Long-term clinical safety and efficacy of drug-eluting stents in real-world patients

ISBN: 978-94-6169-131-6

Layout and printing: Optima Grafische Communicatie, Rotterdam, The Netherlands
Printed with financial support from Abbott Vascular and Cardialysis

Long-term clinical safety and efficacy of drug-eluting stents in real-world patients

Lange-termijn klinische veiligheid en werkzaamheid van drug-eluting stents in real-worldpatiënten

Thesis

to obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
Rector Magnificus

Prof.dr. H.G. Schmidt

and in accordance with the decision of the Doctorate Board

The public defense shall be held on
Wednesday 7th September (Arminius Church) om 09:30 uur

by

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PART 5: CHRONIC TOTAL OCCLUSIONS

PART 6: PATIENTS WITH MULTIVESSEL DISEASE

PART 7: SAPHENOUS VEIN GRAFTS

PART 8: BIFURCATION LESIONS

PART10: STENT THROMBOSIS

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Introduction

INTRODUCTION

Since the first balloon angioplasty was performed in the late 1970's, percutaneous coronary intervention (PCI) has undergone rapid transformation to become an essential treatment option for coronary artery disease as an alternative to surgery. PCI is now widely accepted across the globe, with over half a million procedures being performed annually in the United States alone. Coronary stents were developed in the mid-1980s, and the first randomized trials comparing stenting to balloon angioplasty demonstrated improved angiographic and clinical outcomes. Consequently, coronary artery stenting has progressively replaced balloon angioplasty as the preferred method of PCI. In these initial trials, acute stent thrombosis was a major concern because of high morbidity and mortality. The introduction of dual-antiplatelet therapy with aspirin and a thienopyridine (such as Clopidogrel) as well as improved PCI techniques, decreased the risk of thrombosis to an acceptable level, although the incidence of stent thrombosis remained higher when bare metal stents (BMS) were placed in more complex patients and lesions.

Subsequently, the development of in-stent restenosis emerged as the main clinical problem with BMS with reported rates varying between 15% to 60% depending on patient co-morbidity, including vessel size, and lesion complexity. The widespread adoption of drug-eluting stents (DES) has reduced the rates of restenosis by 60-75% across all lesion and patient subsets. The success of DES is reflected by the fact that they were quickly embraced by the entire interventional cardiology community as the ultimate approach to prevent restenosis. In the years since their approval, DES have become the predominant devices used in PCI, regardless of indication. For example, up to December 2006, more than 2 million patients had received the Cypher sirolimus-eluting stent (SES) worldwide.

However, a temporary break in the increasing DES success story was caused by the so-called European Society of Cardiology (ESC) Firestorm, when proceedings of the congress in September 2006 hypothesized that the use of DES was associated with increased rates of death and myocardial infarction (MI) as compared to BMS [1-3]. Soon, the worldwide DES market crashed (see Figure 1), forcing the American Food and Drug Administration (FDA) to organize a panel meeting on DES on December 7th and 8th, 2006.

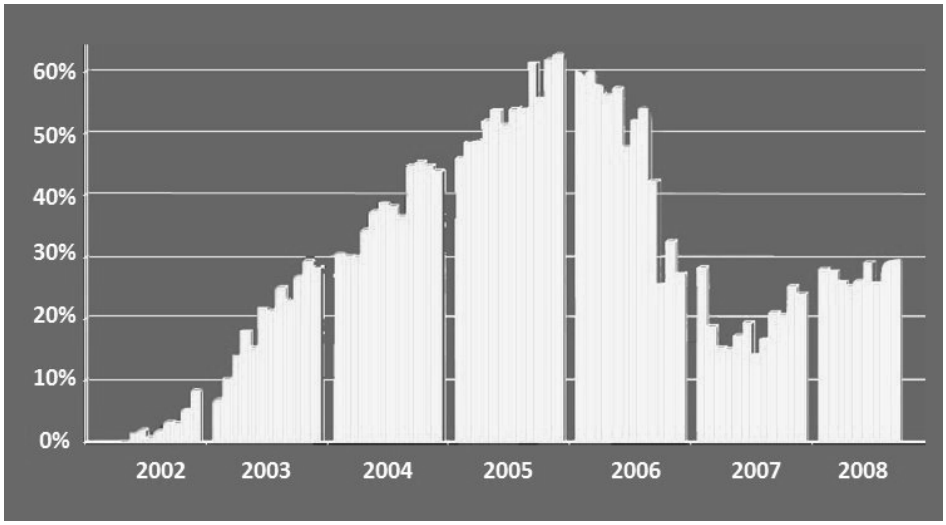

Figure 1. Percentage Drug-eluting stent use in Sweden 2002-8.

After two days of intense debate between key opinion leaders in interventional cardiology, industry and regulatory bodies, the FDA concluded that the use of DES was safe, at least for on-label indications. This conclusion was predominantly based on several investigator-driven meta-analyses of patient level data, based on the pivotal randomized Cypher and Taxus trials. Almost a year later, again at the ESC congress, this time in Vienna, Austria, the focus was on real-world large scale registries, which suggested a better survival when DES were used. Evidence that was initially ignored and widely disputed, suddenly became a consistent finding in over 75,000 patients reported in at least 10 registries and quickly raised the question whether the worldwide cardiology community was *eagerly* mislead in September 2006.

Nevertheless, the concerns about increased rates of death, MI and stent thrombosis ushered in a new era of research in the field of interventional cardiology. Relatively small scale randomized controlled trials with 1-year angiographic primary endpoints were no longer considered sufficient to provide adequate and reassuring information regarding the safety and efficacy of DES. Collaboration between various American and European academic units sought to standardize clinical definitions and endpoints to improve the clarity and consistency of clinical trials. While the DES era started by simply adding a drug to an existing platform, new generations of complex platforms, polymers and coatings are currently being meticulously studied.

In this thesis, the long-term results from the 1st generation of DES are investigated using the all-comer real-world population in Rotterdam, where the Cypher sirolimus-eluting

stent (Cordis, Warren, NJ) was used as the default stent for all patients undergoing PCI since the commercial launch in 2002. In February 2003, SES was replaced by the Taxus Paclitaxel-eluting stent (Boston Scientific, Natick, Massachusetts) as the default stent. Finally in March 2007, the Xience V everolimus-eluting stent (Abbott Vascular, Santa Clara, California) was used for all patients. The use of a single stent type at any 1 time period enables the investigation of complex patients found in real life, many of whom would have been excluded from randomised clinical trials. The long-term data on the first generation DES are explored in a variety of patient subgroups ranging from those with ST-elevation myocardial infarction in Part 3, patients with multivessel disease in Part 6. In Part 9, the incidence and impact of late stent thrombosis, the Achilles heel of DES is examined. Finally in Part 10, the newer generations of drug-eluting stents are evaluated.

The aims of this thesis are to scrutinize the long-term efficacy and safety of 1st generation DES, and to evaluate the benefits of improvements in coronary stent technology.

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CHAPTER 1

The future of drug-eluting stents

Kukreja N, Onuma Y, Daemen J, Serruys PW.

Pharmacol Res. 2008 Mar; 57(3):171-80.

ELSEVIER

Pharmacological Research 57 (2008) 171–180

Pharmacological research

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Perspective☆

The future of drug-eluting stents

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Accepted 29 January 2008

Abstract

This review aims to provide a glimpse into the future of drug-eluting stents (DES). Since their arrival in 2002, DES have transformed the practice of interventional cardiology by drastically reducing restenosis and the need for repeat revascularization. However, data about the potentially fatal long-term risk of stent thrombosis have spurred on research and development to improve upon the first generation of devices. The initial commercially available DES used a stainless steel platform coated with a permanent polymer to provide controlled release of the anti-restenotic drug. The platform, polymer and drug are all targets for improvement. More advanced metallic and fully biodegradable stent platforms are currently under investigation. The permanent polymer coating, a likely contributor adverse events, is being superseded by biocompatible and bioabsorbable alternatives. New drugs and drug combinations are also a research goal, as interventional cardiologists and the industry strive towards safer anti-restenotic DES.

Keywords: Angioplasty; Drug-eluting stent; Polymer

Contents

1. Introduction

Percutaneous revascularization for coronary artery disease has seen rapid and drastic technological advances since its introduction 30 years ago. The technique has been adopted worldwide and is now the commonest modality of revascularization, with increasing numbers of patients being treated each year (almost 2 million procedures were performed in Europe in 2003) [1]. In 2002, the field of interventional cardiology entered a new era with the advent of the first drug-eluting stent (DES) [2]. These expensive and novel devices were quickly embraced by cardiologists and have already had a major impact on coronary revascularization: patients traditionally referred for coronary artery bypass surgery are now revascularized percutaneously, despite a lack of evidence-based medicine. However worrisome data on late stent thrombosis in the first generation of DES have recently emerged. The drugs used are potent cytostatic or cytotoxic agents with detrimental effects on endothelialization. Physician-driven

☆ Perspective articles contain the personal views of the authors who, as experts, reflect on the direction of future research in their field.

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doi:10.1016/j.phrs.2008.01.012

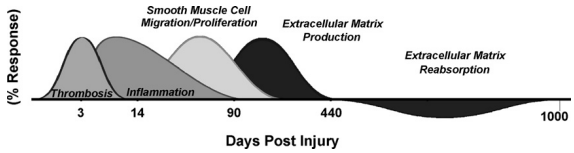

Fig. 1. Vessel healing response following bare-metal stent implantation.

registries with long follow-up suggest an unabated rate of late stent thrombosis even up to 4 years [3–5]. New pharmacologic strategies (e.g. non-polymeric reservoirs, dual drug elution with antithrombotic and anti-inflammatory agents) and new bioabsorbable metallic or non-metallic platforms are currently being tested. The primary goal of DES is no longer the complete abolition of neointimal hyperplasia but the restitution of a healthy, functionally active endothelial lining (e.g. by capturing progenitor endothelial cells or by releasing pro-healing drugs, e.g. nitric oxide), capable of modulating the healing process without a permanent metallic implant. Each DES comprises three components: the stent platform, the active pharmacologic compound, and a drug carrier vehicle (usually a polymer), which controls drug elution. Research for the development of the next generations of DES has focused on each of these components.

2. The rationale behind drug-eluting coronary artery stents

Balloon dilatation as a treatment for obstructive coronary artery disease was first performed in 1977 [6]. The initial shortfalls of this therapy included acute recoil and abrupt vessel closure, which frequently necessitated emergency surgical revascularization [7]. The advent of metallic stents in 1987, initially as a "bailout" for complications of balloon angioplasty but subsequently used as a default revascularization strategy, addressed these problems by providing a mechanical scaffold, thereby reducing rates of emergency bypass surgery to less than 0.5% and reducing restenosis rates from 30 to 40% with balloon angioplasty to 20–25% with bare-metal stents (BMS). However, stent implantation introduced the iatrogenic problem of acute stent thrombosis, whilst restenosis due to neointimal hyperplasia still remained a concern [8–11] (Fig. 1).

Coronary stents are foreign bodies and as such trigger platelet adhesion and activation of the coagulation cascade. Furthermore, high-pressure implantation may cause vessel injury, exposing the thrombogenic subintima, media and atherosclerotic plaque components to the circulation. Stent thrombosis occurred despite the use of heparin and vitamin K antagonists, but has been resolved with the standard use of dual antiplatelet therapy with aspirin and a thienopyridine (either ticlopidine or clopidogrel) until the thrombogenic stent struts have been endothelialised (within 30 days for conventional stents) [12,13].

Neointimal hyperplasia is an exaggerated healing response to vessel trauma resulting from the angioplasty and stent procedure: this has been the major limitation of percutaneous coronary intervention (PCI) in the bare-metal stent era, occurring in 20–30% of cases [14] and has therefore been the pre-eminent focus of recent developments including drug-eluting stents (DES), which utilize the stent itself as a vehicle for local intracoronary drug delivery. In 2002–2003, DES were approved by regulatory bodies in Europe and the USA after initial studies showed a dramatic reduction in rates of restenosis compared with BMS [2,15–17]. Subsequent data from patients with more challenging lesions and clinical presentations have confirmed this benefit with a reduction in restenosis of 60–80% across the board [18–21]. Consequently, the use of DES has been swiftly embraced with market penetration of up to 90% in certain countries.

3. Current commercially available DES

The sirolimus-eluting Cypher stent (Cordis, Warren, New Jersey) is approved for use in the USA, Europe and Japan. The stent consists of a stainless steel platform coated with a permanent polymer (polyethylene-co-vinyl acetate [PEVA] and poly-*n*-butyl methacrylate [PBMA]) containing sirolimus 140 mcg/cm^2, 80% of which is released in 30 days [2,22]. Sirolimus (also known as rapamycin) is a naturally occurring macrolide which is also a potent immunosuppressant licensed for use in transplant recipients. The lipophilic sirolimus binds to FK506-binding protein 12 (FKBP12) and subsequently the mammalian target of rapamycin (mTOR) and thereby blocks the cell cycle, inhibiting the transition from the G1 to S phase, resulting in inhibition of smooth muscle cell (SMC) migration and proliferation [23,24] (Fig. 2). The initial reports of the sirolimus-eluting stent (SES) demonstrated almost complete abolition of neointimal growth [25]. This profound effect on restenosis and repeat revascularization has subsequently been confirmed in larger industry-sponsored randomized trials as well as physician-driven registries including more complex lesions and patients [15,18,20,26–30]. However, potential adverse biological actions of sirolimus include the inhibition of endothelial progenitor cells (EPCs), the upregulation of tissue factor and an increase in the expression of plasminogen activator inhibitor-1 (PAI-1) [31–33]. In clinical practice, SES has been found to unfavorably affect endothelial function [34], which may contribute to adverse clinical events.

The Taxus (Boston Scientific, Natick, Massachusetts) paclitaxel-eluting stent (PES) has also been widely studied in a range of patient and lesion subsets [16,17,35–38]. This stent also incorporates a stainless steel platform with a permanent polymer coating (polystyrene-b-isobutylene-b-styrene [SIBS]) combined with 1 mcg/mm^2 paclitaxel [22]. The release of

paclitaxel is biphasic, with a 48 h early burst followed by low-level release for 2 weeks; however, 90% of the drug remains bound to the polymer [39]. Paclitaxel is an antimitotic microtubule inhibitor, which suppresses cell division in the G0/G1 and G2/M phases, resulting in disruption of SMC migration and proliferation (Fig. 2). However, paclitaxel also increases expression of tissue factor in endothelial cells and increases the expression of PAI-1 [33,40].

The Xience V (Abbott Vascular, Santa Clara, California) everolimus-eluting stent (EES) consists of a Cobalt Chromium (CoCr) platform with a nonerodable polymer and 100 mcg/cm^2 everolimus, a synthetic analogue of sirolimus (40-*O*-(2-hydroxyethyl)-rapamycin) [41] (Fig. 3). The EES has shown favourable results when compared to both BMS and PES in randomised controlled trials [42–46].

The Endeavor (Medtronic Vascular, Santa Rosa, California) zotarolimus-eluting stent (ZES) is also currently in use in Europe. This is also a CoCr platform loaded with a permanent polymer (phosphorylcholine) and a sirolimus analogue (70% released over 30 days), which is therapeutically beneficial when compared to BMS [47–53].

4. Scope for improvement?

Despite the beneficial effects of DES on restenosis and repeat revascularization, there are concerns regarding late (>30 days) and very late (>1 year) stent thrombosis due to delayed endothelialisation despite prolonged dual antiplatelet therapy [5,54–57] (Fig. 4). Features associated with an increased risk of stent thrombosis include small minimal lumen diameter, stent malapposition (either immediately after implantation or as a result of positive remodeling), increasing stent length, residual dissections, geographical miss of the diseased target, poor left ventricular function, diabetes mellitus, increasing age, acute coronary syndrome at presentation, renal failure, treat-

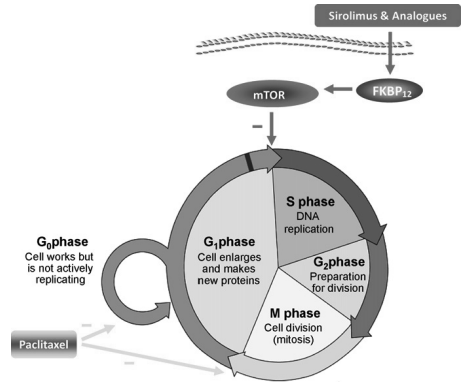

Fig. 2. Effects of sirolimus analogues and paclitaxel on the cell cycle.

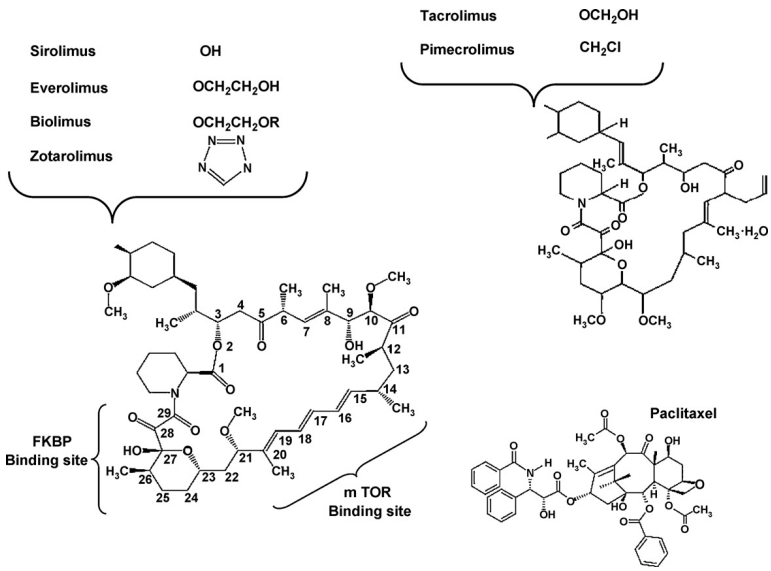

Fig. 3. Chemical structure of sirolimus analogues, calcinuerin inhibitors and paclitaxel.

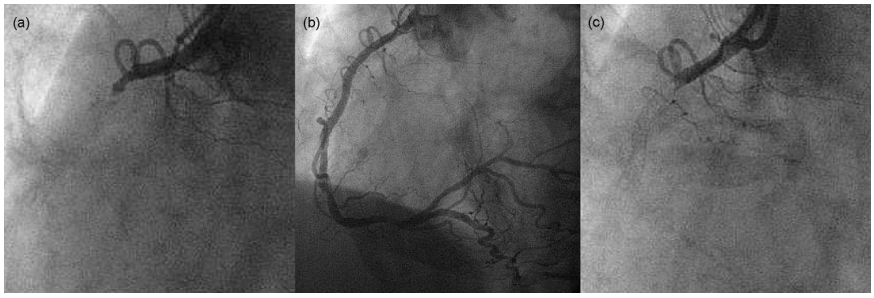

Fig. 4. This patient initially presented with an ST-elevation myocardial infarction due to occlusion of the right coronary artery (a), which was successfully treated with implantation of a paclitaxel-eluting stent (b). One year later the patient suffered another ST-elevation myocardial infarction, this time due to stent thrombosis (c).

ment of bifurcations and treatment of instent restenosis (ISR) [4,5,58–61].

Pathological autopsy studies showed an association between lack of neointimal strut coverage and stent thrombosis [62,63]. More recently, from a registry totalling 81 human autopsies of drug-eluting stents, Finn et al. demonstrated that the most powerful histological predictor of stent thrombosis was endothelial coverage [56]. Recent angioscopic studies also supported this association, demonstrating incomplete neointimal coverage as long as 2 years after implantation of sirolimus-eluting stents [64,65]. Therefore, one of the targets in current research is restitution of a healthy but not hyperproliferative endothelial lining.

To allow controlled drug release, the first generation of DES were coated with a permanent polymer, which persisted after drug release. The presence of such a polymer coating may contribute to stent thrombosis as a result of delayed healing and a hypersensitivity reaction in some cases [63,66–68]. Since these hypersensitivity reactions can occur more than 4 months after DES implantation (long after the period of drug release), it is possible that these events are due to the polymer coating [63]. A principal target of current research is the evaluation of biocompatible polymer coatings, with the aim of permitting controlled drug release whilst minimizing any such adverse effects. Another alternative is to avoid the use of polymers altogether.

5. New permanent metallic platforms

The first two available DES were composed of a 316L stainless steel platform, since this material is radiopaque with adequate radial strength. However, cobalt chromium (CoCr) exhibits superior radial strength and improved radiopacity allowing for thinner stent struts which may reduce restenosis in bare-metal stents (BMS) [69,70], whilst reducing device profile and hence improving its deliverability to the target lesion. CoCr is the platform for the second generation Xience V (EES) and Endeavor (ZES) stents (Table 1).

The Conor DES (Conor Medsystems, Menlo Park, California) has utilized initially a stainless steel and subsequently a CoCr platform with multiple intra-strut wells (Fig. 5). The stent struts are linked to flexible sinusoidal bridges by specially contoured features called ductile hinges. Stent deformation during deployment is confined to the 10% of the stent comprising the ductile hinges, rendering the struts as passive elements, permitting them to utilize reservoirs for drug delivery with no detrimental effect on the strength or crush resistance of the struts. The advantage is that these holes can be loaded with polymer/drug that will not deform or separate from the stent during expansion [71,72].

Beyond "workhorse" DES, new stents are under evaluation for specific lesion types, which historically are associated with worse angiographic and clinical outcomes, namely bifurcations and small vessels. The anatomy of bifurcation lesions produces difficulties in ensuring adequate scaffolding whilst preserving the side-branch ostium—stent underexpansion at this site is common and is associated with increased restenosis and thrombosis rates [73]. The Axxess Plus stent (Devax, Irvine, California) is a nitinol (nickel–titanium) self-expanding thin-strut stent, coated with abluminal PLA and biolimus A9, another sirolimus analogue [74].

The Cardiomind self-expanding nitinol stent (Cardiomind, Sunnyvale, California) has been designed to improve deliverability to distal or tortuous segments of the coronary tree. The stent is incorporated in a 0.014-in. guidewire and has a far lower crossing profile than balloon-expandable stents. The clinical feasibility of a bare cardiomind stent has already been tested with promising results, and the evaluation of a biodegradable polymer-coated stent is expected to commence shortly [75].

Another novel concept is the Xtent custom NX stent (Xtent, Menlo Park, California). This is a CoCr platform coated with PLA and biolimus A9. The unique feature is that the stent consists of multiple 6 mm interdigitating segments, which can be deployed either in combination or separately. This system allows for in situ customization of stent length instead of relying on fixed-length stents. This stent has already been investigated in humans, with further studies in progress [76].

6. Novel stent coatings

The first generation of DES incorporates a polymer to allow controlled drug release. The next generations of DES are utilizing more complex biocompatible materials to achieve these aims. For example, the phosphorylcholine polymer used in the second generation Endeavor ZES, although nondegradable, is a natural component of the cell membrane and as such is considered biocompatible. A multitude of new stents have been investigated incorporating fully biodegradable polymers – the most commonly used being polylactic acid (PLA) and polylactic-co-glycolic acid (PLGA), which are fully metabolized to water and carbon dioxide, leaving in situ a bare-metal stent after all the drug has been released. Preliminary promising data are available on three different stainless steel stents coated with sirolimus and PLA: Excel (JW Medical Systems, China), Cura (Orbus Neich, Fort Lauderdale, Florida) and Supralimus (Sahajanand Medical Technologies, India), although large-scale trials have yet to be performed [77,78]. Paclitaxel has also shown encouraging results when incorporated with PLGA (Conor Medsystems, Menlo Park, California) and PLA (Infinnium; Sahajanand Medical Technologies, India) [71,72,79].

Other concepts include avoiding the use of a polymer completely. A titanium–nitric oxide alloy has been applied to stainless steel stents with encouraging results, including decreased platelet adhesion and neointimal hyperplasia compared with BMS [80]. A microporous stainless steel stent (Yukon, Translumina, Germany) offers the potential to customise drug doses and combinations [81]. The system is therapeutically effective with rapamycin [82]. A nanoporous hydroxyapetite (a biocompatible crystalline derivative of calcium phosphate) coating, which can be impregnated with anti-restenotic drugs, is currently under development [83]. A stainless steel stent coated with nanoporous aluminium oxide and tacrolimus showed disappointing results however, with evidence of particle debris shed from the coating contributing to increased neointimal hyperplasia [84].

7. New drugs and combinations

Another sirolimus analogue under investigation is biolimus A9. This has been evaluated in two biodegradable (PLA) polymer-coated stainless steel stents (Biomatrix; Biosensors International, Singapore and Nobori; Terumo, Japan), where approximately 70% of the drug is eluted over 30 days followed by sustained release with polymer degradation over several months [85,86]. The biolimus-eluting stent has proved effective when compared to both BMS and PES [87].

Tacrolimus is another macrolide immunosuppressant drug licensed for recipients of organ transplantation. However the cellular mechanisms of tacrolimus differ from sirolimus: tacrolimus acts by binding FKBP12 and subsequently inhibiting calcineurin (and thereby decreasing the expression of pro-inflammatory cytokines, e.g. interleukin-2) and suppressing T cell proliferation [24]. The cellular effect is to hold cells in the G0 phase, where they are able to function but unable to replicate. Furthermore, tacrolimus has a preferential effect on SMCs as apposed to endothelial cells and unlike the mTOR inhibitors and paclitaxel, does not increase expression of tissue factor [31,40,88,89]. However, a stainless-steel stent loaded with tacrolimus in abluminal reservoirs (Janus; Sorin Biomedica Cardio, Italy) performed no better than a BMS [90]. A CoCr stent coated with PLGA and tacrolimus (Mahoroba; Kaneka, Japan) is currently under investigation [91].

Pimecrolimus, a tacrolimus analogue has been investigated on its own, but also in combination with paclitaxel. It exerts multiple anti-inflammatory effects including inhibition of IL-2 synthesis via calcineurin inhibition (Table 2).

The Synchronnium stent (Sahajanand Medical Technologies, India) consists of a stainless steel stent coated with a biodegradable polymer incorporating heparin and sirolimus. The addition of heparin aims to decrease the thrombogenicity of the stent. Both drugs are released simultaneously over approximately 50 days. The initial clinical results are promising.

Genistein, a natural isoflavanoid phytoestrogen is currently under investigation in combination with sirolimus. Flavanoids have a number of potentially beneficial characteristics including anti-platelet aggregation, anti-inflammatory and anti-oxidant properties.

An alternative approach, concentrating on healing as opposed to SMC inhibition, is used in the Genous endothelial progenitor cell (EPC) capture stent (Orbus Neich, Fort Lauderdale, Florida). This is a stainless steel stent coated with murine monoclonal antihuman CD34 antibodies, which attract circulating EPCs thereby encouraging rapid endothelialisation and reducing the risk of thrombosis. The EPC capture stent appears effective in stable patients [92–94] and also in the setting of acute myocardial infarction [95].

Another novel target is the local delivery of anti-VEGF, which might decrease the formation of vaso vasorum and thereby promote atheromatous plaque stability. Investigation into the anti-VEGF bevacizumab (Avastin) eluting BiodivYsio stent (Biocompatibles Ltd., London, UK) is currently in progress [96].

8. Fully biodegradable platforms

An option that is currently attracting a great deal of interest is the development of fully biodegradable stents. The required characteristics are the ability for controlled, sustained drug release, sufficient mechanical strength to prevent negative vessel remodeling and avoid stent deformity/strut fractures and compatibility with non-invasive coronary angiography (MRI and CT). Conceptually, once they are fully absorbed, only the healed vessels are left behind with no residual prosthesis and therefore no potential adverse interactions with the coronary artery. Accordingly, long-term antiplatelet therapy may not be warranted as the risk of late or very late stent thrombosis should be low. Additionally, following absorption, vasomotion is restored, and there is less difficulty with future percutaneous or surgical revascularization.

The safety of an uncoated fully degradable poly-L-lactic acid (PLLA) stent (Igaki-Tamai; Igaki Medical Planning, Japan) has

Fig. 5. The CoStar stent (Conor Medsystems, Menlo Park, California), showing the ductile hinges, bridge elements and reservoirs.

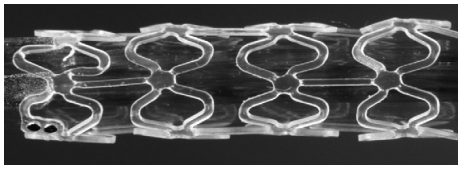

Fig. 6. The fully biodegradable everolimus-eluting poly-L-lactic acid stent (BVS; Abbott Laboratories, IL, USA). Two radiopaque markers are visible on the lower left hand corner of the stent.

already been established [97]. The deployment procedure is technically more complex than a typical balloon-expandable metal stent (the Igaki-Tamai stent is partially self-expanding, but deployment requires the use of a balloon containing heated contrast). Although the acute recoil of the stent was measured as 22% by quantitative coronary angiography, the clinical results were encouraging with a target lesion revascularization rate of 10.5% after 6 months.

An everolimus-eluting PLLA stent (BVS; Abbott Laboratories, IL, USA) has recently undergone clinical evaluation, with promising results. The mechanical properties of the stent appear favourable: acute recoil (the difference between mean diameter during balloon dilatation and mean diameter at the end of the procedure) was similar to a CoCr EES (6.9% vs. 4.9%) [98]. The stent is radiolucent, but contains two platinum markers at each end, to allow identification on both conventional and non-invasive angiography [99] (Fig. 6).

Another polymer-based degradable stent currently undergoing clinical evaluation is the tyrosine-derived polycarbonate REVA stent (REVA medical, San Diego, Ca, USA). This has the advantage of being radiopaque, permitting direct visualization under standard fluoroscopy. The stent structure is unique and utilizes a "slide & lock" design rather than the usual material deformation for deployment.

Apart from polymer-based fully degradable stents, magnesium is a promising alternative. The absorbable metal stent (AMS; Biotronik, Bülach, Switzerland) consists of a bioabsorbable magnesium alloy. The stent is completely radiolucent: accurate positioning during deployment is possible due to two radio-opaque markers at the balloon ends. Although clearly visible on intravascular ultrasound, the stent itself is not visible by

Table 1
Drug-eluting stents in clinical use or under investigation

Drug category	Drug	Stent platform	Coating	Stent name	Company	Approval status
mTOR inhibitors	Sirolimus	SS	DP	Cypher select	Cordis	FDA/CE
		SS	BP	Supralimus	Sahajanand	CE
		SS	BP	CURA	Orbus Neich	
		SS	BP	Exel	JW Medical	
		SS	None	Yukon	Translumina	CE
		CoCr	BP	Supralimus-Core	Sahajanand	
	Everolimus	CoCr	DP	Xience V	Abbott	CE
		PLLA	BP	Absorb	Abbott	Trial
	Zotarolimus	CoCr	DP	Endeavour	Medtronic	CE
		CoCr	DP	Endeavour resolute	Medtronic	Trial
	Biolimus	SS	BP	Biomatrix	Biosensors	CE
	A9	SS	BP	Nobori	Terumo	CE
		CoCr	BP	Xtent	Xtent	Trial
Calcineurin inhibitors	Tacrolimus	SS	None	Janus	Sorin	CE
		CoCr	BP	Maharoba	Kaneka	Trial
	Pimecrolimus	CoCr	BP	Corio	Conor	
		CoCr	BP	Prolimus	Biotronik	Trial
		Magnesium	BP	Dreams	Biotronik	Trial
Microtubule sta-bi-lizer	Paclitaxel	SS	DP	Taxus Liberte	Boston Scientific	FDA/CE
		SS	BP	Infinnium	Sahajanand	CE
		CoCr	BP	CoStar	Conor	CE
		SS	None	Axxion	Biosensors	CE
		Tyrosine polycarbonate	BP	REVA	REVA	Trial
EPC capture	Anti-CD34	SS	DP	Genous	Orbus Neich	CE

mTOR: mammalian target of rapamycin; SS: stainless steel; CoCr: cobalt chromium; DP: durable polymer; BP: biodegradable polymer; PLLA: poly-L-lactic acid; EPC: endothelial progenitor cell; CE: Conformité Européenne; FDA: Food and Drug Administration; late lumen loss = difference between minimal lumen diameter post-procedure and at follow-up angiography in first-in-man trials; binary angiographic restenosis = % of cases with ≥50% diameter stenosis at follow-up angiography in first-in-man trials.

Table 2
Combination drug-eluting stents under clinical investigation

Drug 1	Drug 2	Stent platform	Coating	Stent name	Company
Sirolimus	Genistein				Sahajanand
Pimecrolimus	Paclitaxel	CoCr	BP	Symbio	Conor
Sirolimus	Heparin	SS	BP	Synchronnium	Sahajanand
Zotarolimus	Dexamethasone			Zodiac	Abbott
Sirolimus	Estradiol	SS	None		Translumina

SS: stainless steel; CoCr: cobalt chromium; BP: biodegradable polymer.

conventional or non-invasive imaging [100,101]. The clinical results of the bare AMS were disappointing with high rates of repeat revascularization (45%): a drug-eluting version is eagerly anticipated [102].

9. The future

From these historical developments, we can see that the ideal coronary stent should have several properties. The first is to provide a scaffold to prevent acute recoil and to seal any significant dissection flaps. The stent should also be deliverable and visible, with adequate radiopacity (or the presence of radiopaque markers) to enable precise positioning under X-ray fluoroscopic guidance. The second is to allow sufficient endothelialisation to prevent stent thrombosis whilst minimizing the natural vessel healing reaction, which results in neointimal hyperplasia [103]. The use of biocompatible and biodegradable polymer coatings is commonplace in the next generations of DES. Fully degradable stents offer potential solutions to these conundrums, whilst the use of new or combinations of drugs have the theoretical advantage of producing less toxicity.

10. Conclusion

Since 2002, drug-eluting stents have emerged as the default treatment for many patients with coronary artery disease. However, the provision of a permanent mechanical scaffold with complete inhibition of the endothelium no longer seems sufficient. A large number of devices are currently under investigation, with particular emphasis on new metallic platforms, biocompatible stent coatings, new drug combinations and fully biodegradable platforms. The optimal composition of the next generation of DES has yet to be resolved.

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CHAPTER 2

Four-year clinical follow-up of the rapamycin-eluting stent evaluated at Rotterdam Cardiology Hospital registry

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Am J Cardiol. 2008 Apr 15; 101 (8):1105-11.

Four-Year Clinical Follow-Up of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital Registry

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Although the safety of drug-eluting stents has been under considerable scrutiny, limited real-world follow-up data extending up to 4 years are available. The randomized clinical trials carefully selected patients and are not reflective of everyday practice. From April to October 2002, 508 consecutive patients treated with sirolimus-eluting stents (SES) were enrolled. The control group consisted of 450 patients treated with bare-metal stents during the preceding 6 months. After 4 years of follow-up, the incidence of composite major adverse clinical events (all-cause death, myocardial infarction, or target vessel revascularization) was found to be significantly lower in the SES group (23.0% vs 28.7%, adjusted hazard ratio 0.66, 95% confidence interval 0.51 to 0.86), as were rates of target vessel revascularization (12.2% vs 17.8%, adjusted hazard ratio 0.57, 95% confidence interval 0.39 to 0.83). There were no differences in all-cause mortality (10.5% for SES vs 10.6% for bare-metal stents, p = 0.9) or in the rates of cardiac death (4.5% vs 6.9%, p = 0.1). Although there was no difference in overall stent thrombosis (2.3% vs 2.2%, p = 1.0), SES had a higher rate of very late stent thrombosis (1.4% vs 0%, p = 0.02), balanced by a lower rate of early stent thrombosis (0.4% vs 1.8%, p = 0.05). In conclusion, after 4 years, SES were found to remain safe and effective compared with bare-metal stents. Nevertheless, the higher rate of very late stent thrombosis remains a concern. Longer term follow-up will be required to determine the extent of this problem. **(Am J Cardiol 2008;101:1105–1111)**

Long-term analyses of randomized trials of drug-eluting stents (DES) show a persisting benefit of DES on restenosis and target lesion revascularization, whereas mortality rates with DES and bare-metal stents (BMS) are equivalent, despite concerns regarding late stent thrombosis.[1–5] Inevitably, these randomized trials have selective inclusion criteria, but in the real world, DES are often used beyond their labeled indications, for example, in bifurcation lesions, coronary artery bypass grafts, chronic total occlusions, long lesions requiring multiple overlapping stents, and acute myocardial infarction (MI).[6] Despite using sirolimus-eluting stents (SES) for "off-label" indications in a considerable number of cases, we have previously reported an ongoing benefit of SES after 3 years of follow-up in real-world consecutive patients.[7] Here, we present the clinical outcomes after 4 years.

Methods

The Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry has already been described.[8] On April 16, 2002, our institution commenced the use of SES (Cypher; Cordis Corporation, Miami Lakes, Florida) as the default strategy for every percutaneous coronary intervention. In the first 6 months of enrollment, 508 patients with de novo lesions were treated exclusively with SES (the SES group) and compared with a group of 450 consecutive patients treated with BMS for de novo lesions in the preceding 6 months (the pre-SES group), matched for stent diameter.[9] The protocol was approved by the hospital's ethics committee and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

All procedures were performed following current standard procedural guidelines as previously reported.[10] Angiographic success was defined as residual stenosis <30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow. All patients were advised to maintain lifelong aspirin. At least 1 month of clopidogrel treatment (75 mg/day) was recommended for patients treated in the pre-SES phase. For patients treated with SES, clopidogrel was prescribed for ≥3 months, unless 1 of the following was present: multiple SES implantation (>3 stents), total stented length >36 mm, chronic total occlusion, or bifurcation treatment. In these patients, clopidogrel was maintained for ≥6 months.

The prespecified primary end point was major adverse clinical events (MACEs), defined as a composite of all-cause death, nonfatal MI, or target vessel revascularization (TVR).[8] MI was diagnosed by an increase in creatine kinase-MB fraction of 3 times the upper limit of normal, according to American Heart Association and American College of Cardiology guidelines.[11,12] Stent thrombosis was defined as angiographically documented thrombus with

Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands. Manuscript received October 17, 2007; revised manuscript received and accepted November 29, 2007.

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0002-9149/08/$ – see front matter
doi:10.1016/j.amjcard.2007.11.074

Table 1
Baseline characteristics

Variable	BMS (n = 450)	SES (n = 508)	p Value
Men	70.4%	67.9%	0.4
Age (yrs)	60.8 ± 11.0	61.1 ± 11.0	0.7
Body mass index (kg/m^2)	26.6 ± 3.6	27 ± 4	0.1
Previous MI	39.7%	30.2%	0.02
Previous coronary bypass surgery	8.0%	9.3%	0.5
Previous percutaneous intervention	18.0%	18.8%	0.8
Multivessel coronary disease	47.8%	54.2%	0.05
Hypercholesterolemia*	55.3%	55.3%	1.0
Hypertension‡	37.6%	41.3%	0.2
Family history of coronary disease	28.2%	32.5%	0.2
Current smoker	34.0%	30.7%	0.3
Diabetes mellitus	14.9%	17.7%	0.2
Clinical presentation			0.6
Stable angina pectoris	47.6%	44.7%	
Unstable angina pectoris	34.7%	37.2%	
Acute MI	17.8%	18.1%	
Cardiogenic shock†	11.3%	9.8%	0.7

Data are expressed as mean ± SD or percentages.
* Defined as fasting total cholesterol >5mmol/L (193 mg/dl) or the use of lipid-lowering therapy.
† Refers to patients with acute MIs.
‡ Defined as blood pressure >140/90 mm Hg or treatment for hypertension.

Table 2
Procedural characteristics

Variable	BMS (n = 450)	SES (n = 508)	p Value
Coronary vessel treated*			
Left anterior descending	59.3%	58.7%	0.8
Right	34.0%	38.6%	0.1
Left circumflex	33.1%	31.7%	0.6
Saphenous vein graft	2.0%	3.3%	0.2
Left main	2.2%	3.0%	0.5
ACC/AHA lesion type			
A	19.6%	21.9%	0.4
B1	31.8%	30.7%	0.7
B2	49.6%	48.6%	0.8
C	29.8%	42.5%	<0.01
Bifurcation	7.8%	15.7%	<0.01
Nominal stent length ≥33 mm	9.8%	35.0%	<0.01
No. of stents	1.8 ± 1.1	2.2 ± 1.4	<0.01
Total stent length (mm)	30.1 ± 19.6	38.8 ± 27.9	<0.01
Glycoprotein IIb/IIIa inhibitor used	33.3%	19.3%	<0.01
Average stent diameter (mm)	3.15 ± 0.31	2.85 ± 0.21	<0.01
Angiographic success	97.3%	97.2%	0.9
Clopidogrel duration (mo)	1 ± 0.1	4.2 ± 2	<0.01

Data are expressed as mean ± SD or percentages.
* Patients with each vessel type, hence total >100%.
ACC = American College of Cardiology; AHA = American Heart Association.

Table 3
Cumulative incidence of adverse events

Variable	BMS	SES	p Value
Death	48 (10.6%)	53 (10.5%)	0.9
MI	23 (5.2%)	21 (4.2%)	0.5
TVR	78 (17.8%)	60 (12.2%)	0.02
Composite MACEs	127 (28.7%)	115 (23.0%)	0.05
Stent thrombosis	10 (2.2%)	12 (2.3%)	1.0

TIMI grade 0 or 1 flow, accompanied by acute symptoms (consistent with the definition of definite stent thrombosis as recommended by the Academic Research Consortium).[13,14] The timing of stent thrombosis was categorized into early (<30 days after implantation), late (30 days to 1 year), or very late (>1 year).[14]

Follow-up survival data for all patients were obtained from municipal civil registries. The causes of death were classified according to the International Classification of Diseases and Related Health Problems, 10th Revision. A health questionnaire was subsequently sent to all living patients with specific inquiries on rehospitalization and MACEs. Because ours is the principal regional cardiac referral center, repeat procedures (percutaneous and surgical) are normally performed at our institution and recorded prospectively in our database. For patients who had adverse events at other centers, medical records or discharge summaries from the other institutions were systematically reviewed. General practitioners, referring cardiologists, and patients were contacted as necessary if further information was required.

Continuous variables were compared using Student's *t* test and are presented as mean ± SD. Categorical variables were compared using either Fisher's exact test or Pearson's chi-square test (both 2-sided) and are presented as counts and percentages. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method, and curves were compared using the log-rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Separate Cox regression analyses were performed to identify predictors of adverse events, using the clinical, angiographic, and procedural variables listed in Tables 1 and 2. Variables with a significance of $p < 0.05$ were entered into a Cox multivariate regression analysis; the final results are presented as adjusted hazard ratios (HRs) with 95% confidence intervals (CIs).

Results

Complete follow-up was available for 95.5% of patients. The baseline clinical characteristics of the 2 groups were similar except for a higher prevalence of multivessel disease in the SES group (54.2% vs 47.8%, $p = 0.05$) and a lower incidence of previous MI (30.2% vs 39.7%, $p = 0.02$). Full baseline and procedural details are listed in Tables 1 and 2. Overall, patients treated with SES underwent more complex treatment (more type C lesions, more bifurcations, more stents used, longer total stent length, and smaller average stent diameter). As previously reported, overall 38% of SES group underwent repeat coronary angiography in the first year, while none of the BMS group underwent a scheduled restudy.[9] After the first year, all cases of repeat angiography were clinically mandated.

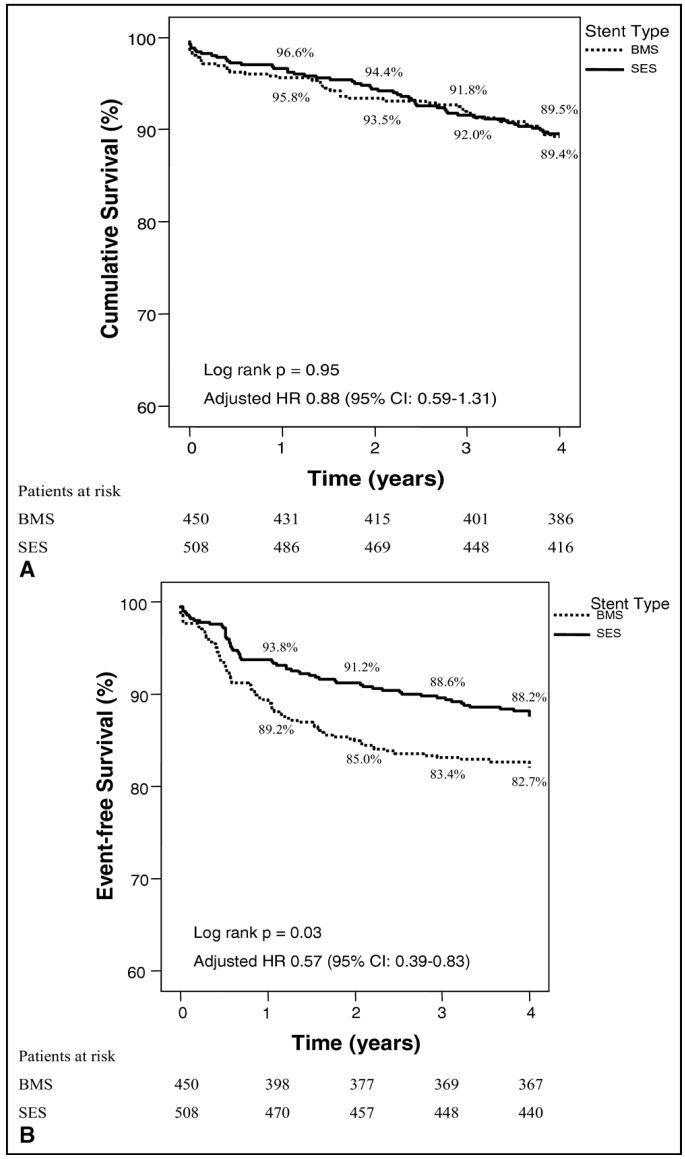

Figure 1. Kaplan-Meier survival curves for *(A)* freedom from death, *(B)* freedom from TVR, *(C)* freedom from composite MACEs (defined as death, MI, or TVR), and *(D)* freedom from stent thrombosis.

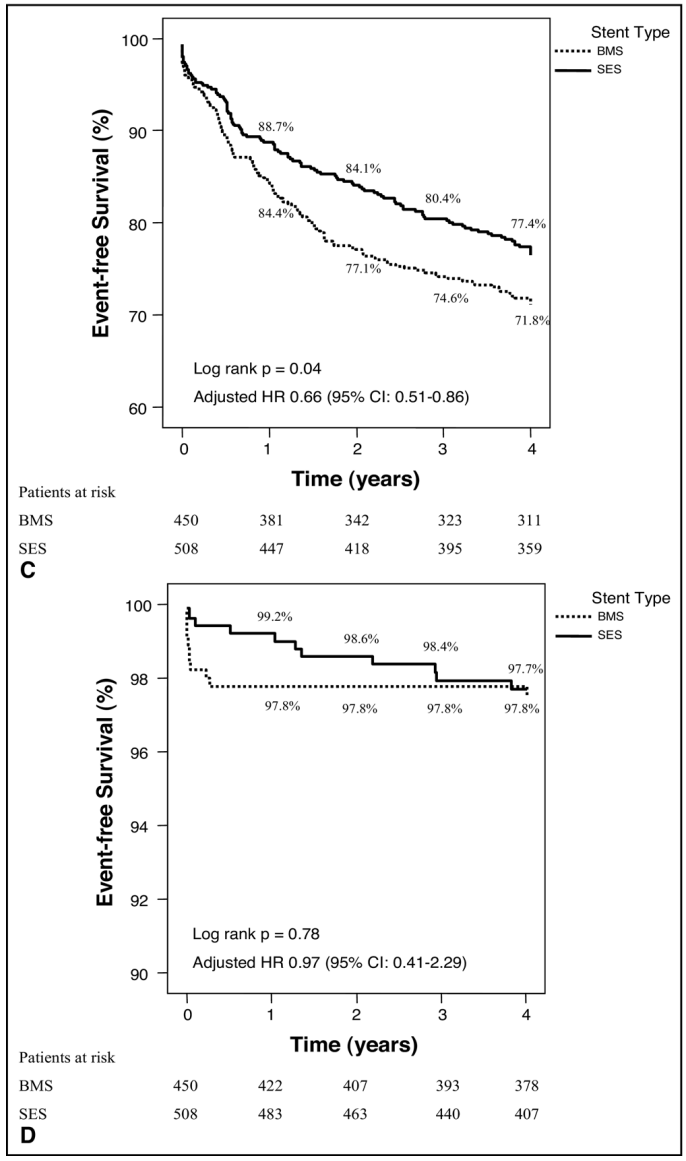

Figure 1. *(continued).*

Table 4
Events between 3 and 4 years of follow-up

Variable	BMS	SES	p Value
Death	11 (2.4%)	10 (2.0%)	0.66
MI	1 (0.2%)	2 (0.4%)	1.0
TVR	5 (1.1%)	10 (2.0%)	0.31
Composite MACEs	13 (2.9%)	19 (3.7%)	0.48
Stent thrombosis	0 (0%)	1 (0.1%)	1.0
Other revascularization	2 (0.4%)	4 (0.8%)	0.69

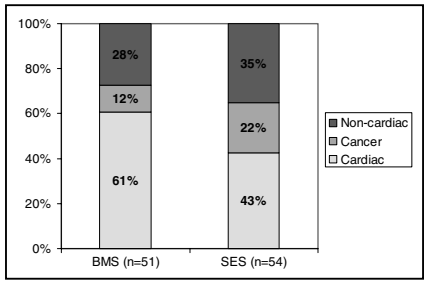

Figure 2. Causes of death expressed as percentages of all deaths in each group. There were no statistically significant differences for any of the categories.

Table 5
Timing of definite stent thrombosis

Variable	BMS	SES	p Value
Early	8 (1.8%)	2 (0.4%)	0.05
Acute	4 (0.9%)	1 (0.2%)	0.2
Subacute	4 (0.9%)	1 (0.2%)	0.2
Late	2 (0.4%)	2 (0.4%)	1.0
Very late	0 (0%)	7 (1.4%)	0.02
Total	10 (2.2%)	11 (2.2%)	1.0

Early stent thrombosis was defined as occurring within 30 days of the index procedure, acute stent thrombosis within 24 hours, subacute stent thrombosis from 24 hours to 30 days, late stent thrombosis from 30 days to 1 year, and very late stent thrombosis >1 year after the index procedure.

The clinical outcomes after 3 years of follow-up have already been reported.[7] The event rates after 4 years are listed in Table 3. The cumulative survival rates for death, TVR, overall MACEs, and stent thrombosis are displayed in Figure 1. As indicated in Table 4, there were no statistically significant differences in the occurrence of any clinical end point between 3 and 4 years of follow-up, although there was a trend toward a higher rate of TVR in the SES group. The cause of death was ascertained in all cases. Analysis of the causes of death showed no significant differences between the 2 groups during 4 years of follow-up, as demonstrated in Figure 2.

Further examination of patients with stent thrombosis revealed that despite no statistically significant difference in overall stent thrombosis rates between the 2 groups, the BMS group had a higher incidence of early stent thrombosis, whereas the SES group had a higher incidence of very late stent thrombosis, as listed in Table 5. The status of antiplatelet therapy at the time of stent thrombosis was available for 18 of the 21 patients. One BMS patient with early stent thrombosis and 1 DES patient with very late stent thrombosis had recently stopped clopidogrel (within 1 week). The details of antiplatelet therapy at the time of stent thrombosis are shown in Figure 3.

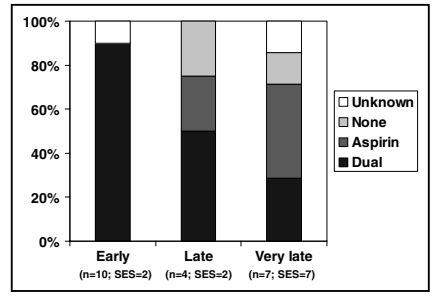

Figure 3. Antiplatelet therapy at the time of stent thrombosis.

Table 6
Independent predictors of target vessel revascularization and major adverse clinical events

Variable	HR	95% CI
TVR		
Diabetes mellitus	1.80	1.18–2.77
AHA/ACC lesion type B2 or C	1.78	1.08–2.95
Previous percutaneous intervention	1.62	1.06–2.46
Treatment with SES	0.57	0.39–0.83
Prespecified composite MACEs		
Cardiogenic shock	3.59	1.81–7.14
Left main treatment	1.98	1.06–3.73
Diabetes mellitus	1.81	1.34–2.43
Previous percutaneous intervention	1.52	1.12–2.05
Total stent length (per 10-mm increment)	1.11	1.00–1.23
Treatment with SES	0.66	0.51–0.86

Abbreviations as in Table 2.

The independent predictors of mortality were cardiogenic shock (HR 5.79, 95% CI 2.46 to 13.6), left main coronary artery treatment (HR 2.17, 95% CI 1.00 to 4.17), diabetes mellitus (HR 1.78, 95% CI 1.11 to 2.85), age (per 10-year increment HR 1.42, 95% CI 1.16 to 1.74), and angiographic success (HR 0.43, 95% CI 0.19 to 0.98). The only independent predictors of definite stent thrombosis were the presence of insulin-dependent diabetes (HR 3.87, 95% CI 1.13 to 13.3), acute MI at presentation (HR 2.58, 95% CI 1.03 to 6.44), and treatment of the left anterior descending artery (HR 0.33, 95% CI 0.11 to 0.99). The presence of diabetes was the only independent predictor of MI (HR 2.16, 95% CI 1.12 to 4.15). All independent predictors for TVR or composite MACEs are listed in Table 6. Treatment with SES did not predict

death (adjusted HR 0.88, 95% CI 0.59 to 1.31), MI (adjusted HR 0.67, 95% CI 0.36 to 1.23), or overall stent thrombosis (adjusted HR 0.97, 95% CI 0.41 to 2.29) but was protective against TVR (adjusted HR 0.57, 95% CI 0.39 to 0.83) and composite MACEs (adjusted HR 0.66, 95% CI 0.51 to 0.86).

Discussion

In this report, we have described long-term clinical outcomes after the use of SES in an all-comers, real-world registry. We have previously reported results after 1, 2, and 3 years of follow-up, all of which have demonstrated no difference in mortality but a continued benefit of SES with respect to TVR and overall MACEs.[7,9,15] To date, there appears to be no diminution of the protective effect of SES treatment with time; after 2 years, the HR for TVR was 0.53 (95% CI 0.36 to 0.79), and the HR for composite MACEs was 0.68 (95% CI 0.50 to 0.91), while after 4 years, these values were 0.57 (95% CI 0.39 to 0.83) and 0.66 (95% CI 0.51 to 0.86), respectively.[15] Thus, after 4 years, the beneficial treatment effect of SES on TVR and composite MACEs was maintained, with no evidence of any late "catch-up" effect of restenosis. Although 4-year follow-up data are available for the randomized trials of SES, our data provide the longest possible follow-up for more complex patients because we used SES as a default treatment strategy for all patients as soon as they became commercially available.

There have been several recent reports addressing the safety of DES, particularly with regard to mortality and stent thrombosis.[1–5,16] Two analyses examined 1,748 patients enrolled in the 4 main randomized SES trials (the Randomized Study With the Sirolimus-Eluting Velocity Balloon-Expandable Stent [RAVEL], Sirolimus-Eluting Stent in Coronary Lesions [SIRIUS], Canadian Sirolimus-Eluting Stent in Coronary Lesions [C-SIRIUS], and European Sirolimus-Eluting Stent in Coronary Lesions [E-SIRIUS]).[3,4] They found no significant differences in 4-year rates of mortality or stent thrombosis between SES and BMS. Another meta-analysis of 4,958 patients enrolled in randomized trials, including some complex patients such as those presenting with acute MI and those who underwent saphenous vein or chronic total occlusion treatment, also found no difference in the rate of death or stent thrombosis between SES and BMS patients after a maximum of 5 years of follow-up.[1] A recently reported network analysis of >18,000 patients enrolled in 38 randomized DES trials (including 6,771 patients treated with SES and 4,921 patients treated with BMS) also found no differences between SES and BMS with regard to mortality or stent thrombosis after up to 4 years of follow-up.[5] However, treatment with SES was protective against MI (HR 0.81, 95% CI 0.66 to 0.97).

The findings in this report are consistent with these recent meta-analyses: we also found no difference in mortality or stent thrombosis, although our overall mortality rates were higher than those reported in the meta-analyses of the randomized trials.[1,3,4] In our patients, we found no significant differences in mortality between the BMS and SES groups, although the SES patients underwent more complex treatment. Reassuringly, there was a trend toward a reduced rate of cardiac death with SES compared with BMS (4.5% vs 6.9%, $p = 0.1$).

Similarly, the rate of definite stent thrombosis (2.3% for SES vs 2.2% for BMS) was higher in our cohort than in a meta-analyses of the randomized trials (1.2% for SES vs 0.6% for BMS using the trial definitions for stent thrombosis and 1.5% for SES vs 1.7% for BMS using the Academic Research Consortium definitions for definite and probable stent thrombosis).[16] An analysis of >8,000 patients treated with DES (paclitaxel-eluting stents and SES) demonstrated an overall stent thrombosis rate of 2.9% after 3 years, with an ongoing incidence of late stent thrombosis of 0.6% per year.[2] Among the 3,875 patients treated with SES, the stent thrombosis rate was 2.7% after 4 years of follow-up.[17] In the present cohort, the early stent thrombosis rate was lower in the DES group, despite the DES patients' receiving glycoprotein IIb/IIIa antagonists less frequently and having undergone treatment of smaller vessels and longer lesions. Although early stent thrombosis is associated with suboptimal angiographic and intravascular ultrasound findings,[18] the pathophysiologic mechanisms of late stent thrombosis are quite different (related to delayed healing and incomplete endothelialization[19,20]); late stent thrombosis was more common in our DES cohort, although there were no significant differences in overall stent thrombosis. Most patients with stent thrombosis were on some form of antiplatelet therapy at the time of the event, but our patient numbers were too small to draw any conclusions from this. It remains unclear whether prolonged dual-antiplatelet therapy would have prevented these adverse events.

Data are available from several large registries from across the globe, all of which demonstrate decreased mortality with DES compared with BMS.[21–25] The Swedish Coronary Angiography and Angioplasty Registry (SCAAR) initially reported on 19,771 patients and found that after 3 years, treatment with DES was associated with a 32% increase in mortality.[26] However, subsequent data from SCAAR conformed to those found by the other registries, namely, that DES are associated with improved survival (although not reaching statistical significance in all).[23,27]

Although these registries included much larger numbers of patients, they tended to investigate patients treated at institutions at which DES and BMS were used concomitantly, raising the possibility of selection bias. Furthermore, only approximately 1/3 of these patients were treated with DES, and the maximum published follow-up data are for 3 years. As such, the mortality rates in our 2 patient groups were higher than in the other registries, whose outcomes data reflect the randomized trials more closely.

Our study also highlights the particular risk endured by diabetic patients: diabetes was an independent predictor of all clinical events, serving a reminder that these patients need aggressive risk factor and lifestyle management. Furthermore, treatment of the left main stem was associated with an increased 4-year risk for overall MACEs and death, suggesting that coronary artery bypass surgery should remain the preferred strategy for such patients. Ongoing randomized multicenter studies will shed further light on this issue.

In conclusion, after 4 years, therefore, it appears that the

safety of SES is maintained in real-world patients. Mortality rates for the BMS and SES groups were higher than those reported in the randomized trials; presumably, this reflects the higher risk and more complex nature of our series of consecutive all-comers as opposed to carefully selected randomized trial patients.

The major weakness of this study is that it was a single-center registry using a historically lower risk BMS control group. Furthermore, the patient numbers may have been too small to detect small differences in mortality.

Acknowledgment: The following operators were involved in the procedures of this patient population: Chourmouzios A. Arampatzis, MD, Eugene McFadden, MD, PhD, Pim J. de Feyter, MD, PhD, Willem J. van der Giessen, MD, PhD, Sjoerd H. Hofma, MD, PhD, Angela Hoye, MBChB, MRCP, Evelyn Regar, MD, PhD, Georgios Sianos, MD, PhD, and Pieter C. Smits, MD, PhD.

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CHAPTER 3

The relative safety and efficacy of bare-metal and drug-eluting stents in low and high-risk patient subsets. An epidemiological analysis of three sequential cohorts of consecutive all comers (n = 6129)

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EuroIntervention. 2009 Jan; 4(4): 464-474.

EuroIntervention

The relative safety and efficacy of bare-metal and drug-eluting stents in low and high-risk patient subsets.

An epidemiological analysis of three sequential cohorts of consecutive all comers (n=6129)

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All of the authors have no conflict of interest to declare.

KEYWORDS
Sirolimus-eluting stent, paclitaxel-eluting stent, long-term safety

Abstract

Aims: Sirolimus- and paclitaxel- eluting stents (SES and PES respectively) have been shown to produce a sustained reduction in restenosis and repeat revascularisations as compared to bare-metal stents (BMS) up to four years. There is still limited data about the long-term safety and efficacy of DES in high-risk subgroups.

Methods and results: A total of 6,129 consecutive patients were treated during three sequential periods with BMS (n=2,428; January, 2000 to April, 2002), SES (n=866; April 2002 to February 2003) or PES (n=2,835; February 2003 to December 2005). A stratified analysis (including age, gender, diabetes, clinical presentation, treated vessel, multivessel disease, AHA lesion class, bifurcation, in-stent restenosis, average stent diameter ≤2.5 mm and total stented length ≤30 mm) was performed to evaluate possible heterogeneities in treatment effect. At four years, all-cause mortality was identical between the drug-eluting stent (DES) and BMS cohorts (13.5% vs. 13.4%, respectively; Adjusted HR 1.10, 95% CI 0.90 - 1.34) without evidence of heterogeneity in the high-risk patient subsets. Both DES significantly reduced the risk for target vessel revascularisation (TVR) as compared to BMS (TVR: 11.9% vs. 15.7% respectively; Adjusted HR 0.69, 95% CI 0.58 - 0.82) along with a reduced risk for post-operative MI (adjusted HR 0.75, 95% CI 0.57 - 0.98), but counterbalanced by a non-significantly higher risk for stent thrombosis (3.1% vs. 1.6%; adjusted HR 1.26, 95% CI 0.82 - 1.95). DES failed to show superiority to BMS in patients with acute myocardial infarction (TVR 10.5% vs. 9.2% respectively; Adjusted HR 1.26, 95% CI 0.82 - 1.93).

Conclusions: In a real world patient population, after four years, the overall use of DES was associated with similar all-cause mortality rates and a significantly reduced risk for post-operative MI and TVR as compared to BMS.

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Introduction

While the superior anti-restenotic properties of drug-eluting stents (DES) have been extensively demonstrated, their impact on hard clinical endpoints like death and myocardial infarction (MI) was never appropriately studied. Although pivotal randomised controlled trials and meta-analyses demonstrated similar rates of death, post-operative MI and stent thrombosis in DES as compared to bare-metal stents (BMS), they were underpowered to detect meaningful differences in these hard clinical endpoints, particularly when the relative safety and efficacy were questioned in high-risk subgroups.[1-4] Although the randomisation was a key feature, the main limiting factors in the pivotal randomised trials were the highly selected patient populations (approximately 40% of the daily clinical practice) and the use of angiographic primary endpoints in many of them. These constraints limited the ability to generalise the conclusions to an all-comer population and precluded proper subgroup analysis. Meta-analyses of randomised controlled trials, including trials in higher risk patients, using aggregate data rather than patient-level data, partially resolved the long-term safety concerns but were again unable to study high-risk subgroups.

Registries including higher risk patients have recently shown a consistent trend towards an increased rate of late stent thrombosis, but an improved survival rate when DES are used.[5-9] However, the majority of the registries suffer from a severe selection bias due to concomitant non-randomised use of DES and BMS. Thereby, the "DES" cohorts in these studies were often a mixture of different types of DES (often mixed with BMS), and ignored the fact that there is a clear difference in the safety and efficacy of different types of DES.[4,10-12]

In the present study, we analysed the relative safety and efficacy of three sequential cohorts of all-comers (n=6.129) treated with either BMS, sirolimus- or paclitaxel-eluting stents (SES and PES respectively). In particular, we performed a stratified analysis to study the efficacy of both types of DES among high-risk patient subsets.

Methods

Study design and patient population

Between January 1, 2000 and December 31, 2005, a total of 7,217 percutaneous coronary interventions were performed in our institution using BMS, SES or PES. From January 2000 until April 16th 2002, 2,681 percutaneous coronary interventions were performed using exclusively bare metal stents, from April 16, 2002, until February 23, 2003, 1,035 interventions were performed using SES (Cypher®, Cordis Corp., Johnson & Johnson, Warren, NJ, USA), as part of RESEARCH registry[13], and from February 23, 2003 to December 31, 2005, 3,339 interventions using PES (TAXUS™ Express2™ or Liberté™, Boston Scientific, Natick, MA, USA), as part of the T-SEARCH registry.[14] Procedures in which two different types of stents (BMS and either SES or PES; SES and either BMS or PES; PES and either SES or BMS) were used were excluded (n=162).

Although a total of 784 patients underwent multiple procedures, only patients initially enrolled in one of the sequential cohorts (BMS, SES or PES group) were maintained for analytical purposes throughout the follow-up period in their original cohort, even if a repeat intervention was performed using a different type of stent. A total of 6,129 patients fulfilled these criteria. (Figure 1)

This study was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Procedures and post-intervention medications

All procedures were performed following previously defined current standard procedural guidelines.[15] Baseline, clinical and procedural patient characteristics were prospectively entered into a dedicated database.

Patients were prescribed aspirin plus clopidogrel 75 mg/day (after a loading dose of 300 mg) before or during baseline coronary interventions. Patients treated with BMS received at least one month of clopidogrel (mean 2.4±2.3 months). Patients treated with SES, received at least three months of clopidogrel (mean 4.5±3.2 months), and patients treated with PES received at least six months of clopidogrel (mean 6.4±3.4 months). All patients were advised to remain on aspirin indefinitely.

Planned angiographic follow-up was performed in 12.0%, 25.9% and 14.3% in the BMS, SES and PES groups respectively.

Baseline definitions

Angina was categorised according to the Canadian Cardiovascular Society (CCS) classification for stable angina and according to the Braunwald classification for unstable angina.[16,17] Hypertension was defined as a blood pressure ≥140 systolic or ≥90 mmHg diastolic or based on the current use of antihypertensive treatment. Dyslipidaemia was classified as a total serum cholesterol level ≥6.2 mmol/l or the use of lipid lowering drugs. Diabetes was defined as treatment with either an oral hypoglycaemic agent, insulin, or through diet. Complete procedural success was defined as the achievement of <50% diameter stenosis (visual assessment) and Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow in all

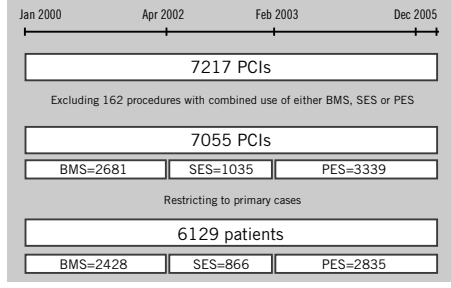

Figure 1. Flowchart depicting the number of procedures in the three sequential periods and the number of patients fulfilling the inclusion criteria in each cohort. Primary cases indicates the number of patients undergoing their first intervention in the study period (2000-2005). SES indicates sirolimus-eluting stent, BMS bare metal stent, PES paclitaxel-eluting stent, PCI percutaneous coronary intervention.

lesions intended to treat. Clinical success was defined as procedural success without death or (re) infarction during the index hospitalisation.

Endpoint definitions and clinical follow-up

The primary safety endpoint was all-cause death and post-operative MI and the primary efficacy endpoint was target vessel revascularisation (TVR) at 4-years of follow-up. Secondary endpoints were the itemised outcome parameters: all-cause death, cardiac death and death from cancer, post-operative MI, TVR and stent thrombosis. Survival data for all patients were obtained from municipal civil registries on a yearly basis for each of the three patient cohorts. The most recent follow-up was performed in October 2007. Causes of death were obtained from the Central Bureau of Statistics, The Hague, The Netherlands. Causes of death were classified according to the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).[18] For the present analysis, death from ischaemic heart disease (I-20 - I-25), sudden cardiac death (I-46), sudden death undefined (R-96), or death from heart failure (I-50) were considered to be cardiac. Death from cancer was defined as any death from malignant neoplasms (C-00 - C-97). All the remaining deaths were classified as being due to other causes and no further distinctions were made. Follow-up was complete for 98.7% of the BMS patients, 100% of the SES patients and 98.4% of the PES patients. Target vessel revascularisation was defined as a re-intervention driven by any lesion located in the same epicardial vessel.[19] Myocardial infarction at follow-up was diagnosed by a rise in creatine kinase-MB fraction (CK-MB) of three times the upper limit of normal, according to American Heart Association/American College of Cardiology guidelines.[20] Stent thrombosis (ST) was defined as angiographically defined thrombosis with TIMI grade 0 or 1 flow or the presence of a flow limiting thrombus, accompanied by acute symptoms, irrespective of whether there had been an intervening reintervention.[21] The timing of ST was categorised as early (within 30 days after implantation), late (between 30 days and 1 year) or very late (more than 1 year).[22] Additionally, a difference was made between primary stent thrombosis (occurring directly after the index procedure) and secondary stent thrombosis (stent thrombosis occurring following a repeat target vessel revascularisation).

Statistical analysis

Continuous variables are presented as mean ±standard deviation. Categorical variables are expressed as percentages. Comparisons among the three groups were performed by the F-test from an analysis of variance for continuous variables and Pearson's Chi-Square test for categorical variables. All statistical tests are 2-tailed. The incidence of events over time was studied with the use of the Kaplan-Meier method, whereas log-rank tests were applied to evaluate differences between the treatment groups. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Cox proportional-hazards regression analyses were applied to further study treatment effects, adjusting for potential confounders listed in Table 1. The number of co-variables in the final model was limited to variables ($p<0.10$) in Cox multivariable regression, and variables considered clinically relevant for each specific endpoint. Final results are presented as adjusted hazard ratios with 95% confidence interval. Subsequent analyses were performed to evaluate possible heterogeneities in treatment effects on mortality and TVR according to the following clinically relevant characteristics: age, gender, diabetes, clinical presentation, treated vessel, multivessel disease, AHA lesion class, bifurcation, in-stent restenosis, average stent diameter≤2.5 mm and total stented length >30 mm. Treatment effects were evaluated with the use of Cox regressions that included a term for the interaction between each characteristic of interest and the assigned treatment, adjusted for the previously defined clinically relevant characteristics. Given the differential follow-up in the three treatment cohorts, additional stepwise logistic regression analyses were performed on the 2-year endpoints of all-cause mortality and TVR to check whether these results were in line with the Cox proportional hazards regression analyses on the 4-year endpoints.

Results

Baseline and procedural characteristics

Both baseline and procedural characteristics are depicted in Table 1. Mean age increased slightly over time from 61.5±11.8 in the BMS group to 62.2±11.5 in the PES group ($p=0.04$). Treatment for acute MI increased from 22.4% in the BMS group to 36.1% in the PES group ($P<0.001$). Procedural complexity increased over time, illustrated by an increase in the treatment of type C lesions, bifurcations and left main stem lesions. Over time, total stented length and number of stents increased, while the average stent diameter decreased.

Clinical outcomes

At thirty days, the cumulative incidence of all-cause mortality was 3.5% in both the DES and BMS groups (adjusted HR 0.84, 95% CI 0.63 - 1.13). However, there was a trend towards a lower 30-day mortality rate in the SES group (2.2%) compared to the PES group (4.0%) (adjusted HR 0.73, 95% CI 0.44 - 1.22). At four years, the mortality rates in the DES and BMS group remained remarkably similar (13.5% vs. 13.4% respectively; adjusted HR 1.10, 95% CI 0.90 - 1.34); however, a trend remained towards a lower mortality rate in the SES group as compared to the PES group (11.2% vs. 14.0% respectively; adjusted HR 1.16, 95% CI 0.88 - 1.53) (Table 2, Figure 2).

The majority (57%) of all deaths were due to cardiac causes, 15% were due to cancer and 28% of the patients died of other causes. While cardiac mortality was similar in the overall DES group as compared with the BMS group, the cardiac mortality rate was significantly lower in the SES group as compared with the PES group (5.8% vs. 8.0% respectively, adjusted HR 0.69 95% CI 0.49 - 0.97). Death due to cancer occurred at a similar rate in both DES groups as in the BMS group (Table 2).

Although the cumulative incidence of post-operative MI was similar among the DES and BMS groups (4.8% vs. 4.9% respectively)

Table 1. Clinical and procedural characteristics of the study population stratified according to stent type.

Variables	Bare metal stent (n=2428)	Drug-eluting stent (n=3701)	Sirolimus-eluting stent (n=866)	Paclitaxel-eluting stent (n=2835)	p* value
Age, years (SD)	61.5 (11.8)	62.1 (11.4)	61.5 (11.0)	62.2 (11.5)	0.04
Male gender	1768/2428 (72.8)	2767/3701 (72.3)	609/866 (70.3)	2067/2835 (72.9)	0.30
Indication SA	1005/2428 (41.4)	1444/3701 (39.0)	373/862 (43.3)	1071/2832 (37.8)	0.003
Indication UA	878/2428 (36.2)	1043/3701 (28.2)	303/862 (35.2)	740/2832 (26.1)	<0.001
Indication MI	545/2428 (22.4)	1207/3701 (32.6)	186/862 (21.6)	1021/2832 (36.1)	<0.001
Cardiogenic shock	24/2428 (1.0)	75/3701 (2.0)	24/862 (2.8)	51/2832 (1.8)	<0.001
DM	320/2428 (13.2)	619/3701 (16.7)	150/866 (17.3)	469/2835 (16.5)	0.001
IDDM	32/2428 (1.3)	155/3701 (4.2)	47/866 (5.4)	108/2835 (3.8)	<0.001
NIDDM	288/2428 (11.9)	471/3701 (12.7)	104/866 (12.0)	367/2835 (12.9)	0.46
Hypertension	793/2428 (32.7)	1944/3701 (33.0)	357/866 (41.2)	1172/2835 (41.3)	<0.001
Hypercholesterolaemia	1057/2428 (43.5)	1944/3701 (52.5)	479/866 (55.3)	1465/2835 (51.7)	<0.001
Family history	523/2428 (21.5)	1220/3701 (33.0)	267/866 (30.8)	953/2835 (33.6)	<0.001
Current smoking	588/2428 (24.1)	997/3701 (26.9)	254/866 (27.9)	743/2835 (25.7)	0.011
Previous PCI	384/2422 (15.9)	416/3675 (11.2)	102/864 (11.8)	314/2811 (11.2)	<0.001
Previous CABG	289/2425 (11.9)	286/3675 (7.7)	61/865 (7.1)	225/2810 (8.0)	<0.001
Previous MI	847/2403 (35.2)	965/3636 (26.1)	269/859 (31.3)	696/2777 (25.1)	<0.001
Treated vessel					
RCA	957/2428 (39.4)	1415/3701 (38.2)	351/866 (40.5)	1064/2835 (37.5)	0.18
LAD	1291/2428 (53.2)	2009/3701 (54.3)	514/866 (59.4)	1495/2835 (52.7)	0.002
LCX	732/2428 (30.1)	115/3701 (30.1)	283/866 (32.7)	832/2835 (29.3)	0.17
LM	86/2428 (3.5)	174/3701 (4.7)	27/866 (3.1)	147/2835 (5.2)	0.003
Bypass graft	135/2428 (5.6)	118/3701 (3.2)	17/866 (2.0)	101/2835 (3.6)	<0.001
AHA Lesion class					
Type A	432/2428 (17.8)	421/3701 (11.4)	162/866 (18.7)	259/2835 (9.1)	<0.001
Type B1	814/2428 (33.5)	978/3701 (26.4)	295/866 (34.1)	683/2835 (24.1)	<0.001
Type B2	1109/2428 (45.7)	1610/3701 (43.5)	426/866 (49.2)	1184/2835 (41.8)	<0.001
Type C	883/2428 (36.4)	1556/3701 (42.0)	372/866 (43.0)	1184/2835 (41.8)	<0.001
Bifurcation	87/2428 (3.6)	437/3701 (11.8)	88/866 (10.2)	349/2835 (12.3)	<0.001
Multivessel disease	1280/2426 (52.8)	1911/3692 (51.6)	40/866 (54.3)	1441/2826 (51.0)	0.18
Multivessel treatment	690/2428 (28.4)	1014/3701 (27.4)	284/866 (32.8)	730/2835 (25.7)	<0.001
ISR	164/2417 (6.8)	132/3605 (3.6)	43/864 (5.0)	89/2741 (3.2)	<0.001
Previous brachytherapy	150/2428 (6.2)	23/3701 (0.6)	11/866 (1.3)	12/2835 (0.4)	<0.001
Number of stents (SD)	1.8 (1.1)	2.2 (1.4)	2.2 (1.5)	2.2 (1.4)	<0.001
Average stent diameter	3.3 (0.6)	2.9 (0.5)	2.8 (0.3)	2.9 (0.6)	<0.001
Total stented length	28.3 (20.0)	42.7 (31.0)	42.8 (30.1)	42.7 (31.1)	<0.001
Clinical success rate	2377/2424 (98.1)	3467/3541 (97.9)	838/859 (97.6)	2629/2682 (98.0)	0.64
Complete procedural success rate	2314/2425 (95.4)	3373/3547 (95.1)	819/862 (95.0)	2554/2685 (95.1)	0.84
IIb/IIIa Inhibitor	791/2428 (32.6)	371/3701 (19.8)	184/866 (21.2)	547/2835 (19.3)	<0.001
Duration of clopidogrel in months (SD)	2.4 (2.3)	6.1 (3.5)	4.5 (3.2)	6.6 (3.4)	<0.001
Planned angiographic follow-up	280/2330 (12.0)	602/3521 (17.1)	221/854 (25.9)	381/2667 (14.3)	<0.001

Figures are represented as absolute numbers and percentages or means and standard deviations as appropriate. SD indicates standard deviation; IDDM: insulin dependant diabetes mellitus; NIDDM: non-insulin dependent diabetes mellitus; SA: stable angina; UA: unstable angina; MI: myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; RCA: right coronary artery: LM: left main coronary artery; SVG: saphenous vein bypass graft; AHA: American Heart Association; ISR: in-stent restenosis.
* P-values are based on comparison BMS, SES and PES.

adjusting for independent predictors resulted in a significantly lower risk for post-operative MI in the DES group (adjusted HR 0.75, 95% CI 0.57 - 0.98). No statistically significant differences were observed between the SES and PES group (adjusted HR 0.84, 95% CI 0.57 - 1.24). (Table 2)

The cumulative incidence of angiographic stent thrombosis was significantly higher in the DES group as compared to the BMS group (3.1% vs. 1.6%; HR 1.80, 95% CI 1.23 - 2.64)(Figure 3). Cox multivariable regression analysis revealed that in the BMS group previous brachytherapy and MI at presentation were significant

Table 2. All cause and specified mortality rates at 4 years.

	Bare metal stent (n=2428)		Drug-eluting stent (n=3701)		Sirolimus-eluting stent (n=866)		Paclitaxel-eluting stent (n=2835)		Drug-eluting vs. bare-metal stent	Sirolimus- vs. Paclitaxel-eluting stent
	N	%	N	%	N	%	N	%	Adjusted HR [95% CI]	Adjusted HR [95% CI]
All-cause death	318	13.4	400	13.5	93	11.2	307	14.0	1.10 [0.90-1.34]	1.16 [0.88-1.53]
Cardiac death	176	7.5	233	7.5	48	5.8	185	8.0	1.00 [0.80-1.25]	0.69 [0.49-0.97]
Death due to cancer	50	2.3	58	2.3	16	2.1	42	2.4	1.16 [0.77-1.75]	0.98 [0.53-1.81]
Myocardial infarction (MI)	111	4.9	153	4.8	34	4.1	119	5.1	0.75 [0.57-0.98]	0.84 [0.57-1.24]
Cardiac death or MI	274	11.7	370	11.7	79	9.5	291	12.4	0.90 [0.75-1.07]	0.76 [0.58-0.90]
Angiographic stent thrombosis	37	1.6	93	3.1	22	2.7	71	3.2	1.26 [0.82-1.95]	0.82 [0.50-1.34]
Target vessel revascularisation (TVR)	355	15.7	356	11.9	99	12.2	257	12.0	0.69 [0.58-0.82]	0.99 [0.77-1.28]
All-cause death, MI or TVR	676	28.4	778	25.3	189	22.4	589	26.6	0.83 [0.74-0.94]	0.85 [0.71-1.01]

SES: sirolimus-eluting stent; BMS: bare metal stent; PES: paclitaxel-eluting stent; HR: hazard ratio; CI: confidence interval. Percentages are based on Kaplan Meier estimates. All hazard ratios are adjusted hazard ratios considering potential confounders listed in Table 1.

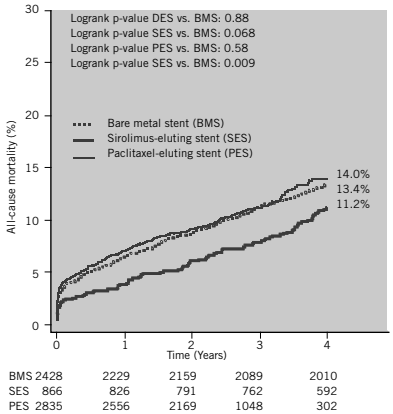

Figure 2. Kaplan Meier all-cause mortality curves for all patients receiving bare-metal stents (BMS), sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES).

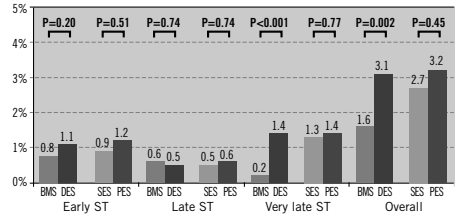

Figure 3. Chart depicting the cumulative incidence of early (<30 days), late (>30 days, <365 days) and very late (>365 days) angiographic stent thrombosis in the bare-metal stent group (BMS), sirolimus-eluting stent (SES) group, paclitaxel-eluting stent group (PES) and drug-eluting stent (DES) group (combined SES and PES). P values are based on the Logrank test.

predictors of stent thrombosis while in the DES group, MI at presentation, diabetes, treatment of the LAD and age significantly increased the risk for stent thrombosis (Table 3). When correcting for independent predictors of stent thrombosis, the adjusted risk for stent thrombosis in the DES group decreased to 1.26 (95% CI 0.82 - 1.95). Additionally, there were no significant differences in the occurrence of stent thrombosis between both DES groups (adjusted HR 0.82, 95% CI 0.50 - 1.34). Among patients with stent thrombosis, secondary stent thrombosis (stent thrombosis occurring after a target lesion revascularisation) occurred in 10.8% of the BMS patients compared to the 4.3% of the DES patients (p=0.22). None (0%) of the patients in the BMS group vs. one (0.1%) patient in the SES group and eight (0.3%) patients in the PES group experienced a second episode of stent thrombosis. In the BMS group 22/111 (19.8%) post-operative MIs were due to ST versus 59/153 (38.6%) in the DES group (p=0.016).

TVR was performed significantly more often in the BMS group (15.7%) as compared to the two DES groups (12.2% vs. 12.0% in the SES and PES groups, respectively)(Table 3, Figure 4). The use of DES was associated with a 31% lower risk for TVR at 4-years compared to BMS (adjusted HR 0.69, 95% CI 0.58 - 0.82). As compared to PES, the use of SES was associated with an equal risk for TVR at 4-years (adjusted HR 0.99, 95% CI 0.77 - 1.28).

Finally, given the differential follow-up between the three treatment cohorts, a stepwise logistic regression analyses with follow-up truncated at two years was used to test the estimated 4-year treatment effect using Cox proportional hazards regression analyses. At two years, the adjusted HR for all-cause mortality in the DES group was 0.92, 95% CI 0.77 - 1.10, which was comparable to initial adjusted HR of 1.04, 95% CI 0.80 - 1.34 derived from a Cox proportional hazards regression model including all univariate significant (p<0.1) predictors of all-cause mortality. Similarly, for TVR, the adjusted HR at two years was 0.55, 95% CI 0.46 - 0.65, which was comparable to initial adjusted HR of 0.60, 95% CI 0.50 - 0.73 derived from a Cox proportional hazards regression model including all univariate significant (p<0.1) predictors of TVR.

Table 3. Univariate and multivariate predictors of stent thrombosis at 4 years in the bare metal- and drug-eluting stent groups.

	BMS		DES	
	Univariate HR [95% CI]	Adjusted HR [95% CI]	Univariate HR [95% CI]	Adjusted HR [95% CI]
Age	–	–	0.97 [0.95-0.98]	0.97 [0.95-0.99]
Clinical presentation				
Stable angina (ref)	–	–	–	–
Unstable angina	2.46 [1.06-5.70]	2.54 [1.08-5.97]	1.86 [1.07-3.24]	2.04 [1.17-3.57]
Myocardial infarction	3.00 [1.23-7.35]	3.56 [1.40-9.09]	2.62 [1.57-4.39]	3.45 [1.99-5.97]
Diabetes	–	–	1.50 [0.92-2.44]	1.83 [1.10-3.00]
Family history	–	–	1.42 [0.94-2.14]	1.44 [0.94-2.19]
Previous brachytherapy	2.84 [1.18-6.80]	3.70 [1.48-9.29]	–	–
Treatment of RCA	0.24 [0.09-0.61]	0.42 [0.14-1.23]	–	–
Treatment of LAD	2.11 [1.04-4.26]	2.01 [0.80 -5.03]	2.15 [1.36-3.38]	1.92 [1.20-3.05]
Treatment of bypass graft	2.65 [1.03-6.79]	3.22 [0.99-10.4]	–	–
Bifurcation treatment	–	–	1.77 [1.06-2.96]	1.33 [0.77-2.31]
Number of stents	0.69 [0.45-1.03]	1.01 [0.50-2.05]	1.22 [1.09-1.37]	1.19 [0.89-1.61]
Total stented length	0.98 [0.95-1.00]	0.98 [0.98-1.02]	1.01 [1.00-1.01]	1.00 [0.99-1.02]
AHA lesion type B2/C	–	–	1.97 [1.10-3.54]	1.48 [0.81-2.70]

BMS: indicates bare-metal stent; DES: drug-eluting stent; RCA: right coronary artery; LAD: left anterior descending coronary artery; AHA: American Heart Association

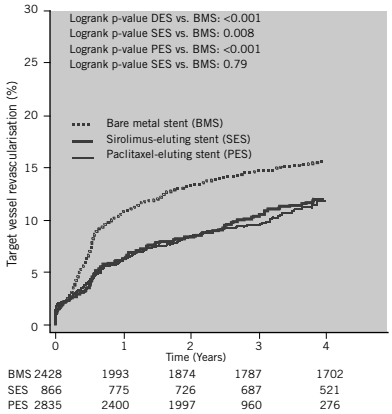

Figure 4. Kaplan Meier curves for target vessel revascularisation up to 4 years for all patients receiving bare-metal stents (BMS), sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES).

Stratified analysis among subgroups

When more specifically analysing the heterogeneity of the treatment effect (DES vs. BMS) on the 4-year TVR rates, a trend towards heterogeneity was observed among patients presenting with MI (p heterogeneity 0.086).(Figure 5a) When assessing the treatment effect of SES vs. PES, which was remarkably similar in the overall population (Figure 4), significant heterogeneity was observed in patients with diabetes (p heterogeneity 0.045), and bifurcation lesions (p heterogeneity 0.036).(Figure 5b)

A stratified analysis to detect heterogeneity in the treatment effect between DES vs. BMS and SES vs. PES did not reveal any significant differences in the 4-year all-cause mortality rates.

ST segment elevation MI subgroup

While in patients presenting with stable or unstable angina, the risk for TVR at 4-years was 38% lower in patients treated with DES as compared to BMS (adjusted HR 0.62, 95% CI 0.51 - 0.75), the risk for TVR in patients presenting with MI was 26% higher (adjusted HR 1.26; 95% CI 0.82 - 1.93) in patients treated with DES as compared with BMS (p heterogeneity 0.086). There was no difference between SES and PES at four years (Figure 5b). The cumulative incidence of all-cause mortality was 16.9% in the DES group vs. 18.7% in the BMS group (Adjusted HR 1.15, 95% CI 0.76 - 1.74) with no significant difference between the SES and PES groups (14.8% vs. 17.0% respectively; adjusted HR 0.82, 95% CI 0.53 - 1.29). Furthermore, there was no difference in the combined endpoint of cardiac death or post-operative MI in DES (18.6%) and BMS (17.9%) group (adjusted HR 1.05, 95% CI 0.60 - 1.84). Stent thrombosis however, occurred in 5.0% of the DES (SES: 4.9%, PES 4.7%) patients as compared to 2.4% of the BMS patients (p=0.06) and very late stent thrombosis (>1 year) was significantly more frequent in the DES as compared to the BMS group (2.7% vs. 0% respectively; p=0.0007).

Diabetes subgroup

Although the 4-year cumulative incidence of TVR in the diabetic subset was significantly lower in the overall DES group as compared to the BMS group (16.2% vs. 24.6%; Adjusted HR 0.53, 95% CI 0.36 - 0.78) significant heterogeneity in the treatment effect was found between SES and PES.(Figure 5b) While in the non-diabetics, the risk for TVR in the SES group was 11% lower than in the PES group (adjusted HR 0.89, 95% CI 0.67 - 1.19), the risk was 41%

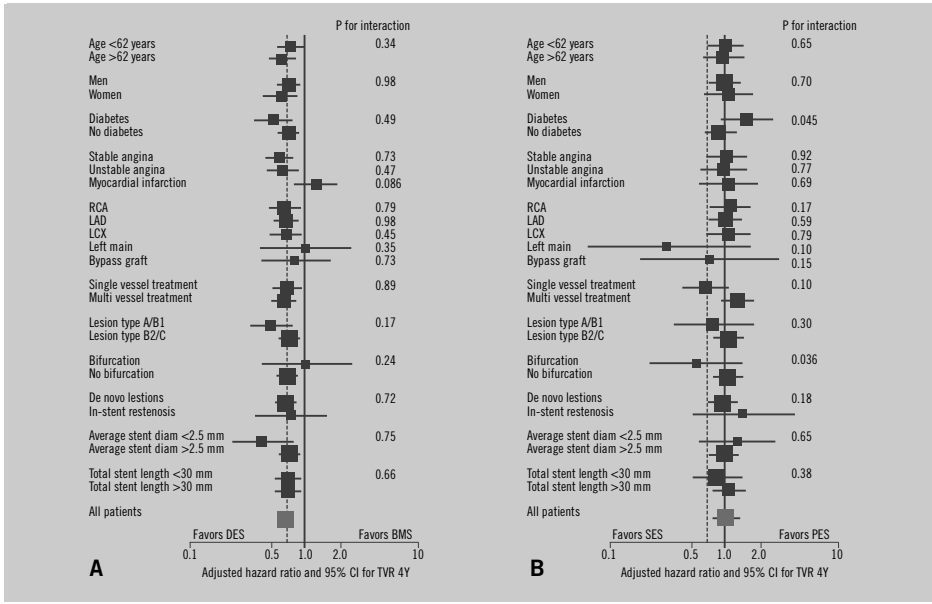

Figure 5. Exploratory analyses to evaluate possible heterogeneity in treatment effects on 4-year target vessel revascularisation rates according to drug-eluting vs. bare-metal stent cohort (A) and according to the sirolimus- vs. paclitaxel-eluting stent treatment cohort (B) and the following clinically relevant characteristics: age, gender, diabetes, clinical presentation, treated vessel, multivessel disease, AHA lesion class, bifurcation, in-stent restenosis, average stent diameter≤2.5 mm and total stented length≤30 mm. The size of the squares corresponds to the amount of statistical information. For the continuous variables (age, average stent diameter and total stented length), medians were used as cut-off. Results of tests for heterogeneity in treatment effect were considered significant if P was <0.05. SES indicates sirolimus-eluting stent; BMS: bare metal stent; PES: paclitaxel-eluting stent; AHA: American Heart Association; LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; RCA: right coronary artery.

higher in the patients with diabetes (adjusted HR 1.41, 95% CI 0.85 - 2.35) (p heterogeneity 0.045). In diabetics, the cumulative incidence of TVR at 4-years was 20.9% in the SES patients as compared with 13.9% in the PES group (Logrank p-value 0.048). There were no significant differences in the hard clinical endpoints between SES and PES treated patients: four-year all-cause mortality was 19.4% in the SES group as compared to 18.4% in the PES group (Adjusted HR 1.38, 95% CI 0.86 - 2.19), whilst the cumulative incidence of cardiac death or post-operative MI was 17.7% in the SES group as compared to 14.6% in the PES group (Adjusted HR 1.09 95% CI 0.64 - 1.83) and stent thrombosis occurred in 6.5% of the SES patients as compared to 4.1% of the PES patients (adjusted HR 1.41; 95% CI 0.56 - 3.56).

Bifurcation lesions

Finally, significant heterogeneity in the 4-year TVR rates between SES and PES was observed in patients treated for bifurcation lesions. While in patients without bifurcations there was no difference between the TVR rates in both DES groups (12.7% in the SES group vs. 11.7% in the PES group; adjusted HR 1.04, 95% CI 0.80 - 1.36), in patients with bifurcation lesions conversely, there was a strong trend towards a lower TVR risk in patients treated with SES as compared to PES (7.1% vs. 14.3% respectively; adjusted HR 0.56, 95% CI 0.23 - 1.36) (p heterogeneity 0.036).(Figure 5b) The difference in all-cause mortality did not reach statistical significance (SES: 6.2% vs. PES: 15.2%; adjusted HR 0.62, 95% CI 0.21 - 1.84). However, the cumulative incidence of cardiac death or post-operative MI was significantly lower in the SES group as compared to the PES group (4.5% vs. 14.2%; adjusted HR 0.30, 95% CI 0.10 - 0.88). Additionally, the cumulative incidence of stent thrombosis was lower in the SES group (1.3%) than in the PES group (5.2%) (adjusted HR 0.21, 95% CI 0.03 - 1.67).

Discussion

The results of the present study show that in a real world patient population, after four years, the overall use of DES was associated with similar all-cause mortality rates and a significantly reduced risk of post-operative MI and TVR as compared to BMS. As compared to patients treated with PES, the use of SES was associated with a significantly lower cardiac mortality and a strong trend towards

lower all-cause mortality as compared to PES. Although the cumulative incidence of stent thrombosis was significantly higher in the DES group, adjustment for confounders resulted in a non-significant 26% increased risk for stent thrombosis at four years in the DES group.

The findings of the present study need to be interpreted in the context of a tertiary referral centre that decided to adopt a policy of default DES use for all-comers (including acute MI at presentation, post-CABG, in-stent restenosis etc.) since the first day of commercial availability of the first approved drug-eluting (Cypher®) stent in Europe on April 16, 2002. On February 23, 2003, for financial reasons, our institution replaced the Cypher® stent by the second CE-mark approved drug-eluting stent (TAXUS™).[23] These two sequential cohorts were complemented by an equally sized cohort of consecutive patients treated with BMS in the two years preceding the commercial introduction of the Cypher® stent.

With the exception of a slightly longer follow-up in the pivotal randomised trials of the two DES[24], the follow-up of the present registry (mean 3.8 years) exceeds that of previously reported registries.[5,6,25-28] Another unique feature of this registry is that it was conducted in a small European country with a sedentary population and a very accurate registration of the vital status and cause of death of its citizens by a well-organised governmental administration. These features reinforce the strength of our observations.

Comparing our results to a recently performed network meta-analyses of 38 drug-eluting stent trials revealed a significantly lower absolute risk reduction for TVR at four years in the present study (3.8% vs. approximately 12% in the meta-analysis). Additionally, a higher overall mortality rate was observed in the present study as compared to the network meta-analysis (13.3% vs. approximately 7.5%, without significant differences between DES and BMS).[4] Yet, it is difficult to compare our results to other published meta-analyses and registries for three reasons. First, meta-analyses using patient level data of the pivotal randomised trials included only highly selected patients, and are representative of only ~40% of the clinical population of a tertiary medical centre.[29] Secondly, in comparable registries, the use of either a DES or BMS was often operator and procedure dependent, resulting in an even greater degree of heterogeneity of the patients treated with DES or BMS, thereby introducing a major potential for selection bias. For example, whereas diabetics would be likely to receive a DES because they are at increased risk of restenosis following BMS placement, patients presenting with acute MI are generally more likely to receive a BMS. It is unlikely that extensive regression and propensity analyses can completely compensate for this inherent type of bias. Thirdly, the vast majority of these registries pooled the outcomes of different devices into one "DES" group, despite the widely acknowledged differences between different types of DES.[4,10-12]

Recently, at least six large-scale real world registries demonstrated similar to significantly lower mortality rates in patients treated with DES compared to BMS.[5-8,30,31] Considering the different features of the present study, our findings demonstrated a similar safety profile for DES and BMS with a significantly lower risk of cardiac death (or post-operative MI) in patients treated with SES compared to PES. The survival benefit in patients treated with SES was already apparent at one week and remained so at one month. Exploring clinical- and procedural success rates, including mortality due to cardiogenic shock at presentation could not account for this difference, and clopidogrel was mandated for at least one month in all patients. Of note, both the short- and long-term survival in the PES group was remarkably similar to the BMS. Several other large-scale registries have also found a similar survival benefit with DES in the first six months which sustained in the longer term.[6,7,25] Our sequential registry analysis does not eliminate the possibility of confounders, but sheds additional light on the late survival after BMS, SES and PES implantation in all comers and demonstrates that pooling the outcomes of different types of DES may not always be appropriate. This is an important lesson as new DES, eluting different drugs form different polymers over different periods of time, enter the market.

We performed a stratified analysis to assess the relative safety of DES. The safety of DES appeared to be consistent among several pre-selected high-risk patient subsets, without a significantly superior safety profile, as expressed by all-cause mortality, between SES and PES. However, we found a strong trend towards heterogeneity in the 4-year TVR rates between DES and BMS in patients presenting with MI. As compared to BMS, the adjusted risk for TVR was 26% higher in patients treated with DES. Although this difference in performance did not reach statistical significance, the observation was in clear contrast to the non-MI population, in which the adjusted risk for TVR in the DES group was significantly (38%) lower. Pivotal randomised controlled trial data revealed that the use of SES was equally safe and more efficacious in reducing TVR in this setting as compared to BMS at 1-year, however, PES failed to demonstrate a superior performance as compared to BMS at one and two years.[32-34] These latter controversial findings, together with the fact that MI at presentation appeared to be a strong predictor of stent thrombosis in patients treated with DES[12,27,35,36], inevitably leading to repeat revascularisations, together with the results of the present study including 1,752 MI patients (DES group with over 80% PES use), makes the use of DES in this high-risk patient subset disputable.

There was significant heterogeneity in the 4-year TVR risk between SES and PES in patients with diabetes and bifurcation treatment. While both drug-eluting devices had a similar safety profile, there was a trend towards a 41% higher risk for TVR in diabetic patients treated with SES. Several smaller subgroup analyses of randomised controlled trials and registries concur with our findings. In the 1-year results from the SOLACI and MILAN registry and the REALITY trial, the use of PES was associated with non-significantly lower rates of target lesion revascularisation as compared to SES in diabetics.[37,38] The Kaiser Permanente and TC-Wyre registries conversely, even demonstrated a significant difference between SES and PES in reducing target lesion revascularisation in diabetics, in favour of PES.[39,40] Indirect evidence of a possible superiority of paclitaxel as compared to the limus family drugs was derived from a pooled analysis of the randomised SPIRIT-II and III trials, which showed a strong trend towards lower major adverse cardiac events rates in patients treated with PES as compared to the Everolimus-eluting XIENCE V stent. (FDA Executive Summary Memo. FDA Panel 29 November

2007; http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4333b1-00-index.html) The sole randomised ISAR-Diabetes trial did not show any significant differences in the clinical endpoints with SES and PES.[41] Large-scale randomised controlled trials are needed to assess the possible superiority of PES as compared to SES in diabetics. The randomised controlled FREEDOM trial (using PES and SES) vs. coronary artery bypass surgery will shed additional light on this issue. [42]

Finally, significant heterogeneity in the treatment effect was observed in patients treated for bifurcation lesions, in which there was a strong trend towards a lower TVR risk and a significantly lower risk (70%) to suffer from cardiac death or post-operative MI when treated with SES as compared to PES. These findings confirm the results of a randomised trial by Pan et al evaluating the safety and efficacy of SES vs. PES in bifurcation lesions.[43] The authors concluded that the overall system of the SES is better than the PES in terms of main vessel restenosis rates, late loss, and neointimal proliferation assessed using intravascular ultrasound.

The present single centre study has several limitations. First, the clinical and procedural complexity increased over time, which resulted in substantial differences in clinical and procedural characteristics between the sequential patient cohorts. Despite the use of extensive regression models, it remains uncertain whether we were able to completely adjust for the differences between the groups. However, the likelihood of a randomised trial comparing BMS with DES in an all-comer population is already remote and will become even more unlikely with the advent of the second and third generation of DES.

A substantial amount of pivotal experiences with DES in several high risk patient and lesion subsets were reported based on the RESEARCH and T-SEARCH registries. Subsequently, late angiographic evaluation was eventually obtained from "complex" patients, typically with DES implanted in bifurcations, left main coronary, chronic total occlusions, very small vessels, long stented length (>36 mm), and acute myocardial infarction (in total, 25.9% patients in the SES group had angiographic follow-up between six and 12 months).[44-50] In the BMS and PES groups, planned angiography was performed in 12.0% and 14.3% respectively. In all other cases, coronary angiography during follow-up was obtained as clinically indicated by symptoms or documentation of myocardial ischaemia. Of note, planned angiographic re-evaluation was used as a co-variable in the Cox proportional hazards regression models.

Due to the sequential nature of the three patient cohorts in the present study, the follow-up in the PES group was shorter than the follow-up in both the BMS and SES groups resulting in a lower number of patients at risk at three years in the PES group. Kaplan Meier survival analyses were performed to reconcile this limitation.

The per patient clinical- and procedural risk profile was linearly associated with time. Given the sequential nature of the three patient cohorts in our study, propensity analyses were considered inappropriate. However, the overall risk profile was more favourable for the BMS group than for either DES group and might even underestimate the real difference.

Finally, the findings derived from the stratified analyses to detect possible heterogeneity in the treatment effect of the different devices should be seen as hypothesis generating. The non-randomised nature of our study precludes any definite statements about the true superiority of one DES above the other in several high-risk subgroups. However it was remarkable that our findings concurred with the few comparative data available in these high-risk subgroups, despite the longer follow-up and subsequent higher event rates in the present study. With the exception of the FREEDOM trial, there are currently no comparative randomised controlled trials ongoing comparing either SES or PES or one of both with BMS in patients with acute MI, bifurcations and/or diabetes properly powered for hard clinical endpoints to confirm our findings.

Conclusion

The results of the present study show that in a real world patient population, after four years, the overall use of DES was associated with similar all-cause mortality rates and a significantly reduced risk for post-operative MI and TVR as compared to BMS. This finding appeared to be consistent among several high-risk patient subsets, with the exception of patients presenting with MI. Furthermore, the use of SES resulted in significantly lower rates of cardiac death and post-operative MI as compared to PES.

Acknowledgement

Dr. Serruys assumes overall responsibility for the integrity of the data, the accuracy of the data analyses, and the completeness of the material reported.

The contribution of the authors is as follows: Conception and design: Daemen, van Domburg, Serruys. Analysis and interpretation of data: Daemen, van Domburg, Boersma, Serruys. Drafting of the manuscript: Daemen, van Twisk, Kukreja, Serruys. Critical revision of the manuscript for important intellectual content: van Twisk, Kukreja, van Domburg, de Jaegere, Daemen, Serruys. Statistical expertise: Boersma, van Domburg, Daemen. Administrative, technical, or logistic support: van Twisk, van Domburg, Serruys. Acquisition of data: van Twisk, Kukreja, van Domburg, Daemen.

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CHAPTER 4

Two-year clinical follow-up of the unrestricted use of the paclitaxel-eluting stent compared to the sirolimus-eluting stent as part of the Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) Registry

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EuroIntervention. 2006 Nov; 2:330-337.

EuroIntervention

Two-year clinical follow-up of the unrestricted use of the paclitaxel-eluting stent compared to the sirolimus-eluting stent as part of the Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry

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The authors have no conflicts of interest to declare.

KEYWORDS
Sirolimus, Paclitaxel, stent, T-SEARCH, two-year

Abstract

Aims: To investigate the medium term (2 year) clinical outcome of the use of the paclitaxel-eluting stent (PES) compared to the sirolimus-eluting stent (SES). To date, there are no direct comparative data on the efficacy of these stents over medium term follow-up. Furthermore, a possible late restenotic phenomenon has not been excluded.

Methods and results: The Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry compared 576 consecutive "all-comer" patients, exclusively treated with PES, with 508 patients who received SES from the RESEARCH registry in the preceding period. Patients were enrolled irrespective of clinical or angiographic features. At 2 years, major adverse cardiac event (death, myocardial infarction or target vessel revascularisation) rates were comparable in the two groups: 15.4% in the SES group versus 18.9% in the PES group (HR 1.26, 95% CI 0.94-1.69, p=0.12). Correcting for differences in both groups resulted in an adjusted HR of 1.11 (95% CI 0.82-1.50, p=0.51, using significant univariate variables). Target vessel revascularisation was 8.0% in the SES group compared with 9.6% in the PES group (HR 1.23, 95% CI 0.81-1.86, p=0.33).

Conclusions: The unrestricted use of SES and PES was safe at two years of follow-up. No significant difference was found between the two devices in terms of death or MI, MACE, TVR or TLR. No late clinical restenotic phenomenon was observed.

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Abbreviations and acronyms

CI: Confidence interval

HR: Hazard Ratio

MACE: Major Adverse Cardiac Event

MI: myocardial infarction

RAVEL: Randomised study with the sirolimus-eluting BxVelocity balloon -expandable stent in the treatment of patients with *de novo* native coronary artery lesions.

RESEARCH: Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital

T-SEARCH: Taxus-Stent Evaluated at Rotterdam Cardiology Hospital

SES: sirolimus-eluting stent

PES: paclitaxel-eluting stent

TLR: target lesion revascularisation

TVR: Target vessel revascularisation

Introduction

Several years have elapsed since the commercial introduction of sirolimus and paclitaxel eluting stents and to date more than 3 million drug-eluting stents have been implanted worldwide.

Both stents, loaded with antiproliferative drugs, have shown to be highly effective in reducing restenosis in stenotic coronary arteries compared to bare metal stents[1-5]. Evidence was seen from the early days of DES with trials describing the effect of the Rapamycin covered SES in relatively simple lesions in the FIM trial[6,7] and the RAVEL trial[8]. Currently, randomised trials, such as the REALITY, TAXI, CORPAL, SIRTAX, ISAR Diabetes trial and BASKET trial, are comparing SES and PES in a wide variety of patient and lesion types[9-14]. Although a recent meta-analysis has demonstrated the efficacy of DES, and the superiority of SES to PES in reducing restenosis and target lesion revascularisation (TLR), the randomised REALITY trial did not show a difference in binary restenosis and neither in major adverse cardiac events (MACE) at 8 and 12 months between both devices[9,15]. Of note, no difference was seen in the rates of death and myocardial infarction after relatively short-term follow-up in both studies.

The purpose of the present study is to report the two-year clinical outcome of an unselected patient cohort compromising 1,084 consecutive patients treated with a sirolimus- or paclitaxel-eluting stent. The study was performed for two reasons: First, to evaluate the incidence of late adverse events – the importance of this issue can be demonstrated by a variety of complications that showed up after several years of clinical experience using multiple drug-eluting devices such as; stent thrombosis more than one year after implantation despite continuation of anti-platelet therapy[16], delayed neointimal growth[17], and a phenomenon of late restenosis in porcine models[18]. Secondly, to see whether both devices were still associated with a comparable outcome at 2 years[19].

Methods

Study design and patient population

The Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry is a single-centre prospective registry with the aim of evaluating the safety and efficacy of the unrestricted use of PES (PES, TAXUS, Boston Scientific Corp., Natick, Massachusetts, USA) implantation in an unselected patient population typical of daily practice. Its design and methodology are similar to that of the RESEARCH registry[20] and follows the dynamic registry design described by Rothman and Greenland[21].

PES was granted *Conformité Européenne* (CE) approval on February 16, 2003 and replaced SES (SES, Cypher, Cordis corporation, Warren, NJ, USA) as the default strategy for every percutaneous coronary intervention (PCI) in our institution. Up to September 30, 2003, a total of 576 patients with *de novo* lesions were treated exclusively with PES and are included in the present report (PES group). In this period, 84% of all patients with *de novo* disease received a PES. Patients not treated purely with PES or patients included in other drug-eluting stent trials were excluded from the present report. This PES group was compared with a control group that comprised the active arm of the RESEARCH registry, including 508 patients with *de novo* disease treated solely with SES (SES group). Written informed consent was acquired for every patient included. Our study fulfilled the criteria of the declaration of Helsinki and was approved by the hospital ethics committee.

Procedures and post-intervention medications

All procedures were performed according to current standards, with the final interventional strategy (including direct stenting, postdilatation and the use of intravascular ultrasound) left to the operator's discretion[20]. Angiographic success was defined as residual stenosis ≤30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow. All patients were pretreated with 300mg clopidogrel. For patients in the SES group post procedure clopidogrel (75 mg/day) was prescribed for at least 3 months. Several exceptions were made for patients treated for long lesions (stented segment >36 mm), chronic total occlusions, bifurcations and patients in whom more that 3 stents were used. These patients received at least 6 months clopidogrel. In the PES population clopidogrel (75 mg/day) was prescribed for at least 6 months according to the protocol of several randomised clinical trials[3,5]. Furthermore, all patients were advised to maintain life-long aspirin treatment (at least 80 mg/day).

End point definitions

Our primary endpoint was MACE at 2 years. MACE was defined as a composite of all cause death, non-fatal myocardial infarction (MI) or target vessel revascularisation (TVR). Secondary endpoints were target lesion revascularisation (TLR), defined as a treatment of a lesion in-stent or within 5 mm of the stent borders, and clinically driven repeat revascularisation, defined as any intervention motivated by a significant luminal stenosis (≥50% diameter stenosis) in the presence of anginal symptoms and/or proven myocardial ischaemia

on the target vessel territory by noninvasive testing. Myocardial infarction was diagnosed by a rise in creatine kinase-MB fraction (CK-MB) of three times the upper normal limit according to American Heart Association/American College of Cardiology guidelines[22,23]. Subacute angiographic stent thrombosis was defined as an angiographically documented complete occlusion (TIMI grade 0 or 1 flow) or a flow-limiting thrombus (TIMI grade 1 or 2 flow) in the first 30 days after a successful procedure. Late angiographic stent thrombosis was defined as late – occurring at least one month after DES implantation with acute symptoms; angiographic – stent thrombosis confirmed angiographically; stent thrombosis – defined as thrombosis with TIMI grade 0 or 1 flow or the presence of a flow limiting thrombus (TIMI flow 1 or 2)[24].

Two-year follow-up data

Long-term survival status was obtained by information provided by the municipal civil registry. Subsequently, questionnaires were sent to all living patients inquiring about new interventions (either surgical or percutaneous), myocardial infarction and medication usage. If patients had an MI or underwent a re-intervention in another hospital, discharge letters from the referring hospitals were requested and analysed for additional information. In cases of doubt, the local cardiologist or general practitioners were contacted. All information was prospectively collected in a dedicated database. We were not able to retrieve complete follow-up information on 30 patients, mostly due to emigration or due to an illegal status in the Netherlands. Finally, follow-up was available for 97% of the patients in both groups.

In both groups, follow-up coronary angiography was clinically driven by symptoms or signs suggestive of myocardial ischaemia or mandated by the operator at the end of the index procedure predominantly for complex procedures. In the PES group 18.4% underwent angiographic follow-up, as part of three specific complex subgroups: left main stenting, crush-bifurcation procedures, and patients who were part of a vulnerable plaque substudy. Of the SES patients, 36.0% underwent angiographic follow-up, as part of the following complex subgroups: bifurcation lesions, chronic total occlusions, very small vessels, left main stenting, long stent length (36 mm), and acute MI.

Statistical analysis

Continuous variables are presented as mean ±SD and were compared by Student's t-test. Categorical variables are presented as counts and percentages and compared by Fisher's exact test. All statistical tests are 2-tailed and a p-value <0.05 was considered significant. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method, and Cox proportional hazards models were used to assess differences between the two strategies. Curves were compared by log-rank test. Separate Cox proportional hazards models were performed to identify independent predictors of adverse events, using clinical, angiographic, and procedural variables contained in Tables 1 and 2. The Cox proportional hazards regression models were used to control for differences between groups, and the final results are presented as

Table 1. Baseline characteristics of patients treated with SES or PES

	SES Group (n=508)	PES Group (n=576)	P- value
Male,%	68	74	0.04
Age, years ±SD	61±11	62±11	0.4
Diabetes,%	18	18	0.8
Non-insulin dependent,%	12	13	0.5
Insulin-dependent,%	6	5	0.2
Hypertension,%	41	42	0.9
Hypercholesterolaemia,%	56	62	0.03
Current smoking,%	31	29	0.6
Previous myocardial infarction,%	30	45	0.13
Previous angioplasty,%	19	18	0.8
Previous coronary bypass surgery,%	9	6	0.05
Single-vessel disease,%	46	44	0.5
Multivessel disease,%	54	56	0.5
Clinical presentation			<0.001
Stable angina,%	45	45	
Unstable angina,%	37	27	
Acute myocardial infarction,%	18	28	
Cardiogenic shock,%*	10	13	

* Relative to patients with acute myocardial infarction.

Table 2. Angiographic and procedural characteristics of patients treated with SES or PES

	SES Group (n=508)	PES Group (n=576)	P- value
Treated Vessel			
Left anterior descending,%	59	55	0.3
Left circumflex,%	32	33	0.6
Right coronary,%	39	38	0.9
Left main coronary,%	3	4	0.3
Bypass graft,%	3	3	1.0
Lesion type*			
Type A or B1%	47	32	<0.001
Type B2 or C%	76	87	<0.001
Multivessel treatment,%	32	29	0.3
Glycoprotein IIb/IIIa inhibitor,%	19	28	0.002
Clopidogrel prescription, months ±SD		6±0	<0.05
Bifurcation stenting,%	16	16	0.9
Number of stented segments ±SD	2.0±1.0	1.7±0.9	<0.001
Number of stented vessels ± SD	1.3±0.6	1.3±0.6	0.8
Number of implanted stents ± SD	2.1±1.4	2.2±1.5	0.09
Total stented length per patient, mm ± SD	38.7±23.7	42.9±31.2	0.02
Nominal stent diameter ≤2.5 mm,%	36	35	0.7
Total stented length >33mm,%	45	48	0.5
Angiographic success of all lesions,%	97	97	0.9

* Percentage of patients with at least 1 lesion type within the category.

adjusted hazard ratios (HRs). Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored.

Results

Baseline and procedural characteristics

Both baseline and procedural characteristics are shown in Tables 1 and 2. In summary, patients were predominantly male and slightly more frequent in the PES group, PES patients had more myocardial infarctions (MIs) and cardiogenic shock as their presenting symptom and hypercholesterolaemia was more often present. Furthermore, PES patients had more complex lesions, received longer total stent lengths and glycoprotein IIb/IIIa inhibitors were administered more frequently (28% versus 19%; p=0.002). Furthermore, fewer PES patients had a history of previous coronary bypass surgery, and fewer segments per patients were stented, although the number of vessels treated per patient was identical. Other baseline and procedural characteristics were similar.

Two-year follow-up

The one-year results of our study have been published previously[19]. At two years of clinical follow-up there was no significant difference in mortality between the SES- and PES-groups, (5.8% versus 7.7% respectively, HR 1.35, 95% CI 0.84 - 2.16, p=0.21) (Figure 1a). No difference was found in the combined endpoint of death or MI in the SES- versus PES-group (9.8% versus 11.9%, HR 1.23, 95% CI 0.85-1.78, p=0.26) (Figure 1b). TLR and TVR rates were similar in both groups. Cumulative incidence of TLR was 6.8% versus 6.3% in the SES group versus the PES group respectively (HR 0.94, 95% CI 0.58-1.51, p=0.79) and TVR was 8.0% in the SES-group versus 9.6% in the PES-group (HR 1.23, 95% CI 0.81-1.86, p=0.33) (Figure 1c). Clinically driven TVR was performed in 7.2% of the SES group compared with 9.4% in the PES group (HR 1.34, 95% CI 0.87-2.06, p=0.18). The two-year cumulative incidence of combined MACE was 15.4% in the SES-population versus 18.9% in the PES-population (unadjusted HR 1.26, 95% CI 0.94-1.69, p=0.12) (Figure 1d). Late stent thrombosis at 2 years occurred in 0.3% of the PES group compared with 0.2% in the SES group. Total rate of stent thrombosis was 1.6% in the PES group versus 0.6% in the SES group (p=0.15).

Table 3. Events between one and two year of clinical follow-up, additional to one-year events

	SES Group (n=508)	PES Group (n=576)	P- value*
Death, n (%)	12 (2.4)	12 (2.1)	0.84
Myocardial infarction, n (%)	2 (0.4)	1 (0.2)	0.60
TLR, n (%)#	11 (2.2)	4 (0.7)	0.065
TVR (including TLR), n (%)‡	13 (2.6)	9 (1.6)	0.28
Non TVR, n (%)	13 (2.6)	5 (0.9)	0.03

target lesion revascularisation; ‡ target vessel revascularisation
* by Fisher exact test

Events between one and two years

In this period a total of 48 events occurred. Twelve patients died in the SES group, two died of a cardiac cause, 6 patients died of a non-cardiac cause, 2 patients died suddenly of unknown cause and of 2 patients the cause of death was unknown. Twelve patients died also in the pre-SES group, 5 of a cardiac cause, 3 patients died of non-cardiac causes and the cause of death of 4 patients was unknown. Three MI's occurred (two in the SES group versus one in the PES group). Furthermore, 13 patients received a TVR in the SES group versus 9 in the PES group, all of them were clinically driven. Eleven patients treated with SES underwent a target lesion revascularisation and only 4 out of the PES population (p=0.065). Additionally, 13 patients treated with SES and 5 with PES required a repeat intervention in a different vessel. One case of late-stent thrombosis was reported between one- and two-years.

Predictors of adverse events

In order to identify independent predictors of MACE at two years of follow-up, Cox regression analysis was performed for all baseline characteristics listed in Tables 1 and 2. The following variables were significant in predicting MACE at two years of follow-up: age > 65, female gender, diabetes mellitus, multivessel disease, left main stenting, bifurcation stenting, lesion type B2 or C and total stented length (per 10 mm increment) (Table 4). A second analysis was performed to determine independent predictors of TVR. Diabetes mellitus, lesion type B2 or C, bifurcation stenting and total stented length per 10 mm increment were found to be significant. Subanalyses were performed in several subgroups according to baseline and procedural characteristics (Figure 2). In patients of normal weight, defined as body mass index (BMI) ≤25, patients

Table 4. Independent predictors of MACE and TVR by COX separate regression analysis. Population tested, includes all patients#

Major Adverse Events*	HR	95% CI
Cardiogenic Shock	3.67	2.09-6.46
Left Main treatment	3.44	2.12-5.60
Lesion type B2 or C	2.96	1.72-5.10
Multivessel disease	1.92	1.40-2.62
Diabetes Mellitus	1.87	1.36-2.59
Female gender	1.64	1.22-2.20
Bifurcation stenting	1.62	1.15-2.30
Total stented length (per 10 increment)	1.13	1.07-1.21
Age	1.01	1.00-1.03
Target Vessel Revascularisation	**HR**	**95% CI**
Lesion type B2 or C	4.17	1.69-10.28
Bifurcation stenting	2.00	1.25-3.19
Diabetes	1.73	0.98-2.76
Total stented length (per 10mm increment)	1.18	1.08-1.28

* Including death, myocardial infarction and target vessel revascularisation
# Stent type was not an independent predictor when entered into the model

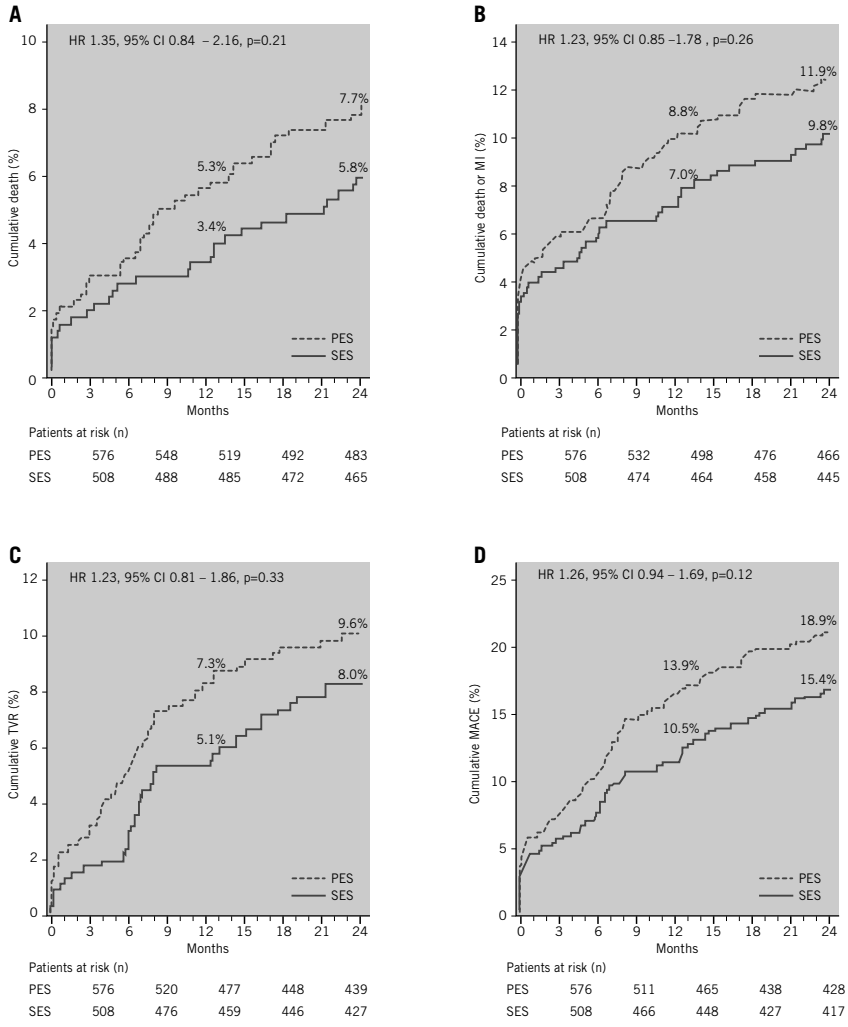

Figure 1. Two-year adverse events in patients treated with sirolimus- and paclitaxel-eluting stents (SES and PES). Cumulative risk of death (A); death or myocardial infarction (MI) (B); target vessel revascularisation (C); death, myocardial infarction or target vessel revascularisation (MACE) (D).

treated with SES had a significantly lower rate of TVR compared to the PES group (p=0.02). In all other subgroups no superiority was noticed between SES and PES.

Adjustment for differences between both groups

The Cox proportional hazards regression model was used to adjust the two groups by correcting for multiple potential confounders in the baseline and procedural characteristics. First, a model was built forcing stent type and all independent predictors listed in Table 4. All previously significant variables remained significant except for bifurcation treatment, age and total stented length. The adjusted HR for use of PES became even less significant, decreasing from HR 1.26 (95% CI 0.94-1.69, p=0.12) to HR 1.12 (95% CI 0.83-1.51, p=0.44), after controlling for the increased complexity in the PES group.

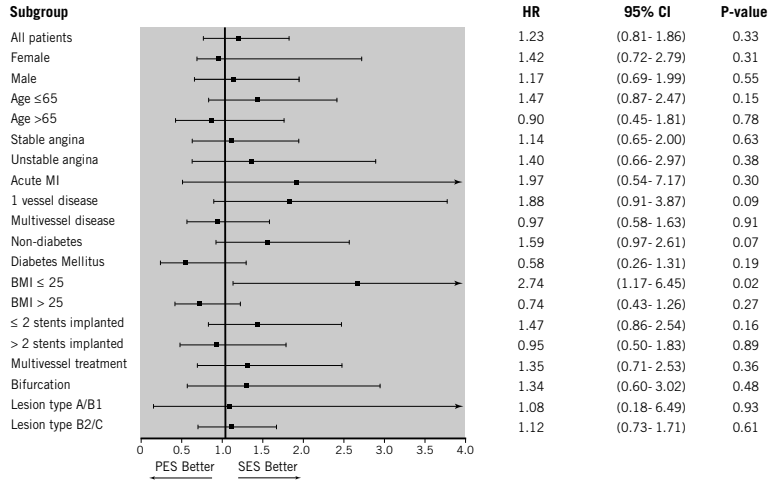

Figure 2. Hazard ratios (HR) of stent type at two-year follow-up for target vessel revascularisation in subgroups of patients according to baseline and procedural characteristics. MI=myocardial infarction.

A second model was then built forcing stent type and significant univariate variables (independent predictors plus number of stents), and the adjusted outcome of MACE at two year was similar between SES and PES (adjusted HR 1.11, 95% CI 0.82 to 1.50, p=0.51). Finally, stent type was also not a significant predictor of TVR when adjusted for lesion type, bifurcation stenting, diabetes and total stented length (adjusted HR 1.09, 95% CI 0.72-1.66, p=0.68).

Discussion

The present study reports on the 2-year clinical outcome of the use of SES and PES in a real world patient cohort and confirms that neither one of both devices is superior to the other in preventing MACE. Additionally, no differences were found in the occurrence of death and MI, TLR and TVR between both groups.

Death and MI occurred in a similar amount in both groups, which is in accordance with randomised trials[15]. Additionally, there was a trend towards a higher incidence of stent thrombosis in the PES group. It has to be mentioned that in the second year, 2 patients in the SES group and 3 patients in the PES group died of sudden death of unknown cause or of a fatal out-of-hospital cardiac arrest. It cannot be excluded these patients also suffered late thrombotic events.

Whether the SES is superior to PES in terms of late luminal loss and the ability to reduce the need for re-interventions, is still a topic of debate. In terms of target lesion revascularisation, both the SIRTAX and ISAR-DESIRE showed TLR rates favouring SES[12,25]. However, the TAXI, REALITY, ISAR-DIABETES and CORPAL studies did not show a difference between both devices[9,10,13,26]. In terms of angiographic restenosis, both the SIRTAX and ISAR-DIABETES showed results favouring the SES. Although, it has to be mentioned that in the SIRTAX trial the incomplete angiographic follow-up may have resulted in an overestimation of the difference owing to attrition bias. However, the medium to long-term difference remains unknown. The present study reports the 2-year clinical follow-up of the use of the sirolimus- and paclitaxel- eluting stents in a real world patient cohort and confirms that neither one of the devices is superior to the other in preventing the need for revascularisations or the occurrence of overall MACE. The incidence of baseline characteristics with a predictive value towards a worse outcome was higher in the PES cohort and the lesions treated in the PES patients were more difficult overall. This is reflected in the adjusted MACE rate, in which the difference becomes even smaller. Additionally it has to be mentioned that between one and two years, the TLR rate is in favour of the paclitaxel-eluting stent (2.2% versus 0.69%; p=0.065).

When compared to the PES patients, a significantly higher amount of SES patients underwent angiographic follow-up. Of all patients with angiographic follow-up, only 6 (6.6%) underwent a TVR because of a significant (>50% stenosis) without "documented" anginal symptoms. Of note, 2 were because of severe proximal stenosis with large areas of myocardium at risk. Thereby, all TVRs performed in the second year were clinically driven. It is for this reason, that we did not choose clinically driven TVR as a primary endpoint.

An additional rebound phenomenon, as seen in porcine models and brachytherapy, does not seem to occur, at least after two years of follow-up. This latter is supported by the FIM study with 4 years of angiographic follow-up, which demonstrated the absence of a catch-up phenomenon of restenosis in a small patient population[7]. Although both sirolimus- and paclitaxel-eluting stents have been shown to reduce neointimal proliferation, their mechanisms of action are different. Both devices modify the healing process after stent injury, which is the most likely explanation for the reduction in

restenosis[27]. Nevertheless, both drugs interfere with a different part of the cell cycle and both stents have different polymer coatings and dissimilar drug-release kinetics[28,29]. The clinical implications in the differences between both devices still have to be determined.

Looking at the independent predictors of MACE (table 4), it can be concluded that patients treated for left main stenosis or complex lesions (type B2/C) had a significantly higher risk of adverse events at 2 years. Several trials, like the FREEDOM, COMBAT, SYNTAX and CARDIA trial, are currently ongoing to see whether these patients would benefit more from coronary artery bypass surgery[30,31].

In the subgroup analyses, we found that patients with a BMI $\leq$25 treated with SES had a superior outcome with respect to the need for TVR when compared to PES. A paradox in the relationship between BMI and late mortality after PCI with bare-metal stents has been previously described, however, repeat revascularisation rates were not shown to be affected by body mass[32]. Whether the "obesity paradox" will extend to repeat revascularisations in the DES-era and will be influenced by the type of DES needs further investigation.

We realize this is an observational, non-randomised cohort study and thus suffers from its design. For instance, the two sequential cohorts are separated by a 4-month interval, resulting in several differences in both baseline and procedural characteristics. In general, the PES population was more complex overall. More primary PCIs were performed, because of the implementation of a pre-hospital protocol that triaged more patients to primary PCI. More complex (Type B2/C) lesions were treated and more stents were implanted. This latter is likely due to the growing confidence in the superior properties of DES compared to BMS.

However, our study comprises an all-inclusive unrestricted patient population which is able to represent the daily clinical practice of a large catheterisation laboratory and thus may possess a greater generalisability than has been possible with randomised trials.

Conclusion

The medium term follow-up of the T-SEARCH registry shows that the unrestricted use of SES and PES was still safe at two years. No significant difference was found in the adjusted outcome of both devices in terms of death or MI, TLR, TVR or MACE. The inferior trend in crude outcome seen in PES was, in part, due to its higher-risk population. A trend towards less TLR in the PES group between one and 2 years was also observed. No late clinical restenotic phenomenon was seen in either group and stent thrombosis after one year occurred in only one patient.

Acknowledgement

The following operators were involved in the procedures of the discussed patient population:
Chourmouzios A. Arampatzis, MD
Eugene McFadden, MD, PhD
Pim J. de Feyter, MD, PhD
Willem J. van der Giessen, MD, PhD
Sjoerd H. Hofma, MD, PhD
Angela Hoye, MBChB, MRCP
Peter P.T. de Jaegere, MD, PhD
Evelyn Regar, MD, PhD
Patrick W. Serruys, MD, PhD
Georgios Sianos, MD, PhD
Pieter C. Smits, MD, PhD

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CHAPTER 5

Primary percutaneous coronary intervention for acute myocardial infarction: long-term outcome after bare metal and drug-eluting stent implantation

Kukreja N, Onuma Y, Daemen J, van Twisk P, Piazza N, van Domburg R, Serruys PW.

Circ: Cardiovasc Interv. 2008 Oct: 1; 103-110.

Primary Percutaneous Coronary Intervention for Acute Myocardial Infarction

Long-Term Outcome After Bare Metal and Drug-Eluting Stent Implantation

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Background—Primary percutaneous coronary intervention (PPCI) for ST-elevation myocardial infarction with bare metal stents (BMS) is well established, while randomized trials suggest equivalent safety and reduced repeat revascularization with drug-eluting stents (DES) in this setting. However, long-term data on DES in PPCI is lacking, especially in those ineligible for inclusion in randomized trials. Our aim was to investigate the long-term outcomes of unselected patients undergoing PPCI with BMS and DES.

Methods and Results—We analyzed all patients (n=1738) undergoing PPCI for a de novo lesion in our institution from 2000 to 2005. Patients from 3 sequential consecutive cohorts of BMS (n=531), sirolimus-eluting (SES, n=185) or paclitaxel-eluting stents (PES, n=1022) were included. The median duration of follow-up was 1185 days (interquartile range, 746 to 1675). There were no differences in all-cause mortality or repeat revascularization between DES and BMS, although there was a nonsignificant trend toward improved survival with SES compared with both BMS (propensity score-adjusted hazard ratio, 0.63; [95%CI, 0.33 to 1.18]) and PES (hazard ratio, 0.71; [95% CI, 0.40 to 1.26]). SES were associated with lower rates of the composite end point of all-cause death, nonfatal myocardial infarction, or target vessel revascularization (hazard ratio, 0.62; 95%CI, 0.40 to 0.96) when compared with PES. Very late stent thrombosis only occurred in the DES groups.

Conclusions—Although DES are not associated with an increase in adverse events compared with BMS when used for PPCI, neither DES reduced repeat revascularizations. Appropriately powered randomized trials with hard clinical end points and an "all-comer" design are required to further assess the benefit of DES in PPCI. **(*Circ Cardiovasc Intervent*. 2008;1:103-110.)**

Key Words: angioplasty ■ mortality ■ myocardial infarction ■ stents

Primary percutaneous coronary intervention (PPCI) with stent implantation is the preferred modality for treating patients with ST-elevation myocardial infarction (STEMI).[1] However, the role of drug-eluting stents (DES) in these patients is less well established, because these patients were excluded from the pivotal randomized trials comparing DES with bare metal stents (BMS).[2–4] Although there have been randomized trials evaluating DES in STEMI patients, these trials included relatively small numbers of patients with the majority only reporting 1-year follow-up.[5–9] The extent of registry data are similarly limited.[10–13] Data from 4 meta-analyses demonstrate a significant benefit in terms of repeat revascularization, with no difference in mortality or stent thrombosis rates between DES and BMS.[14–17] With the paucity of long-term data, concerns remain about the potential risk for late adverse events, particularly as acute coronary syndromes at the time of PCI is a predictor of stent thrombosis.[18,19] Our aim was to investigate the long-term clinical outcomes of unselected patients (including those with cardiogenic shock) treated with bare metal and DES at a single academic medical center.

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Clinical Perspective see p 110

Methods

Between January 2000 and December 2005, 1738 consecutive patients presenting with STEMI underwent PPCI for a de novo lesion with a single stent type as their standard treatment. During this time period, PPCI was the default strategy for all patients with STEMI presenting within 6 hours of symptom onset. The patients are transferred directly to our cath laboratory either by the ambulance service or by local emergency departments, thus minimizing any potential delays in call- and door-balloon times. Initially, all patients

Received April 22, 2008; accepted August 18, 2008.
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Circ Cardiovasc Intervent **is available at http://circinterventions.ahajournals.org** **DOI: 10.1161/CIRCINTERVENTIONS.108.787762**

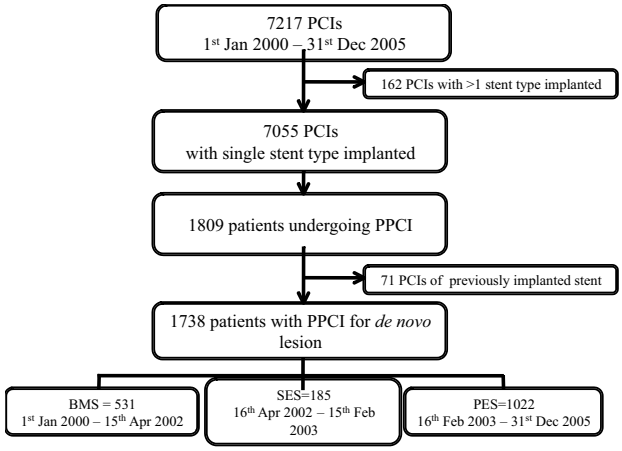

Figure 1. Flowchart showing patient recruitment.

were treated with BMS, but on April 16, 2002, our institution adopted the use of sirolimus-eluting stents (SES: Cypher; Cordis, Warren, N.J.) as the default strategy for all coronary interventions. On February 16, 2003, SES was replaced by paclitaxel-eluting stents (PES: Taxus; Boston Scientific, Natick, Mass.) as the default stent. This single-center registry, therefore, consists of 3 sequential groups of consecutive patients: BMS (n=531; January 2000 to April 2002), SES (n=185; April 2002 to February 2003), and PES (n=1022; February 2003 to December 2005) (Figure 1). All patients undergoing PPCI were enrolled, including those in cardiogenic shock. The only exclusion criteria were the implantation of more than one different stent type during the index procedure or PCI for a previously stented lesion.

All procedures were performed following standard procedural guidelines at the time.[20] The use of glycoprotein 2b/3a inhibitors or adjunctive devices was left up to the operator's discretion. Angiographic success was defined as residual stenosis <30% by visual estimation and thrombolysis in MI grade 3 flow. All patients were advised to maintain lifelong aspirin. Hypercholesterolemia was defined as fasting total cholesterol >5 mmol/L (193 mg/dL) or the use of lipid-lowering therapy. Hypertension was defined as blood pressure >140/90 mm[ths]Hg or the use of antihypertensive medications. Renal impairment was defined as a serum creatinine >150 μmol/L (1.7 mg/dL).

The primary end point was all-cause mortality. Secondary end points included MI, target vessel revascularization (TVR), target lesion revascularization (TLR), definite stent thrombosis, and the composites of all-cause death or nonfatal MI and major adverse clinical end points (defined as all-cause death, nonfatal MI, or TVR). MI included reinfarction (defined as recurrence of symptoms together with ST-elevation or new left bundle branch block and an increase in cardiac enzymes following stable or decreasing values) or spontaneous MI (diagnosed by a rise in creatine kinase-MB fraction of 3 times the upper limit of normal together with symptoms and either new ST-elevation or left bundle branch block). Stent thrombosis was adjudicated in accordance with the Academic Research Consortium classification of definite stent thrombosis.[21] The timing of stent thrombosis was categorized into early (within 30 days after

Table 1. Patient Demographics

	Overall (n=1738)	BMS (n=531)	SES (n=185)	PES (n=1022)	BMS vs SES (*P*)	BMS vs PES (*P*)	SES vs PES (*P*)
Age, years	59.1±11.9	57.7±12.1	59.4±11.7	59.8±11.7	0.28	0.03	1.00
Male	78.5%	81.0%	75.1%	77.8%	0.09	0.14	0.43
Hypertension	26.4%	21.1%	27.76	29.0%	0.07	0.001	0.70
Hypercholesterolemia	29.5%	24.9%	36.2%	30.6%	0.003	0.02	0.13
Family history of coronary disease	25.1%	20.5%	29.7%	26.6%	0.01	0.008	0.38
Smoking history	48.0%	37.3%	61.15%	51.2%	<0.001	<0.001	0.01
Current smoker	38.9%	35.6%	48.6%	38.8%	0.002	0.2	0.01
Ex-smoker	9.2%	2.1%	12.4%	12.3%	<0.001	<0.001	0.97
Diabetes mellitus	9.8%	9.6%	11.9%	9.6%	0.38	0.99	0.34
Type 2	8.3%	9.2%	9.7%	7.5%	0.84	0.22	0.31
Type 1	1.7%	0.4%	2.7%	2.3%	0.01	0.005	0.60
Renal impairment	1.2%	1.1%	1.6%	1.1%	0.70	0.92	0.46
Previous myocardial infarction	12.7%	20.2%	12.5%	8.8%	0.02	<0.001	0.11
Previous coronary artery bypass surgery	2.1%	3.0%	1.6%	1.8%	0.43	0.11	1.00
Previous percutaneous coronary intervention	3.9%	4.4%	3.8%	3.8%	0.73	0.56	0.99
Cardiogenic shock	5.6%	4.3%	13.0%	5.0%	<0.001	0.56	<0.001

BMS indicates bare metal stents; SES, sirolimus-eluting stents; PES, paclitaxel-eluting stents.

Table 2. Angiographic and Procedural Details

	Overall (n=1738)	BMS (n=531)	SES (n=185)	PES (n=1022)	BMS vs SES (*P*)	BMS vs PES (*P*)	SES vs PES (*P*)
No. of diseased vessels	1.6±0.8	1.7±0.8	1.6±0.8	1.6±0.8	1.00	0.11	1.00
Multivessel disease	43.3%	46.3%	44.3%	41.5%	0.64	0.07	0.47
Coronary vessel treated*							
Right coronary	40.3%	39.4%	41.6%	40.5%	0.60	0.66	0.78
Left anterior descending	52.2%	56.3%	54.6%	49.6%	0.73	0.01	0.21
Circumflex	16.0%	16.2%	16.2%	15.9%	1.00	0.86	0.90
Left main coronary artery	3.4%	3.6%	2.7%	3.4%	0.57	0.88	0.61
Saphenous vein graft	1.3%	2.3%	0%	1.1%	0.04	0.07	0.39
ACC/AHA lesion classification†							
Type B2	37.9%	40.7%	40.5%	35.9%	0.97	0.07	0.23
Type C	45.3%	41.2%	53.5%	45.9%	0.004	0.08	0.06
Bifurcation	5.9%	2.6%	4.9%	7.7%	0.14	<0.001	0.17
Multivessel treatment	13.3%	15.6%	13.5%	12.0%	0.49	0.05	0.57
No. of lesions treated	1.4±0.8	1.5±0.7	1.8±0.9	1.2±0.7	<0.001	<0.001	<0.001
No. of stents implanted	1.7±1.0	1.6±0.9	1.9±1.2	1.7±1.1	0.001	0.03	0.09
Mean stent diameter	3.2±0.5	3.5±0.5	2.9±0.2	3.1±0.4	<0.001	<0.001	<0.001
Total stent length	32.2±21.3	25.9±16.2	34.4±22.6	35.1±22.6	<0.001	<0.001	1.00
Glycoprotein 2b/3a inhibitor	43.4%	48.0%	34.6%	42.6%	0.002	0.04	0.04
Angiographic Success	95.4%	96.8%	94.0%	94.9%	0.10	0.09	0.62
Clopidogrel duration, months	5.0±3.1	1.8±1.1	4.2±2.0	6.8±2.4	<0.001	<0.001	<0.001
Medications at discharge							
ACE inhibitor/ARB	30.2%	19.8%	24.3%	36.7%	0.19	<0.001	<0.001
Statin	57.4%	40.5%	53.0%	67.0%	0.003	<0.001	<0.001
β-blocker	45.5%	41.1%	44.3%	47.9%	0.44	0.01	0.36

BMS indicates bare metal stents; SES, sirolimus-eluting stents; PES, paclitaxel-eluting stents; ACC, American college of cardiology; AHA, American heart association; ACE, angiotensin converting enzyme, ARB, angiotensin receptor blocker.

*Expressed as percentage of patients with each vessel type, hence total >100%.

†Expressed as percentage of patients with each lesion type.

implantation), late (between 30 days and 1 year), or very late (>1 year).

Follow-up survival data for all patients were obtained annually from municipal civil registries. A questionnaire was subsequently sent to all living patients with specific enquiries about repeat hospital admission and adverse events. As the principal regional cardiac center, repeat revascularizations are normally performed at our institution and recorded prospectively in our database. For patients who suffered an adverse event at another center, medical records from the other institutions were systematically reviewed. General practitioners and patients were contacted as necessary if further information was required. The protocol was approved by the hospital ethics committee and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Statistical Analysis

Categorical variables are presented as percentages and were compared by Pearson χ^2 test or Fisher exact test. Continuous variables are presented as mean±standard deviation and were compared by means of the *F* test for analysis of variance and the Bonferroni method, using a 2-sided probability value of <0.0167 (0.05/3) to indicate statistical significance. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method, and curves were compared using the log-rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Separate Cox multivariable regression analyses were performed for each paired treatment comparison. Stent type was forced into forward stepwise models using all the 34 variables listed in Tables 1 and 2. Variables with a significance of $P<0.1$ were entered into the next step; the final results are presented as adjusted hazard ratios (HR) with 95% CI. To account for baseline differences in the 3 cohorts, individual propensity scores for each paired treatment comparison were calculated by logistic regression using all significantly different pretreatment variables in Tables 1 and 2.[22] Stent type and the appropriate propensity scores were then forced into separate forward stepwise Cox multivariable regression analyses using the variables in Tables 1 and 2 as above to obtain propensity score-adjusted HRs. Further, Cox multivariable analyses were performed to identify independent predictors of adverse clinical events. All statistical analyses were performed using SPSS for windows version 12.0.1 (SPSS Inc., Chicago, Ill.).

Results

Fifty-six patients (3.2%) were lost to follow-up. The overall mean duration of clinical follow-up was 1185 days (interquartile range [IQR], 746 to 1675). Because of the sequential nature of the 3 consecutive patient cohorts, there were significant differences ($P<0.001$) in the duration of follow-up for each stent type: BMS median 2132 days (IQR, 1588 to 2350), SES 1516 days (IQR, 1406 to 1643) and PES 884 days (IQR, 558 to 1209). Baseline demographics are

Table 3. Clinical Outcomes After 3 Years Follow-Up

	Overall (n=1738)	BMS (n=531)	SES (n=185)	PES (n=1022)		SES vs BMS adjusted HR (95% CI)	PES vs BMS adjusted HR (95% CI)	SES vs PES adjusted HR (95% CI)
Death	13.8%	16.4%	11.4%	12.9%	*	0.66 (0.37–1.18)	0.93 (0.65–1.32)	0.72 (0.41–1.25)
					†	0.63 (0.33–1.18)	0.93 (0.63–1.33)	0.71 (0.40–1.26)
Myocardial infarction	5.4%	5.7%	3.8%	5.6%	*	0.73 (0.31–1.69)	1.04 (0.62–1.75)	0.70 (0.31–1.56)
					†	0.79 (0.31–2.01)	1.07 (0.64–1.80)	0.65 (0.27–1.58)
Death or nonfatal myocardial infarction	18.4%	20.4%	14.6%	18.1%	*	0.69 (0.43–1.12)	1.01 (0.75–1.36)	0.68 (0.43–1.09)
					†	0.64 (0.38–1.10)	1.06 (0.78–1.42)	0.59 (0.36–0.97)
Target vessel revascularization	7.3%	8.0%	7.0%	6.9%	*	0.83 (0.44–1.56)	0.93 (0.61–1.41)	0.90 (0.49–1.65)
					†	0.81 (0.40–1.66)	0.94 (0.62–1.42)	0.87 (0.46–1.64)
Target lesion revascularization	5.2%	5.7%	5.4%	4.9%	*	0.64 (0.30–1.35)	0.67 (0.40–1.12)	0.96 (0.47–1.94)
					†	0.54 (0.22–1.32)	0.82 (0.50–1.33)	1.02 (0.49–2.12)
Composite major adverse cardiac events‡	22.2%	25.0%	17.8%	21.5%	*	0.66 (0.43–1.01)	0.97 (0.75–1.26)	0.68 (0.45–1.03)
					†	0.63 (0.39–1.02)	0.97 (0.74–1.25)	0.62 (0.40–0.96)
Definite stent thrombosis	2.9%	1.9%	3.2%	3.4%	*	0.92 (0.32–2.62)	1.16 (0.53–2.52)	0.79 (0.32–1.95)
					†	0.90 (0.27–2.97)	1.54 (0.73–3.26)	0.84 (0.33–2.18)
Early	1.4%	1.5%	0%	1.5%	*	—	0.76 (0.30–1.92)	—
					†	—	0.74 (0.29–1.87)	—
Late	0.7%	0.4%	0.5%	0.9%	*	1.10 (0.10–12.17)	1.46 (0.28–7.53)	0.75 (0.09–6.45)
					†	1.70 (0.15–19.21)	1.49 (0.29–7.66)	0.75 (0.08–7.28)
Very late	0.8%	0%	2.7%	0.9%	*	—	—	2.21 (0.70–7.03)
					†	—	—	2.20 (0.63–7.70)

BMS indicates bare metal stents; SES, sirolimus-eluting stents; PES, paclitaxel-eluting stents; HR, hazard ratio.
*Conventional multivariable analysis.
†Propensity score adjusted.
‡Defined as all-cause death, nonfatal myocardial infarction or target vessel revascularization.

shown in Table 1, whereas angiographic and procedural details are described in Table 2. There were significant baseline differences between the groups: in particular, the patients were older in the DES groups, although in the SES group this did not reach statistical significance.

Angiographic success rates were similar among the 3 cohorts (overall 95.4%). The total stented length was higher, and the mean stent diameter was smaller in the DES groups. The recommended duration of clopidogrel and the use of statins and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers at discharge from hospital progressively increased.

Clinical event rates after 3 years follow-up, together with HR adjusted both by conventional Cox multivariable regression analysis and propensity score-adjustment, are shown in Table 3.

From the Kaplan-Meier estimates, there were no statistically significant differences between the 3 groups in terms of all-cause mortality, MI, TLR, or TVR (Figure 2a through 2c). The SES group had a significantly lower rate of the composite end point of all-cause mortality, nonfatal MI, or TVR compared with BMS (logrank $P=0.04$) and demonstrated a trend toward superiority over PES (logrank $P=0.09$) (Figure 2d). SES also exhibited a trend toward lower rates of the composite of all-cause death or nonfatal MI when compared with BMS (logrank $P=0.07$), whereas PES showed a trend toward increased rates of definite stent thrombosis (logrank $P=0.07$) (Figure 2e and 2f).

Although there was a trend toward improved survival with SES compared with both BMS and PES, this was not statistically significant with conventional multivariable adjustment or after propensity score adjustment (Table 3). Any differences between the 3 groups in terms of TVR or TLR did not reach statistical significance. There were no differences in overall, early, or late stent thrombosis rates, although there were no cases of very late stent thrombosis in the BMS group versus 2.7% in SES ($P=0.001$; Fisher exact test) and 0.9% in PES ($P=0.03$; Fisher exact test). SES had a trend toward increased rates of very late stent thrombosis.

The multivariable predictors of mortality are shown in Table 4. Independent predictors of other clinical events are shown in Table 5, and those for composite end points in Table 6. The use of particular stent types did not predict any adverse event. Renal impairment, increasing age, previous MI, and the number of diseased vessels were independent predictors of all-cause mortality and both composite end points. Treatment of the right coronary artery (RCA) or the use of β-blockers at the time of discharge independently predicted improved outcome. Although patients with cardiogenic shock did have higher 3-year mortality than hemodynamically stable patients (overall 44.9% versus 11.9%, $P<0.001$; BMS 26.1% versus 16.0%, $P=0.24$; SES 45.8% versus 6.2%, $P<0.001$; PES 52.9% versus 10.7%, $P<0.001$), this was not an independent predictor of outcome after multivariable adjustment.

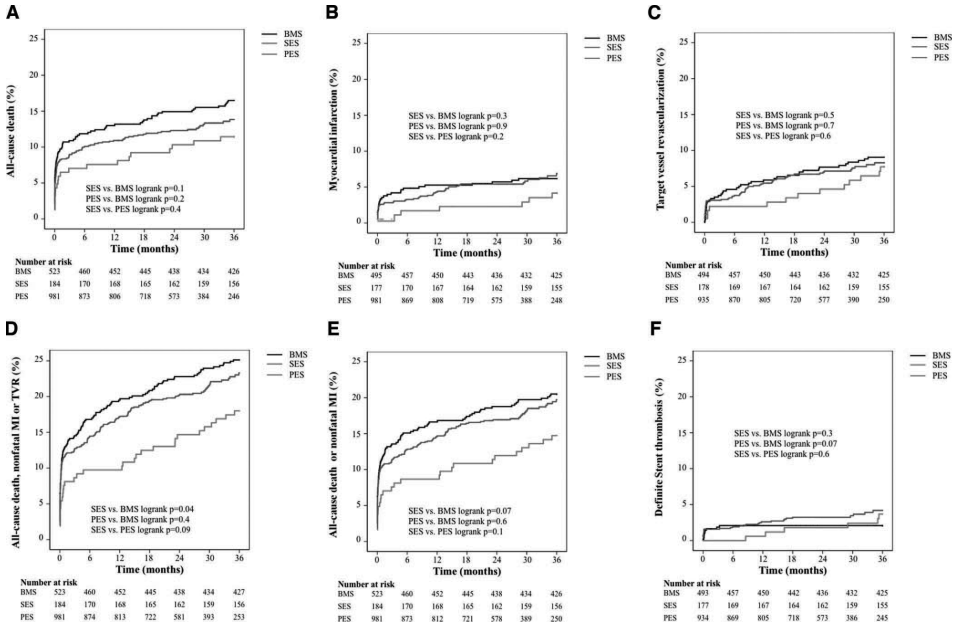

Figure 2. Kaplan-Meier estimates of cumulative 3-year clinical events. (a) all-cause mortality; (b) myocardial infarction; (c) target vessel revascularization; (d) composite major adverse cardiac events (death, nonfatal myocardial infarction, or target vessel revascularization); (e) composite all-cause mortality or nonfatal myocardial infarction; (f) definite stent thrombosis.

Discussion

Our results provide some evidence as to the long-term safety of DES in a large cohort of patients undergoing PPCI. The use of DES in this setting has been questioned since firstly, delayed healing may predispose these and other patients to late and very late stent thrombosis with potentially fatal clinical repercussions.[23,24] Secondly, eventual resolution of any thrombus trapped between the stent and vessel wall at the time of implantation may result in late acquired malapposition, which is another potential risk factor for stent thrombosis.[25,26] Finally, adverse effects on endothelial function and vasomotion may also contribute.[27–30] Although existing data suggest that DES are safe and reduce repeat revascularization in patients undergoing PPCI, long-term data are lacking: the majority of randomized trials have reported only 1-year follow-up, although some data are available up to 2 years.[14,31]

Table 4. Multivariable Predictors of 3-Year All-Cause Mortality

Variable	Adjusted HR	95% CI	*P*
Renal impairment	5.29	2.64–10.59	<0.001
Left main coronary artery treatment	2.51	1.37–4.60	0.003
Previous myocardial infarction	1.67	1.14–2.46	0.009
Type C lesion	1.49	1.07–2.08	0.02
No. of diseased vessels*	1.33	1.09–1.61	0.005
Age†	1.06	1.04–1.08	<0.001
Right coronary artery treatment	0.61	0.43–0.86	0.005
β-blocker treatment at discharge	0.59	0.42–0.84	0.003

HR indicates hazard ratio.
*Per each extra vessel.
†Per each extra year.

Table 5. Independent Predictors of Other 3-Year Clinical Events

	Adjusted HR	95% CI	*P*
Myocardial infarction			
Bifurcation treatment	2.76	1.42–5.39	0.003
Target vessel revascularization			
No. of diseased vessels*	1.29	1.01–1.64	0.04
Right coronary artery treatment	0.53	0.35–0.81	0.004
Angiographic success	0.30	0.16–0.57	<0.001
Target lesion revascularization			
Left anterior descending artery treatment	2.10	1.28–3.46	0.003
Definite stent thrombosis			
Bifurcation treatment	2.44	1.07–5.60	0.04
Left anterior descending artery treatment	2.25	1.09–4.62	0.03
Family history of coronary artery disease	2.12	1.12–3.98	0.02
Mean stent diameter	0.41	0.22–0.76	0.004

HR indicates hazard ratio.
*Per each extra vessel

Table 6. Independent Predictors of 3-Year Composite End Points

	Adjusted HR	95% CI	*P*
All-cause death or nonfatal myocardial infarction			
Renal impairment	3.98	2.01–7.87	<0.001
Left main coronary artery treatment	1.98	1.10–3.56	0.02
Previous myocardial infarction	1.44	1.02–2.03	0.04
No. of diseased vessels*	1.24	1.05–1.47	0.01
Age†	1.03	1.02–1.05	<0.001
β-blocker treatment at discharge	0.62	0.47–0.83	0.001
Right coronary artery treatment	0.59	0.44–0.79	<0.001
All-cause death, nonfatal myocardial infarction or target vessel revascularization			
Renal impairment	3.20	1.63–6.26	0.001
Previous Myocardial infarction	1.37	1.00–1.87	0.05
No. of diseased vessels*	1.34	1.16–1.56	<0.001
Age†	1.03	1.02–1.04	<0.001
Right coronary artery treatment	0.59	0.45–0.76	<0.001
β-blocker treatment at discharge	0.71	0.55–0.91	0.007

HR indicates hazard ratio.
*Per each extra vessel.
†Per each extra year.

The Massachusetts registry has reported 2-year data on 1221 propensity score-matched pairs of DES and BMS patients, which showed reductions in mortality and repeat revascularization with DES.[32] The New York State Registry also found a reduction in mortality with DES.[33] We have found that after a median of 1185 days (IQR, 746 to 1675) follow-up, there were no differences in any clinical end point including all-cause mortality and repeat revascularizations between both DES types and BMS. In fact, compared with BMS, there was a trend toward improved survival and the composites of all-cause death or nonfatal MI and all-cause death, nonfatal MI or TVR with SES. The relatively smaller numbers in our SES cohort may explain why this difference did not reach statistical significance. When examining PES, we were unable to demonstrate benefits over BMS in terms of any of the clinical end points. Furthermore, after propensity score adjustment, PES had higher rates of the composite of all-cause death or nonfatal MI and all-cause-death, nonfatal MI, or TVR when compared with SES. Our results for the PES cohort are consistent with the randomized paclitaxel-eluting stent versus conventional stent in myocardial infarction with ST-segment elevation (PASSION) trial comparing PES with BMS, which found no significant difference in any of the clinical end points with PES.[8]

The lack of benefit in terms of repeat revascularization with both types of DES is surprising. Published randomized trials of DES in STEMI patients have demonstrated a consistent reduction in repeat revascularization with the use of SES,[6,7,9,34] although this benefit did not reach statistical significance in a randomized trial comparing PES with BMS.[8] All of these trials found no difference in mortality with DES. Recent meta-analyses of randomized-controlled trials demonstrated a consistent benefit with DES in terms of reducing repeat revascularization with a risk reduction of approximately 60%.[14–17] Analysis of our data revealed a trend toward decreased TLR with both types of DES (conventional HR, 0.64; 95% CI, 0.30 to 1.35 and propensity score-adjusted HR, 0.54; 95% CI, 0.22 to 1.32 for SES; and conventional HR, 0.67; 95% CI, 0.40 to 1.12 and propensity score-adjusted HR, 0.82; 95% CI, 0.50 to 1.33 for PES), which was not statistically significant. Our patients, however, differed from those in the randomized trials: for example, the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (TYPHOON) study excluded patients with excessive tortuosity or calcification, ostial or multiple lesions, massive thrombus in the infarct-related artery, bifurcations, or left main coronary artery (LMCA) disease.[9] Restrictions on the maximum lesion length permitted in the TYPHOON study (30 mm) meant that the mean stented length was 22.1 and 20.3 mm for SES and BMS in TYPHOON, compared with the overall mean length of 32 mm in our patients. Part of the explanation may be that in our patients, the DES groups had longer and smaller diameter stents implanted than the BMS group; both of these features increase the relative risk of restenosis. Another reason for a lack of benefit with regards to repeat revascularization in our study is the very low TLR and TVR rates for our BMS patients: for example, the TLR rate in our BMS cohort was remarkably low at 6.0% after 3 years, compared with approximately 13% after 1 year in the meta-analysis by Kastrati et al.[17] One potential explanation for this is that our patients did not undergo routine angiographic follow-up, which may partly explain the higher revascularization rates in some randomized trials: for example, the 1-year TVR rate of 13.4% in the BMS group of the TYPHOON study and 13.2% in the MISSION! Intervention study (both with routine angiographic follow-up) appears excessive when compared with our 3-year BMS TVR rate of 8.0% and the 1-year TLR rate of 7.8% found in the PASSION study, where patients did not undergo routine angiographic follow-up.[6,8,9] Furthermore, ST-elevation MI is often the consequence of plaque rupture in the proximal segments of coronary arteries, hence the lumen tends to be larger and the absolute risk of restenosis is lower. The all-comer Basel Stent Kosten Effektivitäts Trial found that patients with vessel diameter $\geq$3.0 mm derived no clinical benefit from DES as opposed to BMS implantation.[35] Another possibility is that the balance between neointimal suppression and late acquired malapposition with DES may even out clinical event rates. Close inspection of the survival curves suggests that there might be late catch-up in repeat revascularization in the SES group.

Although current guidelines recommend 12 months of dual antiplatelet therapy after DES implantation, the duration of clopidogrel given to our patients was based on the protocols from the pivotal DES randomized-controlled trials[2,4]; therefore, initially patients treated with SES were routinely given 3 months clopidogrel, except for complex cases (bifurcations, multiple stents) who were given 6 months. All PES patients

were routinely given 6 months. Although the multivariable analysis adjusted for the recommended duration of clopidogrel, it is possible that the differences in dual antiplatelet therapy may have affected the results due to the shorter duration given to the SES group.

In summary, DES are not associated with increased overall 3-year adverse events when used for PPCI. However, given the cost difference compared with BMS, our results do not support the use of PES in patients with STEMI as these stents confer no clinical benefit over BMS. SES, however, are associated with a trend toward improved mortality compared with PES and BMS, although this did not reach statistical significance. Very late stent thrombosis only occurred in the DES cohorts, and ongoing follow-up is required to assess this continued risk.

Appropriately powered randomized trials with an "all-comer" design, hard clinical end points, and long-term follow-up are required to further assess the role of DES in the treatment of patients with STEMI. Routine intravascular ultrasound after stent implantation coupled with angiographic and intravascular ultrasound follow-up, which although increasing the rate of repeat revascularization due to the oculostenotic reflex, may nevertheless shed some light onto the mechanistic reasons why PES do not appear to reduce adverse clinical events in these patients.

Limitations

The patients included in the study are all from a single institution and were not randomized. Nevertheless, these unselected patients represent real-world practice, whereas patients enrolled in clinical trials are carefully selected. Furthermore, although there are significant differences between the historical cohorts, the use of single stent types at any one time period eliminates some bias, for example, treating higher risk patients with DES. We have attempted to account for differences between the cohorts in terms of baseline demographics by using a propensity score, although we acknowledge that each statistical method has limitations and there is no consensus method for adjusting for these differences, and there may be other potential confounding features that we have not accounted for. Unfortunately, time to reperfusion, LV function, and data relating stent thrombosis to antiplatelet therapy are unavailable.

Acknowledgments

We acknowledge the senior cardiologists involved in the PCI procedures: E. McFadden, MD, PhD; P.J. de Feyter, MD, PhD; P.P.T. de Jaegere, MD, PhD; S.H. Hofma, MD, PhD; E. Regar, MD, PhD; G. Sianos, MD, PhD; P.C. Smits, MD, PhD; M.J. van der Ent, MD, PhD; W.J. van der Giessen, MD, PhD; C.A. van Mieghem, MD. We also acknowledge the contribution of Dick Goedhart, PhD, for his statistical advice.

Disclosures

All authors have approved the final manuscript, which has not been published and is not under consideration elsewhere.

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CLINICAL PERSPECTIVE

Primary percutaneous coronary intervention (PPCI) is the optimal treatment for ST-elevation myocardial infarction. Randomized trials suggest equivalent safety and reduced repeat revascularization with drug-eluting stents (DES) when compared with bare metal stents (BMS) in this setting. However, long-term data on DES in PPCI is lacking. We therefore investigated the long-term outcomes of all patients undergoing PPCI with BMS and DES (n=1738) for a de novo lesion in our institution from 2000 to 2005. Patients from 3 sequential consecutive cohorts of BMS (n=531), sirolimus-eluting (SES, n=185), or paclitaxel-eluting stents (PES, n=1022) were included and followed for a median of 1185 days. There were no differences in all-cause mortality or repeat revascularization between DES and BMS, although there was a nonsignificant trend towards improved survival with SES compared with both BMS (propensity score-adjusted hazard ratios HR, 0.63; 95% CI, 0.33–1.18) and PES (HR, 0.71; 95% CI, 0.40–1.26). SES were associated with lower rates of composite major adverse cardiac events when compared with PES (HR, 0.62; 95% CI, 0.40–0.96). Very late stent thrombosis only occurred in the DES groups. In summary, we found that although DES were not associated with an increase in adverse events compared with BMS when used for PPCI, they did not reduce the need for repeat revascularizations, a finding which conflicts from previously reported studies. We conclude that appropriately powered randomized trials with hard clinical end points and an "all-comer" design are required to further assess the benefit of DES in PPCI.

CHAPTER 6

Comparison of three-year clinical outcome of sirolimus- and paclitaxel-eluting stents versus bare metal stents in patients with ST-segment elevation myocardial infarction (from the RESEARCH and T-SEARCH Registries)

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Am J Cardiol. 2007 Apr 15; 99(8): 1027-32.

Comparison of Three-Year Clinical Outcome of *Sirolimus*- and *Paclitaxel*-Eluting Stents Versus Bare Metal Stents in Patients With ST-Segment Elevation Myocardial Infarction (from the RESEARCH and T-SEARCH Registries)

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Sirolimus-eluting stents (SESs) recently proved to be superior to bare metal stents (BMSs) in decreasing the need for repeat revascularization in patients with ST-segment elevation myocardial infarction (STEMI) at 1 year. Whether this also holds for paclitaxel-eluting stents (PESs) is currently unclear and the long-term relatively efficacy of the 2 drug-eluting stents is currently unknown. We investigated the 3-year efficacy of SESs and PESs versus BMSs in patients with STEMI. Primary angioplasty was performed in a consecutive group of 505 patients (BMSs in 183, SESs in 186, PESs in 136). At 3 years, the cumulative mortality rate was comparable in the 3 groups: 13.3% in the BMS group, 11.5% in the SES group, and 12.4% in the PES group (nonsignificant for all). The rate of target vessel revascularization (TVR) was 12.0% in the BMS group compared with 8.0% and 7.7% in the SES and PES groups, respectively (p = 0.12 for BMS vs SES, 0.30 for BMS vs PES, 0.62 for SES vs PES). The cumulative incidence of death, MI, or TVR was 25.5% in the BMS group compared with 17.9% and 20.6% in the SES and PES groups, respectively (p = 0.06 for BMS vs SES, 0.32 for BMS vs PES, 0.45 for SES vs PES). Angiographic stent thrombosis occurred in 2.4% of all patients (BMS 1.6%, SES 2.7%, PES 2.9%). In conclusion, in this relatively small consecutive patient cohort, the use of SESs and PESs was no longer associated with significantly lower rates of TVR and major adverse cardiace events in patients with STEMI after 3 years of follow-up. A high frequency of stent thrombosis was observed in the 2 drug-eluting stent groups. **(Am J Cardiol 2007;99:1027–1032)**

Primary percutaneous coronary intervention, with or without stenting, has been shown to result in superior long-term outcome compared with thrombolytic therapy in patients with acute myocardial infarction (MI).[1] Recently, several studies have reported that sirolimus-eluting stents (SESs) and paclitaxel-eluting stents (PESs) are more effective in decreasing restenosis and the frequency of repeat interventions than are bare metal stents (BMSs), which rapidly resulted in an unrestricted use of drug-eluting stents also in patients with ST-segment elevation MI (STEMI).[2–4] Shortly after the introduction of SESs in 2002 the first studies appeared, hypothesizing that the therapeutic range of SESs could be extended to use in patients presenting with MI. Compared with BMSs, SESs were associated with less restenosis and target vessel revascularization (TVR) up until 1 year of follow-up.[3,5] Currently it is unclear whether this also holds for PESs.[4,6] To date, there are no data on the long-term outcome of the use of SESs and PESs in patients with STEMI, a growing high-risk subgroup that is becoming a substantial recipient of the total number of percutaneous coronary interventions in many centers all over the world. For that reason, we evaluated the 3-year clinical outcomes of a series of consecutive patients with STEMI treated with BMSs, SESs, or PESs as part of a primary percutaneous coronary intervention strategy.

Methods

On April 16, 2002, our institution commenced the use of SESs (Cypher, Cordis Corp., Warren, New Jersey) as the default strategy for every percutaneous coronary intervention, with the aim of including a patient population representing the "real world."[7] Up until January 2003, 186 consecutive patients were treated with primary angioplasty using exclusively SESs for STEMI. In February 2003 the PES replaced the SES as the device of choice for all percutaneous coronary interventions. Until September 2003, 136 primary percutaneous coronary interventions were performed using exclusively PESs for STEMI. A control group of 183 consecutive patients with STEMI treated with BMSs immediately before April 2002 was retrospectively selected. Of note, the 2 study groups were part of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital

Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands. Manuscript received August 10, 2006; revised manuscript received and accepted November 24, 2006.

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0002-9149/07/$ – see front matter
doi:10.1016/j.amjcard.2006.11.070

Table 1
Baseline and procedural characteristics of patients treated with bare metal, sirolimus, or paclitaxel-eluting stents

Variable	BMS Group (n = 183)	SES Group (n = 186)	PES Group (n = 136)	p Value
Men	79%	75%	84%	0.2
Age (yrs)	57 ± 12	60 ± 12	59 ± 12	0.1
Diabetes mellitus	12%	12%	6%	0.1
Hypercholesterolemia*	34%	37%	46%	0.1
Hypertension	26%	27%	24%	0.8
Current smoker	48%	47%	42%	0.5
Previous MI	24%	14%	11%	0.006
Previous coronary angioplasty	9%	7%	6%	0.6
Previous coronary bypass grafting	3%	2%	2%	0.6
No. of coronary arteries narrowed >50%				0.6
1	48%	55%	52%	
2	29%	27%	29%	
3	24%	18%	19%	
Cardiogenic shock	10%	13%	12%	0.6
Time from symptom onset to angioplasty (h)	3.5 ± 3.8	3.3 ± 2.1	3.2 ± 2.4	0.8
Infarct-related coronary vessel				0.7
Left anterior descending	57%	53%	52%	
Left circumflex	10%	8%	9%	
Right coronary	30%	37%	36%	
Left main	1%	2%	2%	
Bypass graft	2%	—	2%	
TIMI flow at baseline				0.8
Grade 0/1	73%	73%	78%	
Grade 2	15%	17%	11%	
Grade 3	13%	10%	10%	
TIMI flow after angioplasty				0.6
Grade 0/1	4%	2%	2%	
Grade 2	17%	15%	12%	
Grade 3	79%	83%	86%	
Bifurcation lesion	4.4%	9.1%	9.6%	0.13
No. of implanted stents	1.7 ± 1.0	1.9 ± 1.2	1.8 ± 1.1	0.1
Total stented length (mm)	30.3 ± 20	34.7 ± 24	35.9 ± 23	0.055
Clopidogrel prescription (mo)	2.3 ± 1.6	4.2 ± 2.0	5.7 ± 1.0	<0.001
Glycoprotein IIb/IIIa inhibitor	56%	37%	55%	<0.001
Peak creatinine kinase (U/L)	3,957 ± 5,135	3,126 ± 3,126	2,875 ± 2,713	0.1
Peak creatinine kinase-MB (IU/L)	319 ± 230	296 ± 255	320 ± 306	0.7

Values are percentages of patients or means ± SDs.
* Defined as a fasting total serum cholesterol level >5.5 mmol/L (210 mg/dl) or use of lipid-lowering therapy.
TIMI = Thrombolysis In Myocardial Infarction.

(RESEARCH) and Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registries, respectively. All patients were enrolled in the analysis including patients in cardiogenic shock (defined as systolic blood pressure persistently <90 mm Hg or the need for inotropic support or intra-aortic balloon pump implantation to maintain a blood pressure >90 mm Hg with evidence of organ end failure and increased left ventricular filling pressures). Patients who underwent rescue percutaneous coronary intervention after failed thrombolysis or who had previous brachytherapy were not included in this study. This protocol was approved by the hospital ethics committee and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

All procedures were performed according to current standard procedural guidelines and their details have been reported previously.[8,9] Baseline and postprocedural flows were evaluated offline according to the Thrombolysis In Myocardial Infarction criteria by cardiologists blinded to stent group and clinical outcomes. All patients were advised to maintain lifelong aspirin. At least 1 month of clopidogrel treatment (75 mg/day) was recommended for patients treated in the BMS group. In the 2 drug-eluting stents groups, clopidogrel was prescribed for ≥3 months unless multiple SES implantation (>3 stents), total stented length >36 mm, persistent total occlusion, or bifurcations was present. In these cases clopidogrel was prescribed for ≥6 months.

Patients were prospectively followed for the occurrence of major adverse cardiac events (defined as a composite of all-cause death, nonfatal MI, or TVR). Reinfarction was diagnosed by recurrent symptoms and/or new electrocardiographic changes in association with increases in creatine kinase and creatine kinase myoglobin levels of >1.5 times the previous value, if within 48 hours, or >3 times the upper normal limit, if 48 hours after the index infarction.[10,11] TVR was defined as a reintervention driven by any lesion located in the same coronary artery. A secondary end point was

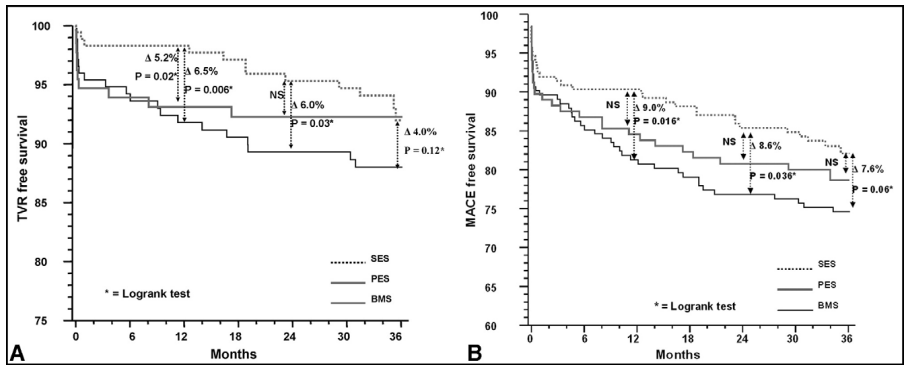

Figure 1. Kaplan-Meier survival curves of *(A)* TVR and *(B)* combined cumulative incidence of major adverse cardiac events (MACE; death, MI, and TVR). Δ = change.

Table 2
Major adverse cardiac events at one year and two and three years

Variable	BMS Group (n = 183)	SES Group (n = 186)	PES Group (n = 136)	p Value
Events in first year				
All-cause mortality	17 (9.3%)	15 (8.1%)	11 (8.1%)	0.89
MI	6 (3.3%)	2 (1.1%)	6 (4.4%)	0.17
TVR (all)	14 (7.7%)	3 (1.6%)	9 (6.6%)	0.021
Stent thrombosis	3 (1.6%)	1 (0.5%)	4 (2.9%)	0.22
Hierarchical MACEs	34 (18.6%)	18 (9.7%)	21 (15.4%)	0.048
Events in second year				
All-cause mortality	5 (2.7%)	4 (2.2%)	3 (2.2%)	0.92
MI	—	1 (0.5%)	—	0.42
TVR (all)	4 (2.2%)	5 (2.7%)	1 (0.7%)	0.45
Stent thrombosis	—	1 (0.5%)	—	0.423
Hierarchical MACEs	8 (4.4%)	9 (4.8%)	4 (2.9%)	0.69
Events in third year				
All-cause mortality	2 (1.1%)	2 (1.1%)	2 (1.5%)	0.94
MI	—	3 (1.6%)	—	0.075
TVR (all)	2 (1.1%)	4 (2.2%)	—	0.21
Stent thrombosis	—	3 (1.6%)	—	0.075
Hierarchical MACEs	4 (2.2%)	6 (3.2%)	2 (1.5%)	0.76

MACEs = major adverse cardiac events.

target lesion revascularization, defined as treatment of a lesion in stent or within 5 mm of the stent borders. Subacute stent thrombosis was defined as an angiographically documented complete occlusion (Thrombolysis In Myocardial Infarction grade 0 or 1 flow) or a flow-limiting thrombus (Thrombolysis In Myocardial Infarction grade 1 or 2 flow) in the first 30 days after a successful procedure. Late stent thrombosis was defined as angiographically defined thrombosis with Thrombolysis In Myocardial Infarction grade 0 or 1 flow or the presence of a flow limiting thrombus occurring ≥1 month after drug-eluting stent implantation accompanied by acute symptoms.[12]

Three-year survival status was obtained through municipal civil registries. Health questionnaires were subsequently sent to all living patients and inquired about post-discharge repeat coronary interventions (surgical or percutaneous) and MI. If a patient had an MI or a reintervention at another center, medical records or discharge letters were requested and systematically reviewed. Local cardiologists or general practitioners were contacted if necessary. Follow-up was available for 98% of patients with BMSs, 98% of patients with SESs, and 97% of patients with PESs.

Continuous variables are presented as mean ± SD. Categorical variables are expressed as percentages. Comparisons across the 3 groups were performed by the F test from an analysis of variance for continues variables and Pearson chi-square test for categorical variables. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method. Patients were censored at 1, 2, and 3

Table 3
Major adverse cardiac events up to three years

Variable	BMS Group (n = 183)	SES Group (n = 186)	PES Group (n = 136)	Relative Risk (95% CI)		
				SES vs BMS	PES vs BMS	PES vs SES
Mortality at 1 yr	9.4%	8.1%	8.1%	0.81 (0.36–1.81)	1.01 (0.66–1.53)	1.24 (0.52–2.95)
Mortality at 3 yrs	13.3%	11.5%	12.4%	0.78 (0.41–1.51)	1.08 (0.77–1.52)	1.62 (0.80–3.27)
Nonfatal MI at 1 yr	3.5%	1.2%	4.7%	0.30 (0.06–1.53)	1.11 (0.62–1.99)	5.40 (1.07–27.6)
Nonfatal MI at 3 yrs	3.5%	4.0%	4.7%	0.95 (0.30–2.98)	1.11 (0.62–1.99)	2.03 (0.63–6.51)
TVR at 1 yr	8.2%	1.7%	6.9%	0.23 (0.06–0.85)	1.11 (0.72–1.72)	10.45 (1.76–62.2)
TVR at 3 yrs	12.0%	8.0%	7.7%	0.65 (0.30–1.37)	0.98 (0.66–1.46)	1.69 (0.70–4.07)
MACEs (death, MI, and TVR) at 1 yr	18.7%	9.7%	15.5%	0.57 (0.32–1.03)	0.99 (0.75–1.31)	1.49 (0.79–2.82)
MACEs (death, MI, and TVR) at 3 yrs	25.5%	17.9%	20.6%	0.77 (0.48–1.23)	0.97 (0.76–1.24)	1.17 (0.69–1.97)

CI = confidence interval; other abbreviation as in Table 2.

years to report the cumulative incidence of major adverse cardiac events and TVR in the 2 Kaplan-Meier curves. Overall incidences were tested using log-rank test. Cox proportional hazards regression analyses were performed to correct for independent predictors of adverse events and differences across groups. Independent predictors were determined for each end point in the 3 compared groups (SES vs BMS, SES vs PES, PES vs BMS) by using all univariate significant ($p < 0.1$) baseline and procedural characteristics listed in Table 1. Independent predictors of outcome were forced into the model, together with stent type used. The final results are presented as adjusted hazard ratios. Patients lost to follow-up were considered at risk until the date of final contact, when they were censored.

Results

Clinical baseline characteristics were comparable among groups, with the exception of previous MI, which was more frequent in the BMS group (24%) than in the SES and PES groups (14% and 11%, respectively, $p = 0.006$; Table 1). There were few differences in procedural characteristics among groups: Glycoprotein IIb/IIIa inhibitor use was higher in the BMS (56%) and PES (55%) groups than in the SES group (37%, $p < 0.001$), and as defined by the study protocol clopidogrel prescription was longer in the 2 drug-eluting stent groups than in the BMS group.

Thirty-day and 1-year outcome have been reported previously.[8,9] At 3 years, the cumulative mortality rate was comparable in the 3 groups (13.3% in the BMS group, 11.5% in the SES group, and 12.4% in the PES group; log-rank $p = 0.63$ for BMS vs SES, 0.78 for BMS vs PES, 0.86 for SES vs PES). Cause of death was cardiac in 62%, unknown in 18%, and noncardiac in 20% of patients. In the BMS group 3.5% developed a new MI compared with 4.0% in the SES group and 4.7% in the PES group (log-rank $p = 0.99$ for BMS vs SES, 0.62 for BMS vs PES, 0.52 for SES vs PES). Target lesion revascularization was performed in 8.4% of patients in the BMS group compared with 6.2% in the SES group and 6.1% in the PES group (log-rank $p = 0.27$ for BMS vs SES, 0.56 for BMS vs PES, 0.58 for SES vs PES). There was a trend toward a higher incidence of TVR in the BMS group (12.0%) compared with the SES (8.0%) and PES (7.7%) groups (Figure 1). The combined cumulative incidence of major adverse cardiac events was 25.5% in the BMS group compared with 17.9% in the SES group and 20.6% in the PES group (Figure 1). Events occurring in the second and third years of follow-up are presented in Table 2.

At 3 years, 12 patients (2.4%) presented with angiographically documented stent thrombosis. Three patients (1.6%) in the BMS group developed stent thrombosis compared with 5 (2.7%) in the SES group and 4 (2.9%) in the PES group ($p = 0.72$ for SES vs BMS, 0.46 for PES vs BMS). Stent thrombosis occurred relatively soon after the index percutaneous coronary intervention at a mean of 8.7 days (range 6 to 11) and 3.5 days (range 0 to 6) in the BMS and PES groups, respectively. In contrast, in the SES group stent thrombosis occurred much later, at a mean of 685 days (range 18 to 1,074). Three of 4 patients with stent thrombosis after 1 year were on single antiplatelet therapy with aspirin and 1 stopped using aspirin 2 days before the event. Two patients presented with unstable angina and 2 with MI. One patient in the PES group had 3 recurrent thrombotic events at 4, 8, and 11 days after the procedure and died during the third event of a subsequent MI despite being on dual antiplatelet therapy. Although beyond the scope of the present analysis, it is worth mentioning that 1 patient in the PES group developed stent thrombosis at 1,100 days after the procedure, 2 days after stopping dual antiplatelet therapy, because of an elective surgical procedure. All cases of stent thrombosis were treated using balloon angioplasty with 100% glycoprotein IIb/IIIa use and additional stents were used in 4 cases.

In Cox multivariate analysis performed in the total population, bifurcation treatment (in which 2 stents were used in 92% of patients) proved to be the strongest predictor of stent thrombosis (hazard ratio 7.84, 95% confidence interval 2.12 to 29.03) followed by female gender, which had a cardioprotective effect (hazard ratio 0.17, 95% confidence interval 0.05 to 0.58). Cox multivariate regression models were also used to correct for differences and independent predictors of adverse events between each pair of groups (SES vs BMS, PES vs BMS, and PES vs SES; Table 3). After adjustment, no significant differences were seen in the 3 comparisons in any clinical end point (death, nonfatal MI, TVR, and major adverse cardiac events).

Discussion

The main findings of the present analysis of 505 consecutive patients presenting with STEMI are (1) the superiority of

SESs in decreasing TVR compared with BMSs and PESs at 1 year was no longer present at 3 years, (2) PESs were not superior to BMS in decreasing the incidence of adverse cardiac events at 1, 2, and 3 years of follow-up, and (3) stent thrombosis in this high-risk subgroup occurred with an overall incidence of 2.4% at a mean of 289 days after the procedure (median 10 days, interquartile range 4.5 to 757) and did not differ significantly across the 3 groups.

Previous (non)randomized studies have reported that the use of the 2 types of drug-eluting stent result in similar rates of death and MI compared with BMSs.[13,14] A recent meta-analysis of randomized trials comparing SESs with PESs also showed no significant difference in these end points.[15] The results of the present study concur with those of the previously mentioned studies and are supported by a recent meta-analysis of the results of SES implantation in patients with acute MI.[5]

The success of drug-eluting stents is primarily driven by their capability to decrease restenosis and the need for repeat interventions, but the currently available long-term follow-up is based on randomized studies, which excluded patients with STEMI.[14] At 1 year, we observed a relative decrease of 80% in the risk for TVR with the use of SESs compared with BMSs ($p = 0.006$). However, at 2 and 3 years, the relative decreases were 59% ($p = 0.003$) and 44% ($p = 0.12$), respectively. PESs showed no significant benefit in decreasing TVR compared with BMSs at 1 years or 2 or 3 years. These 1-year results concur with those of the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (TYPHOON) trial, which randomized >700 patients and showed that SESs were superior to BMSs in patients presenting with acute MI.[3] With regard to PESs, the randomized Paclitaxel-Eluting Stent versus Conventional Stent in Myocardial Infarction with ST-Segment Elevation (PASSION) trial confirmed our findings that PESs were not superior to BMSs in each clinical end point at 1 year of follow-up.[4] The favorable results of the SESs in the TYPHOON trial might have been influenced by the high TVR rate in the BMS control arm and the angiographic follow-up in a considerable number of patients.

The loss of the superiority of SESs compared with BMS after 1 year of follow-up might be partly explained by the occurrence of late stent thrombosis, which occurred in 4 patients (2.1%) in the SES group in the third year of follow-up compared with a 0% incidence in the BMS group. These 4 cases of late stent thrombosis comprised 50% of the total number of TVRs performed in the third year of follow-up and accounted for 100% of all MIs occurring between the first and third year. The increased incidence in very late stent thrombosis in the SES group is in accordance with a recent report by Togni et al,[16] which showed a trend toward a higher incidence of very late stent thrombosis in patients treated with SESs. Although stenting in the setting of MI proved to be a consistent predictor of stent thrombosis, current reports about the occurrence of stent thrombosis after 1 year and especially after 2 years are still scarce.[17–19]

The total incidence of stent thrombosis in this high-risk patient population was 2.4% and was, although mostly due to the longer follow-up, higher than that in previous reports in which stent thrombosis rates were 1.0% to 1.7%.[12,20,21] The incidence of stent thrombosis in the BMS group in the present study was 1.6% and in is agreement with that in previous reports.[22] Stent thrombosis occurred in 2.9% of patients in the PES group, all within the first week after the index percutaneous coronary intervention. No late stent thrombosis was observed from 1 year to 3 years. This latter observation does not concur with a previous study, which reported late stent thrombosis rates of ~0.8% in patients treated with PESs.[23] However, the occurrence and rate of early stent thrombosis in the PES group was comparable to that in the BMS group, occurring mainly within the first 2 weeks after stent implantation.[24] It is unknown whether the late deaths of unknown cause were due to stent thrombosis.

Dual antiplatelet therapy was not able to prevent the 10 early thrombotic events. Whether it would have prevented the late cases of stent thrombosis remains unclear. Thus, the relative efficacy of dual antiplatelet therapy remains unknown, even when taking into account the increased costs, higher bleeding risk, and possibility of aspirin and/or clopidogrel resistance.[25–28]

A limitation of the present study is that the results are based on a nonrandomized patient population without completely identical groups. An example of this is glycoprotein IIb/IIIa prescription, which was lower in the SES group. However, its use did not prove to be protective against adverse events and short- and long-term outcomes in the present study, which is in accordance with the current literature.[29] Further, the results are based on a relatively small patient cohort and therefore may have lack of power. Nevertheless, the present study is the first in the world to complete longer-term follow-up of this high-risk patient subset because Europe was the first to grant Conformité Européenne mark approval for the 2 types of drug-eluting stent, whereas approval by the US Food and Drug Administration was granted >1 year later.

The recently published 1-year results of the randomized, controlled PASSION and TYPHOON trials showed dis-similar outcomes with respect to the different drug-eluting stents used.[3,4] However, until they are able to present longer-term follow-ups, the present single-center prospective registry, which aims to represent a real-world patient population, shows that the "unrestricted" use of SESs and PESs might not be justified in patients presenting with STEMI when taking into account the long-term adverse events.

Appendix

The following operators were involved in the procedures of the discussed patient population: Chourmouzios A. Arampatzis, MD, Eugene McFadden, MD, PhD, Pim J. de Feyter, MD, PhD, Willem J. van der Giessen, MD, PhD, Sjoerd H. Hofma, MD, PhD, Angela Hoye, MBChB, MRCP, Peter P.T. de Jaegere, MD, PhD, Patrick W. Serruys, MD, PhD, Evelyn Regar, MD, PhD, Georgios Sianos, MD, PhD, and Pieter C. Smits, MD, PhD.

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CHAPTER 7

Interventional treatment in diabetics in the era of drug-eluting stents and compliance to the ESC guidelines: lessons learned from the Euro Heart Survey Programme

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EuroIntervention. 2009; 4: 578-587.

EuroIntervention

Interventional treatment in diabetics in the era of drug-eluting stents and compliance to the ESC guidelines: lessons learned from the Euro Heart Survey Programme

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None of the authors have a conflict of interest to declare.

KEYWORDS
Angioplasty, risk factors, drug eluting stent, diabetics, European Heart Survey

Abstract

Aims: The objective of the study is to determine the demographics and the in-hospital outcome of diabetic and non-diabetic patients treated with percutaneous coronary interventions (PCI) in Europe, to report the type of equipment and technology used for PCI procedures in diabetics and to clarify whether the treatment of diabetic patients complies with current European Society of Cardiology (ESC) guidelines.

Methods and results: A total of 14,458 patients treated with PCI were enrolled from 29 member countries of the ESC between June 2005 and January 2006. Data were collected on patient characteristics and treatment, using new Cardiology Audit and Registration Data standards.

In total, 3,603 patients (24.9%) were diabetic. Diabetics were older, more often female and had a higher body mass index than non-diabetics. Diabetics had higher rates of hypercholesterolaemia and hypertension, while current smokers were more frequent in the non-diabetics. Diabetics also had significantly higher rates of previous cardiovascular events. Clopidogrel was administered only in 48.1% of diabetic patients before PCI, while IIb/IIIa inhibitors were 22.9% during PCI. At discharge, there was a major adjustment of treatment with increases in the use of Beta-blocker (80.4%), angiotensin converting enzyme inhibitor (ACEI, 71.3%) and statins (89.8%) compared with on admission (Beta-blocker 60.9%, ACEI 55.0%, statin 63.1%). In-hospital mortality was higher in diabetics (1.8% vs 1.2%) although the in-hospital MACCE rate was not significantly different (3.6% vs 3.0%, p=0.09).

Conclusions: Diabetic patients treated with PCI were older with more comorbidity. According to ESC guideline, the under-usage of clopidogrel, GP IIb/IIIa inhibitors should be improved. PCI is now taken as a good opportunity to adjust the use of appropriate medication.

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Introduction

Diabetic patients are known to have an aggressive form of atherosclerosis with less favourable long-term survival following percutaneous coronary intervention (PCI) as compared to non-diabetic patients[1-4,6-10]. Currently, about 20% of patients with clinically established coronary artery disease have previously diagnosed diabetes and the prevalence of undiagnosed diabetes is also high[11-12].

The European Heart Survey (EHS) Programme is aimed at providing up-to-date information on the current state of cardiovascular disease in Europe[13,14]. The most recent survey was performed in 2005-2006 for the percutaneous coronary intervention (PCI) registry database. General objectives of the survey included the determination of regional variations in the indications for revascularisation, and the assessment of the immediate, in-hospital outcome of patients assigned to different treatment strategies stratified by the clinical presentation and severity of coronary artery disease and patient comorbidities.

In this study, we investigated the EHS PCI database to: i) determine the demographics and the in-hospital outcome of diabetic and non-diabetic patients treated with PCI in Europe; ii) report the type of equipment and technology used for PCI procedures in diabetics and iii) clarify whether the treatment of diabetic patients complies to current European Society of Cardiology (ESC) guidelines[5,15].

Subjects and methods

Study population

Between June 2005 and January 2006, 137 centres from 29 member countries of the European Society of Cardiology (ESC) enrolled 14,458 patients who underwent PCI. Data were collected on patient characteristics and treatment, using new Cardiology Audit and Registration Data standards (CARDS)[16].

Definition

Previous history was obtained from the patients' medical notes, referral letters or information from the patients' family. Myocardial infarction was defined according to ESC/ACC guidelines[5]. MACCE was a combined endpoint of death, stroke or myocardial infarction. Major bleeding was defined as overt clinical bleeding associated with a drop in haemoglobin of greater than 5 g/dl or in haematocrit of 15%.

Statistical methods

Categorical data are presented as percentages. For continuous variables the mean ± standard deviation is shown. Subgroups were compared by Pearson chi-square test with respect to dichotomous or nominal categorical variables, by Mann-Whitney U-test with respect to ordinal and continuous variables, and by log-rank test with respect to the discrete durations of recommended antiplatelet therapy. Independent predictors of hospital mortality were analysed by stepwise selection in a logistic regression model using a significance level for entry of 0.1 and for stay of 0.15. Age, sex, ongoing ACS, elective PCI and the characteristics listed under past history relevant to CAD and risk factors in Table 1 were included as potential predictors. A significance level of 0.05 was assumed and all p-values are the results of two-tailed tests. The statistical computations were performed using SAS, version 9.1 (Cary, NC, USA)

Table 1. Patient characteristics, clinical presentation and angiographic results.

	Diabetics (n=3,603)	Non-diabetics (n=10,855)	p-value
Demographics			
Age, years	65.7±10.3	62.9±11.8	<0.001
Male	67.7	76.9	<0.001
BMI, kg/m^2	29.0±6.3	27.4±8.1	<0.001
Region			<0.001
Northern Europe	6.2	8.6	
Western Europe	24.9	25.0	
Central Europe	25.0	29.0	
Mediterranean	43.9	37.4	
Past history relevant to CAD	60.1	49.7	<0.001
Previous MI	36.4	31.1	<0.001
Previous PCI	25.2	20.9	<0.001
Previous CABG	9.6	6.7	<0.001
Valvular heart disease	2.9	2.1	0.006
Previous CHF	8.1	7.2	0.11
Previous Stroke	6.1	3.6	<0.001
Peripheral vascular disease	10.6	5.7	<0.001
Chronic renal failure	6.1	2.5	<0.001
Risk factors			
Current smoker	19.0	31.6	<0.001
Hypertension	77.5	61.4	<0.001
Hypercholesterolaemia	69.2	61.2	<0.001
Initial clinical assessment			<0.001
ACS with ongoing instability	29.3	33.6	
Stabilised ACS	25.9	24.4	
Elective PCI	44.8	42.0	
ST-elevation MI	15.4	19.6	<0.001
STEMI / primary PCI	13.2	16.9	<0.001
Left ventricular ejection fraction			<0.001#
>50%	62.7	68.0	
41-50%	19.3	18.8	
31-40%	12.1	9.4	
≤ 30%	5.9	3.8	
Angiographic results			
*Stenosed vessels**			
Right coronary artery	61.4	56.0	<0.001
Left main trunk	4.7	4.7	0.96
Left anterior descending artery	73.1	66.8	<0.001
Left circumflex artery	55.7	49.0	<0.001
Arterial bypass graft	1.5	0.9	0.004
Venous bypass graft	4.2	3.2	0.005
No. of vessels diseased			<0.001#
0 vessel	0.5	0.3	
1 vessel	36.2	45.9	
2 vessels	34.2	32.7	
3 vessels	29.1	21.1	

Values are % or mean ± standard deviation. BMI: body mass index, CAD: coronary artery disease, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, CHF: congestive heart failure, ACS: acute coronary syndrome; *: % of patients with each vessel type treated, hence total > 100%; #: Mann-Whitney U-test

Results

In 14,458 enrolled patients, 3,603 patients (24.9%) were diabetic, in which 2.8% were newly diagnosed as diabetic, 15.3% were treated with dietary control, 58.2% with oral medication and 23.6% were on insulin. Prevalence of the diabetics in patients enrolled from each region was 19.4% from Northern Europe, 24.8% from Western Europe, 22.2% from Central Europe and 28.1% from Mediterranean. Patient characteristics, clinical presentation and angiographic results are presented in Table 1. Diabetics were older (65.7 vs. 62.9 years), less often male (67.7% vs. 76.9%) and had a higher body mass index than non-diabetics (29.0 vs. 27.4 kg/m^2). Diabetics had higher rates of hypercholesterolaemia (69.2% vs. 61.2%) and hypertension (77.5% vs. 61.4%), while current smokers were more frequent in the non-diabetics (19.0% vs. 31.6%). Diabetics also had significantly higher rates of previous cardiovascular events. Regarding the clinical presentation, ACS with ongoing instability was less frequent (29.3% vs. 33.6%) and elective PCI was more frequent (44.8% vs. 42.0%) in diabetics. Normal left ventricle ejection fraction (>50%) was less frequent in diabetics than in non-diabetics (p<0.001). Angiographic results showed that 3-vessel disease was present in 29.1% of diabetics vs. 21.1% of non-diabetics (p<0.001).

The use of medical therapy from the time of admission and discharge is presented in Figure 1. On admission, beta-blockers (BB), angiotensin converting enzyme inhibitors (ACE-I) and statins were used in half the patients, while diabetic patients had a strong tendency towards being prescribed more cardiac medications than non-diabetics. At discharge, there was a major adjustment of treatment with increases in the use of BB, ACE-I, angiotensin receptor blockers (ARB) and statins as well as antiplatelet agents. Approximately 80% of patients had beta-blockers and 90% of patients received a statin.

Figure 2 demonstrates the use of antiplatelet therapy before PCI. Aspirin was prescribed in almost 80% of patients, while clopidogrel was given to approximately half of the patients (Figure 2A). In roughly a quarter of those treated with clopidogrel, it was administered within 6 hours before PCI (Figure 2B). The recommended duration of dual antiplatelet therapy is presented in Figure 3. In patients with drug-eluting stents, approximately 8 % of patients were recommended by physicians to have dual antiplatelet therapy for less than 6 months.

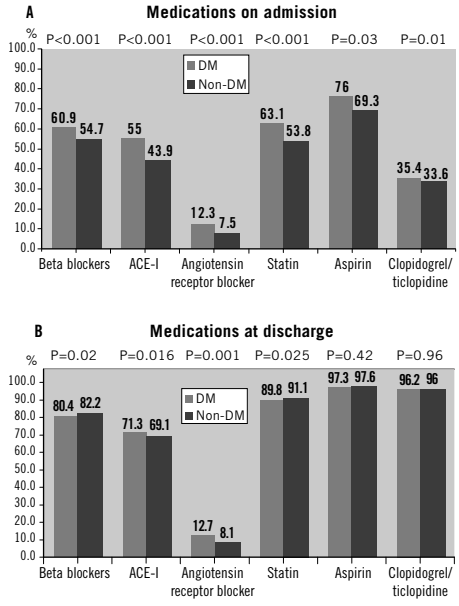

Figure 1 demonstrates medications on admission (A) and at discharge (B). P values are given for comparison between diabetics and non-diabetics. There was a major adjustment at discharge.

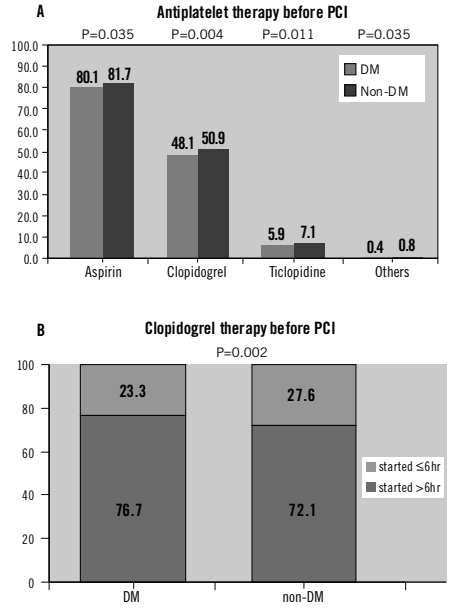

Figure 2 demonstrates anti-platelet therapy before PCI. Clopidogrel / Ticlopidine were given to only 54.0% of diabetics and 58.0% of non-diabetics (A). For the patients receiving clopidogrel, roughly one quarter started the agent less than 6 hours before the PCI procedure (B).

Tables 2 and 3 show the type of arterial access, lesion characteristics and devices used in PCI. There were no differences in the route of arterial access between diabetics and non-diabetics; femoral access was the most frequently used. The left main trunk was treated at similar rates (2.4%) in both diabetics and non-diabetics. Type C and restenotic lesions were more frequently treated in diabetics than non-diabetics. The use of invasive diagnostic tools (intravascular

Table 2. Arterial access and devices used in PCI.

	Diabetics (n=3,603)	Non-diabetics (n=10,855)	p-value
Percutaneous arterial access			0.63
Femoral	89.1	88.6	
Brachial	0.3	0.5	
Radial	10.5	10.8	
Other / unknown	0.1	0.1	
PCI lesions			
*Treated vessels**			
Right coronary artery	37.6	38.1	0.62
Left main trunk	2.4	2.4	0.97
Left anterior descending artery	48.5	47.4	0.22
Left circumflex artery	30.1	28.8	0.15
Bypass graft	2.7	2.0	0.016
No. of treated segments			0.001†
1 segment	66.8	69.4	
2 segments	22.8	22.2	
≥3 segments	10.4	8.4	
Number of stents implanted			0.09†
No stent	6.9	6.5	
1 stent	64.2	66.3	
2 stents	20.3	20.0	
At least 3 stents	8.6	7.1	
Use of drugs			
Aspirin	83.9	85.1	0.11
Clopidogrel	77.2	77.2	0.99
300 mg loading dose#	84.1	82.2	0.14
600 mg loading dose#	15.9	17.8	0.14
Ticlopidine	7.2	8.4	0.03
GP IIb/IIIa-antagonist	23.1	24.5	0.10
GP IIb/IIIa-antagonist in STEMI/Non-STEMI patients	46.5	48.0	0.48
Positive inotropes	3.7	3.4	0.42
Unfractionated heparin	82.6	81.1	0.047
Low-molecular weight heparin	28.8	31.1	0.01
Diagnostic devices			
IVUS	1.6	2.0	0.18
Pressure wire	0.7	1.2	0.03
Flow wire	0.3	0.2	0.76
Therapeutic devices			
Cutting balloon	2.1	2.0	0.62
Intra-aortic balloon pump	1.4	1.8	0.10
Distal protection Device	0.2	0.5	0.04
Rotablator	0.4	0.2	0.04

Values are %. PCI: percutaneous coronary intervention; IVUS: intravascular ultrasound; *: % of patients with each vessel type treated, hence total >100%; #: % of patients loaded with clopidogrel before PCI; †: Mann-Whitney U-test

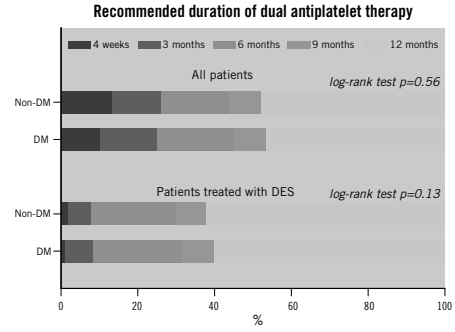

Figure 3. Recommended duration of dual anti-platelet therapy is demonstrated in all patients and in the patients treated with DES.

Table 3. Characteristics of treated lesions.

	Diabetics (n=5,416)	Non-diabetics (n=15,718)	p-value
Lesion characteristics			0.04
Type A	12.6	13.6	
Type B	58.6	59.2	
Type C	28.7	27.2	
Restenosis	6.3	5.0	<0.001
Bifurcation	12.3	13.2	0.09
TIMI flow before PCI			< 0.001#
TIMI 3	64.1	60.3	
TIMI 2	14.6	15.1	
TIMI 1	7.0	6.9	
TIMI 0	14.3	17.7	
Maximal stent/ balloon size			< 0.001#
≤ 3 mm	70.2	64.6	
> 3 mm	29.8	35.4	
Stent implanted	89.1	90.1	0.03
Stent type*			<0.001
Passive stent	43.3	53.3	
Drug eluting stent	56.7	46.7	
DES type†			0.64
Cypher†	46.8	45.7	
Taxus†	49.3	50.4	
Endeavor†	3.9	3.9	

Values are %. TIMI: Thrombolysis in Myocardial Infarction Trial Grade; PCI: percutaneous coronary intervention; DES: Drug eluting stent; #: Mann-Whitney U-test; *: % of known stent types; †: expressed as a % of known drug-eluting stent types

ultrasound [1.6% vs. 2.0%], pressure wire [0.7% vs. 1.2%] and flow wire [0.3% vs. 0.2%]) was low in both groups. Diabetic patients had smaller calibre vessels treated: a maximum stent or balloon size ≤ 3 mm was more frequently used in diabetics. In diabetics, more PCI procedures involved the implantation of at least 3 stents than in non-diabetics. Bare-metal stents were more frequently used in non-diabetics (53.3% of stents implanted), while drug-eluting stents more in diabetics (56.7%).

Periprocedural complications and in-hospital outcome are shown in Table 4. TIMI flow after PCI was not different between diabetics and non-diabetics. Overall, there were no differences in the rates of periprocedural complications between the 2 groups, except that haemorrhage requiring surgery or transfusion occurred more frequently in diabetics than in non-diabetics (0.7% vs. 0.4%, p=0.01). The rates of in-hospital death, renal failure and major bleeding were significantly higher in diabetic patients, however, the

difference in the composite endpoint of death, non-fatal MI and non-fatal stroke was not statistically significant (3.6% vs. 3.0%, p=0.09). In addition, as a result of logistic regression analysis (Table 5), diabetes remained as an independent predictor of mortality. (Odds ratio 1.40, [95% CI: 1.03-1.92])

Table 4. Peri-procedural complications and in-hospital outcome.

	Diabetics (n=3,603)	Non-diabetics (n=10,855)	p-value
Minimal TIMI flow after PCI			0.14#
TIMI 3	92.8	92.1	
TIMI 2	3.9	4.3	
TIMI 1	0.7	0.9	
TIMI 0	2.6	2.7	
Peri-procedural complications	6.0	6.4	0.42
Acute segment closure	0.8	0.6	0.36
Side branch occlusion	1.0	1.3	0.26
Coronary perforation	0.2	0.4	0.08
No reflow	1.9	1.9	0.75
Heart block requiring pacing	0.6	0.6	0.80
DC cardioversion	0.5	0.6	0.59
Distal embolisation	0.7	0.7	0.82
Mechanical Ventilation	0.7	0.5	0.09
Tamponade	0.1	0.1	0.42
Shock induced by procedure	0.3	0.2	0.61
Allergic reactions	0.2	0.3	0.42
Stroke	0.1	0.0	0.10
Emergency CABG	0.1	0.2	0.46
Access complications in total	2.4	2.0	0.17
false aneurysm	0.8	0.7	0.54
haemorrhage requiring surgery or transfusion	0.7	0.4	0.01
Arterial occlusion / dissection	0.2	0.2	0.92
Arteriovenous fistula	0.2	0.1	0.13
Infection	0.4	0.3	0.49
In-hospital outcome			
MACCE	3.6	3.0	0.09
Death	1.8	1.2	0.02
Non-fatal MI	1.6	1.7	0.76
Non-fatal stroke	0.3	0.2	0.37
Stent thrombosis	0.5	0.7	0.26
on the same day as PCI	23.5	54.4	0.02
next day	17.6	7.4	0.19
between day 2 and discharge	58.8	38.2	0.12
Renal failure requiring dialysis	1.0	0.6	0.02
Major bleeding	1.3	0.9	0.04

Values are % or mean ± standard deviation. TIMI: Thrombolysis in Myocardial Infarction Trial Grade; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; MI: myocardial infarction; MACCE: Major Adverse Cardiac and Cerebrovascular event; #: Mann-Whitney U-test

Table 5. Predictors of hospital mortality.

Variable	OR	95%-CI
Diabetes	1.40	1.03-1.92
Age (per 10-year increase)	1.78	1.54-2.07
Male gender	0.76	0.55-1.03
Ongoing ACS	6.56	4.06-10.60
Elective PCI	0.53	0.27-1.03
Current smoker	2.21	1.55-3.15
Previous stroke	2.01	1.23-3.27
Congestive heart failure	1.60	0.97-2.63

Discussion

In this survey of current practice of PCI in Europe, diabetics represented 24.9% out of 14,458 patients. This percentage is threefold higher than the prevalence of diabetics in Europe (7.8%, International Diabetes Federation). Although the diabetic prevalence does not differ from the previous revascularisation survey (23% in PCI treatment arm)[13], the slightly higher prevalence of diabetes in this present survey may reflect the fact that the recruitment of the patients was weighted towards Mediterranean countries (39.0%) having a higher prevalence of diabetics of 28.1%.

The prevalence of smoking was lower in the diabetics (19.0% vs. 31.6%), while that of hypertension and hypercholesterolaemia was significantly higher in this group. This trend was also observed in the EUROASPIRE II survey including 5,650 patients with history of hospitalisation for coronary heart disease, where diabetic patients were more obese and had higher systolic but lower diastolic blood pressure than non-diabetic patients and the prevalence of current smoking was lower in diabetes (17.3%) than non-diabetics (22.0%)[18]. The ESC guidelines on cardiovascular disease prevention in clinical practice in 2003[19] states that in patients with established CVD, lifestyle changes such as stopping smoking, making healthy food choices and increasing physical activity should be encouraged. To achieve these goals, lifestyle intervention programs focusing simultaneously on multiple preventable risk factors seemed to be most successful[20,21].

The ESC guidelines generally pose more ambitious treatment goals for risk factors in diabetic patients than in non-diabetic patients[24]; <130/80 mmHg for blood pressure, <4.5 mmol/l for total cholesterol and <2.5 mmol/l for LDL cholesterol. In achieving these strict goals, hospitalisation for PCI seems to be a good opportunity to review and optimise medications. In the current survey, the usage of ACE-I, ARB, beta-blocker and statins before PCI in diabetics was 55.0%, 12.3%, 60.9% and 63.1%, whilst the use at discharge was 71.3%, 12.7%, 80.4% and 89.8%, respectively. From this point of view, there is improvement in this survey compared with the previous EHS survey on coronary revascularisation[13] in which the usage of ACE-I, beta-blocker and statin at discharge remained 57%, 75% and 67%, respectively. This trend that an admission for revascularisation results in better use of guideline recommended medical treatment is also reported in other registries. In the REACH international outpatient-based registry including 40,450 patients with documented CAD, Steinberg et al reported that use of any lipid-lowering agent in those with previous CABG or PCI was 86% in CABG/PCI groups versus 70% in patients medically managed[22]. The possible reasons for this discrepancy are: i) treatment by cardiologists during and after revascularisation procedures increases the likelihood of the use of guideline-recommended therapies for CAD; ii) having a revascularisation procedure increases the patients' and their physicians' awareness of the CAD diagnosis, thus increasing prescriptions for and adherence to therapies[23].

The ESC guidelines for diabetics with heart disease in 2007 state that in diabetic patients with CVD, statin therapy should be initiated regardless of baseline LDL cholesterol, with a treatment target of <1.8-2.0 mmol/l (Class I level B)[24]: they also indicate that screening for microalbuminuria and adequate blood pressure-lowering therapy

using ACE-inhibitors and angiotensin receptor II blockers improve micro- and macrovascular morbidity in type 1 and type 2 diabetes (Class I level A). Although statin and ACE-I treatment at discharge in this survey is as high as 89.8 and 80.4%, there is room for improvement in pharmacological therapy in diabetic patients.

This survey demonstrated that diabetics had better baseline TIMI flow than non-diabetics. One of the possible causes is that ACS was less frequent in diabetics while elective PCI was more frequent. Interestingly, better baseline coronary flow in diabetics has previously been reported even in the setting of acute myocardial infarction. In 3,742 patients enrolled in the Primary Angioplasty in Myocardial Infarction (PAMI) studies, Harjai et al demonstrated that although diabetics had worse baseline clinical characteristics, longer pain onset-to-hospital arrival time and longer door-to balloon time, they nevertheless had better TIMI flow than non-diabetics[25]. They speculated that diabetics with ACS and poor TIMI flow may have died before reaching the hospital.

The ESC guidelines in 2005 stated that clopidogrel should have been orally administered at least 6 hours before PCI in stable CAD (Class IC recommendation), and that the duration of clopidogrel was recommended to be from 6 to 12 months after DES implantation[15]. The higher loading dose of 600 mg is recommended as pre-treatment for primary PCI, immediate PCI in NSTE-ACS or ad hoc PCI in stable CAD while the lower loading dose of 300 mg is recommended in stable CAD[17]. The current study demonstrates that there was an under-usage of clopidogrel before the PCI procedure. Clopidogrel or ticlopidine was administered to only roughly 50% of patients before PCI (Figure 2A), and approximately 25% of patients were given clopidogrel within the 6 hours preceding the PCI (Figure 2B). The duration of dual antiplatelet therapy was well abided: 92% of the patients having drug-eluting stents were recommended to have dual antiplatelet therapy for at least 6 months. The loading dose of 600 mg was administered in 15.9% of diabetics, while 300 mg was used in 84.1%. Recently, Angiolillo et al reported that high platelet reactivity in type 2 diabetics with coronary artery disease on chronic dual antiplatelet therapy is associated with a higher risk of long-term adverse cardiovascular events, suggesting the need for tailored antithrombotic drug regimens in high-risk patients[26]. The higher loading dose of 600 mg of clopidogrel has been proposed as a strategy to accelerate and enhance platelet inhibition compared with a loading dose of 300 mg and to improve short-term clinical outcomes compared with standard clopidogrel therapy[27]. An alternative approach will be the use of prasugrel, a new thienopyridine, with more potency and rapid onset, which has been evaluated in randomised trial with promising results[28-30].

The previous ESC guidelines in 2005[15] stated that the use of GP IIb/IIIa inhibitors for PCI in stable angina should be considered on an elective basis in cases at high-risk of thrombotic complications (complex interventions, unstable lesions, as bail-out medication in case of threatening/ actual vessel closure, visible thrombus, or no/ slow-reflow phenomenon). In NSTE-ACS, GP IIb/IIIa inhibitors should be added only in high-risk patients, in whom an invasive strategy is planned (IC). In STEMI, guidelines recommend GP IIb/IIIa inhibitors use in all primary PCI (IIa A).

Now, the ESC guidelines for diabetics with heart disease renewed the statement that GP IIb/IIIa inhibitors are indicated also for elective PCI in a diabetic patient (Class IB)[24]. At the time this survey was performed, only the former guideline was published, so that only a small portion of diabetics received GP IIb/IIIa receptor blockers (7% before procedure, 22.9% during procedure). Broader use of GP IIb/IIIa is therefore expected in the future.

In this survey, 63.3% of diabetic patients treated with PCI had multivessel disease, although there is scant evidence demonstrating the benefit of PCI treatment over CABG treatment for multivessel disease. In a meta-analysis using pooled patient-level based 5-year follow-up data from ARTS, ERACI-II, MASS-II and SoS trials, the cumulative incidence of death, stroke or MI in the diabetic population was similar following PCI with stenting and CABG (21.4% vs. 20.9% respectively, p=0.9)[31]. However, the hazard ratio for repeat revascularisation in the diabetic subgroup was 0.19 (95% CI 0.12-0.30) due to a three-fold higher cumulative incidence of repeat revascularisation in the PCI group (29.7% vs. 9.2%; p<0.001)[31]. These results are still inconclusive because they are extracted results from diabetic subgroups without specifically targeting these populations. In addition, the above-mentioned trials were performed before the introduction of drug-eluting stents and accordingly comparison between contemporary CABG and PCI using drug-eluting stents is mandatory. The results of ongoing clinical randomised trials in diabetics such as the future Revascularisation Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM), The Coronary Artery Revascularisation in Diabetes (CARDia) trial and Coronary Artery Revascularisation in Diabetes (VA CARDs) is warranted.

The guidelines for diabetic/ pre-diabetic patients in 2007 state that drug-eluting stents should be used in all diabetic patients (Class IIa recommendation)[24]. In the survey, only 52.5% of diabetic patients were treated with drug-eluting stents. However, the benefit of DES in diabetics still needs further evaluation. In a recent meta-analysis of 18,023 patients by Stettler et al[32], comparing the use of sirolimus-eluting stents, paclitaxel-eluting stents and bare-metal stents, there were no differences in myocardial infarction or death between the three stent groups in the diabetic population. The Ontario registry including 13,353 patients demonstrated a significant benefit of drug-eluting stents over bare-metal stents in reducing the need for repeat TVR especially in subgroups of patients with two or three risk factors for restenosis including diabetics, small diameter and long lesion[33]. For example, the number needed to treat (NNT) in diabetic patients with small diameter vessels (<3 mm) and long lesions (≥ 20 mm) was 10, while the NNT for those with large diameter vessels and short lesions (< 20 mm) but without diabetes was 167.

As for complications, major bleeding was more frequently observed in diabetics (1.3% vs 0.9%). Since major bleeding is known to be associated with poor outcome, special attention should be paid to this particular subset of patients. According to a meta-analysis on the prognostic impact of major bleeding in ACS by Hamon et al, major bleeding is a strong predictor of mortality (7.6-fold), myocardial infarction (3-fold) and stroke (5-fold)[34]. Of interest, in the meta-analysis, diabetes was not identified as a risk factor for bleeding.

The current analysis demonstrated that the rate of in-hospital stent thrombosis is comparable between diabetics and non-diabetics, while stent thrombosis in the same day is relatively lower in diabetics than non-diabetics. This may reflect the fact that the diabetics were less frequently treated in the setting of primary PCI than the non-diabetics, which has been identified as one of the independent predictors of the stent thrombosis[35]. Since late thrombosis is one of the concerns after DES implantation, data with longer-term follow-up in larger patients cohort is warranted.

Study limitations

This survey only involves voluntarily participating hospitals and the sample size only represents a small fraction of all patients treated with PCI throughout Europe in the study period. Of note, the number of diabetics patients treated with DES was about 1,900. Such a sample size represents a very small fraction of the overall diabetic patients treated with DES in Europe. Therefore the present analysis may not be reflective of the current European interventional practice in diabetes patients. However, as the PCI registry has collected data on large numbers of patients, we still believe that it provides a good estimate of disease demographics and therapy and will also enable individual clinicians to compare their own patient population and therapeutic strategies.

Conclusion

The current analysis revealed that diabetic patients treated with PCI were older with more comorbidity and more severe coronary disease than non-diabetics; they were subsequently associated with worse in-hospital mortality. The under-usage of clopidogrel, GP IIb/IIIa inhibitors should be improved. The use of appropriate medications was adjusted at discharge. Follow-up data in this registry will clarify whether optimal medical therapy is maintained. The small sample size is a limitation of this study.

Appendix: Organisation of the Survey

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CHAPTER 8

The long-term value of sirolimus- and paclitaxel-eluting stents over bare metal stents in patients with diabetes mellitus

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Eur Heart J. 2007 Jan; 28(1): 26-32.

The long-term value of sirolimus- and paclitaxel-eluting stents over bare metal stents in patients with diabetes mellitus

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Received 23 August 2006; revised 8 October 2006; accepted 9 November 2006; online publish-ahead-of-print 29 November 2006

KEYWORDS
Diabetes;
Sirolimus-eluting stent;
Paclitaxel-eluting stent;
Restenosis

Aims To investigate the outcome of a real world diabetic patient cohort treated with bare metal stents (BMS), sirolimus-, or paclitaxel-eluting stents (SES and PES, respectively). Due to the different mechanisms of action of both drugs it is currently unknown which device is the best option to treat these high-risk patients.

Methods and results The study compares the 2-year clinical outcome of 708 consecutive diabetic patients (25% insulin treated) treated with either a BMS ($n = 252$), a SES ($n = 206$), or a PES ($n = 250$), as part of the RESEARCH and T-SEARCH registries. Target vessel revascularization was 19.5% in the BMS group, vs. 15.3% in the SES group and 9.7% in the PES group. PES (21.2%), but not SES (28.9%), were superior to BMS (29.7%) in reducing major adverse cardiac events. After propensity analyses, none of the differences remained significant. The incidence of stent thrombosis (ST) was high in both DES groups.

Conclusion There was a trend towards a more favourable outcome associated with the use of PES over BMS. There was no significant difference between SES and PES in each of the clinical endpoints, and neither in the NIDDM patients, which are hypothesized to be better-off with PES.

Introduction

Patients with diabetes mellitus (DM) are known to have a higher incidence of mortality and cardiovascular disease compared with non-diabetic patients.[1] Major reasons are the more diffuse and accelerated form of atherosclerosis, accompanied by longer lesion lengths, smaller vessel size, and greater plaque burden.[2–5] Insulin-requiring diabetics are, especially, more susceptible to adverse cardiac events.[6]

Several trials that pre-date the drug-eluting stent (DES) era showed that the event-free survival was significantly higher in patients treated with coronary artery bypass surgery over percutaneous coronary intervention (PCI) with balloon angioplasty or bare metal stents (BMS), mainly due to the high restenosis rates, inability to fully revascularize multiple ischaemic areas, and the rapid progression of atherosclerosis.[7–11] To date, both sirolimus- and paclitaxel-eluting stents (SES and PES) proved to be more effective in reducing restenosis and target vessel revascularization (TVR) in diabetic patients when compared with BMS up until 1 year of follow-up in several retrospective subset analysis of randomized controlled trials and small single-centre experiences.[12–16] Whether besides these benefits, the long-term hard clinical endpoints as mortality and myocardial infarction (MI) remain comparable between both groups remains questionable.[17,18].

Of interest is that patients with type II diabetes exhibit a breakdown in the PI3-kinase insulin signal transduction pathway, the pathway in which mammalian target of rapamycin (mTOR) is involved.[19] It can be hypothesized that in this situation, inhibiting protein synthesis by blocking mTOR with rapamycin may be less effective. Paclitaxel conversely, inhibits signalling downstream, independent of insulin resistance. Whether this hypothesis can be translated into clinical practice remains puzzling and is currently illustrated by various studies focusing on differences between SES and PES in selected patients up to 1 year of follow-up.[20–22] Our goal is to present the 2-year clinical outcome of 708 consecutive diabetic patients treated with a BMS, SES, or a PES.

Methods

Study design and patient population

In April 2002, our institution began to use SES (Cypher®; Cordis Corporation, Warren, NJ, USA) as a default strategy for all patients undergoing PCI. In February 2003, the PES (Taxus, Boston Scientific Corp., Natick, MA, USA) replaced the SES as the default treatment.

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From April 2002 to February 2003, 206 consecutive patients were treated exclusively with SES. From February 2003 to April 2004, 250 consecutive DM patients received a PES. A group of 252 consecutive diabetic patients treated with BMS immediately before April 2002 were retrospectively selected as a control group. The present diabetic population ($n = 708$) comprises 20% of the patients treated within the framework of the consecutive and similarly designed RESEARCH and T-SEARCH registries, which are described elsewhere.[23,24] Patients were eligible for inclusion if they were undergoing pharmacological treatment with either insulin or hypoglycaemic agents at the time of the index procedure and patients with transient hyperglycaemia were not included in the present analysis.

The protocol was approved by the hospital Ethics Committee and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

Procedures and post-intervention medications

All procedures were performed according to standard clinical guidelines.[24] Angiographic success was defined as a residual stenosis $\leq$30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow. All patients were pretreated with 300 mg of clopidogrel. At least 1-month of clopidogrel treatment (75 mg/day) was recommended for patients treated in the BMS phase. Patients who received a PES were prescribed $\geq$6 months of clopidogrel (75 mg/day), and those who received an SES were prescribed clopidogrel for $\geq$3 or 6 months depending on the complexity of the procedure.[25] All patients were advised to maintain aspirin ($\geq$80 mg/day) lifelong.

Endpoint definitions and clinical follow-up

DM was defined by the presence of therapy: patients taking solely oral medication were classified as non-insulin dependent diabetes mellitus (NIDDM) and those on insulin therapy as insulin-dependent diabetes mellitus (IDDM).

The primary endpoint was the occurrence of major cardiac events, defined as a hierarchical composite of all-cause death, non-fatal MI, or TVR. MI was diagnosed by an increase in creatine kinase-MB fraction of greater than three times the normal upper limit.[26] Target lesion revascularization (TLR) was defined as a repeat intervention (surgical or percutaneous) to control a luminal stenosis within the stent or in the 5-mm proximal or distal segments adjacent to the stent. TVR was defined as a re-intervention of a lesion in the same epicardial vessel. Subacute angiographic stent thrombosis was defined as an angiographically documented complete occlusion (TIMI grade 0 or 1 flow) or a flow-limiting thrombus (TIMI grade 1 or 2 flow) in the first 30 days after a successful procedure. Late-stent thrombosis was defined as angiographically defined thrombosis (TIMI grade 0 or 1 flow or the presence of a flow-limiting thrombus) occurring at least 1 month after DES implantation accompanied by acute symptoms.[27] Creatinine clearance was used as the measure of renal function with the baseline creatinine clearance calculated from most recent preprocedural creatinine value according to the formula proposed by Cockcroft and Gault.[28] Hypercholesterolaemia was defined as a fasting serum cholesterol level $>$5.5 mmol/L or use of lipid-lowering therapy at the time of the procedure.[29]

Two-year follow-up data

Survival data for all patients were obtained from municipal civil registries. A health questionnaire was subsequently sent to all living patients with specific questions on re-hospitalization and major adverse cardiac events. Patients treated with BMS or SES were contacted at 6 months, 1 year, and 2 years post-procedure, whereas patients treated with PES were contacted at 1 and 2 year(s) post-procedure. All repeat interventions and re-hospitalizations were prospectively collected during follow-up and entered into a dedicated database. When needed, referring physicians and institutions were contacted for additional information. Finally, follow-up was available for 98% of the patients in both DES groups and for 97% in the BMS group.

Statistical analysis

Continuous variables are presented as mean $\pm$ SD. Categorical variables are expressed as counts and percentages. Comparisons among the three groups were performed by the *F*-test from an analysis of variance for continues variables and Pearson's χ^2 test for categorical variables. The cumulative incidence of adverse events was estimated according to the Kaplan–Meier method and the log-rank test was used to evaluate differences between groups. Cox proportional hazards regression analysis was performed to correct for independent predictors of adverse events. Independent predictors, using all the baseline and procedural characteristics listed in *Tables 1* and *2*, were determined for each of the endpoints in the three compared groups (SES vs. BMS; SES vs. PES; PES vs. BMS). Independent predictors of outcome ($P < 0.1$), were forced into the model, together with the stent-type (=crude hazard ratios) and the assumptions of the proportional hazards model were tested using Omnibus tests of model coefficients. In order to avoid chance predictors, all predictors were carefully evaluated and none of them was in contrast to previously known risk factors. Control of potential confounders was attempted by constructing a propensity score using logistic regression.[30] The propensity score was the probability that a patient would receive either a BMS, an SES, or a PES, and was computed using an extensive, non-parsimonious, logistic regression model including the following variables: age, gender, clinical presentation, previous PCI, previous MI, previous coronary artery bypass surgery, multivessel disease, hypertension, dyslipidaemia, family history of coronary artery disease, smoking, diabetes, creatinine clearance, body mass index (BMI), glycoprotein IIb/IIIa inhibitor use, bifurcation treatment, vessel treated (RCA, LAD, LCX, LM, bypass graft), lesion type, chronic total occlusion, average stent diameter, number of stents, and total stented length. The selection of the variables was made so as to get the best discriminating model as assessed by the *C*-statistics. Covariate interactions and higher-order terms for the continuous variables proved unnecessary for the balance of baseline characteristics across quintiles. In the PES vs. BMS comparison, the propensity score became significant in the model for which we deleted the first quintile. In the PES vs. SES comparison, we deleted the fifth quintile. The resulting propensity score was then included in the Cox proportional hazards model as a continuous variable. The final results are presented as adjusted HRs. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. In all cases, $P < 0.05$ was considered significant. Statistical analysis were performed with SPSS 12.0.2 for Windows (SPSS Inc., Chicago IL, USA).

Results

Baseline and procedural characteristics

Baseline, angiographic, and procedural characteristics are included in *Tables 1* and *2*. There were more patients requiring insulin treatment in both DES groups: 31% (SES), 28% (PES), than in the BMS group (18%), $P < 0.002$. Both hypertension and hypercholesterolaemia increased over time and so was the presence of multivessel disease and the duration of clopidogrel prescription. The complexity of the procedures also increased over time, reflected by the treatment of type C lesions, incidence of multivessel treatment, number of stented vessels, number of implanted stents, total stented length, average stent diameter, and treatment of chronic total occlusions.

Table 1 Baseline clinical characteristics

	Bare ($n = 252$)	SES ($n = 206$)	PES ($n = 250$)	*P*-value
Male, *n* (%)	162 (64)	136 (66)	82 (67)	0.78
Age (years ± SD)	62.7 ± 10	62.0 ± 10	63.8 ± 11	0.2
NIDDM, *n* (%)	208 (82)	142 (69)	180 (72)	0.002
IDDM, *n* (%)	44 (18)	64 (31)	70 (28)	0.002
Hypertension, *n* (%)	135 (54)	142 (69)	176 (70)	<0.001
Hypercholesterolaemia, *n* (%)	150 (60)	145 (70)	207 (83)	<0.001
Current smoking, *n* (%)	55 (22)	41 (20)	47 (19)	0.69
Previous myocardial infarction, *n* (%)	92 (37)	74 (36)	102 (41)	0.49
Previous angioplasty, *n* (%)	69 (27)	65 (32)	67 (27)	0.49
Previous coronary bypass surgery, *n* (%)	40 (16)	21 (10)	40 (16)	0.14
Multivessel disease, *n* (%)	151 (60)	139 (67)	177 (71)	0.03
Clinical presentation				
Stable angina, *n* (%)	125 (50)	100 (49)	116 (47)	0.77
Unstable angina, *n* (%)	99 (39)	73 (35)	93 (37)	0.70
Acute myocardial infarction, *n* (%)	28 (11)	33 (16)	41 (16)	0.18
Creatinine clearance (mL/min)	107.6 ± 72.4	96.2 ± 35.2	89.5 ± 40.0	0.02
BMI (kg/m^2)	29.5 ± 6	29.0 ± 5	29.1 ± 11	0.76

Table 2 Angiographic and procedural characteristics

	Bare ($n = 252$)	SES ($n = 206$)	PES ($n = 250$)	*P*-value
Treated coronary vessel[a]				
Left anterior descending, *n* (%)	145 (58)	126 (61)	135 (54)	0.31
Left circumflex, *n* (%)	83 (33)	74 (36)	87 (35)	0.79
RCA, *n* (%)	88 (35)	82 (40)	160 (64)	<0.001
LM coronary, *n* (%)	14 (6)	13 (6)	12 (5)	0.78
Bypass graft, *n* (%)	19 (7.5)	6 (3)	23 (9)	0.024
Lesion type [b]				
Type A, *n* (%)	41 (16)	42 (20)	22 (9)	0.002
Type B1, *n* (%)	82 (32)	76 (37)	56 (22)	0.002
Type B2, *n* (%)	122 (48)	107 (52)	125 (50)	0.75
Type C, *n* (%)	100 (40)	86 (42)	132 (53)	0.007
Number of coronary vessels treated, *n* (%)				<0.001
1	166 (66)	124 (60)	137 (55)	
2	71 (28)	68 (33)	63 (25)	
3	15 (6)	14 (7)	50 (20)	
Multivessel treatment, *n* (%)	85 (34)	82 (40)	114 (46)	0.025
Bifurcation stenting, *n* (%)	20 (8)	38 (18)	30 (12)	0.003
No. of stented vessels	1.4 ± 0.6	1.5 ± 0.6	1.7 ± 0.8	<0.001
Number of implanted stents ± SD	1.9 ± 1.2	2.3 ± 1.4	2.3 ± 1.4	<0.001
Total stented length per patient (mm ± SD)	30.5 ± 22.4	44.1 ± 29.2	48.8 ± 32.9	<0.001
Average stent diameter (mm ± SD)	3.27 ± 0.49	2.82 ± 0.25	2.91 ± 0.37	<0.001
Nominal stent diameter ≤2.5 mm, *n* (%)	21 (8.4)	31 (15.1)	52 (20.6)	0.001
Chronic total occlusion (>3 months), *n* (%)	14 (6)	20 (10)	54 (22)	<0.001
Glycoprotein IIb/IIIa inhibitor, *n* (%)	80 (32)	41 (20)	64 (26)	0.02
Clopidogrel prescription (months) ± SD	3.17 ± 3.23	4.68 ± 2.73	6.32 ± 2.58	<0.001
Angiographic success of all lesions, *n* (%)	244 (97)	190 (92)	235 (94)	0.1

Values are means ± SD or percentages.
[a]Expressed as percentage of patients with vessel type treated. Total exceeds 100%.
[b]Expressed as percentage of patients with lesion type. Total exceeds 100%.

Two-year follow-up

Two-year cumulative incidence of mortality was comparable among the three groups: 9.8% in the BMS group vs. 13.3% and 11.5% in the SES and PES groups, respectively (*Figure 1A*). However, a significantly higher number of patients in the SES group died in the second year: 12 (5.8%) when compared with only three (1.2%) in the PES group ($P = 0.007$). Eight patients (3,2%) died in the second year in the BMS group. MI was more frequent in the BMS (7.7%) and SES (5.1%) groups when compared with the PES group (3.4%) ($P = 0.048$ PES vs. BMS). The cumulative incidence of the combined endpoint of death and MI occurred in 15.4% of

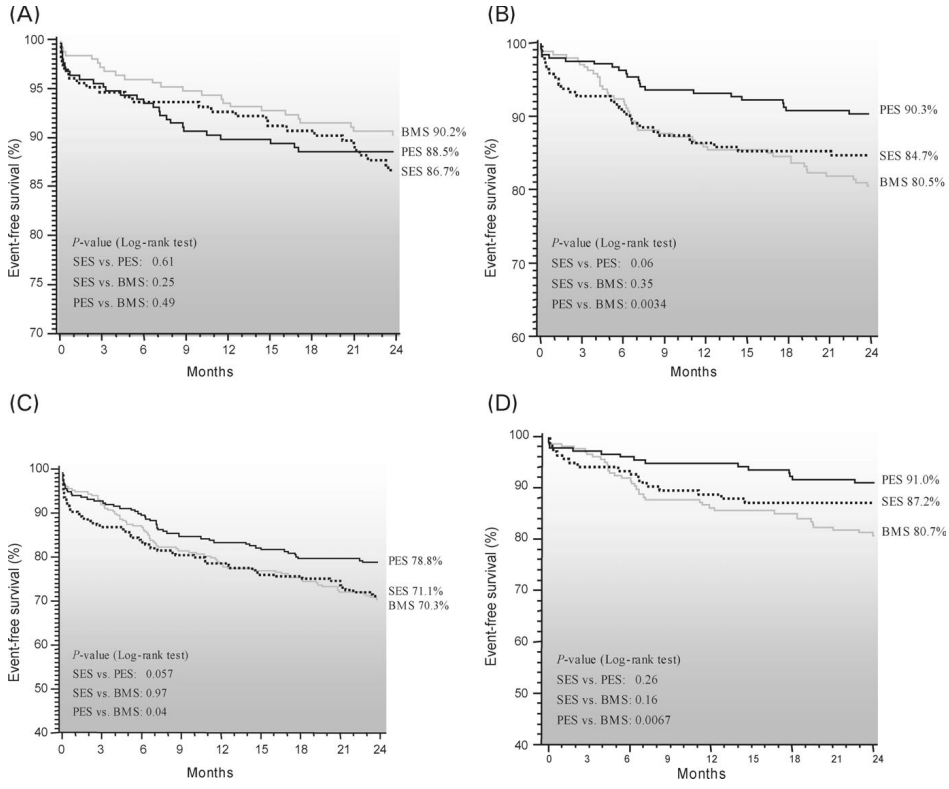

Figure 1 Two-year cumulative incidence of mortality (*A*), TVR (*B*), major adverse cardiac events (*C*), and TVR in NIDDM (*D*), in patients treated with BMS, SES, or PES, respectively.

the BMS patients, vs. 18.2% and 14.7% of the SES and PES patients, respectively ($P = 0.33$ SES vs. PES). TLR was performed in a remarkably low percentage of PES patients (5.3%) when compared with the BMS (15.6%) and SES (13.2%) patients ($P = 0.0037$ SES vs. PES; $P = 0.0004$ PES vs. BMS). Also, TVR was significantly lower in the PES group (9.7%) when compared with the BMS group (19.5%) ($P = 0.0034$). The cumulative incidence of TVR in the SES group was 15.3% and was neither inferior to PES ($P = 0.06$) nor superior to BMS ($P = 0.97$) (*Figure 1B*). The composite endpoint of MACE was found in 29.7% of the BMS patients, almost comparable with the SES group, in which a 28.9% incidence of MACE was found. MACE rates in the PES group (21.2%) were significantly lower when compared with the BMS group (29.7%), $P = 0.04$ (*Figure 1C*). Of interest was the high incidence of ST, which occurred in 4.4% of the SES patients (3.4% early ST) compared with 2.4% in the PES group (2.0% early ST) and only 0.8% in the BMS group (0.8% early ST) (*P*-values: SES vs. BMS, 0.015; PES vs. BMS, 0.18; SES vs. PES, 0.29). Of the total 17 patients with ST, two died, seven presented with an MI, and 12 patients were still on dual-antiplatelet therapy at the time of the event.

When patients were classified with respect to the use of insulin, the cumulative incidence of mortality was significantly higher in IDDM patients (16.7%) compared with the NIDDM patients (9.6%); ($P = 0.013$). TVR was performed in a comparable number of IDDM patients (17.1%) as in NIDDM patients (14.1%); ($P = 0.36$). Comparing TVR rates in the NIDDM patients (*Figure 1D*), the outcomes remained comparable to those of the overall population, showing no significant superiority of PES to SES.

Cox multivariable regression models were used to correct for differences and independent predictors of adverse events between each pair of groups (SES vs. BMS; PES vs. BMS; and PES vs. SES) (*Table 3*). After correcting for independent predictors of adverse events, the use of PES remained significantly superior to BMS in terms of TVR at both 1 (HR 0.66; 95% CI 0.49–0.89) and 2 years (HR 0.69; 95% CI 0.53–0.89), and MACE at 2 years (HR 0.75; 95% CI 0.60–0.94). The use of SES was neither significantly superior

Table 3 Multivariable predictors of major adverse cardiac events at 2 years (Cox proportional hazards model)

	BMS ($n = 252$)	SES ($n = 206$)	PES ($n = 250$)	SES vs. BMS, relative risk (95% CI)	PES vs. BMS, relative risk (95% CI)	PES vs. SES, relative risk (95% CI)
Mortality at 1 year (%)[a]	6.5	7.3	10.2	0.59 (0.23–1.5)]	0.95 (0.61–1.47)	1.72 (0.75–4.00)
Including propensity score				0.65 (0.20–2.14)	1.31 (0.64–2.69)	1.89 (0.69–5.21)
Mortality at 2 years (%)[a]	9.8	13.3	11.5	1.32 (0.76–2.29)	0.89 (0.61–1.31)	0.93 (0.48–1.82)
Including propensity score				1.55 (0.77–3.14)	1.08 (0.58–1.99)	2.31 (0.81–6.58)
Death or non-fatal MI at 1 year (%)[a]	10.9	12.2	12.6	1.04 (0.60–1.78)	0.85 (0.61–1.20)	1.24 (0.66–2.34)
Including propensity score				1.13 (0.58–2.19)	0.92 (0.57–1.51)	1.53 (0.70–3.39)
Death or non-fatal MI at 2 years (%)[a]	15.4	18.2	14.7	1.01 (0.62–1.63)	0.80 (0.59–1.08)	0.78 (0.50–1.24)
Including propensity score				1.20 (0.66–2.19)	0.90 (0.64–1.26)	0.89 (0.44–1.80)
TVR at 1 year (%)[a]	14.1	13.6	6.9	0.99 (0.59–1.65)	0.66 (0.49–0.89)	0.57 (0.29–1.14)
Including propensity score				0.98 (0.52–1.83)	0.69 (0.46–1.03)	0.66 (0.26–1.67)
TVR at 2 years (%)[a]	19.5	15.3	9.7	0.77 (0.48–1.24)	0.69 (0.53–0.89)	0.73 (0.40–1.35)
Including propensity score				0.83 (0.47–1.47)	0.73 (0.51–1.05)	0.65 (0.29–1.47)
MACE (Death, MI, and TVR) at 1 year (%)[a]	21.5	21.4	16.7	0.95 (0.64–1.42)	0.82 (0.65–1.02)	0.75 (0.49–1.15)
Including propensity score				0.97 (0.60–1.58)	0.77 (0.58–1.03)	0.55 (0.32–0.95)
MACE (Death, MI, and TVR) at 2 years (%)[a]	29.7	28.9	21.2	0.99 (0.70–1.40)	0.75 (0.60–0.94)	0.70 (0.49–1.02)
Including propensity score				1.11 (0.72–1.70)	0.77 (0.55–1.07)	0.68 (0.36–1.30)

[a]Crude HRs without propensity scores.

to BMS nor significantly inferior to PES. Of interest was that when the propensity score was added to the models, none of the comparisons remained significant although a trend remained towards a better outcome with PES when compared with both BMS and SES.

Discussion

The present study, comprising a series of 708 consecutive diabetic patients, showed that in contrast to the SES-treated patients, the crude relative risk for both TVR and MACE was significantly lower in the PES group over the BMS group, at 2 years of clinical follow-up. However, after propensity analyses, these differences did not remain significant. Although hypothesized, PES was not superior to SES in the NIDDM subset in reducing TVR or MACE. When compared with IDDM, NIDDM was associated with a better long-term survival.

The 2-year event-free survival rate in this diabetic subset was 24.8%, irrespective of the stent type used, and was substantially lower than reported in DES trials including a general population.[31–33] This latter confirms again the detrimental effect of DM on the prognosis following PCI, despite the use of DES in the majority of our patients.[34]

Both SES and PES have been shown to be superior to BMS in patients with DM up until 1 year of follow-up.[15,16] In a randomized trial by Dibra *et al.*, there was no significant difference between both devices in any of the clinical endpoints at 9 months of follow-up, despite the superiority of SES in reducing late lumen loss and binary restenosis.[20] A meta-analyses of randomized trials comparing either SES or PES to BMS showed that when the diabetic subsets were pooled, the use of SES was associated with a 65% reduction in in-stent restenosis compared with PES, albeit there was again no significant difference between both SES and PES in reducing TVR and MACE.[35] Because of its clinical approach, the present report is not completely comparable to these previous studies with angiographic primary endpoints, which show that inconsistencies between clinical and angiographic endpoints are far from being resolved. Nevertheless, our results are in line with other registries. The STENT registry, including 1680 diabetic patients, confirmed the comparable results achieved with both devices at 9 months of follow-up and the SOLACI registry showed even lower TVR rates in diabetics treated with PES, compared to those treated with SES.[21,36]

Stent thrombosis in both DES arms was high (SES: 4.4%, PES: 2.4%) when compared with the BMS patients (0.8%). Studies focusing on the incidence of ST following treatment with DES in a general population, reported ST rates of 1.0–1.6% and depicted diabetes as an independent predictor of ST.[27,37] The present report emphasizes the need for longer-term follow-up and confirms that ST, mainly in the DES-treated patients, continues to occur after 6–12 months of follow-up.[38] As 78% of the patients with ST were still on dual-antiplatelet therapy, lifelong prescription of clopidogrel, additionally associated with higher bleeding risks, higher costs, and a potential of clopidogrel resistance, does not seem warranted.[39–41] Nevertheless, we feel that these numbers should encourage researchers to continue to follow their patients and not to stop their follow-up when the initial ($\leq$1 year) results look promising.

Of interest are the mechanisms of action of both drugs. Sirolimus is a natural macrocyclic lactone that is capable of inhibiting the mTOR and blocking the cell-cycle during the transition from G1 to S phase.[42] mTOR is dependent of the PI3-kinase pathway, which is hypothesized to be degraded in insulin-resistant diabetics.[19] This latter suggests SES to be less effective in diabetic patients (comprising $\sim$70% NIDDM). Paclitaxel on the other hand stabilizes microtubules, which are known to be responsible for cell division, and acts completely independent of the PI3-kinase pathway. This hypothesis is partly supported by the results of the present study. We observed an almost identical occurrence of MACE in the SES and BMS groups, providing some evidence for the non-superiority of SES in diabetics. Although many would refer to previously published studies, which did prove this superiority, one has to realize that these studies

included only highly selected patients not reflecting daily clinical practice. Not only patients presenting with acute coronary syndrome, chronic total occlusions, and (un)protected left main (LM) stenosis, but also the typical diabetics with diffuse disease in multiple vessels, requiring extensive revascularization were often excluded.[12,14,15] In this study, these high-risk patients comprised ~60% of the present population. Although we were not able to show a superiority of PES over SES, there were two interesting findings. First, MACE rates were significantly higher in the SES group when compared with the PES group at 1 year (propensity analysis), which is in agreement with NIDDM arm, the large-scale STENT registry.[43] Secondly, there was a significantly higher mortality rate during the second year in the SES group. Although this difference could be due to ST, focusing on the combined endpoint of death and MI revealed comparable rates in all three groups, especially when correcting for independent predictors. Moreover, it has to be commented that the overall mortality rate (11.4%) in the present population was higher than reported in previous trials and is most likely related to the high complexity of the present population. Excluding patients presenting with multivessel disease, LM lesions and presentation with acute myocardial infarction resulted in a 2-year mortality rate of only 7.6%.

The present study suffers from the inherent limitations of a non-randomized trial. The compared groups were not completely identical, which was mainly due to the relatively large inclusion period in which the complexity of the procedures increased. In order to partly compensate for the differences in baseline characteristics, with an increasing risk over time, we performed a multivariable analysis and a propensity analysis. Thereby, the TLR rate might be less accurate in predicting clinical restenosis compared with a non-diabetic population, since diabetic patients are known to have a significantly greater incidence of silent ischaemia than non-diabetics and the lack of an angiographic follow-up.[44] Finally, ST related only to angiographically document ST, using a definition consistent with previous reports on ST either after DES or BMS implantation. This latter may have led to an underestimation of the actual incidence of ST, particularly, in patients suffering from sudden cardiac death or silent stent occlusion.

Nevertheless, this report focuses on the 2-year 'clinical' outcome of the unrestricted use of BMS, SES, and PES in diabetic patients in a 'real world' setting and demonstrates the importance of longer-term follow-up. More larger scale and randomized trials are needed to elucidate the best treatment for patients with DM and the possible superiority of one DES compared to another, also taking into account the long-term adverse events like ST.

Conclusion

Although there was a trend towards lower MACE rates in the PES group at 2 years of clinical follow-up, the superiority of both SES and PES over BMS in diabetic patients remains questionable. There was no significant difference between SES and PES in the NIDDM patients, who are hypothesized to be better-off with PES, and ST was more frequent in both DES groups.

Conflict of interest: none declared.

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CHAPTER 9

Contemporary treatment of patients with chronic total occlusion: critical appraisal of different state-of-the-art techniques and devices

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EuroIntervention. 2007; 3:188-196.

EuroIntervention

Contemporary treatment of patients with chronic total occlusion: critical appraisal of different state-of-the-art techniques and devices

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This paper also includes accompanying moving images published at the following website: www.eurointervention.org

KEYWORDS
Chronic Total Occulsion, tapered tip guidewires, retrograde recanalisation, CTO techniques

Abstract

Aims: To describe the contemporary approach of chronic total occlusion (CTO) treatment of patients at the Thoraxcenter, Rotterdam, The Netherlands. Additionally, to make a critical appraisal of the performance of state-of-the-art CTO dedicated guidewires and devices in a prospective registry of patients.

Methods and results: During 20 months, a total of 160 consecutive patients (165 CTOs) were enrolled. The mean age was 61.5±11.1 years and 83.6% were male. In 91.5% of the patients this was the first attempt to open the CTO and 93.8% were *de novo*. The overall success rate was 60.6%. A median of 1 guiding catheter was used per case (Range: 1 to 9) and a median of 4 guidewires (Range: 1 to 11; 13 different types). 74.5% patients required more than one guidewire/device for the treatment of the CTO. The guidewires that most frequently crossed the CTO were the following: PT Graphix™ intermediate 33.0%, Miracle 3 g 27.4% and Crosswire NT 25.5%. The only device tested as a first option for the treatment of the CTOs was the CROSSER™. Overall, the CROSSER™ system was used in 23 (13.9%) patients with a success rate of 60.9%. The Point 9® X-80 Laser catheter was used in 10 (6.1%) patients with a success rate of 60%. Another 3 patients were treated with the Point 7® laser catheter. Both were used either to facilitate the crossing of the balloon, or to treat primarily in-stent restenosis occlusions. The SafeCross® System was used in 15 (9.1%) patients and the success rate in these patients was 46.7%. The most common strategy used in this registry was the use of an over-the-wire balloon in 81.5% of the cases. The parallel wire technique was used in 27.3% of the cases and in 12.7% was converted into a "see-saw" technique. When a large false lumen was created, re-entry into the true lumen was attempted in 21.2% of the cases, by means of IVUS guided approach and/or the use of stiffer guidewires, such as a Confianza guidewire. Retrograde recanalisation was attempted in 10 cases (6.1%), in three cases a graft was used; the remaining cases were treated either via collaterals or the septal branches.

Conclusions: The treatment of CTOs requires the use of a high number of guiding catheters and guidewires, as well as the use of sophisticated devices. The procedure must be carefully planned in advance as far as possible, as well as considering a prompt change in approach during the performance of the procedure to prevent complications derived from long procedures by using specific techniques such as parallel wire, see-saw, anchoring balloon, etc.

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Abbreviations and acronyms
CABG: coronary artery bypass grafting
CTO: chronic total occlusion
GW: guidewire
IVUS: intravascular ultrasound
MNS: magnetic navigation system
MSCT: multislice computed tomography
OTW: over-the-wire
PCI: percutaneous coronary intervention

Introduction

Success in re-opening a chronic total occlusion (CTO) has significant benefits on quality of life as well as conferring a 10-year survival advantage compared with failed revascularisation[1,2]. There has been a significant increase in percutaneous procedural success rates for CTO over the last 10 years without an increase in adverse events[2]. Such successes have stimulated a shift from the conventional practice of treating all CTO patients with coronary artery bypass grafting (CABG) to a strategy that aims to treat these same patients with percutaneous coronary intervention (PCI).

Although a high proportion of CTOs may have a recanalised lumen that may facilitate the passage of a guidewire (GW)[3,4], this passage of the wire across the missing section of vessel or 'crossing' of the lesion is still the most technically demanding phase of the procedure and is the predominant cause of failure. Therefore, many specific guidewires and devices have been introduced to try to overcome this most exacting phase of the CTO procedure. As a result, nowadays interventionalists are overwhelmed by the availability of multiple CTO-dedicated guidewires (stiffer, tapered-tipped and hydrophilic-coated guidewires) and also CTO-dedicated devices (Crosser™, FlowCardia, Inc., USA; Laser Guidewire®, Spectranetics, Colorado Springs, CO, USA; Safe Cross System®, Intraluminal Therapeutics, USA) commercially available for the treatment of the CTO. Some of them have been separately evaluated in randomised trials and registries[5-7]. However, most of the time the treatment of the CTOs requires a synergistic combination of components of this armamentarium. How do they perform? Do we have a predefined sequence of the use of these guidewires/devices? To attempt to answer these questions, we prospectively collected data on 160 consecutive patients undergoing percutaneous treatment of a CTO at the Thoraxcenter, Rotterdam, The Netherlands. We describe in detail the tools and techniques used in the contemporary approach for the treatment of these patients.

Material and methods

Study patients

Those eligible for this study included all consecutive patients presenting with symptomatic coronary artery disease due to a chronic total occlusion. Chronic occlusion was defined as either an occlusion on angiography with no antegrade filling of the distal vessel other than via collaterals or minimal antegrade flow (TIMI flow 0 or 1)[8,9]. All patients included had a native vessel occlusion estimated to be at least one month's duration based on either a history of sudden chest pain, a previous acute myocardial infarction in the same target vessel territory, or the time between the diagnosis made on coronary angiography and PCI. The type of CTO was either *de novo* or in-stent restenosis.

The protocol was approved by the local ethics committee and is in accordance with the principles of Good Clinical Practice for Trials of Medicinal Products in the European Community and the Declaration of Helsinki. All patients signed a written informed consent.

The key point of this registry was the presence of a dedicated research fellow present in the cath lab during all cases, registering every single manoeuvre, technique or approach applied in the treatment of the case. The two most experienced operators in the CTO procedures in our centre treated all patients.

Definitions

Biplane angiography

The use of two simultaneous fluoroscopic C-arms. The angiographic views should be orthogonal and should offer the best visualisation of the missing segment. Ideally, all cases with CTO should be treated in a cath lab with biplane assistance.

Bilateral injection

This improves distal visualisation of the target vessel by doing simultaneous injections in the right and left coronary system. The purpose is also to better localise the position of the tip of the guidewire in the occluded segment and to visualise the distal true lumen. To this aim, bilateral femoral access is established; the non-target vessel is usually engaged with a 5 Fr diagnostic catheter and if, during the procedure, the manipulation of the guiding catheter in the target vessel provoked frequent disengagement of the non-target vessel catheter, a guidewire was placed in the non-target vessel to maintain the catheter engagement.

Guided reopening of CTO: different modalities

Retrograde-guided PCI

When retrograde filling in the occluded vessel is sufficient, it is common to see the distal end of the occlusion. A guidewire can be distally placed through contralateral collaterals. This strategy has usually two purposes: first the GW can be left touching the distal cap of the occlusion as a landmark ("kissing guidewire"); secondly, an attempt to cross the occlusion retrogradely can be performed (Figure 1).

Intravascular ultrasound (IVUS)-guided PCI

This concerns the use of IVUS to facilitate the guidewire (GW), either to cross the occlusion or to re-enter into the true lumen. The former is possible when there is a big side branch at the entry point of the CTO, for instance when the CTO is in the ostium of the left anterior descending artery, the IVUS probe can be placed in the ostium of the left circumflex (and vice-versa) to guide crossing of the occlusion. The latter is possible when there is a large false lumen created after long GW manipulation without angiographic signs of perforation (Figure 2).

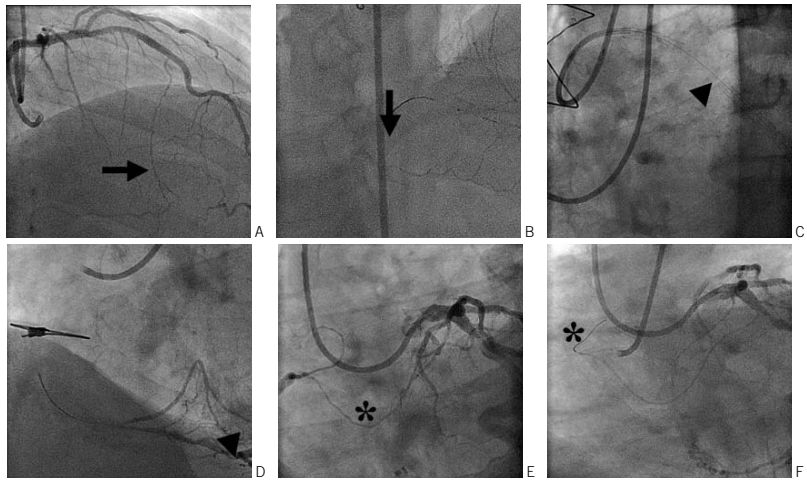

Figure 1. Retrograde technique. A and B via septal branch (arrow). C and D via saphenous vein graft (arrowhead). E and F via epicardial collateral (asterisk).

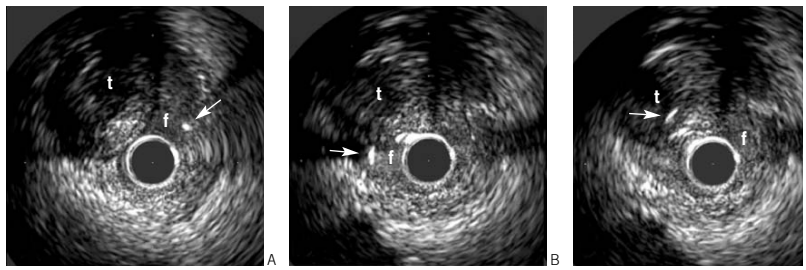

Figure 2. Panel A shows part of the vessel with the true lumen (t) at 11 o'clock. The arrowhead indicates the Crosswire NT guidewire in the false lumen (f) at 2 o'clock. Panel B shows the situation after manoeuvring the guidewire, still in the false lumen (f) now at 9 o'clock. Panel C shows the guidewire manoeuvred into the true lumen (t) at 10 o'clock. The IVUS probe is still positioned in the false lumen (f).

Multislice computed tomography (MSCT)-guided PCI

The 3-D volume-rendered reconstructed images produced by MSCT are imported into the Magnetic Navigation System (MNS) and overlaid on the fluoroscopic images (see also description of MNS below). Following this, a virtual lumen is identified using the vessel navigation tool that is a part of the MNS. This software marks points on both the MSCT and angiographic images using the "store marked position" option in the magnetic navigation software and these images are aligned using the alignment tool on the MNS screen. Finally, the vessel navigation software creates a virtual vessel overlay for the missing segment – namely the segment occupied by the CTO. After creation of the virtual vessel roadmap the operator can manoeuvre a guidewire through the vessel by indicating the desired point on a virtual roadmap that is synchronised to the fluoroscopic image (viewed from the same angle) and is displayed on a touch screen. The MNS computes a vector needed to navigate the guidewire and orientates the magnetic field that aligns the tip of the guidewire (Avi file 1).

Stent-guided PCI

This is is always the situation in cases of occlusive in-stent restenosis, where a permanent roadmap provided by the existing stent is present. This offers a particular situation where the interventionalist has instantaneous feedback of any manoeuvre performed with the guidewire.

Injection of contrast through the over-the-wire balloon (OTW)

Frequently, during CTO procedures there is uncertainty whether the GW is in the true lumen. The interventionalist can advance carefully the OTW balloon up to the tip of the GW, or as far as possible; then the GW is taken out and an injection of 1 or 2 cc of contrast media through the lumen of the OTW is performed. This allows you to visualise whether the GW is in the true lumen.

Improving support

In crossing CTOs it is essential to have optimal guiding catheter support; the following are some strategies to achieve this.

Guiding catheter selection

This is crucial in getting optimal support; for instance, in the treatment of the right coronary artery, an Amplatz left catheter was commonly used. Large size (7 or 8 Fr) guiding catheters are usually used in order to accommodate two balloons when there is the need for anchoring the balloon.

Stenting the proximal segment

When the proximal segment of the coronary artery is also diseased, stenting may facilitate deep engagement of the guiding catheter.

Anchoring technique

This consists of the placement of an inflated balloon in a non-target side branch[10] (Figure 3).

Child in Mother catheter technique or five-in-six system[11]

This is a method of inserting a 5 Fr guiding catheter into a 6 Fr or 7 Fr guiding catheter to increase backup support. Usually, the 5 Fr guiding catheter is 120 cm and the 6 Fr 100 cm long. The 5 Fr must have a soft tip to better negotiate any tortuosity it might encounter with the least possible damage (Figure 4).

Guidewiring of the non-target vessel

When one of the left coronary arteries is the target vessel a GW in the non-target vessel can be placed to increase support.

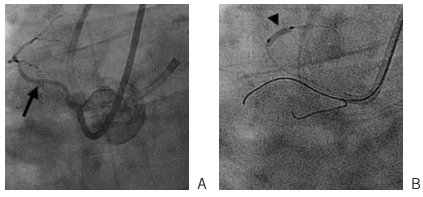

Figure 3. The anchor balloon technique. A. The arrow indicates the atrial branch of the Right Coronary Artery. B. A 2.0x12mm Maverick balloon (arrowhead) has been inflated in the atrial branch to improve guiding catheter support.

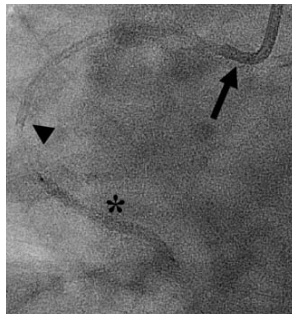

Figure 4. The "child-in-mother" technique. A 6 Fr mother guiding catheter (arrow) combined with a 5 Fr child catheter (arrowhead) facilitates delivery of a stent (asterisk).

Manoeuvres to facilitate advancement of the balloon once the GW is placed distally

After crossing the chronic occlusion, the operator may find either that the balloon does not cross the occluded segment or that the occlusion is undilatable. Here are some strategies to facilitate the placement of the balloon in the occluded segment:

Crosser™

The Crosser™ CTO Recanalisation System (FlowCardia Inc, CA, USA) is mainly a CTO device for primary crossing of the lesion. However, it can also help when the lesion is undilatable. The Crosser™ system has been described elsewhere[7,12]. The catheter is monorail, hydrophilic, and 0.014 inch guidewire and 6 Fr guiding catheter compatible (Avi file 2). In this cohort of patients, in three cases the Crosser™ was specifically used to facilitate advancement of the balloon catheter.

Point 9® X-80 Laser catheter

There are two product configurations of the Point 9® X-80 laser catheter (Spectranetics, Colorado Springs, CO, USA): Vitesse (Rx) 110-004 or Extreme (OTW) 110-002. The Point 9® catheter has a 0.9 mm tip diameter and is 0.014 inch guidewire and 6 Fr guide catheter compatible. The maximum laser parameters are: 80 fluence, 80 hertz. In addition, a new Point 7® (0.7 mm tip) laser catheter has been also tested in this registry. The point 7 was used in 3 cases (Figure 5).

Laser guidewire

The Laser guidewire® (Spectranetics, Colorado Springs, CO, USA) consists of a 0.018 inch shapeable guidewire containing 12 silica fibres with a 45 micron diameter. The guidewire was designed to function as an exchange guidewire. The fluence typically used

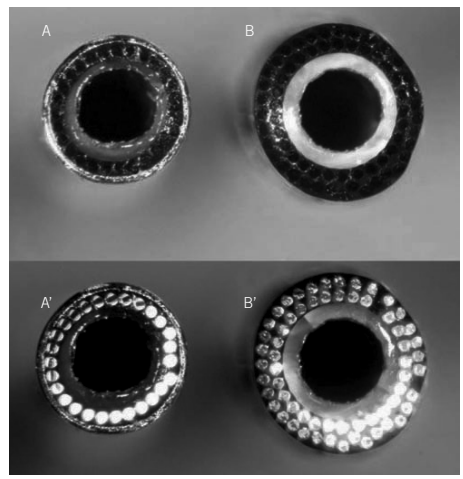

Figure 5. Point 7® (A) and Point 9® (B) laser catheters. In A' and B' the optical fibres are visualised. In the Point 7® laser catheter (A and A') there is one single line of optical fibres, while in Point 9® laser catheter (B and B') there are two lines.

during a laser guidewire procedure was 60 mJ/mm^2, with a pulse repetition rate of 25 Hz. The laser guidewire was used in one case (Avi file 3).

"Open mouth" technique

This is used once the GW has broken the proximal cap of the CTO and it is not able to advance further. A balloon inflation in the proximal segment of the occluded segment results in a larger space, enabling CTO guidewires and CTO-dedicated devices to perform better. However, some complications may occur if the guidewire is in a false lumen such as perforation. Thus, it is recommended to perform in cases of totally occluded stents, where a permanent and visible roadmap is present and also when the operator is certain the guidewire is in the true lumen.

Over-the-wire balloon exchange

Commonly, CTO treatment includes, as a first choice, the use of an over-the-wire balloon to back up the guidewire. When the guidewire is placed distally, the OTW has to be pulled back to advance other balloons or the stent. To try to keep in place the guidewire while the OTW is being pulling back, an indeflator filled with saline is used. The indeflator is connected to the lumen of the OTW and then saline solution is irrigated at a constant pressure (roughly 16 atm), while the OTW balloon is being pulled back during fluoroscopy, to reduce the risks of GW displacement.

Parallel wire technique

This is the use of two guidewires for crossing the CTO, when one subintimal track has been created. With this method, the wire which enters the subintimal space is left there, and a second wire (stiffer than the first one) is inserted alongside it to find a new channel[13] (Figure 6).

The see-saw technique

This also involves the use of two guidewires, but instead of leaving one of them in the false lumen, both are used sequentially to re-enter in the true lumen.

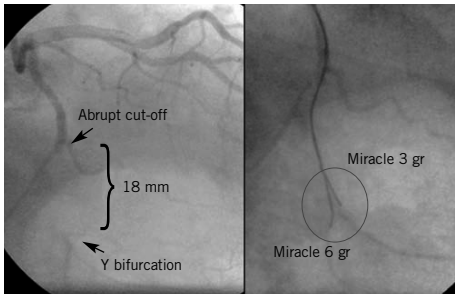

Figure 6. Parallel wire technique. In the right hand side panel the length of the occluded segment in the left circumflex was measured. Of note, the occlusion has a side branch at the entry point and ends in Y-bifurcation, these three angiographic characteristics have been associated with failure. On the left hand side, two guidewires are in place, both are clearly in a false lumen.

Partial reopening of the occlusion

Procedures where the GW crossed only half way through the occlusion and an important side branch was reached, but it was impossible to go further through the occlusion were considered a partial reopening.

Rentrop classification[14]

Grading of collateral filling was as follows: 0 = none, 1 = filling of side branches only, 2 = partial filling of the epicardial segment, 3 = complete filling of the epicardial segment.

Retrograde recanalisation

This is the opening of the CTO from the distal segment of the occluded vessel to the proximal segment of the occluded vessel. There are three possible routes to reach the distal cap: a) via arterial or vein grafts anastomosed to the native vessel distal to the site of occlusion in patients who have previously undergone CABG, b) via epicardial collaterals mainly between RCA and LCx through atrial branches or between distal RCA and LAD over the apex and c) septal collaterals. Bilateral arterial access is given for any route of retrograde approach (Figure 1).

SafeCross System[15]

The SafeCross System® (Intraluminal Therapeutics, Carlsbad, CA) is comprised of the Intraluminal guidewire, which is plugged directly into a console. The wire itself is 0.014 inch diameter and notably has a blunt tip; the distal 10 mm is radiopaque. The system uses optical coherence reflectometry to enable accurate guidance of the wire and a reduced risk of wire perforation. In addition, it enables the system to be forward looking with a very high resolution of up to 15 microns. The current Intraluminal guidewire has the capability of radiofrequency ablation with short-duration bursts (100 msec pulses) of low-frequency energy (250–500 kHz) delivered at the tip to enhance forward wire passage.

Venture® control catheter[16]

The Venture® is a 6 Fr, 0.014" compatible, 140 cm long over-the-wire, flexible and torqueable support catheter with a mechanically activated deflectable tip (90° degrees). It is intended to direct, steer, support, and control a guidewire (Avi file 4).

Magnetic navigation system

The use of a magnetic navigation system is a new option that may facilitate navigation in complex coronary anatomy[17]. The Stereotaxis Niobe® MNS has been extensively described elsewhere[18]. In brief, there are two permanent magnets positioned on either side of the fluoroscopic table. The MNS generates a composite magnetic field of 0.8 Tesla that is uniform in a 15 cm volume within the chest of the patient. This creates a magnetic field vector that can be rotated, translated and tilted in 360º in each plane, this allows fine control of the orientation of the tip of a magnetically enabled guidewire.

Statistical analysis

The analysis was done according to the principle "intention-to-use", which means that all the manoeuvres and armamentarium employed during the procedure independently of the duration of the use were included. Continuous variables are presented as mean±SD and categorical variables are presented as counts and percentages.

Results

From October 2004 to April 2006, 160 (165 CTOs) consecutive patients were enrolled in this prospective, research-fellow witnessed registry of patients with a chronic total occlusion treated in a single centre. Five patients had two occluded vessels and were treated in the same index procedure.

The mean age 61.5±11.1 years, mostly being male 83.6% (Table 1). For the majority of the patients (91.5%) this was the first attempt to open the CTO. Most of the occlusions were *de novo* lesions (93.8%), and the most frequently treated coronary artery was the right coronary artery (RCA) in 51.8% (Table 2). The angiographic characteristics are also shown in Table 2.

Table 1. Baseline characteristics, n=160.

Age, years (mean+SD)	61.5±11.1
Male (%)	83.6
Diabetes mellitus (%)	22.4
Hypertension (%)	49.7
Family history of CHD (%)	46.7
Current smoking (%)	35.2
Hypercholesterolaemia (%)	58.2
Previous ACS (%)	41.8
Previous PCI (%)	27.9
Previous CABG (%)	9.7
Vessel disease (%)	
One vessel disease	28.9
Two vessel disease	48.7
Three vessel disease	22.4
Attempts to reopen the CTO (%)	
First	91.5
Second	7.9
Third	0.6

SD = standard deviation; CHD = cardiovascular heart disease; ACS = acute coronary syndrome; PCI = percutaneous coronary intervention; MI = myocardial infarction

Guiding catheter selection

A total of 226 guiding catheters were used for the treatment of 165 CTOs. Overall, the median was 1 (Range: 1 to 9). Specifically, in the left anterior descending (LAD) and left circumflex (LCX) the median was 1 (Range: 1 to 9), whereas in the RCA the median 1 but the range went from 1 to 5.

For the LAD the first choice of guiding catheter was the Amplatz left 2 in 51.0% of the cases. While in the LCX the Judkins left guiding catheter was the most frequently used (41.1%). Lastly, in the RCA the Judkins right was the first option in 68.0% (Table 3). Of note, in the LAD, 23.5% of the patients required more than one guiding catheter; while in the LCX, 29.4% patients required more than one. Lastly, in the RCA, 17.9% patients required more than one guiding catheter.

Guidewire selection

Thirteen different types of guidewires were used. Overall, a total of 467 guidewires were used for the treatment of 165 CTOs. The median was 4 (Range: 1 to 11). Specifically, in the LAD the median was 3 (range: 1 to 11) and in the LCX the median was 1 (Range: 1 to 9), whereas in the RCA the median 2 (range: 1 to 11). The first choice in 69.9% of the cases was the PT Graphix™ Intermediate (Boston Scientific Corporation, USA), followed by Miracle 3 g (ASAHI, INTEC, Co, Japan) in 12.9% of the cases and 5.5% of the cases were primarily treated using a Choice™ PT (Boston Scientific Corporation, USA). The magnetically enabled Cronus moderate support and Assert guidewires were used as the first option in 4 cases (Table 4).

Seventy-four and a half percent (74.5%) of the patients required more than one guidewire/device for the treatment of CTO. Of note, as a second option, the PT Graphix™ Intermediate usage showed an important drop (11.4%), while the use of Miracle 3 g increased significantly (43.9%).

The guidewires most frequently used to cross the CTO in this registry were the following: PT Graphix™ Intermediate at 33.0%, Miracle 3 g at 27.4% and Crosswire NT at 25.5%. In total these three guidewires achieved 85.9% of the overall success rate.

Table 2. Procedure and angiographic characteristics, n=165.

Type of CTO (%)	
De novo	93.8
In-stent restenosis	6.3
Target vessel (%)	
Left anterior descending	31.1
Left circumflex	10.4
Right coronary artery	51.8
Obtuse marginal	5.5
Left main coronary artery	0.6
Stump morphology (%)	
Central	17.5
Eccentric	37.8
Blunt	44.8
Ostial involvement (%)	15.2
Side branch at entry (%)	67.3
Bridging collaterals (%)	42.4
Collateral filling [Rentrop Classification (%)]	
0/1	21.0
2	32.5
3	46.5
Calcification (%)	
None/mild	56.5
Moderate	26.7
Severe	16.7
PCI in at least one additional (non-occluded) major vessel during the index procedure (%)	
Two arteries	25.6
Three arteries	6.1
Number of vessels treated	1.4±0.6
Total number of stents	2.2±1.8
Number of stents in the target vessel	1.5±1.5
Average target vessel stent length (mm)	24.5±7.3
Average target vessel stent diameter (mm)	2.9±0.4
Contrast used (ml)	457.5±191.6
Procedure time (min)	128.0±58.9
Fluoroscopic time (min)	67.2±44.7
Radiation exposure (DAP)	12,395.9±8,320.7
Total cost of the procedure (Euros)	5,544.9±3,366.2
Overall success rate (%)	60.6

SD = standard deviation; CHD = cardiovascular heart disease; ACS = acute coronary syndrome; PCI = percutaneous coronary intervention; MI = myocardial infarction

Table 3. Guiding catheter selection.

	1st choice	2nd choice	3rd choice	4th choice	5th choice	Last GC used
LAD	n=51	n=12	n=1	n=1	n=1	
	100.0%	23.5%	0.02%	0.02%	0.02%	
Judkins left	6.4	25.0	100.0			42.5
Contralateral support (CLS)	38.3	25.0		100.0		34.0
Amplatz left 2	51.0	8.3				19.1
Amplatz left 3	4.3	41.7				4.3
LCX	n=17	n=5	n=3	n=3	n=3	
	100.0%	29.4%	17.6%	17.6%	17.6%	
Judkins left	41.2			33.3		41.2
Contralateral support (CLS)	29.4	40.0		66.7	100.0	41.2
Amplatz left 2	29.4	20.0	100.0			11.8
Amplatz left 3		40.0				5.9
RCA	n=78	n=14	n=6	n=5	n=4	
	100.0%	17.9%	7.7%	6.4%	5.1%	
Judkins right	68.0	28.6	20.0	20.0	50.0	59.0
Amplatz left 2	29.5	50.0	20.0	20.0	25.0	34.6
Amplatz left 3	1.3	7.1			25.0	2.6
Amplatz right	1.3					1.3
Amplatz left 1		7.1				1.3
Multi-purpose		7.1	20.0	20.0		
El Gamal			40.0	40.0		

LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery; GC = guiding catheter

Table 4. Guidewires selection to cross the CTO.

	1st choice n=165 100.0 %	2nd choice n=123 74.5 %	3rd choice n=81 49.1 %	4th choice n=57 34.5 %	5th choice n=36 21.8 %	6th choice n=24 14.5 %	7th choice n=12 7.3 %	8th choice n=8 4.8 %	9th choice n=5 3.0 %
PT Graphix™ Intermediate	69.9	11.4	21.0	8.8	30.6	8.3	16.7	50.0	20.0
Miracle 3 g	12.9	43.9	19.8	24.6	11.1	29.2		25.0	20.0
Choice™ PT	5.5	3.3	3.7	3.5	5.6			12.5	
Crosswire NT	4.3	24.4	22.2	21.1	11.1	20.8	8.3	12.5	20.0
Cronus moderate support	0.6								
Assert	1.8								
Miracle 4.5 g		0.8	1.2	1.8					
Miracle 6 g		1.6	4.9	12.3	11.1	8.3	16.7		
Confianza		3.3	4.9	5.3	2.8	12.5	8.3		
BMW	1.2		4.9	3.5	5.6	4.2			
PT Graphix™ supper support		1.6							
Miracle 12 g	0.6				5.6				
Terumo 40 g			1.2		2.8				
SafeCross® system		2.4	3.7	8.8	8.3	8.3	25.0		
Crosser™	3.1	4.1	7.4	7.0					20.0
Laser wire®		1.6	2.5	1.8	5.6		16.7		20.0
Laser catheter® 0.9			1.2	1.8		8.3	8.3		
Laser catheter® 0.7		1.6	1.2						

Dedicated CTO device selection

Crosser™

Table 4 shows the frequency of the use of these different devices. The only device tested as a first option for the treatment of the CTOs was the Crosser™. Five patients were treated, in 2 patients with non-calcified CTO (multislice computed tomography analysis) the device was able to cross the occlusion from the beginning to end. The other three patients were successfully treated with a combined approach using Crosser™ and CTO dedicated guidewires. After the initial guidewire failed to cross the CTO, the most frequently used device was the Crosser™ (Table 4). Overall, the Crosser™ system was used in 23 (13.9%) patients with a success rate of 60.9%.

Laser

The Point 9® X-80 Laser catheter was used in 10 (6.1%) patients with a success rate of 60%. Another 3 patients were treated with the Point 7® laser catheter. Both were used either to facilitate the crossing of the balloon, or primarily to treat in-stent restenosis occlusions. The Laser® guidewire was used in 7 (4.2%) patients as a last opportunity to cross the lesions; the success rate was 28.6%.

SafeCross® System

This system was used in 15 (9.1%) patients with a success rate of 46.7%.

Other devices

The Venture catheter was used in 4 patients (2.4%). Some issues were found with the use of this device. The steerability is far from

being close to 1:1. There must be some room for the free movement of the device. On the other hand, it could be effectively used to direct the guidewire towards the entry point.

The magnetic navigation system was used in 5 cases (3.0%). Three cases were successfully treated by using multislice computed tomography coronary angiography guidance combined with highly precise guidewire steering (Magnetic Navigation System).

Rotational atherectomy was unsuccessfully used in 1 case (0.6%) to allow the passage of the balloon.

Techniques to open CTOs

Many techniques and strategies were employed in the treatment of these patients. The most common in this study was the use of an OTW balloon in 81.5% of the cases. Bilateral injection was used in 63.5% of the procedures. The parallel wire technique was used in 27.3% of the cases and in 12.7% was converted into a see-saw technique. When a large false lumen was created, re-entry into the true lumen was attempted in 21.2% of the cases, by means of IVUS-guided approach and/or the use of stiffer guidewires, such as a Confianza guidewire. The open-mouth technique was used in 9.8% of the cases. A contrast injection through the OTW was performed in 4.9% of the cases.

Retrograde recanalisation was attempted in 10 cases (6.1%), in three cases a graft was used; the remaining cases were treated either via collaterals or the septal branches.

Forty-six patients (26.1%) in this cohort underwent MSCT scanning before the CTO procedure.

The mean volume of contrast used was 457.5±191.6 ml. The mean procedure time was 128.0±58.9 min, with a fluoroscopic time of 67.2±44.7 min and radiation exposure of 12,395.9±8,320.7 DAP. It is worth mentioning that the mean overall cost of the procedure was 5,544.90±3,366.20 Euros, including stent cost.

Discussion

The invasive treatment of CTO by means of PCI is still one of the most challenging procedures for the interventional cardiologist. It is also one of the most unpredictable procedures as well. The original intended strategy is usually changed during the procedure according to the different issues the operator may encounter. Thus, there is no universal approach capable of successfully treating this subset of lesions. However, there are some guidelines that can help us to easily and smoothly overcome these issues. This paper reports, in detail, a single-centre's experience in the treatment of chronic total occlusions using nearly all the current available guidewires, devices and techniques. This report attempts to be a narrative of these real time CTO procedures. There is growing evidence in favour of opening a CTO[1,2,6], but this benefit must be balanced by the potential disadvantages for the patients which may arise from all these multiple issues that come together with the procedure itself. Even when there is no comparative group, it appears that treating CTOs using these types of procedures are more challenging, time consuming, risky (in terms of radiation safety, contrast use and the risk inherent in the employment of specific CTO dedicated techniques/guidewires/devices) and expensive than any of the others in the field of interventional cardiology. For instance, if only the contrast medium is considered, in this cohort alone there was, on average, 457.5 ml used. It has been reported that for each 100 ml there is an increment in the overall risk of contrast-induced nephropathy (CIN); therefore in this population, on average, the risk of CIN would be thus 7.5%, with the risk of dialysis of 0.04%[19]. Comparing the mean contrast used in this study (457.5 ml) with recently published data on non-chronic occlusions – as reported by Marenzi et al[20] where the mean contrast used was 274±113 ml, or in the report by Le Feuvre et al[21] where the mean contrast used were 267 ml and 276 ml in the two studied groups – it is clear that in considering this all comers registry of those treated for chronic total occlusions that the contrast use is much higher.

In addition, long procedure times and high radiation exposure still are the sine qua non in the PCI of the CTO patients. Reduction in total radiation dose might prevent acute and long-term radiation effects such as skin injuries[22].

From the hardware development point of view, CTO dedicated guidewires/devices have gone through several waves of technological advances in the past few years in order to meet the very high technical demand required by this type of lesion. Saito et al[23] reported on the comparison between two clearly defined periods, which differed mainly due to the use of tapered tip guidewires in the latest period; with a change in success rate that was documented from 67% to 81%. Thus, the introduction of these guidewires has been one of the major breakthroughs in the treatment of CTO lesions. With respect to this report, it is clear that our centre is in a period of transition from the use of standard/stiffer guidewires to the early use of tapered tip guidewires. As far as the approach is concerned, one of the challenges lying ahead is the retrograde approach, which offers a kind of dual alternative in the same patient. In other words, when the antegrade approach has been unsuccessful, the retrograde is still an option under certain conditions in carefully selected patients. This approach is technically demanding and requires not only operator skills but also special equipment. In parallel, we have explored some other novel alternatives as the combined approach of the use of MSCT and magnetic navigation, integrating the actual images of the coronary tree (MSCT images) of the patient into the MNS software for use as a roadmap, and the ablation capabilities of some of the CTO devices such as the SafeCross® system and laser. These three components constitute for us the ideal trifecta (forward looking, highly precise steerability and ablation capabilities) needed to treat CTOs. In non-calcified and non-tortuous CTOs we have also assessed the performance of the Crosser™ system in a few cases with encouraging results that prompted us to start a registry of CTO patients treated with this system as a first option. In these long-lasting procedures it is important to consider any short-cut to save time, effort and more importantly to reduce risks, for both the patient and the operator. Therefore many techniques described in the methods section could help us reach this goal. One important lesson is the early use of tapered tip GW during the procedure: the operator should not waste time using stiffer hydrophilic guidewires if a large false lumen has been created or non-significant progress has been made, instead a tapered tip GW should be used. The success rate is still far from being optimal. However, now that we have a deep insight into our way of treating these patients, sev-

eral actions have been started to launch a new approach to treat these patients, mainly with the widely use of tapered tip GWs and the retrograde approach.

Conclusion

The treatment of CTOs is more complex that we had thought. It requires the use of a high number of guiding catheters and guidewires, as well as the use of sophisticated devices. Pre-procedural evaluation of the CTO lesion by means of multislice computed tomography is becoming routine. Above all, the procedure must be carefully planned in advance – as far as possible – taking into consideration, as well, the possible necessity of promptly changing this approach during the procedure in order to prevent complications derived from its lengthy duration, and accomplishing this by using specific techniques such as parallel wire, see-saw, anchoring balloon, etc.

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Online data supplements

Video 1. Imaging co registration (MSCT on angiography for the treatment of CTO)

Video 2. The Crosser™ device

Video 3. The laser wire

Video 4. Venture steering catheter

CHAPTER 10

Three-year clinical outcomes after coronary stenting of chronic total occlusion using sirolimus-eluting stents: insights from the rapamycin-eluting stent evaluated at Rotterdam cardiology hospital-(RESEARCH) registry

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Catheter Cardiovasc Interv. 2007 Oct 24; 70 (5): 635-639.

Three-Year Clinical Outcomes After Coronary Stenting of Chronic Total Occlusion Using Sirolimus-Eluting Stents: Insights From the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital—(RESEARCH) Registry

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Background: We previously reported that the 1-year survival-free from target lesion revascularization was 97.4% in patients with chronic total occlusion (CTO) treated with sirolimus-eluting stents (SES). There are currently no long-term results of the efficacy of SES in this subset of lesions. We assessed the 3-year clinical outcomes of 147 patients with CTO treated with either SES or bare metal stents (BMS). Methods and Results: A total of 147 (BMS = 71, SES = 76) patients were included. Four patients died in the BMS group while five patients died in the SES group, $P = 0.8$; two myocardial infarctions occurred in both groups, $P = 0.9$; and target vessel revascularization was performed in nine patients in the BMS and seven in the SES group, $P = 0.5$. The cumulative event-free survival of MACE was 81.7% in BMS group and 84.2% in SES group, $P = 0.7$. Two patients of the SES group had a coronary aneurism at 3-year angiographic follow-up. Conclusions: The use of SES was no longer associated with significantly lower rates of target vessel revascularization and major adverse cardiac events in patients with CTOs after 3 years of follow-up compared with BMSs.

Key words: drug-eluting stents; angiography; coronary; total occlusions; percutaneous coronary intervention; restenosis

INTRODUCTION

Drug-eluting stents (DES) are superior in terms of clinical outcomes and restenosis rate to bare-metal stents (BMS) in every angiographic and patient subset [1–3]. In particular, in patients with chronic total occlusion (CTO) DES have shown a significant decrease in need for repeat revascularization and restenosis rate [4–7], although this subset remains still in the DES era a predictor of restenosis [8]. Our group has previously reported the 6-month angiographic and clinical outcomes of sirolimus-eluting stent (SES) in patients with CTOs [9]. In this study, we showed a marked reduction in restenosis rate and major adverse cardiac events (MACE) compared with BMS. This observation was confirmed in the PRISON II study [10], a prospective, randomized trial that included a total of 200 patients treated either with a SES or BMS with both clinical and angiographical follow-up at 6 months. However, among the interventionalists, the clinical and angiographic long-term follow-up of the DES is still a major concern, especially in high-risk populations. We therefore investigated the 3-year clinical and angiographic follow-up of patients with CTO in a consecutive series of 147 patients, with comparison between the bare metal stents and SESs.

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Received 30 November 2006; Revision accepted 16 April 2007

DOI 10.1002/ccd.21249
Published online 24 October 2007 in Wiley InterScience (www.interscience.wiley.com).

MATERIALS AND METHODS

From April 2002 to February 2003, 76 patients with CTOs were treated solely with SES. In this period SES (Cypher®; Cordis Corporation, Warren, NJ) was the device of first choice for every PCI performed in our institution as part of the rapamycin eluting stent evaluated at rotterdam cardiology hospital (RESEARCH) registry, a prospective single center study set-up with the aim of evaluating the safety and efficacy of SES in a "real world" scenario, following the dynamic registry design described by Rothman and coworkers [11,12]. Except for contraindications to clopidogrel treatment, no exclusion criteria were made. All consecutive patients treated successfully were enrolled irrespective of clinical presentation and CTO lesion characteristics. Those patients treated with SES implantation were compared with all those treated for a CTO in the preceding 1 year with bare metal stents (BMS), identified from the departments' dedicated database. The same operators utilizing standard techniques treated all groups; the only difference being the type of stent.

This protocol was approved by the hospital ethics committee and is in accordance with the principles of Good Clinical Practice for Trials of Medicinal Products in the European Community and the Declaration of Helsinki. Written informed consent was obtained from every patient.

CTO Definition

CTO was defined as a complete occlusion on angiography with no antegrade filling of the distal vessel other than via collaterals. All the occlusions in a native vessel with at least 3-month duration based on the clinical history or a previous coronary angiogram were included [9].

Angiographic Analysis

Quantitative coronary analysis in those patients with angiographic follow-up was performed as previously described [9]. Briefly, three segments were analyzed: (1) stent segment; (2) the 5 mm proximal to the stent; and (3) the 5 mm distal to the stent. The target lesion comprised the in-stent plus the proximal and distal edge segments. Binary restenosis was considered as $>50\%$ diameter stenosis within the target lesion.

All patients were pretreated with 300 mg of clopidogrel, which was then prescribed at a dose of 75 mg/day for 6 months. All patients were advised to maintain aspirin ($\geq$80 mg/day) lifelong.

Our primary endpoints were the 3-year incidence of MACE, a compound endpoint of all-cause mortality, nonfatal myocardial infarction and target-vessel revascularization, in both groups. Secondary endpoints were target vessel revascularization (TVR) and myocardial infarction (MI). MI was defined by a rise in creatine kinase-MB fraction (CK-MB) of three times the upper limit of normal, according to American Heart Association/American College of Cardiology guidelines [13]. TVR was defined as a percutaneous reintervention or coronary artery bypass grafting (CABG) of a lesion in the same epicardial vessel. Subacute angiographic stent thrombosis was defined as an angiographically documented complete occlusion (TIMI grade 0 or 1 flow) or a flow-limiting thrombus (TIMI grade 1 or 2 flow) in the first 30 days after a successful procedure. Late stent thrombosis was defined as angiographically defined thrombosis with (TIMI grade 0 or 1 flow or the presence of a flow limiting thrombus), occurring at least 1 month after DES implantation accompanied by acute symptoms. Angiographic follow-up was performed in a subset of 30 patients in the SES group.

Three-Year Follow-Up Data

Patients were followed-up prospectively and evaluated for MACE-free survival of using both municipal civil registries and health questionnaires inquiring about postdischarge repeat coronary interventions (either surgical or percutaneous) and MI. Since our hospital is a tertiary referral center for our region, with a catchment area of $\sim$1.3 million people, most of the repeat interventions were performed at our institution. Follow-up information was prospectively entered into a dedicated database. If a patient had an MI or a reintervention at another center, medical records or discharge letters were requested and systematically reviewed. Local cardiologists or general practitioners were also contacted as necessary. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored.

Statistical Analysis

Continuous variables are presented as mean $\pm$ SD and were compared by the Student's t test. Categorical variables are presented as counts and percentages and compared by Fisher's exact test. The cumulative incidence of adverse events was estimated according to the Kaplan–Meier method and curves were compared using the log-rank test. Separate Cox regression analyses were performed to identify independent predictors of adverse events. Preselected variables were: age, gender, hypertension, diabetes, renal impairment, previous intervention, old MI, smoking, treatment of the left main coronary artery, and previous CABG. The final results are presented as adjusted hazard ratios (HRs).

Catheterization and Cardiovascular Interventions DOI 10.1002/ccd.
Published on behalf of The Society for Cardiovascular Angiography and Interventions (SCAI).

TABLE I. Baseline Patient Characteristics

	BMS $n = 71$	SES $n = 76$	P value
Mean age (years)	60.9 ± 10.5	61.1 ± 10.6	0.9
Male sex (%)	76.7	65.8	0.1
Current smoker (%)	27.4	18.4	0.2
Diabetes mellitus (%)	5.5	14.5	0.07
Hypertension (%)	35.6	42.1	0.3
Hypercholesterolemia (%)	57.5	67.1	0.3
Previous myocardial infarction (%)	50.7	51.3	0.8
Previous CABG (%)	0	3.9	0.2
Glycoprotein IIb/IIIa inhibitor usage (%)	21.9	18.4	0.8
Target vessel			0.1
LAD (%)	27.5	46.1	
LCX (%)	27.5	19.7	
RCA (%)	44.9	36.8	
Mean number of stents	1.9 ± 0.8	2.2 ± 1.2	0.9
Mean diameter of the stent (mm)	3.1 ± 0.58	2.8 ± 0.3	<0.001
Mean length of stent (mm)	21.7 ± 6.3	22.5 ± 6.1	0.5

SES: sirolimus-eluting stents, PES: paclitaxel-eluting stents, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention, LAD: left anterior descending artery, LCX: circumflex artery, RCA: right coronary artery.

TABLE II. Clinical Events at Three-Year Follow-Up

	BMS, $n = 71$	SES, $n = 76$	P value
Death, n(%)	4(5.6)	5(6.6)	0.8
MI, n(%)	2(2.8)	2(2.6)	0.9
TLR, n(%)	8(11.3)	6(7.9)	0.5
TVR, n(%)	9(12.7)	7(9.2)	0.5
TLR/Death, n(%)	12(16.9)	11(14.5)	0.7
TVR/Death, n(%)	13(18.3)	12(15.8)	0.7
MI/Death, n(%)	4(5.7)	6(8.1)	0.6
MACE, n(%)	13(18.3)	12(15.8)	0.7

MI, myocardial infarction; TLR, target lesion revascularization; MACE, major adverse cardiac events.

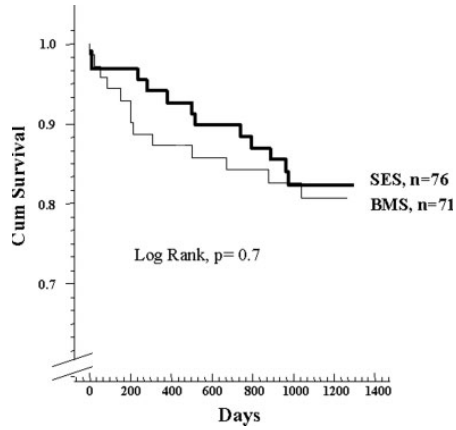

Fig. 1. Three-year cumulative incidence of major adverse cardiovascular events.

RESULTS

Baseline and Procedural Characteristics

A total of 71 and 76 patients were included in the BMS group and in the SES group, respectively. There were no significant differences between the groups with respect to baseline patient characteristics (Table I). In the BMS group 76.1% and in the SES group 65.8% were male ($P = 0.1$) and the mean age was 60.9 ± 10.5 and 61.1 ± 10.6 years, respectively ($P = 0.9$). Although not statistically significant, in the SES group the number of diabetic patients and patients treated in the LAD were higher. Glycoprotein IIb/IIIa inhibitor use was low in both the BMS group (21.9%) and SES group (18.4%) ($P = 0.08$); as defined by protocol, clopidogrel prescription was longer in SES group (6 months) as compared with the BMS group (1 month).

Three-Year Clinical Follow-Up

Both 6-month and 1-year outcomes have been reported previously [9,14]. At 3 years, follow-up was available in 87.3% of the patients in the BMS group and in 96% of the SES group. Four patients died in the BMS group, two of unknown cause, one of noncardiac cause, and one of cardiac death; while five patients died in the SES group, $P = 0.8$; in this group, three deaths were of cardiac cause, one patient died of cancer, and the cause of one patient was unknown.

Two MI's occured in both groups, $P = 0.9$; and TVR was performed in nine patients in the BMS and seven in the SES group, $P = 0.5$. The cumulative survival-free of MACE was 81.7% in BMS group and 84.2% in SES group, $P = 0.7$ (Table II and Fig. 1). No cases of late stent thrombosis were identified in these two groups.

In the multivariate analysis the only variable that was an independent predictor of MACE was age, HR 1.04 (95%CI, 1.01, 1.07).

Three-Year Angiographic Follow-Up

Thirty patients underwent angiography at 3-year; the in-stent minimum lumen diameter was 1.9 ± 0.6 mm, the in-stent diameter stenosis was 30.5%, and the late loss 0.35 ± 0.50; four patients had binary restenosis; out of this four, two CTOs were found to be reoccluded (Fig. 2). One of these patients with reocclusion

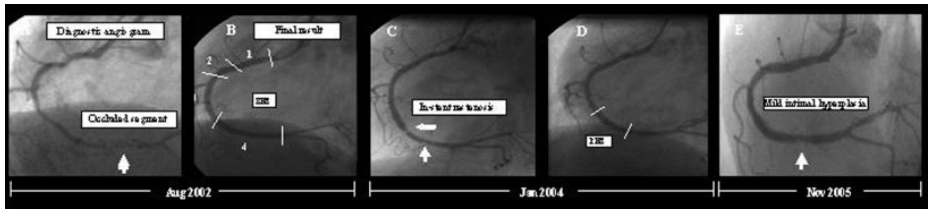

Fig. 2. A patient with a chronic total occlusion in the distal right coronary artery (panel A) was treated with four sirolimus stent (SES), in panel B the final result. Seventeen months later the patient underwent coronary angiogram due to stable angina and focal stent restenosis was seen in the gap between SES 3 and 4 (panel C). In addition, mild intimal hyperplasia was observed in the body of the SES number 4. Patient was treated with a PES (panel D). In the three-year angiographic follow-up an increase was seen in the intimal hyperplasia (panel E).

was treated due to the presence of symptoms, while the other patient was left untreated due to the absence of symptoms and it is awaiting noninvasive ischemia testing. Two patients had a coronary aneurism.

DISCUSSION

This report describes the 3-year clinical and angiographic follow-up of patients with CTO treated with either BMS or sirolimus stents.

There have been some publications comparing BMS vs. DES treatment for CTOs with 6-month follow-up [7,9,15], and recently the first randomized trial in the DES era that included exclusively CTO patients was published [10]; pooling these studies despite the different nature of data (e.g. registries vs. randomized trial), the analysis showed a decrease in TVR and MACE with DES, OR 0.25 (95%CI, 0.16, 0.40) and OR 0.36 (95%CI, 0.24, 0.53), respectively. Three 1-year follow-up studies have been published [5,6,14], (all registries), which also showed a sustained benefit of DES in terms of TVR and MACE, OR 0.1 (95%CI, 0.05, 0.20) and OR 0.17 (95%CI, 0.07, 0.43), respectively. Clinical reports including up to 1-year clinical follow-up, neither individually or globally, showed a decrease in terms of all cause death or MI.

Although due to the study design some baseline characteristics are different between the two groups such the presence of diabetes, treatment of the LAD (no statistically significant), and diameter of the stent, in the 6-month [9] and 1-year [14] reports in patients treated with SES a marked reduction in restenosis rate and MACE was observed compared with BMS. In turn, this 3-year follow-up report showed no difference whatsoever in any of the MACE components. This is in agreement with other two long-term follow-up substudies of the RESEARCH registry, patients with diabetes mellitus and acute MI [16]. The former report compared the 2-year clinical outcome of 708 consecutive diabetic patients treated with either a BMS (n = 252), a SES (n = 206), or a PES (n = 250). TVR rates were 19.5% in the BMS group, vs. 15.3% in the SES group and 9.7% in the PES group. PES (21.2%) but not SES (28.9%), were superior to BMS (29.7%) in reducing MACEs. However, after propensity analyses, none of the differences remained significant. The second report where primary angioplasty was performed in a consecutive group of 505 patients (BMS, n = 183; SES, n = 186; PES, n = 136), showed that the cumulative incidence of death or MI was comparable in the three groups: 16.6% in the BMS group, 14.6% in the SES group, and 16.9% in the PES group. At 3 years, TVR was 12.0% in the BMS group, compared with 8.0 and 7.7% in the SES and PES groups, respectively. The cumulative incidence of death, MI or TVR was 25.5% in the BMS group compared with 17.9 and 21.4% in the SES and PES groups, respectively. In light of these results, it seems that a late clinical restenotic phenomenon is observed in specific subsets of patients, and that the beneficial effects in restenosis rates of DES observed in the first year might drop over the time.

The present study has all the intrinsic limitations of a registry. Although in our center only in a limited period of time all comers were treated with sirolimus eluting stent and the number of CTO patients treated was relatively small, all consecutively treated CTO patients were included in this registry. A word of caution in interpreting the present findings as confirmative must be given, since the sample size is small. However, so far, in this subset of patients, this is the only registry with clinical and angiographic long-term follow-up.

CONCLUSIONS

Despite clinical benefit after 1 year, the use of sirolimus stent was no longer associated with significantly lower rates of TVR and MACEs in patients with

CTOs after 3 years of follow-up compared with bare metal stents.

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CHAPTER 11

Chronic total occlusion treatment in post-CABG patients: saphenous vein graft versus native vessel recanalization-long-term follow-up in the drug-eluting stent era

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Catheter Cardiovasc Interv. 2007 Jul 1;70(1):21-5.

Chronic Total Occlusion Treatment in Post-CABG Patients: Saphenous Vein Graft Versus Native Vessel Recanalization—Long-term Follow-up in the Drug-Eluting Stent Era

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Objective: To compare the postprocedural and long-term clinical outcomes of two groups of patients, all presenting with chronic saphenous vein graft (SVG) occlusion, who underwent either SVG or native vessel reopening. Background: Chronic total occlusions (CTO) treatment in patients who underwent previous surgical revascularization is a dilemma and the choice of performing native vessel or SVG recanalization is not always easy. Methods: Between July 2002 and October 2004, a total of 260 patients were successfully treated for a CTO. Of them, we selected all patients (*n* = 24) who had previous bypass surgery with graft occlusion. Of this final group, 13 patients underwent a percutaneous graft recanalization while 11 underwent native vessel reopening. Results: Primary end points were in-hospital and 3-year rates of death, myocardial infarction, target lesion revascularization, and target vessel revascularization. No events occurred in either group during the in-hospital period. Cumulative 3-year event-free survival in the native vessel and SVG group was 81.8% and 83.9% respectively (*P* = NS). One death and one TVR occurred in each group. Conclusion: In selected cases, SVG reopening instead of the native vessel is feasible. In such a high-risk population, drug-eluting stent implantation in both SVG and native CTO lesions is associated with good long-term outcomes.

Key words: percutaneous coronary intervention; total occlusions; bypass grafts; coronary

INTRODUCTION

Chronic total occlusions (CTOs) remain one of the most challenging problems for interventionists as the procedural success rate and acute outcome are still relatively poor [1–6]. Percutaneous treatment of saphenous vein grafts (SVGs) occlusions, notwithstanding the use of drug-eluting stent (DES) and new protection devices, remains exacting [7]; the atherosclerotic disease in SVGs is pathologically different from the native vessel, showing soft and friable lesions usually with a poorly developed fibrous cap and large and bulky thrombi that tend to occupy the entire length of the graft [8–12]. Which revascularization treatment should we then recommend to patients with chronic SVG occlusions? Is it worthwhile to treat the SVG occlusions or should we avoid this approach and always attempt to treat the native bypassed coronary arteries?

To clarify this issue better we compared the clinical outcomes of two groups of patients, all presenting

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Received 12 October 2006; Revision accepted 20 December 2006

DOI 10.1002/ccd.21100
Published online 22 June 2007 in Wiley InterScience (www.interscience.wiley.com).

chronic SVG occlusion, who underwent either SVG or native vessel reopening.

METHODS

Population

Demographic and procedural data regarding all patients undergoing PCI at our centre were prospectively entered into a dedicated database. Between July 2002 and October 2004, a total of 351 patients had a CTO treatment attempt in our center; 260 were successfully treated (74.1%). Of them, we retrospectively selected only those patients ($n = 24$) who had undergone previous saphenous vein bypass grafting and subsequently had total occlusion of one or more grafts. Of this final group, 13 patients underwent a percutaneous reopening treatment on the occluded graft while 11 underwent percutaneous reopening of the native vessel (Table I).

Exclusion criteria were unsuccessful attempt and intolerance or contraindication to clopidogrel. No other predefined clinical inclusion or exclusion criteria were considered, and the indication for PCI was decided on clinical and angiographic characteristics.

TABLE I. Baseline Clinical Characteristics

	SVG group ($N = 11$)	Native group ($N = 13$)	P value
Age (years)	67.8 ± 12.4	60.8 ± 10.9	NS
Women, *n* (%)	1 (7.6)	2 (18.1)	NS
Diabetes mellitus, *n* (%)	5 (38.4)	3 (27.2)	NS
Hypertension, *n* (%)	7 (53.8)	4 (36.6)	NS
Current smoking, *n* (%)	2 (15.3)	2 (18.1)	NS
Familiarity, *n* (%)	7 (53.8)	6 (54.5)	NS
Dislipidemia, *n* (%)	10 (76.9)	9 (81.1)	NS
Prior myocardial infarction, *n* (%)	7 (53.8)	6 (54.5)	NS
Prior PCI, *n* (%)	5 (38.4)	7 (63.6)	NS
Clinical presentation (ACS), *n* (%)	6 (46.1)	1 (9)	<0.05

SVG, saphenous vein graft; PCI, percutaneous coronary intervention; ACS, acute coronary syndrome.

End Points

The primary outcome measures investigated were the occurrences of death, myocardial infarction (MI), target vessel revascularization (TVR), target lesion revascularization (TLR), and major adverse cardiac events (MACE) defined as a nonhierarchical composite of all cause death, nonfatal MI, or repeat revascularization during hospital stay and at 3 years.

Definitions

CTO was defined as a complete coronary obstruction (TIMI flow grade 0) with an estimated duration of >3 months. Technical success was defined as the ability to cross and open the occluded segment with no more than 40% residual stenosis in all views; procedural success was defined as a technical success with no in-hospital MACE. MI was defined as a threefold CK-MB increase; hemodynamic instability was defined as the occurrence of sustained ventricular arrhythmias or prolonged hypotension (BP < 90/60 mm Hg). TLR was defined as any revascularization performed on the treated segment; TVR was defined as any reintervention performed on the treated vessel.

Interventional Technique

The operators performed the procedure according to standard techniques of the time via the femoral or brachial approach. All procedural and technical details and the choice of devices were left to the operator's judgment. In the cardiac catheterization laboratory, patients received a bolus of 10,000 units of heparin followed by repeated boluses per a weight-based protocol to achieve an activated clotting time >250 sec. All the lesions were treated with DES implantation. Periprocedural abciximab was administered at the operator's discretion. After the procedure, clopidogrel (75 mg daily) was prescribed to all patients for 6 months after stent implantation; aspirin was given indefinitely.

Follow-up

A follow-up visit or telephone interview was scheduled at 30 days, 6 months, 1 year, and then yearly. Civil registries were queried in case of death, to determine whether it was or not a cardiac death. A health questionnaire was subsequently sent to all living patients with specific questions on rehospitalization and MACE [13,14]. All repeat interventions and rehospitalizations were prospectively collected during follow-up and entered into a dedicated database. An exercise tolerance test was recommended after 6 months in event-free patients; angiographic follow-up was performed only in those patients with recurrence of symptoms or with a positive stress test.

Statistical Analysis

Variables with normal distribution were analyzed using parametric tests while variables with a non-normal distribution were analyzed with nonparametric tests. Continuous variables are expressed as mean ± SD or median ± SD and differences were compared using Student's t test or Mann–Whitney test. Categorical variables are expressed as counts and percentages; differences were assessed by Fisher's exact test or χ^2 test, as appropriate. All statistical tests were two-tailed. When more than one clinical event occurred in a patient, all the events occurring were considered for survival analysis. All analyses were performed using SPSS version 12 statistical software (SPSS Inc., Chicago, IL). A P value < 0.05 was considered significant.

Catheterization and Cardiovascular Interventions DOI 10.1002/ccd.
Published on behalf of The Society for Cardiovascular Angiography and Interventions (SCAI).

TABLE II. Angiographic and Procedural Characteristics

	SVG group ($N = 11$)	Native group ($N = 13$)	P value
Three vessel disease, n (%)	13 (100)	7 (63.6)	<0.05
TL location, n (%)			
LAD	2 (15.3)	0 (0)	NS
LCX	4 (30.7)	7 (63.6)	NS
RCA	7 (53.8)	4 (36.6)	NS
Baseline RVD (mm)	3.04 ± 0.36	2.71 ± 0.31	<0.05
Postprocedure RVD (mm)	3.28 ± 0.24	2.89 ± 0.29	<0.05
Ostial location, n (%)	11 (84.6)	2 (18.1)	<0.05
Calcified lesions, n (%)	3 (23)	5 (45.4)	NS
Number of guiding catheters/patient	1.07 ± 0.2	1.7 ± 0.9	<0.05
Number of guide wires/patient	2.15 ± 1.34	2.17 ± 1.1	NS
Number of balloons/patient	1.53 ± 0.87	1.63 ± 0.8	NS
TL number of placed stents/patient	3.3 ± 1.54	2.27 ± 0.46	<0,05
TL average diameter stent (mm)	3 ± 0.3	2.62 ± 0.24	<0.05
TL average length stent (mm)	22.9 ± 6.5	21.5 ± 4.4	NS
Total number of treated lesions	1.76 ± 0.92	1.72 ± 0.78	NS
Total number of placed stents/patient	4 ± 1.65	3 ± 1.54	<0.05
Total average diameter stent (mm)	2.97 ± 0.35	2.6 ± 0.1	<0.05
Total average length stent (mm)	22.4 ± 4.94	21.4 ± 3.7	NS
Use of distal protection, n (%)	5 (38.4)	0 (0)	NS
Procedural time (min)	148 ± 39	135 ± 36	NS
Contrast amount (ml)	360 ± 112	399 ± 133	NS
Periprocedural abciximab, n (%)	8 (61.5)	5 (45.4)	NS

RVD, reference vessel diameter; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; TL, target lesion; SVG, saphenous vein graft.

TABLE III. Procedural and In-Hospital Outcomes

	SVG group ($N = 11$)	Native group ($N = 13$)	P value
Procedural success rate (%)	100	100	NS
Final TIMI flow grade 3, n (%)	11 (100)	13 (100)	NS
Hemodynamic instability, n (%)	2 (15.3)	0 (0)	NS
IABP, n (%)	1 (7.6)	0 (0)	NS
Temporary pacing, n (%)	1 (7.6)	0 (0)	NS
Perforation, n (%)	0 (0)	0 (0)	NS
In-hospital death, n (%)	0 (0)	0 (0)	NS
Postprocedural MI, n (%)	0 (0)	0 (0)	NS
Urgent TVR, n (%)	0 (0)	0 (0)	NS
Postprocedural CK levels (UI)	123 ± 66	99 ± 50	NS

IABP, intra aortic balloon pump; TVR, target vessel revascularization; TIMI, thrombolysis in myocardial infarction; SVG, saphenous vein graft; MI, myocardial infarction; CK, creatine-kinase.

RESULTS

Baseline and Procedural Variables

Baseline clinical and angiographic characteristics are shown in Tables I and II.

In our population, the median time from bypass surgery to the index percutaneous was 10 years (range: 10 months to 20 years). In the SVG group, distal embolic protection was used in 38.4%. There were no significant differences in the two groups except that patients with PCI for SVG versus native artery occlusion presented more often with acute coronary syndrome (46.1% vs. 9.0%; $P < 0.05$), three vessel disease (100% vs. 63.6%; $P < 0.05$), received a slightly higher number of stents (4 ± 1.65 vs. 3 ± 1.54; $P < 0.05$) and with a larger mean diameter (2.97 ± 0.35 vs. 2.6 ± 0.1 mm; $P < 0.05$).

Procedural and In-Hospital Outcomes

Procedural and In-Hospital Outcomes are summarized in Table III.

Both technical and procedural success rates were 100%. No death, postprocedural infarction, or urgent re-PCI occurred in either group. Two patients experienced hemodynamic instability, both in the SVG group. One patient needed an intra-aortic balloon pump (none in native vessel group) and one patient needed temporary pacing (none in native vessel group).

Follow-up Clinical Outcomes

Three-year follow up clinical outcomes are shown in Table IV.

One patient dropped out after 9.2 months (276 days). One patient in the native vessel group died 11 months (335 days) after the procedure; one patient in the SVG group died 24 months (720 days) after the procedure. There was one TVR in the native vessel group (13 months after the index procedure) and one in the SVG group (5.2 months after the index procedure). No MI or re-CABG occurred in the follow-up period. The cumulative MACE free survival rate at 36 months was 81.8% in native vessel versus 83.9% in the SVG group.

DISCUSSION

The main findings of this study are that SVG reopening instead of the native vessel is a feasible and an interesting option in selected cases and that DES use in this population is safe with good long-term outcomes. Undoubtedly this can be considered one of the most challenging and highest risk populations ever treated in the DES era: patients with previous CABG, treated with a PCI in SVGs or native vessels for a CTO. What today can be considered "real world clinical practice," albeit still not so common, was discouraged a few years ago; in an editorial published by our group in 1993 [1] it was suggested to avoid percutaneous treatment of SVG lesions and to opt for revascularization of the native vessel if re-CABG, as a serious alternative, was not feasible.

TABLE IV. Three-Year Follow-up Clinical Outcomes

	SVG group ($N = 11$)	Native group ($N = 13$)	P value
Deaths, *n* (%)	1 (7.6)	1 (9)	NS
MI, *n* (%)	0 (0)	0 (0)	NS
Re-CABG, *n* (%)	0 (0)	0 (0)	NS
Re-PCI, *n* (%)	1 (7.6)	1 (9)	NS
MACEs, *n* (%)	2 (15.3)	2 (18.1)	NS

MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; MACE, major adverse cardiac events; SVG, saphenous vein graft.

The 2005 ACC/AHA guidelines for PCI indicate that the average technical success rate of recanalizing CTO is 65%; advances in technical skills and introduction of new devices have enabled in some centers to reach a 70% or greater technical success rate, which anyway is still considerably lower compared with the 92% success rate of PCI for overall lesions [15–18].

Consistent with these data, technical success rate between July 2002 and October 2004 in our centre was 74.1%. It is well known that interventional maneuvers on vein grafts are difficult and often associated with a high risk of complications; lesion crossing, balloon inflation, and stent deployment can easily perforate the vein wall or dislodge friable atherosclerotic and thrombotic material, causing distal embolization and slow-flow or no-reflow phenomenon [1,19].

Which therefore were the elements that led the interventionist to attempt reopening a SVG instead of the native vessel?

The decision was basically taken on angiographic features: the presence of diffuse, complex, or ostial blunt lesions in tortuous, calcified native vessels deterred their recanalization while, on the other hand, good graft conditions, short shaft or ostial tapered SVG lesions or the presence of sequential grafts encouraged a reopening attempt.

DES, new protection devices, and antiplatelet drugs make the attempt easier. Recent studies reported that DES implantation (both sirolimus and paclitaxel eluting stents) reduced in-stent restenosis and improved both short- and long-term revascularization rates after successful CTO recanalization in native vessels compared with bare metal stents [20–22]. Moreover, distal protection devices (e.g. FilterWire EX) and platelet glycoprotein IIb/IIIa inhibitors have been shown to be effective in elective PCI in SVGs by reducing distal embolization and slow-flow or no-reflow phenomena [23–25].

In this study, the use of DES for CTO recanalization, associated with the use of antiplatelet drugs led to excellent postprocedural and in-hospital outcomes. No death, MI, urgent TVR, or distal embolization occurred in either group. Additionally, only two patients with PCI for SVG occlusion had in-hospital hemodynamic instability (15.3%), one requiring an IABP and one requiring temporary pacing.

Three-year follow-up outcomes are good especially considering the high baseline risk profile of our population: prior CABG, advanced age, prior infarction, three-vessel and diffuse coronary disease, and diabetes mellitus were common characteristics of this population. However, despite the encouraging outcomes of DES use, up to 50% of late cardiac events in patients with SVG lesions are due to disease progressions at different sites rather than the initial target [26,27]; so a high MACE rate should be expected in this population.

At 3 years, two patients died (one in each group) and two underwent a re-PCI (one in each group). MACE-free survival rate at 36 months in the native vessel and SVG groups were 81.8% and 83.9% respectively, without statistical difference between the groups.

This compares favorably with existing data on DES use for native vessel CTO treatment, with reported overall MACE-free survival rate at 6 and 12 months of 90–91% and 87–84% respectively [20,28,29], although still few data are available on DES use for SVGs CTO treatment. A recent report by Ge et al. showed an overall MACE-free survival at 6 months of 88.5% in SVG lesions [30], in line with the results of DES use on native vessels. Though based on a very small, highly selected population with peculiar angiographic features and though should be interpreted with great caution, these results show encouraging follow-up results probably thanks to DES, new guide wires generation, and new specific devices introduction. In selected cases, SVG recanalization instead of the native vessel with DES can therefore be an interesting option with a high procedural success rate; moreover, DES implantation in both SVG and native CTO lesions is associated with an equal effect on MACE-free survival at 3-year follow-up.

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Catheterization and Cardiovascular Interventions DOI 10.1002/ccd.
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CHAPTER 12

Revascularization in the high-risk patient: multivessel disease

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Minerva Cardioangiol. 2007 Oct; 55(5): 579-92.

Revascularization in the high-risk patient: multivessel disease

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The aim of this article is to review the treatment of patients with multi-vessel coronary artery disease. Percutaneous coronary intervention (PCI) has been challenging coronary artery bypass grafting (CABG) as the gold standard of care for patients with multi-vessel disease; however, the application of PCI to these patients has been mainly limited by restenosis. Up to the late 1990s, numerous large-scale, randomized trials addressed this issue comparing CABG to PCI with balloon angioplasty or bare-metal stents. These studies demonstrated similar rates of death and myocardial infarction in both groups, while the need for revascularization remained significantly lower in the CABG group. Drug-eluting stents (DES) have dramatically reduced restenosis and repeat revascularization rates. CABG has also progressed with improvements in perioperative management, a higher use of arterial grafting, and advanced techniques with the implementation of minimally invasive and off-pump surgery as options. Therefore, the results of previous trials in the pre-DES era can no longer be extrapolated into the "real world". As intermediate steps preceding a fully-fledged, randomized trial, several trials have compared PCI with DES and the historical control of CABG, but the results are still inconclusive. Several dedicated randomized trials are currently ongoing to compare PCI with DES and CABG using contemporary techniques. Until the results of these randomized trials are presented, the choice for each strategy should be based on the patients' individual risk and anatomy.

Key words: **Coronary artery disease - Angioplasty, transluminal, percutaneous coronary - Stents.**

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The treatment of coronary artery disease has been evolving over the last 40 years. Coronary artery bypass graft surgery (CABG) was introduced in 1968 and has been accepted as the gold standard of treatment for patients with multi-vessel disease.[1-4] CABG has progressed with more effective perioperative management, a higher use of arterial grafting, and contemporary techniques with minimally invasive and off-pump surgery as options.[5, 6] Percutaneous coronary intervention (PCI) commenced in 1977 with the first percutaneous transluminal balloon angioplasty as a non-surgical alternative.[7] After the publication of the BENESTENT and STRESS trials in 1994, coronary artery stenting with improved antiplatelet therapy has progressively replaced balloon angioplasty as the preferred method of PCI.[8, 9] The introduction of drug-eluting stents (DESs) in 2001 has enabled PCI to reduce both angiographic and clinical restenosis to less than double figures

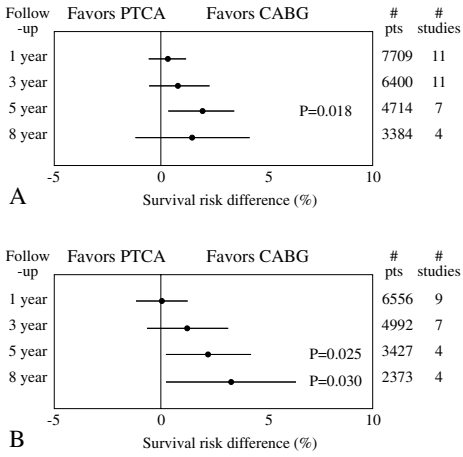


Figure 1.—Risk difference for all-cause mortality for years 1, 3, 5 and 8 post-initial revascularization. All trials (A) and multivessel coronary artery disease (B). The lines represent 95% confidence intervals. (From Hoffman *et al.*[3]).

in simple cases, resulting in a significant reduction in the need for repeat revascularizations. Although evidence stemming from randomized trials has been accumulating on the use of DES in low-risk patients presenting with relatively simple lesions, in real life their use has been extended to higher risk populations and lesions, including diabetic patients, those with diffuse coronary stenosis, and those with chronic total occlusions, who comprise a large proportion of patients with multivessel disease.[10, 11] In addition to DES, new devices have been developed to overcome chronic total occlusions, which have been a major limitation to complete revascularization.

Although PCI has been challenging CABG as the treatment of choice for patients with multivessel disease, the application of PCI to these patients has been mainly limited by restenosis, which develops in 30-40% with balloon angioplasty and 20-25% with bare-metal stents (BMS).[12] In the mid- to late 1990s, several large, multicenter, randomized trials were performed to compare CABG to PCI with BMS for the treatment of multi-vessel disease and demonstrated that at follow-up, mortality and myocardial infarction were not significantly different between the two groups but the need for repeat revascularization procedures was significantly more frequent in the PCI rather than the CABG group. In these trials comparing PCI to CABG, restenosis was the major limiting factor for PCI; since DES has partially resolved the problem of restenosis, it seems reasonable to expect that PCI with DES in multi-vessel disease could become equivalent to CABG. In the absence of a definitive clinical trial to support this view, several dedicated randomized trials are ongoing to directly compare CABG and contemporary PCI using DES in patients with multivessel disease.

Thus, due to developments in PCI as well as CABG, the findings of the previous trials with balloon angioplasty or bare-metal stents cannot be extrapolated to current clinical practice although those trials highlighted several important topics also relevant in the DES-era. We have therefore distinguished in the review a pre-DES era and a DES (modern) era.

Pre-DES era: balloon angioplasty and bare-metal stent

Between the late 1980s and the early 1990s, six randomized trials listed in Table I compared CABG with PCI with balloon angioplasty to select the most appropriate revascularization modality.[13-18] All these trials included patients who were eligible for either CABG or PCI. A meta-analysis comparing one- to three-year outcomes of the randomized trials found no significant differences in the rates of death or myocardial infarction.[19, 20] As to long-term outcome, Hoffman *et al.* calculated a trend favoring CABG over PTCA for survival at 5 (risk difference [RD] 2.3%, CI 0.29-4.3%, P=0.025) and 8 years (RD 3.4%, CI 0.32 to 6.4%, P=0.03) in patients multi-vessel disease [3] (Figure 1). More recently, the 10-year follow-up results from the BARI trial demonstrated that there was no significant difference in mortality and MI event rates between the randomized treatment groups.[21]

The development of coronary stents ope-

TABLE I.—*Summary of randomized trials in the pre-DES era.*

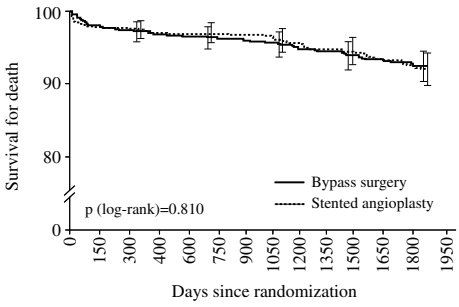
Trials	Bare-metal stent use	Clinical parameters			Angiographic end points	Cost assessment
		Mortality and MI	Angina relief	Repeat revascularization		
GABI	No	PCI	PCI	CABG	No difference	No difference
EAST	No	No difference	CABG	CABG	CABG	No difference (8 yr)
RITA	No	No difference	CABG	CABG	No difference	No difference (5 yr)
ERACI	No	No difference	CABG	CABG	No difference	PCI (3 yr)
CABRI	No	No difference	CABG	CABG	No difference	No
BARI	No	No difference	No difference	CABG	No difference	No difference (10 yr)
MASS-2	Yes	CABG (MI)	No difference	CABG	No difference	No difference (1 yr)
AWESOME	Yes	No difference	No difference	CABG	No difference	No difference
ERACI-2	Yes	PCI	CABG	CABG	CABG	CABG (5 yr)
SoS	Yes	CABG (mortality)	CABG	CABG	No difference	No difference
ARTS	Yes	No difference	CABG	CABG	No difference	PCI (3 yr)

PCI: in favor of percutaneous intervention; CABG; in favor of coronary artery bypass grafting; No: not available; MI: myocardial infarction. GABI: German Angioplasty Bypass Surgery Investigation, EAST: Emory Angioplasty versus Surgery Trial (1994), RITA: Randomized Intervention Treatment of Angina (1993), ERACI: Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease (1996), CABRI: Coronary Angioplasty versus Bypass Revascularization Investigation (1995), BARI: Bypass Angioplasty Revascularization Investigation (1996).

ned a second avenue for PCI. In 1994, the BENESTENT trial demonstrated that clinical and angiographic outcomes were better in patients who received a stent than in those who received standard balloon angioplasty. In the United states, the STRESS trial mirrored the finding of BENESTENT.[8, 9] Following these two trials, stents became widely used all over the world. Consequently, five randomized, controlled trials were performed to compare surgery to PCI with stenting in the mid- to late 1990s. These were Arterial Revascularization Therapy Study (ARTS; 2001),[2] ERACI-II (2001),[22] Stent or Surgery (SOS; 2002),[23] the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) [24] and the Medicine, Angioplasty or Surgery Study for multi-vessel coronary artery disease (MASS II).[25] The Results of these randomized surgery *vs* BMS trials are also summarized in the Table I.

In the largest trial (ARTS), a total of 1 205 patients with the potential for equivalent revascularization were randomly assigned to CABG (n= 605) or stent implantation (n=600). The primary endpoints were measured in terms of major adverse cardiac and cerebrovascular events (MACCE) at 1-year comprising all-cause death, any cerebrovascular event, non-fatal myocardial infarction, or any repeat revascularization. At one year, there was no significant difference between the CABG and stent groups in terms of the rates of death, stroke, or myocardial infarction. Among patients who survived without a stroke or a myocardial infarction, 16.8% of those in the stenting group underwent a second revascularization, as compared with 3.5% of those in the surgery group. At 5 years, there were 48 and 46 deaths in the stent and surgical groups, respectively (8.0% *versus* 7.6%; P=0.83; relative risk [RR] = 1.05 [0.71-1.55]). Importantly, the 5-year outcome from this trial was the first to demonstrate a similar mortality rate for PCI with stenting *versus* CABG (Figure 2). The incidence of repeat revascularization was significantly higher in the stent group (30.3%) than in the CABG group (8.8%; P<0.001, RR=3.46 [2.61-4.60]).[4]

In most randomized trials, patients treated with stenting were shown to be similar to those treated with CABG in terms of death and myocardial infarction. In a meta-analysis of 1-year patient-based data from ARTS, ERACI II, MASS II and SoS, Mercado *et al.* reported that the cumulative incidence of death, MI, or stroke at 1-year follow-up was similar in both groups (PCI 8.7% *vs* CABG 9.1%, P=



Pat. at risk	1 year	2 year	3 year	4 year	5 year
CABG	588	583	577	568	559
Stent	585	582	576	567	552

Figure 2.–Kaplan-Meier curves showing 5-year mortality in the ARTS trial. (From Serruys *et al.*[4]).

0.63; Figure 3). The need for repeat revascularization was considerably higher (18.0% *vs* 4.4%, P<0.001), although the observed gap with CABG surgery has narrowed from approximately 30% reported in the balloon-angioplasty era to approximately 18% with BMS.[26] Most recently, a meta-analysis of 5-year data employed from the same trials was available, in which Daemen *et al.* reported that PCI and CABG were associated with a similar safety profile in terms of death, stroke and myocardial infarction. However, the need for repeat revascularization procedures still remained significantly more frequent in the PCI than the CABG group (personal communication with Joost Daemen).

Another study worth mentioning is a non-randomized study reported by Hannan *et al.*[27] Inconsistent with other studies, risk-adjusted survival rates were significantly higher in patients treated with CABG than in those patients treated with coronary stenting. They used New York's cardiac registries (n=59 314) to determine the rates of death and subsequent revascularization within three years after the procedure in various groups. The rates of adverse outcomes were adjusted by means of proportional-hazards methods to account for differences in patients' severity of illness before revascularization. The adjusted hazard ratio (HR) for the long-term risk of death after CABG relative to stent implantation was 0.64 (95% CI 0.56-0.74) for patients with 3-vessel disease and a proximal LAD lesion (Figure 4C) and 0.76 (95% CI, 0.60-0.96) for patients with 2-vessel disease without involvement of the proximal LAD (Figure 4A). However, we have to interpret these data with prudence because baseline characteristics were different between the PCI and CABG groups in addition to the unadjustable characteristic: "judgment of physician to assign the patients for either PCI or CABG".

Complete revascularization

The concept of complete revascularization arose from the early studies on CABG surgery.[28-32] In a seminal publication from the coronary artery surgery study (CASS) registry, 3 372 patients with 3-vessel disease (including left main disease) who underwent isolated first-time CABG between July 1974 and June 1979 were analyzed with a mean follow-up of 4.9 years.[32] The degree of revascularization for this study was defined as the number of the 3 major vessels (or their branches) that received a bypass graft. Patients with severe angina in whom more complete revascularization was performed enjoyed improved overall and event-free survival independently of any baseline differences. More recently, a single-center retrospective analysis of 1 034 patients who underwent first-time CABG with a mean follow-up of 3.3 years was performed.[33] The authors employed a functional definition in which complete revascularization was achieved when at least one bypass graft was placed distal to a 50% or greater narrowing in each diseased territory. In this study, compared with completely revascularized patients, incomplete revascularization was associated with an increased 5-year unadjusted overall mortality (47.4% *vs* 17.6%, respectively, P<0.001) and cardiac mortality rates (25.5% *vs* 6.9%, P<0.001).

Several studies have compared long-term outcomes of complete revascularization and incomplete revascularization with the use of PCI.[34-38] In the study by Ijsselmuiden *et al.*,

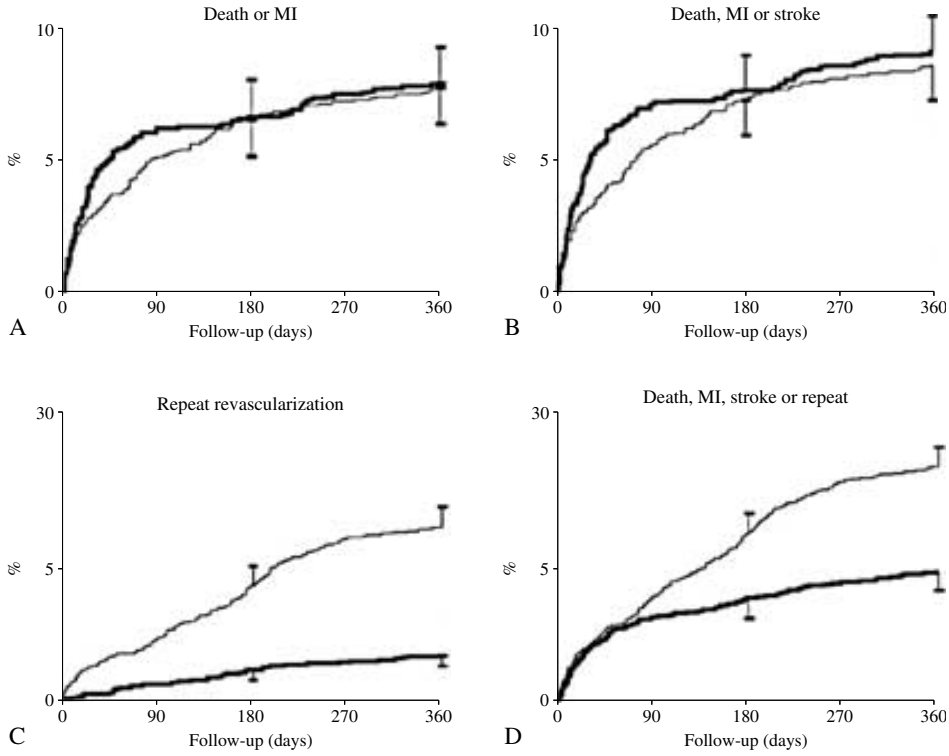


Figure 3.–Incidence of adverse cardiovascular events and repeat revascularization procedures during 1-year follow-up in patients allocated PCI with multiple stenting or CABG surgery (bold line). (From Mercado *et al.*[26]).

they randomized 219 patients with multivessel disease to either PCI limited to the culprit vessel or PCI of all vessels with over 50% stenosis. This study demonstrated that at long-term follow-up of 4.6 years, the overall need for repeat PCI was significantly lower (21.2% *versus* 31.2%, P=0.06) in the completely revascularized group although target-lesion revascularization rates were similar in the completely revascularized group and the culprit vessel–treated group (17.3% *versus* 12.0%, P=0.3). Overall long-term MACCE rates were similar between groups (34.6% *versus* 40.4% respectively, P=0.4), as were estimated costs (P=0.8). More recently, using New York State's Percutaneous Coronary Interventions Reporting System (n=21 945), the non-randomized study by Hannan *et al.* demonstrated that the incompletely revascularized patients had significantly worse 3-year survival than completely revascularized patients, even after adjustment for patient risk (adjusted HR=1.15; 95%CI, 1.01 to 1.30).[39]

There has been only one report from a randomized trial that compared the end point of complete revascularization between CABG and PCI. The ARTS trial in which equivalent revascularization was mandatory has published the one-year outcomes of patients who were completely or incompletely revascularized. All lesions with a >50% diameter in a segment with a reference diameter of ≥1.50 mm were scored as potentially amenable to treatment. If all such segments were treated according to the case report form, they were classified as a complete revascularization.

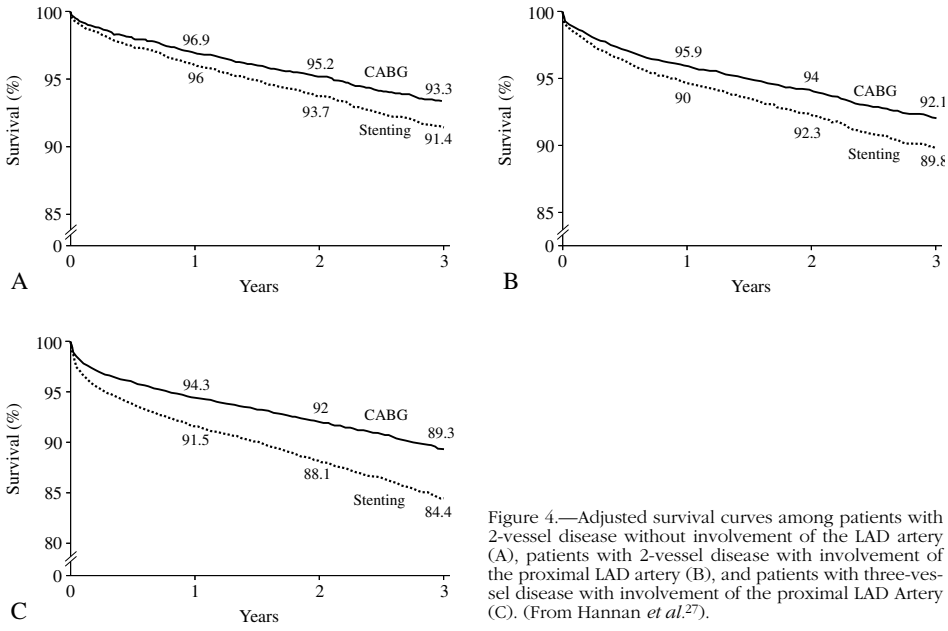


Figure 4.—Adjusted survival curves among patients with 2-vessel disease without involvement of the LAD artery (A), patients with 2-vessel disease with involvement of the proximal LAD artery (B), and patients with three-vessel disease with involvement of the proximal LAD Artery (C). (From Hannan *et al.*[27]).

Despite the potential for equivalent revascularization, complete revascularization was more frequently achieved in CABG-treated patients (84.1%) than in stented patients (70.5%, P<0.001). Although no differences in mortality or the combined end point of death/stroke/myocardial infarction were seen in the comparison of the four groups, overall MACCE rates were significantly higher in the incompletely revascularized stented group, driven by an increased need for CABG within the first year of follow-up.[40]

There is no universal definition for what is meant by complete revascularization. Each trial to date has employed different definitions like anatomical and functional revascularization, depending on whether the reperfused ischemic myocardial territory is taken into consideration. In the BARI trial, the authors attempted to establish different definitions and apply them to the available results.[41] They used with four different definitions; 1) traditional complete revascularization with one graft to each major diseased artery system; 2) functional complete revascularization with one graft to all diseased major or primary segmental vessels; 3) patients were grouped according to whether or not the number of distal anastomoses was less, equal to, or more than the number of diseased coronary segments; 4) patients were grouped by whether they had 2 or more grafts to both the left anterior descending coronary artery and to a non-left anterior descending coronary artery system, or whether no system had multiple grafts. The authors found that by either the traditional or functional definition, complete revascularization conferred no independent advantage, but the risk estimates on late mortality were in the direction that favored complete revascularization.

Although little evidence is available on this aspect of the comparison of CABG and PCI and various definitions are present, the overall trends support complete revascularization. The goal should always be complete revascularization whether the treatment choice is surgery or PCI, although the presence of chronic total occlusions (CTO) remains the

highest hurdle to achieve complete revascularization for the percutaneous approach.

Cost-effectiveness

Another crucial aspect to be mentioned is cost-effectiveness. In the BARI randomized trial, the cost of the initial revascularization procedure was 35% lower among PCI patients, but this difference had narrowed to 5% by 5 years of follow-up mostly as a result of the greater need for additional revascularization procedures among PCI patients. After 10-12 years, these early differences between PTCA and CABG in economic and quality-of-life outcomes were no longer significant.[42] In the EAST trial, Weintraub *et al.* reported that the cost advantage of PCI in the initial procedure was largely or even completely lost for randomized patients after 8 years follow-up because of additional procedures after a first revascularization by PCI.[43] In the ERACI trial, the cumulative cost at 3-year follow-up was greater for the bypass surgery group than for the coronary angioplasty group.

In the more recent MASS II trial with stenting, comparison of CABG and PCI showed no difference in the incidence of death, although the greater occurrence of repeat revascularization procedures in the PCI group elevated its costs to that of CABG in one-year.[44] In the ARTS trial, the one-year results demonstrated that PCI was less expensive than CABG and offered the same degree of protection against death, stroke, and myocardial infarction. However, at 3 years, the additional costs generated by the higher rate of revascularization in the stented patients reduced the cost saving of € 2779 in favor of stenting observed at 1 year to € 1798. The incremental cost for each event-free patient treated by surgery decreased substantially from € 19257 at 1 year to € 10492 at 3 years.[45] In the five-year follow-up of ERACI-II, comparison of average cost per patient showed a higher cost with PCI than CABG ($13,584 in PCI and $11,362 in CABG, P=0.04), although that is partly explained by the liberal use of stents and high proportion of glycoprotein inhibitors used in the PCI arm.[46]

Thus, in most trials, PCI had an advantage in initial procedure costs, although the advantage in favor of PCI becomes less significant or lost in long-term follow-up due to repeat revascularization.

Diabetic patients

Diabetic patients are known to have an aggressive form of atherosclerosis with less favorable long-term survival following both PCI and CABG as compared to non-diabetic patients.[47-50] Due to their smaller vessel size, longer lesion length and greater plaque burden, diabetics are inextricably connected to multivessel disease. Furthermore, they have a differently acting restenotic cascade as compared to non-diabetics and show higher restenosis rates.

Diabetic patients with multivessel disease who are treated with CABG derive a survival benefit over those treated with PCI. The BARI study demonstrated that the 5-year all-cause mortality rate was 34.5% in randomized diabetic patients assigned to PTCA *versus* 19.4% in CABG patients (P=0.0024; RR=1.87); the corresponding cardiac mortality rates were 23.4% and 8.2%, respectively (P=0.0002; RR=3.10). The CABG benefit was more apparent amongst patients requiring insulin.[51] The EAST trial included a small cohort of treated diabetic patient who underwent PCI (n=29) or CABG (n=30) with a non-significant trend towards improved 8-year survival in the surgical group (60.1% *vs* 75.5%, respectively, P=0.23).[52]

In the BMS era, the survival advantage of CABG might be less significant, although PCI is still associated with higher rates of repeat revascularization. The ARTS-I trial showed that in the subgroup of diabetic patients (n=208), there was no statistical difference in one-year mortality, although there was a trend in favor of CABG (6.3% *vs* 3.1%, P=0.294). The patients treated with stenting had a significantly lower event-free survival (63.4%) than those with CABG (84.4%), due to the higher necessity for repeat revascula-

rizations in the PCI arm. Results from the diabetic subgroup of the SoS trial (n=142) showed similar rates of death or Q-wave MI in the PCI and CABG cohorts (10% *vs* 12%, respectively), but a higher repeat revascularization rate in patients assigned PCI (25% *vs* 5%). In a meta-analysis using pooled patient-level based 1-year follow-up data from ARTS, ERACI-II, MASS-II and SoS trials, 1-year mortality rates were 5.6% of patients allocated to PCI with multiple stenting and 3.5% of those allocated to CABG surgery (HR 1.6, 95% CI 0.72-3.6, P=0.3).[26]

These results are inconclusive because they extracted results from diabetic subgroups without specifically targeting these populations. Furthermore, there seems reason to believe that due to the rapid disease progression and greater atherosclerotic burden of the diabetic patient with multivessel disease, CABG should be the preferred treatment, mainly because of its ability to bypass this large amount of plaque burden, which could make repeat revascularizations less of a necessity.

Drug-eluting stents: contemporary era

Since their introduction in 2002, drug-eluting coronary-artery stents have decreased late luminal loss and angiographic restenosis by reducing neointimal hyperplasia after vascular injury and enabled PCI to halve repeat reintervention rates without affecting short and long-term safety.[53, 54]

Immediately after the revelation of the low restenotic rate in PCI with DESs, the first PCI-CABG trials added a DES arm to the historical CABG arms in the previously published trials. The ARTS-II trial was one of the first trials, which added a prospectively collected arm of 607 consecutive patients to the ARTS-I study.[55] The ARTS-I trial randomized 1 205 patients with multivessesl disease to CABG or PCI with bare-metal stents. The ARTS-II 1-year results showed that PCI with DES was not inferior to CABG with respect to the combined endpoint of MACCE. The need for repeat revascularizations, was still significantly higher than in the historical CABG arm of ARTS-I, although overall MACCE rates in ARTS II approached the surgical results and were significantly better than bare metal stenting in ARTS I. The 3-year results of ARTS-II study demonstrated the same tendency with comparable MACCE rates in ARTS-II PCI and ARTS-I CABG (80.6 *vs* 83.8%, P=0.21). Freedom from revascularization in ARTS-II was 85.5%, lower than in ARTS-I CABG (93.4%; P<0.001).[56] The ERACI-III study was performed in a similar approach as ARTS-II by adding a group of 225 DES patients to the ERACI-II trial.[57] At one-year follow-up, freedom from MACCE was significantly greater among patients treated with DES (88%) than the ERACI-II CABG arm (80.5%, P=0.038) and ERACI-II PCI patients (78%, P=0.006). Freedom from repeat revascularization was similar between patients with DES and CABG (91.2% *vs* 95.1%, P=NS).

Recent developments of PCI to overcome chronic total occlusions

The presence of a CTO has remained the highest hurdle and the most important technical challenge to achieve complete revascularization with PCI. CTOs occur relatively frequently, appearing in up to 20% of patients undergoing diagnostic coronary angiography and making 10% of PCIs in the contemporary practice of a tertiary referral catheterization laboratory. Historically, the success rate of crossing CTOs approximates to 60% with conventional techniques.[58] This success rate is dependent on operator experience, the number of attempts performed, anatomic considerations, and the choice of devices available.

Parallel with the emergence of DES, numerous devices have been developed for the percutaneous treatment of CTOs. Multi-slice computed tomography coronary angiography has provided additional information such as occlusion length and degree of calcification, features that predict procedural success and that are often underestimated by conventional coronary angiography.[59] In the randomized TOTAL trial (total occlusion trial with angioplasty by using laser guidewire), laser tipped guidewires were no better than con-

ventional wires.[60] Local delivery of thrombolytic therapy to the site of occlusion via a specialized catheter to facilitate wire crossing was recently reported with promising results.[61] New devices in development include a blunt dissection catheter, a helical screw-like-tipped microcatheter, and a specific system that uses optical coherence reflectometry together with radiofrequency ablation. The retrograde approach using collaterals is also regarded as promising.[62, 63] However, higher rates of technical success do not result in higher rates of procedural success, including the avoidance of complications.

After successful recanalization, the implantation of drug-eluting stents has been shown to improve the mid-term outcome of patients with CTOs. Three registries, all with angiographic follow-up, convincingly demonstrate a sustained reduction in restenosis rates, need for reintervention, and occurrence of MACCE with drug-eluting stents compared with bare-metal stents.[58, 64, 65] In the recent randomized PRISON II trial (Primary Stenting of Totally Occluded Native Coronary Arteries II), Suttorp *et al*. showed that use of silorimus-eluting stents were superior to bare metal stents with a significant reduction in angiographic binary in-segment restenosis (SES 11% *vs* BMS 41%, P<0.0001), resulting in significantly less necessity for target lesion revascularization.[66]

Ongoing trials

SYNTAX study

The relevance of the above-mentioned trials to compare PCI and CABG might be in dispute because of the following reasons. Firstly, they might not mirror the "real world" because only 2-12% of the patients screened are actually randomized because of numerous exclusion criteria and disagreement between the surgeons and the interventional cardiologists.[3] In the "real world", both interventional cardiologists and surgeons are often confronted with complex anatomy. Secondly, patients are heterogeneic in the severity of coronary artery disease and the complexity of the lesion. For example, a patient with a distal left-main trifurcation lesion and an occluded right coronary artery is routinely classified as "3-vessel disease" together with a patient having three focal lesions in the mid portions of the three coronary arteries. However, the former clearly poses a greater therapeutic challenge for the interventional cardiologist and is different from the latter in prognosis regardless of the revascularization strategy.

Taking these arguments into consideration, the Synergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) study was planned. SYNTAX is a prospective, multicenter, multinational, randomized clinical trial with an all-comers design. The overall study goal of SYNTAX is to assess the best revascularization treatment for patients with de novo 3-vessel disease or LM disease by randomizing patients to either PCI with paclitaxel-eluting TAXUS stents or CABG. Of note, SYNTAX employs a unique scoring system named the "SYNTAX score" to quantify the complexity of coronary artery disease.[67-70] It focuses on not only the number of significant lesions and their location, but also the complexity of each lesion independently. The SYNTAX score was calculated using dedicated software that integrates 1) the number of lesions with their specific weighting factors based on the amount of myocardium distal to the lesion according to the score of Leaman *et al*.;[71] and 2) the morphologic features of each single lesion, as previously reported.[67] An example of SYNTAX score calculation in 1 subject is shown in Figure 5. The development of the SYNTAX score should provide guidance to physicians as a predictive tool on the optimal revascularization strategy for patients with high-risk lesions.

FREEDOM and CARDIA

Diabetic patients showed less favorable long-term survival following both PCI and CABG as compared to non-diabetic participants in the previous trials. Recently, the non-randomized diabetes subgroup of the ARTS-II trial, which included patients with siroli-

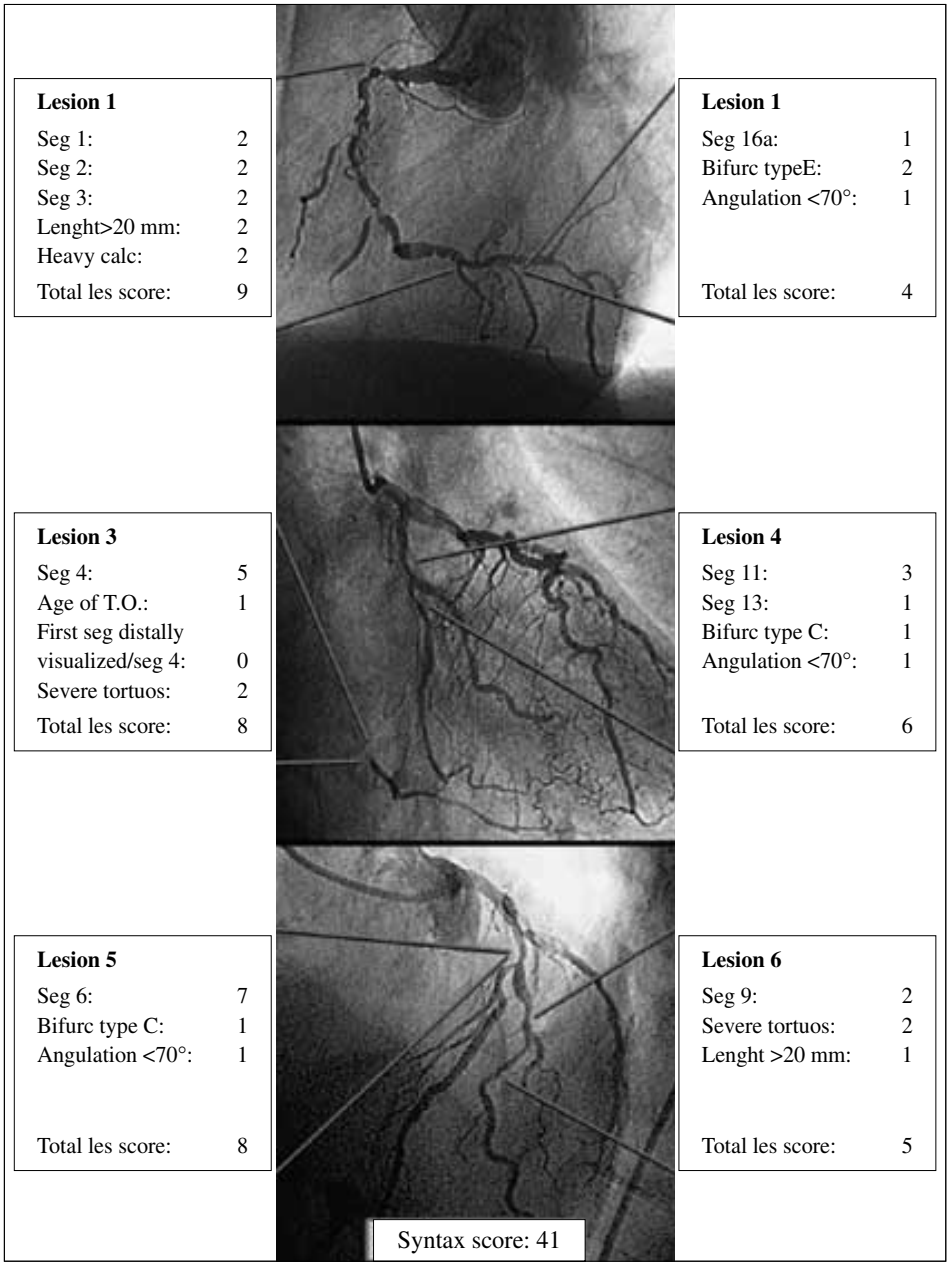


Figure 5.–Calculation of overall SYNTAX score based on coronary lesion angiographic characteristics in a representative patient. Bifurc: bifurcation; calc: calcification; les: lesion; Seg: segment; TO: total occlusion. (From Valgimigli *et al.*[68]).

mus-eluting stents, showed that the 1-year event-free survival was equal in the CABG arm and ARTS-II PCI arm.[72] This result might be inconclusive because they extracted results from subgroups rather than specifically targeting these populations at the onset. Thus, focusing on this high-risk population, two trials have been planned. The Future Revascularization Evaluation in Patients with Diabetes Mellitus; Optimal Management of Multivessel Disease (FREEDOM) trial, a randomized unblended two-sided superiority trial, is enrolling 2 400 diabetic patients with multivesssel disease to treatment with PCI with sirolimus-eluting stent or paclitaxel-eluting stent *versus* CABG. The other ongoing trial is the Coronary Artery Revascularisation in Diabetes (CARDIA) study, a prospective, randomized, multicenter UK investigation of 600 diabetic patients, designed to address the hypothesis that PCI with SES is not inferior to CABG as a revascularization strategy.

Conclusions

As outlined above, there is little evidence to believe that a specific revascularization strategy would imply a better survival in the general population with multivessel disease. With drug-eluting stents as well as the multitude of new devices and techniques to overcome CTOs, the ongoing trials will provide new contemporary data on the completeness of revascularization and outcomes in patients randomized to CABG or PCI in multivessel coronary disease. Until the results of these trials are published, the choice for each strategy should be based on the patients' individual risk and anatomy.

Riassunto

Rivascolarizzazione nel paziente ad alto rischio: malattia multivasale

L'obiettivo di questo articolo è quello di presentare una revisione critica del trattamento dei pazienti con cardiopatia ischemica multivasale. L'angioplastica coronarica percutanea (*percutaneous coronary intervention*, PCI) è in competizione con il bypass arterioso coronarico (*coronary artery bypass grafting*, CABG) per il ruolo di gold standard nel trattamento dei pazienti con coronaropatia multivasale. Tuttavia, l'applicazione della PCI a questi pazienti è stata principalmente limitata dal fenomeno della ristenosi. Fino alla fine degli anni '90, numerosi studi randomizzati su larga scala hanno confrontato il CABG con la PCI mediante pallone o stent convenzionali. Questi studi hanno dimostrato simili tassi di mortalità ed infarto miocardico in entrambi i gruppi, ma con una ridotta necessità di rivascolarizzazione nel gruppo CABG. Da recenti acquisizioni è emerso che gli stent a rilascio di farmaci (*drug eluting stents*, DES) hanno drammaticamente ridotto la ristenosi e la necessità di ripetuta rivascolarizzazione. Anche la tecnica del CABG è migliorata, in particolare nella gestione perioperatoria, con un più alto tasso di grafting arterioso e con migliori tecniche di opzioni mini-invasive e intervento off-pump. Pertanto, i risultati degli studi pre-DES non possono essere più sostanzialmente estrapolati al mondo reale di oggi. Nell'attesa di adeguati studi randomizzati, numerosi trial hanno tuttavia già confrontato la PCI con DES con il CABG tradizionale, ma i risultati non sono conclusivi. Numerosi studi randomizzati mirati sono in corso per il confronto fra PCI con DES e CABG al loro stato attuale. Fino alla disponibilità dei risultati di questi studi, la scelta della strategia da adottare per ciascun paziente dovrebbe essere fatta in base alle sue caratteristiche individuali di rischio ed anatomiche.

Parole chiave: Malattia coronarica - Angioplastica coronarica percutanea - Stent.

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CHAPTER 13

Sirolimus-eluting stents, bare metal stents or coronary artery bypass grafting for patients with multivessel disease including involvement of the proximal left anterior descending artery: analysis of the Arterial Revascularization Therapies study part 2 (ARTS-II)

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Heart. 2009 Jul;95(13):1061-6.

Sirolimus-eluting stents, bare metal stents or coronary artery bypass grafting for patients with multivessel disease including involvement of the proximal left anterior descending artery: analysis of the Arterial Revascularization Therapies study part 2 (ARTS-II)

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Accepted 10 March 2009
Published Online First 19 March 2009

ABSTRACT

Objective: The The Arterial Revascularization Therapies Study (ARTS)-II trial found no differences in survival or overall adverse events between sirolimus-eluting stents (SES) and the surgical arm of ARTS-I. Nevertheless, existing data suggest that patients with disease of the proximal left anterior descending artery (LAD) may derive particular benefit from coronary artery bypass grafting (CABG). We therefore analysed the clinical outcome of patients in ARTS-I and ARTS-II with proximal LAD involvement.

Design: Multicentre observational study.

Setting: Forty-five European academic hospitals.

Patients: Patients with multivessel coronary artery disease.

Interventions: Patients in ARTS-II with proximal LAD disease treated with SES (289/607, 48%) were compared with 187/600 (31%) bare metal stent patients (ARTS-I BMS) and 206/605 (34%) surgical patients (ARTS-I CABG) with proximal LAD involvement from ARTS-I.

Main outcome measures: Major adverse cardiac and cerebrovascular events after 3 years.

Results: The Arterial Revascularization Therapies study part 2 (ARTS-II) subgroup had better survival than both ARTS-I groups (ARTS-II 98.6% vs ARTS-I BMS 95.7%, $p = 0.05$ and vs ARTS-I CABG 94.7%, $p = 0.01$) and lower rates of the hard clinical composite endpoint of death or non-fatal myocardial infarction (ARTS-II 3.1% vs ARTS-I BMS 9.6%, $p = 0.002$ and vs ARTS-I CABG 9.7%, $p = 0.002$). Although the ARTS-I CABG patients had a lower need for repeat revascularisation than ARTS-II (5.3% vs 13.1%, $p = 0.002$), the overall composite adverse event rates (death, myocardial infarction, stroke or any repeat revascularisation) were not significantly different between the ARTS-I CABG and ARTS-II patients (15.0% vs 18.0%, $p = 0.4$).

Conclusions: SES are not inferior to CABG or bare metal stents for the treatment of patients with multivessel coronary disease including involvement of the proximal LAD.

Randomised trials have shown no difference in mortality with coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) with bare metal stents (BMS) for patients with multivessel disease.[1–3] However, CABG has been the historical gold standard treatment for patients with multivessel disease due to a reduced need for repeat revascularisation compared with PCI. The advent of drug-eluting stents (DES) has threatened this superiority of CABG, since they reduce restenosis and the need for repeat revascularisation in simple lesions and demonstrate equivalent survival when compared with CABG in patients with multivessel disease.[4–7]

Nevertheless, the optimal treatment for patients with multivessel disease and involvement of the proximal left anterior descending artery (LAD) is less clear. These patients have a poor prognosis if left untreated,[8] and historical registry data have suggested improved survival with CABG over PCI for patients with three-vessel disease or two-vessel disease involving the proximal LAD.[9–11] In addition, long-term analyses of patients enrolled in randomised trials of CABG versus BMS for multivessel disease have found equivalent survival in the subgroups of patients with proximal LAD disease.[12 13] Nevertheless, long-term follow-up data after contemporary PCI with DES implantation in these patients are limited. A recent registry report found no difference in unadjusted clinical outcome between DES and CABG, irrespective of proximal LAD disease, although after adjustment for differences in baseline risk factors, CABG was associated with overall improved survival.[14]

The Arterial Revascularization Therapies Study part 2 (ARTS-II) enrolled multivessel disease patients with the same inclusion criteria as ARTS-I: these patients were treated with sirolimus-eluting stents (SES) and compared with the historical BMS and CABG groups in ARTS-I.[15] The overall results after 5 years' follow-up in ARTS-I and 3 years' follow-up in ARTS-II have already been published.[6 16] In this report, we describe the 3-year outcome of a prespecified subgroup of patients ARTS-I and ARTS-II with multivessel disease including involvement of the proximal LAD.

METHODS

The methods, enrolment criteria and baseline characteristics of ARTS-I and ARTS-II have already

been described in detail.[1 15] Briefly, in ARTS-I, 1205 patients with unstable angina, stable angina or silent ischaemia with multivessel disease (≥50% stenosis in at least two major epicardial vessels including the LAD) were randomised to PCI with BMS or CABG between April 1997 and June 1998 in 67 centres. Patients with previous PCI, previous CABG, left main coronary artery disease, left ventricular ejection fraction <30%, previous cerebrovascular accident (CVA), myocardial infarction (MI) within the preceding week, severe hepatic or renal disease, neutropenia or thrombocytopenia, intolerance of or contraindications to acetylsalicylic acid or ticlopidine, and the need for concomitant major surgery were excluded. The study protocol specified that CABG should be performed "on-pump" with the use of a left internal mammary artery (LIMA) graft for the LAD if possible. In ARTS-II, 607 patients with the same inclusion and exclusion criteria as ARTS-I were enrolled for treatment with sirolimus-eluting stents between February and November 2003 in 45 centres. The overall 5-year clinical results of ARTS-I and 3-year results of ARTS-II have already been published elsewhere.[6 16]

In this prespecified subgroup analysis, we investigated the 3-year clinical outcome of patients with a significant lesion (defined as ≥50% diameter stenosis) in the proximal LAD (defined as the segment between the branching point of the left main stem and the first major septal branch, that is segment 6 in the American Heart Association classification).[17] The primary endpoint was the incidence of major adverse cardiac and cerebrovascular events (MACCE, defined as all-cause death, non-fatal MI, non-fatal CVA or any repeat revascularisation) after 3 years. Secondary endpoints were the rates of all-cause mortality, cardiac mortality, MI, CVA, any repeat revascularisation, target lesion revascularisation (TLR) and the composites of (i) all-cause death or non-fatal MI and (ii) all-cause death, non-fatal MI or non-fatal CVA. Within 7 days of the index procedure, MI was defined as the presence of new abnormal Q waves and either a ratio of creatinine kinase (CK)-MB isoenzyme to total CK of >0.1 or a total CK-MB greater than five times the upper limit of normal. Beyond this time period, MI was defined as either new abnormal Q waves or cardiac enzyme changes.[1] Details of the occurrence of stent thrombosis according to Academic Research Consortium (ARC) definitions[18] were recorded for the patients in ARTS-II.

The Syntax score was also calculated for all patients in ARTS-II. Briefly, this is an assessment of the angiographic severity of coronary artery disease taking into account the area of myocardium supplied by a lesion, together with a detailed angiographic assessment of lesion characteristics including presence of a bifurcation, trifurcation, chronic occlusion, calcification, thrombus, vessel tortuosity, long lesion or diffuse small vessel disease.[19]

STATISTICAL ANALYSIS

Continuous variables are expressed as means (SD) and compared with the unpaired Student t test. Categorical variables are expressed as percentages and were compared with the χ^2 or Fisher exact test. Clinical endpoints are expressed as percentages and compared in terms of relative risk (RR) with 95% CIs. All statistical tests were two-tailed. Cumulative survival free from adverse events was calculated using the Kaplan–Meier method, and differences were assessed using the logrank test. A p value ≤ 0.05 was considered statistically significant without correction for multiplicity. To compensate for differences in baseline and procedural characteristics between patients enrolled in ARTS-I and ARTS-II, propensity scores were calculated for each paired treatment comparison using logistic regression. These scores were then entered into separate proportional hazards models, with the final results expressed as adjusted hazard ratios (HR) and 95% CI.

RESULTS

The overall 3-year results of ARTS-II and the 3-year results of patients in ARTS-I with proximal LAD disease have already been published elsewhere.[6 13] Out of 607 patients in ARTS-II, 289 (48%) had involvement of the proximal LAD. For ARTS-I, 187 out of 600 (31%) BMS patients and 206 out of 605 (34%) CABG patients also had involvement of the proximal LAD. The

Table 1 Demographics and angiographic characteristics for patients with proximal left anterior descending artery involvement

	ARTS-II (n = 289)	ARTS-I bare metal stents (n = 187)	ARTS-I coronary artery bypass grafting (n = 206)
Age, years	63.0 (10.2)	60.1 (9.5)**	62.0 (9.0)
Body mass index, kg/m²	27.5 (4.1)	26.9 (3.6)	27.4 (3.4)
Male	80.6%	78.1%	81.1%
Diabetes mellitus	24.9%	11.2%**	14.6%*
Hypertension	65.7%	41.2%**	44.2%**
Hypercholesterolaemia	74.0%	63.1%*	58.5%**
Peripheral vascular disease	8.0%	5.3%	5.3%
Previous myocardial infarction	32.5%	44.4%*	37.9%
Chronic obstructive pulmonary disease	4.8%	6.4%	4.4%
Smoking history			
Current	17.6%	27.4%*	20.4%
Former	39.1%	43.5%	51.9%*
Clinical presentation			
Unstable angina	32.9%	41.7%	34.5%
Stable angina	57.4%	53.5%	59.7%
Silent ischaemia	9.7%	4.8%	5.8%
Left ventricular ejection fraction, %	59.2 (11.5)	60.8 (12.2)	60.5 (13.3)

*p<0.05 versus proximal LAD SES group.
**p<0.005 versus proximal LAD SES group.
ARTS, Arterial Revascularization Therapies study; LAD, left anterior descending artery.

ARTS-II patients with proximal LAD involvement had a significantly higher Syntax score than the remaining ARTS-II patients (22.9 (9.7) vs 18.8 (8.9), p<0.0001). The baseline characteristics of patients with involvement of the proximal LAD are shown in table 1, and the angiographic and procedural details are demonstrated in table 2. For the patients with proximal LAD involvement, the ARTS-II group had more extensive coronary disease and more extensive revascularisation, with a higher incidence of three-vessel coronary disease and Type C lesions. They also had more lesions treated, more stents implanted and a greater total stented length than patients in ARTS-I.

The clinical endpoints after 1 and 3 years are shown in table 3 and depicted in fig 1. When compared with the surgical group in ARTS-I (ARTS-I CABG), the ARTS-II patients had a lower risk of the individual endpoints of all-cause death, cardiac death and myocardial infarction at 3 years (table 3). The hard clinical composite endpoints of death or non-fatal MI and death, non-fatal MI or non-fatal stroke were also less frequently reached in the ARTS-II cohort. The CABG patients required repeat revascularisation less often, and as a result, the overall MACCE rates were similar between the ARTS-I CABG and ARTS-II patients. As shown in table 4, after adjustment for differences in patient characteristics, there was no difference in the rates of MACCE between ARTS-II and ARTS-I CABG, although ARTS-II patients had a significantly lower rate of the composite of death or non-fatal MI. ARTS-II patients demonstrated a non-significant trend towards a reduction in the individual endpoints of all-cause mortality or any myocardial infarction, although they had a trend towards increased repeat revascularisations.

When comparing ARTS-II with the bare metal stent group in ARTS-I (ARTS-I BMS), the composites of MACCE and death or non-fatal MI were lower in the ARTS-II patients, although there were no significant differences in overall mortality. The ARTS-II patients also had a lower rate of myocardial infarction, any repeat revascularisation and target lesion revascularisation (table 3). After adjustment, we still found a significant reduction in MACCE, any repeat revascularisation and TLR (table 4).

Definite stent thrombosis according to ARC definitions occurred in 2.4% of the ARTS-II proximal LAD patients (early 0.7%; late 0.7%; very late 1.0%), while the composite of definite or probable stent thrombosis occurred in 3.8% (early 1.0%; late 1.0%; very late 1.0%).

DISCUSSION

The treatment of patients with multivessel disease and involvement of the proximal LAD has been of particular concern ever since data from medically treated patients enrolled in the mid-late 1970s in the Coronary Artery Surgery Study (CASS) registry showed poorer survival in those with proximal vessel disease.[8] This is presumably due to the large area of left ventricular myocardium at risk with proximal LAD disease, since approximately 58% of the total coronary blood flow to the left ventricle is via the LAD in a right dominant coronary artery system.[19 20] This information is taken into account by the Syntax score:[19] the mean Syntax score for ARTS-II patients with proximal LAD involvement was 22.9 (SD 9.7) compared with 18.8 (8.9) for the remaining ARTS-II patients.

Data from the New York State registry in the early 1990s revealed that surgical revascularisation provided better survival than balloon angioplasty in patients with three-vessel disease or two-vessel disease with proximal LAD involvement.[10] A further report from the New York State registry found that the adjusted hazard ratio for the long-term mortality after CABG relative to BMS implantation was 0.64 (95% CI 0.56 to 0.74) for patients with three-vessel disease with involvement of the proximal

Table 2 Angiographic and procedural characteristics of patients with proximal left anterior descending artery involvement

	ARTS-II (n = 289)	ARTS-I bare metal stents (n = 187)	ARTS-I coronary artery bypass grafting (n = 206)
Two-vessel coronary disease	45.3%	67.4%**	60.2%**
Three-vessel coronary disease	54.0%	29.4%**	36.9%**
No of diseased vessels	2.5 (0.5)	2.3 (0.5)**	2.3 (0.5)**
No of diseased lesions	3.7 (1.3)	3.0 (1.0)**	3.0 (1.1)**
Location of lesions†			
Right coronary artery	28.6%	29.3%	29.0%
Circumflex artery	28.5%	24.3%	25.7%
American College of Cardiology/American Heart Association lesion classification			
Type A	7.1%	5.2%	6.1%
Type B1	21.9%	28.0%*	30.6%**
Type B2	56.6%	58.2%	57.0%
Type C	14.4%	8.6%**	6.4%**
Chronic total occlusion	1.7%	0.2%**	1.0%
Bifurcation lesion	35.2%	34.1%	32.5%
Ostial lesion	7.0%	12.2%**	9.5%
No of stented lesions	3.3 (1.2)	2.7 (1.0)**	
No of stents implanted	3.8 (1.6)	2.9 (1.2)**	
Total stented length, mm	73.9 (33.4)	48.3 (21.5)**	
No of anastomoses			3.0 (1.0)
Left internal mammary graft			94.5%

*p<0.05 versus ARTS-II.
**p<0.005 versus ARTS-II.
†Expressed as a percentage of all lesions.
ARTS, Arterial Revascularization Therapies study.

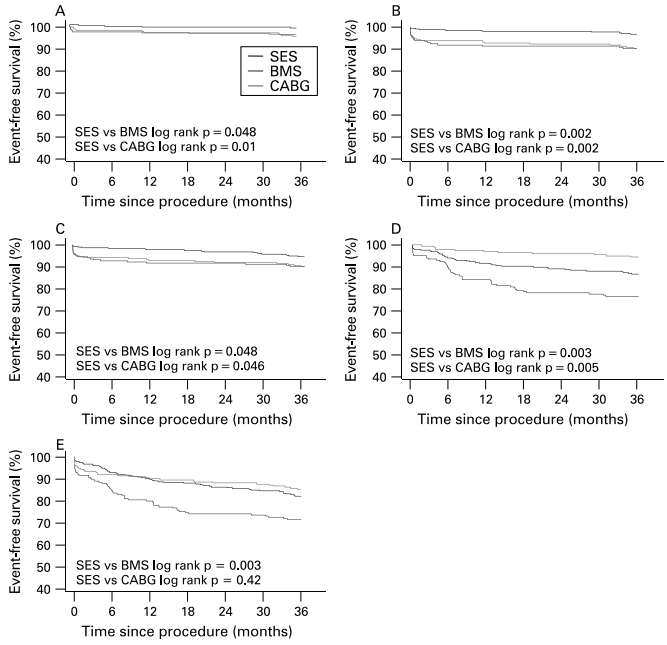

Figure 1 Kaplan–Meier curves for event-free survival from (A) all-cause death, (B) all-cause death or non-fatal myocardial infarction, (C) all-cause death or non-fatal myocardial infarction or stroke, (D) any repeat revascularisation and (E) major adverse cardiac and cerebrovascular events, defined as all-cause death, myocardial infarction, stroke or any repeat revascularisation. BMS, bare metal stent; CABG, coronary artery bypass grafting; SES, sirolimus-eluting stents.

LAD, compared with 0.74 (0.62 to 0.90) for those with three-vessel disease without proximal LAD involvement.[11] However, these registry data conflict with information from the randomised ARTS-I trial, which found no difference in all-cause mortality of the hard clinical composite of death, stroke or myocardial infarction in patients with multivessel disease and proximal LAD involvement treated with CABG or BMS implantation. The BMS patients in ARTS-I did have a significantly higher need for repeat revascularisation within 3 years (RR 4.63, 95% CI 2.41 to 8.90) which was the main contributor towards a higher overall adverse event rate in the BMS patients (RR 1.92, 95% CI 1.34 to 2.75).[13]

More contemporary data from the New York State registry found no difference in survival rates between multivessel disease patients treated with CABG or DES. However, after adjustment for differences in baseline characteristics, patients with two- or three-vessel disease had improved survival with CABG, irrespective of proximal LAD involvement.[14] These findings conflict with those from the overall results of ARTS-II, which found no difference in survival between DES and the BMS or CABG patients in ARTS-I. Although the CABG patients required repeat revascularisation less frequently than DES or BMS within 3 years (6.5% vs 14.3% vs 26.3% respectively), DES treatment reduced this difference sufficiently so that the overall adverse event rates were not significantly different between ARTS-I CABG and ARTS-II (16.1% vs 19.3%; RR 1.20, 95% CI.94 to 1.53).

In this analysis of patients with proximal LAD involvement, we found a lower rate of death and hard clinical endpoints in the SES patients when compared with both the surgical and BMS arms of ARTS-I. Careful inspection of the Kaplan–Meier survival curves shows that this may be due to an early reduction in death and MI in the ARTS-II group when compared with both arms of ARTS-I. Given the high incidence of CK-MB elevation after CABG, this might be expected,[21] although it is unclear whether this finding truly represents superior safety of sirolimus-eluting stents or indicates improvements in periprocedural patient management between 1997 and 1998 (ARTS-I) and 2003 (ARTS-II). However, these potential improvements are not clearly evident when examining complications following PCI across Europe: in 1997, the in-hospital mortality was 0.4% vs 0.6% in 2003, although this might be explained by a higher rate of PCI for acute myocardial infarction (9% in 1997 vs 17% in 2003).[22] Inspection of the data from the New York State registries does not suggest any major changes in outcomes after CABG: patients with three-vessel disease including proximal LAD involvement had a 1-year mortality of 5.3% for those treated in 1993–5 compared with 5.7% in those treated in 1997–2000; the 1-year mortality of all three vessel disease patients treated in 2003–4 (irrespective of proximal LAD involvement)

Table 3 Unadjusted clinical endpoints in Arterial Revascularization Therapies study (ARTS)-I and ARTS-II patients with proximal left anterior descending artery involvement

	ARTS-II (n = 289)	ARTS-I BMS (n = 187)	ARTS-I CABG (n = 206)	ARTS-II versus ARTS-I bare metal stents relative risk (95% CI)	ARTS-II versus ARTS-I coronary artery bypass grafting relative risk (95% CI)
All-cause death					
1 year	1.0%	3.7%	3.4%	0.28 (0.07 to 1.06)	0.31 (0.08 to 1.17)
3 years	1.4%	4.3%	5.3%	0.32 (0.10 to 1.06)	0.26 (0.08 to 0.80)
Cardiac death					
1 year	0.7%	2.7%	2.4%	0.26 (0.05 to 1.32)	0.29 (0.06 to 1.46)
3 years	0.7%	3.2%	3.4%	0.22 (0.04 to 1.06)	0.20 (0.04 to 0.97)
Any myocardial infarction					
1 year	0.7%	5.3%	4.9%	0.13 (0.03 to 0.58)	0.14 (0.03 to 0.64)
3 years	1.7%	5.9%	5.8%	0.29 (0.10 to 0.83)	0.30 (0.11 to 0.83)
Stroke					
1 year	0.7%	1.1%	1.0%	0.65 (0.09 to 4.55)	0.71 (0.10 to 5.02)
3 years	2.8%	2.1%	1.9%	1.29 (0.40 to 4.24)	1.43 (0.44 to 4.67)
Any repeat revascularisation					
1 year	8.3%	15.5%	2.9%	0.54 (0.32 to 0.89)	2.85 (1.19 to 6.85)
3 years	13.1%	23.0%	5.3%	0.57 (0.38 to 0.85)	2.46 (1.29 to 4.70)
Target lesion revascularisation					
1 year	3.8%	12.3%	2.4%	0.31 (0.15 to 0.62)	1.57 (0.55 to 4.45)
3 years	7.6%	15.5%	3.4%	0.49 (0.29 to 0.83)	2.24 (0.98 to 5.15)
Death or myocardial infarction					
1 year	1.7%	8.6%	7.3%	0.20 (0.08 to 0.54)	0.24 (0.09 to 0.64)
3 years	3.1%	9.6%	9.7%	0.32 (0.15 to 0.70)	0.32 (0.15 to 0.69)
Death or stroke or myocardial infarction					
1 year	2.4%	9.1%	7.8%	0.27 (0.11 to 0.63)	0.31 (0.13 to 0.74)
3 years	5.9%	10.7%	10.7%	0.55 (0.30 to 1.02)	0.55 (0.30 to 1.01)
MACCE					
1 year	10.4%	20.3%	10.2%	0.51 (0.33 to 0.79)	1.02 (0.60 to 1.73)
3 years	18.0%	28.9%	15.0%	0.62 (0.45 to 0.87)	1.20 (0.80 to 1.80)

MACCE, major adverse cardiac or cerebrovascular event (all-cause death, stoke, myocardial infarction or any repeat revascularisation).

was 5.2%.[10 11 14] A large study from the UK found that although patient comorbidity increased significantly between 1995 and 2003, long-term event-free survival improved.[23] Nonetheless, any direct comparison of adverse event rates between patients treated over different time period are inevitably complicated by changes in clinical practice (eg, older patients treated, and more with acute coronary syndromes) as well as improvements in pharmacotherapy and catheter laboratory equipment.

The overall adverse event rates with SES were no different when compared with the CABG group, despite the CABG patients requiring repeat revascularisation less frequently (as found in the overall ARTS-II comparison). Furthermore, the risk

Table 4 Comparison of 3-year endpoints after adjustment for baseline and procedural characteristics with and without propensity score correction

	ARTS-II versus ARTS-I bare metal stents		ARTS-II versus ARTS-I coronary artery bypass grafting	
	Hazard ratio (95% CI)		Hazard ratio (95% CI)	
	Without propensity score	With propensity score	Without propensity score	With propensity score
All-cause death	0.32 (0.10 to 1.05)	1.03 (0.05 to 21.23)	0.25 (0.08 to 0.80)	0.37 (0.09 to 1.49)
Cardiac death	0.53 (0.10 to 2.89)		1.26 (0.23 to 6.99)	0.18 (0.00 to 11.21)
Any myocardial infarction	0.28 (0.10 to 0.81)	0.46 (0.05 to 3.94)	0.29 (0.10 to 0.81)	0.35 (0.10 to 1.18)
Stroke	1.27 (0.38 to 4.20)	0.75 (0.07 to 7.54)	1.40 (0.42 to 4.63)	1.03 (0.26 to 4.06)
Any repeat revascularisation	0.53 (0.34 to 0.81)	0.33 (0.14 to 0.76)	2.53 (1.29 to 4.94)	1.92 (0.91 to 4.07)
Target lesion revascularisation	0.45 (0.26 to 0.78)	0.27 (0.10 to 0.73)	2.23 (0.95 to 5.22)	1.35 (0.52 to 3.51)
Death or myocardial infarction	0.31 (0.14 to 0.69)	0.60 (0.10 to 3.56)	0.31 (0.14 to 0.68)	0.37 (0.14 to 0.94)
Death or stroke or myocardial infarction	0.53 (0.28 to 1.00)	0.65 (0.16 to 2.62)	0.53 (0.28 to 1.00)	0.57 (0.26 to 1.22)
MACCE	0.57 (0.39 to 0.83)	0.41 (0.19 to 0.89)	1.19 (0.77 to 1.86)	1.11 (0.65 to 1.89)

ARTS, Arterial Revascularization Therapies study; MACCE, major adverse cardiac or cerebrovascular event (all-cause death, stoke, myocardial infarction or any repeat revascularisation).

of late and very late definite stent thrombosis with DES (2.4% in this ARTS-II subgroup) did not translate into an overall excess of MI or cardiac death when compared with both the BMS and CABG cohorts, as found with the overall ARTS-II population.[6] Although incomplete strut apposition and lack of strut coverage occurs with a significantly higher frequency in SES than in BMS[24 25] and the ongoing risk of stent thrombosis with DES remains a concern, in our patients at least, this risk seems counterbalanced by the benefit of DES. The non-significant reduction in the rates of MI in the ARTS-II patients suggests that either the clinical sequelae of stent thrombosis may not be as devastating as previously thought, or restenosis in BMS is not a benign phenomenon.[26–30] Furthermore, graft failure should not be forgotten or ignored as a potential cause of adverse events in patients undergoing CABG.[31 32]

These findings suggest that treatment with sirolimus-eluting stents is a safe and effective alternative to CABG in patients with multivessel disease involving the proximal LAD and, given the reduction in hard clinical endpoints, may even be the preferred strategy.

LIMITATIONS

ARTS-I was a randomised controlled trial and therefore suffers from the inherent limitations of this type of study including patient selection. Therefore, the results of this study may not be applicable to other populations. Additionally, this is a subgroup analysis: the sample size was chosen to detect differences in the entire population and hence lacks adequate statistical power to provide definitive results. We acknowledge that contemporary improvements in surgical and perioperative management may have improved the outcomes in patients currently treated with CABG compared with the historical group from ARTS-I. It is possible that improved outcomes might be achieved with higher rates of arterial grafting in surgical patients. Due to different recruitment periods, patients in ARTS-II had more intensive pharmacological therapy than those in ARTS-I, which may also confound the results.

Funding: The ARTS-II trial was sponsored by Cordis EMEA, a Johnson & Johnson company.

Competing interests: NM and HPS are employees of Cordis EMEA, a Johnson & Johnson company.

Ethics approval: Ethics approval was provided by the ethics committee of each participating site.

Patient consent: Obtained.

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CHAPTER 14

Three-year survival following multivessel percutaneous coronary intervention with bare-metal or drug-eluting stents in unselected patients

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Am J Cardiol. 2009 Jan 15;103 (2):203-11.

Three-Year Survival Following Multivessel Percutaneous Coronary Intervention With Bare-Metal or Drug-Eluting Stents in Unselected Patients

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Drug-eluting stents (DESs) have been shown to reduce the rate of repeat revascularization compared with bare-metal stents (BMSs) after multivessel percutaneous coronary intervention in carefully selected patients. However, the long-term safety and efficacy of DESs in patients with multivessel disease outside the setting of randomized trials was unknown. Therefore, all patients undergoing multivessel percutaneous coronary intervention with BMSs, sirolimus-eluting stents (SESs), or paclitaxel-eluting stents (PESs) from January 2000 to December 2005 were investigated. The primary end point was all-cause mortality. A total of 1,720 patients were recruited in 3 consecutive sequential groups of BMS (n = 701; January 2000 to April 2002), SES (n = 293; April 2002 to February 2003), and PES (n = 726; February 2003 to December 2005). Overall median follow-up was 1,440 days. There was improved 3-year survival in the SES group (93.7%) compared with both the BMS (86.1%) and PES groups (87.3%), which remained significant after propensity score adjustment for differences in baseline and procedural characteristics (SES vs BMS, adjusted hazard ratio 0.53, 95% confidence interval 0.30 to 0.94; SES vs PES, adjusted hazard ratio 0.49, 95% confidence interval 0.28 to 0.87). There was no difference in mortality between the PES and BMS groups. Both DES types significantly reduced the need for clinically driven target-vessel and target-lesion revascularization without an excess in myocardial infarction or stent thrombosis. In conclusion, both SESs and PESs significantly reduced the need for repeated revascularization in these patients with no excess in mortality. SESs might reduce mortality in patients undergoing multivessel percutaneous coronary intervention. **© 2009 Elsevier Inc. (Am J Cardiol 2009;103:203–211)**

Historically, coronary artery bypass grafting has been the gold standard of treatment for patients with multivessel coronary artery disease.[1] Trials comparing percutaneous coronary intervention using bare-metal stents (BMSs) have shown equivalent mortality, but an increased need for repeated revascularization compared with coronary artery bypass grafting.[2–4] The Arterial Revascularization Therapies Study Part II (ARTS-II) found equivalent 3-year survival with drug-eluting stents (DESs) compared with historic coronary artery bypass grafting and BMS groups from ARTS-I, although freedom from revascularization was still inferior to coronary artery bypass grafting.[5] Nonetheless, with recent revelations about late and very late stent thrombosis, there were concerns regarding the long-term safety of DESs, particularly in patients treated for "off-label" indications.[6–8] Although there were reports of short-term clinical outcomes after multivessel percutaneous coronary intervention with DESs,[9–11] longer term comparisons between BMSs and different DESs in unselected patients with multivessel disease were scarce. We therefore analyzed all patients undergoing multivessel percutaneous coronary intervention in our institution to ascertain the long-term safety of BMSs, sirolimus-eluting stents (SESs), and paclitaxel-eluting stents (PESs).

Methods

From January 2000 to December 2005, all patients undergoing multivessel percutaneous coronary intervention with a single stent type as their standard treatment were enrolled. We defined multivessel percutaneous coronary intervention as intervention to ≥2 major epicardial coronary arteries or bypass grafts during the same procedure. Initially, all patients were treated with BMSs, but on April 16, 2002, our institution adopted the use of SESs (Cypher; Cordis, Warren, New Jersey) as the default strategy for all coronary interventions. On February 16, 2003, SESs were replaced by PESs (Taxus; Boston Scientific, Natick, Massachusetts) as the default stent. This single-center registry therefore consisted of 1,720 patients divided into 3 groups of consecutive patients of BMS (n = 701; January 2000 to April 2002), SES (n = 293; April 2000 to February 2003), or PES (n = 726; February 2003 to December 2005). The sole exclusion criterion was implantation of ≥1 different stent

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0002-9149/09/$ – see front matter © 2009 Elsevier Inc.
doi:10.1016/j.amjcard.2008.08.068

Table 1
Baseline patient demographics

Variable	BMS (n = 701)	SES (n = 293)	PES (n = 726)	Overall (n = 1,720)	p Value
Men	71.0%	74.1%	72.7%	72.3%	0.6
Age (yrs)	64.0 ± 11.1	63.5 ± 10.5	64.2 ± 10.8	64.0 ± 10.9	0.7
Hypertension*	39.2%	45.1%	46.7%	43.4%	0.01
Hypercholesterolemia†	48.6%	60.4%	62.4%	56.5%	<0.001
Family history of coronary artery disease	21.4%	25.3%	33.7%	27.3%	<0.001
Smoking history	26.7%	35.5%	41.6%	34.5%	<0.001
Current	21.7%	21.2%	19.0%	20.5%	0.4
Exsmoker	5.0%	14.3%	22.7%	14.1%	<0.001
Diabetes mellitus	15.8%	24.6%	20.9%	19.5%	0.003
Type 1	2.4%	8.2%	5.0%	4.5%	<0.001
Type 2	13.4%	16.4%	16.4%	15.2%	0.2
Renal impairment	1.7%	3.8%	2.6%	2.4%	0.2
Previous myocardial infarction	42.7%	37.2%	35.8%	48.8%	0.02
Previous coronary artery bypass grafting	12.0%	7.8%	9.4%	10.2%	0.09
Previous percutaneous coronary intervention	18.4%	19.8%	19.4%	19.1%	0.8
Previous brachytherapy	5.4%	1.4%	0.3%	2.6%	<0.001
Clinical presentation					
ST-Elevation myocardial infarction	13.6%	8.5%	14.3%	13.0%	0.04
Unstable angina/non–ST-elevation myocardial infarction	40.8%	38.2%	34.3%	37.6%	0.04
Stable angina	45.6%	53.2%	51.4%	49.4%	0.04
Cardiogenic shock	1.3%	2.0%	2.1%	1.7%	0.5

Values expressed as mean ± SD or percent.
* Blood pressure >140/90 mm Hg or treatment for hypertension.
† Fasting total cholesterol >5 mmol/L (193 mg/dl) or use of lipid-lowering therapy.

type during the index procedure. All patients were prospectively entered into a dedicated database. For patients undergoing multiple procedures, the first procedure at our institution from January 2000 to December 2005 was recorded as the index procedure. All subsequent procedures were counted as repeated revascularizations. For patients with in-stent restenosis lesions, patients had either undergone previous single-vessel treatment, these lesions were treated before January 2000 at our hospital, or patients had been initially treated at other hospitals.

All procedures were performed following current standard procedural guidelines at the time.[12] The use of glycoprotein 2b/3a inhibitors or adjunctive devices was left up to the operator's discretion. Complete procedural success was defined as residual stenosis <50% using visual estimation in the presence of Thrombolysis in Myocardial Infarction grade 3 flow in all attempted lesions.[13] Hypercholesterolemia was defined as fasting total cholesterol >5 mmol/L (>193 mg/dl) or use of lipid-lowering therapy. Hypertension was defined as blood pressure >140/90 mm Hg or use of antihypertensive medications. Renal impairment was defined as serum creatinine >150 μmol/L (>1.7 mg/dl).

The primary end point was all-cause mortality. Secondary end points included any nonfatal myocardial infarction, target-vessel revascularization, target-lesion revascularization, definite stent thrombosis, and the composites of all-cause death or myocardial infarction and major adverse cardiac events (defined as all-cause death, nonfatal myocardial infarction, or target-vessel revascularization). Myocardial infarction at follow-up consisted of either reinfarction or spontaneous myocardial infarction, diagnosed by an increase in creatine kinase-MB fraction of 3 times the upper limit of normal, together with symptoms and electrocardiogram changes.[14] Stent thrombosis was defined as angiographically documented thrombus with Thrombolysis in Myocardial Infarction grade 0 or 1 flow accompanied by acute symptoms (consistent with the definition of definite stent thrombosis recommended by the Academic Research Consortium).[15,16] The timing of stent thrombosis was categorized into early (≤30 days after implantation), late (30 days to 1 year), or very late (>1 year).

Follow-up survival data for all patients were obtained from municipal civil registries. Causes of death were classified according to the *International Classification of Diseases and Related Health Problems, 10th Revision*. A health questionnaire was subsequently sent to all living patients with specific enquiries about repeated hospital admissions and major adverse cardiac events. As the principal regional cardiac referral center, repeated procedures (percutaneous and surgical) were normally performed at our institution and recorded prospectively in our database. For patients who experienced an adverse event at another center, medical records or discharge summaries from the other institutions were systematically reviewed. General practitioners, referring cardiologists, and patients were contacted as necessary if further information was required. The protocol was approved by the hospital ethics committee and was in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

Categorical variables were presented as percentages and compared using Pearson's chi-square test or Fisher's exact test. Continuous variables were presented as mean ± SD and compared using F test for analysis of variance. A 2-sided $p < 0.05$ was used to indicate statistical significance. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method, and curves were

Table 2
Angiographic and procedural data

Variable	BMS (n = 701)	SES (n = 293)	PES (n = 726)	Overall (n = 1,720)	p Value
No. of diseased vessels	2.38 ± 0.5	2.37 ± 0.5	2.44 ± 0.5	2.40 ± 0.5	0.05
No. of treated vessels	2.16 ± 0.38	2.16 ± 0.37	2.18 ± 0.41	2.17 ± 0.39	0.5
Coronary vessel treated*					
Right	60.1%	60.1%	55.8%	48.3%	0.2
Left anterior descending	74.0%	75.1%	75.3%	74.8%	0.8
Left circumflex	65.6%	70.6%	68.3%	67.6%	0.3
Left main coronary artery	10.1%	7.8%	14.9%	11.7%	0.002
Saphenous vein graft	6.0%	2.7%	4.0%	4.6%	0.05
ACC/AHA lesion classification†					
Type A	26.0%	20.5%	12.8%	19.5%	<0.001
Type B1	48.8%	43.3%	36.5%	42.7%	<0.001
Type B2	58.1%	64.8%	60.6%	60.3%	0.1
Type C	47.5%	51.9%	52.2%	50.2%	0.2
Bifurcation	4.4%	12.3%	20.0%	12.3%	<0.001
In-stent restenosis	8.9%	9.9%	8.1%	8.7%	0.6
Chronic occlusion	11.8%	9.6%	13.9%	12.3%	0.1
No. of lesions treated	2.6 ± 0.9	2.8 ± 0.9	2.4 ± 1.0	2.6 ± 1.0	<0.001
Mean no. of stents implanted	2.7 ± 1.5	3.2 ± 1.5	3.4 ± 1.6	3.1 ± 1.6	<0.001
Stent diameter (mm)	3.19 ± 0.5	2.78 ± 0.2	2.90 ± 0.4	3.00 ± 0.4	<0.001
Total stent length (mm)	42.3 ± 26.4	60.2 ± 34.2	66.6 ± 36.3	55.7 ± 34.1	<0.001
Complete procedural success	89.7%	91.1%	89.0%	89.7%	0.6
Intravascular ultrasound use	16.1%	10.2%	19.0%	16.3%	0.003
Glycoprotein 2b/3a inhibitor	31.8%	21.8%	20.1%	25.2%	<0.001
Recommended duration of clopidogrel (mo)	2.9 ± 2.8	5.3 ± 3.6	6.8 ± 3.6	5.0 ± 3.7	<0.001

Values expressed as mean ± SD or percent.
* Expressed as percentage of patients with each vessel type; hence, total >100%.
† Expressed as percentage of patients with each lesion type; hence, total >100%.
ACC = American College of Cardiology; AHA = American Heart Association.

Table 3
Three-year clinical outcomes

Variable	BMS (n = 701)	SES (n = 293)	PES (n = 726)	Overall (n = 1,720)		SES vs BMS Adjusted HR (95% CI)	PES vs BMS Adjusted HR (95% CI)	SES vs PES Adjusted HR (95% CI)
Death	13.9%	6.8%	12.7%	12.2%	*	0.47 (0.27–0.80)	0.88 (0.62–1.25)	0.53 (0.31–0.92)
					†	0.53 (0.30–0.94)	0.90 (0.63–1.30)	0.49 (0.28–0.87)
Myocardial infarction	3.9%	4.4%	3.3%	3.8%	*	0.69 (0.32–1.46)	0.47 (0.23–0.95)	1.46 (0.70–3.03)
					†	0.74 (0.33–1.66)	0.45 (0.22–0.93)	1.43 (0.68–3.00)
Death or nonfatal myocardial infarction	16.5%	10.9%	15.9%	15.3%	*	0.61 (0.39–0.94)	0.82 (0.59–1.15)	0.74 (0.48–1.15)
					†	0.66 (0.42–1.05)	0.82 (0.58–1.16)	0.70 (0.45–1.10)
Target-vessel revascularization	9.0%	6.1%	6.8%	7.6%	*	0.34 (0.18–0.62)	0.42 (0.26–0.67)	0.81 (0.44–1.49)
					†	0.35 (0.19–0.67)	0.45 (0.28–0.73)	0.78 (0.42–1.45)
Target-lesion revascularization	6.9%	5.5%	5.5%	6.1%	*	0.36 (0.19–0.69)	0.37 (0.22–0.64)	0.97 (0.51–1.84)
					†	0.37 (0.19–0.73)	0.41 (0.24–0.69)	0.98 (0.51–1.88)
Death, nonfatal myocardial infarction, or target-vessel revascularization	23.7%	14.7%	20.9%	21.0%	*	0.51 (0.35–0.74)	0.73 (0.55–0.98)	0.69 (0.47–1.01)
					†	0.51 (0.34–0.76)	0.73 (0.55–0.98)	0.68 (0.46–1.00)
Definite stent thrombosis	1.0%	1.4%	1.4%	1.2%	*	0.75 (0.21–2.72)	0.53 (0.16–1.72)	1.41 (0.40–5.02)
					†	0.69 (0.17–2.79)	0.46 (0.13–1.61)	1.47 (0.41–5.26)

* Conventional multivariate adjustment.
† Propensity score adjusted.

compared using log-rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Separate Cox multivariate regression analyses were performed for each paired treatment comparison (SES vs BMS, PES vs BMS, and SES vs PES). Stent type was forced into a forward stepwise model using all variables listed in Tables 1 and 2. Variables with a significance of $p < 0.1$ were entered into the next step. Final results were presented as adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). Individual propensity scores for each paired treatment comparison were calculated using parsimonious logistic regression to account for dif-

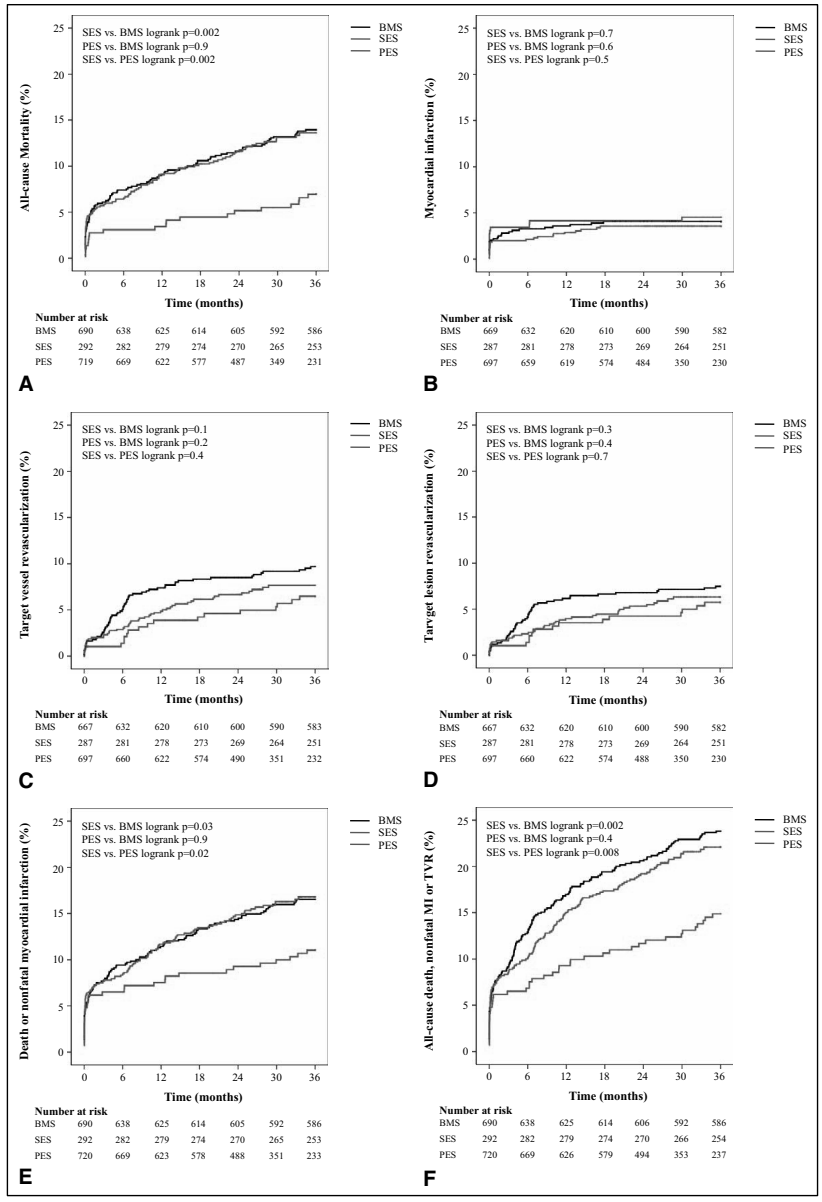

Figure 1. Kaplan Meier curves for cumulative *(A)* all-cause mortality, *(B)* myocardial infarction (MI), *(C)* target-vessel revascularization (TVR), *(D)* target-lesion revascularization, and the composite end points of *(E)* all-cause death or nonfatal MI and *(F)* all-cause death, nonfatal MI, or TVR.

Table 4
Timing of definite stent thrombosis

	BMS (n = 701)	SES (n = 293)	PES (n = 726)	Overall (n = 1,720)	SES vs BMS p Value	PES vs BMS p Value	SES vs PES p Value
Early	0.9%	1.0%	1.0%	0.9%	0.7	0.8	1.0
Late	0.1%	0.3%	0%	0.1%	0.5	0.5	0.3
Very late	0%	0%	0.4%	0.3%	—	0.3	0.6

Table 5
Independent predictors of all-cause mortality after 3 years

Variable	Adjusted HR	95% CI	p Value
ST-Elevation myocardial infarction	3.46	2.14–5.60	<0.001
Renal impairment	2.67	1.42–5.01	0.002
Left main coronary artery treatment	2.61	1.77–3.87	<0.001
Unstable angina/non–ST elevation myocardial infarction	1.98	1.35–2.91	<0.001
Type C lesion treatment	1.92	1.35–2.73	<0.001
Diabetes mellitus	1.71	1.19–2.47	0.004
Age*	1.05	1.03–1.06	<0.001
Complete procedural success	0.58	0.38–0.90	0.01
SES use	0.51	0.31–0.83	0.006

* Per each extra year.

Table 6
Independent predictors of 3-year repeated revascularization

Variable	Adjusted HR	95% CI	p Value
Target-vessel revascularization			
Previous brachytherapy	2.91	1.38–6.15	0.005
BMS use	1.85	1.22–2.80	0.004
Diabetes mellitus	1.73	1.12–2.66	0.01
No. of stents implanted*	1.18	1.05–1.33	0.005
Target-lesion revascularization			
BMS use	1.98	1.26–3.10	0.003
Diabetes mellitus	1.86	1.16–3.00	0.01
No. of stents implanted*	1.26	1.11–1.43	<0.001

* Per each extra stent.

ferences in the 3 cohorts using all significantly different variables listed in Tables 1 and 2.[17] Stent type and appropriate propensity scores were then forced into separate forward stepwise Cox multivariate regression analysis using the variables listed in Tables 1 and 2, as described. The propensity score–adjusted results were presented as adjusted HRs with 95% CIs. Cox multivariate regression analyses were also performed using stent type and all variables listed in Tables 1 and 2 to identify independent predictors of adverse clinical events. Because of the small number of definite stent thrombosis events, univariate predictors were initially identified and then entered into a limited Cox multivariate analysis together with stent type.

Results

A total of 1,720 patients were recruited in 3 groups of consecutive patients according to stent type and date of enrollment as BMS (n = 701; January 2000 to April 2002), SES (n = 293; April 2002 to February 2003), or PES (n = 726; February 2003 to December 2005). The overall median duration of follow-up was 1,440 days (interquartile range 899 to 1,842). Because of the sequential consecutive nature of the 3 cohorts, there were significant differences in median durations of follow-up among the groups of BMS (2,071 days, interquartile range 1,635 to 2,341); SES (1,517 days, interquartile range 1,395 to 1,610), and PES (968 days, interquartile range 748 to 1,260; p <0.001 for each comparison). Thirty-five patients (2%) were lost to follow-up. Although all patients were advised to maintain lifelong aspirin use, there were significant differences in the recommended duration of clopidogrel treatment after percutaneous coronary intervention. There were significant differences in patient demographics among the 3 groups (Table 1). Angiographic and procedural details are listed in Table 2.

There was no difference in all-cause mortality between the PES and BMS groups (Table 3; and Figure 1). However, the crude mortality rate was lower with SESs compared with both BMSs and PESs. There were no significant differences in unadjusted rates of myocardial infarction, target-vessel revascularization, target-lesion revascularization, or definite stent thrombosis among the 3 groups after 3 years (Table 3; Figure 1). The composite end point of all-cause mortality or nonfatal myocardial infarction was reached less frequently in the SES group (Figure 1). A similar reduction in the composite of all-cause mortality, nonfatal myocardial infarction, or target-vessel revascularization was also found with SESs (Figure 1). There were no differences comparing PESs with BMSs in either composite end point. Evaluation of clinical events at 7 and 30 days found a higher incidence of myocardial infarction in the SES group compared with the PES group (adjusted HR 2.69, 95% CI 1.10 to 6.57). Nevertheless, there were no differences in mortality or the composite of death or nonfatal myocardial infarction among the 3 stent types.

After multivariate and propensity score adjustment, the mortality rate in the SES group was significantly lower than in the BMS group (Table 3). The PES group had a lower rate of myocardial infarction than the BMS cohort. Both DES types were associated with significant reductions in the adjusted rate of repeated revascularization compared with BMSs, with no significant difference between the 2 DES types. The composite end point of all-cause death, nonfatal myocardial infarction, or target-vessel revascularization was reached more often in the BMS group compared with both DES groups. For this end point, there was also improved outcome with SESs compared with PESs. The 48 patients with BMSs undergoing target-lesion revascularization had no significant difference in 3-year mortality rates compared with the remaining patients with BMSs (8.3% vs 13.9%; p = 0.25). The timing of definite stent thrombosis is listed in Table 4. There were no significant

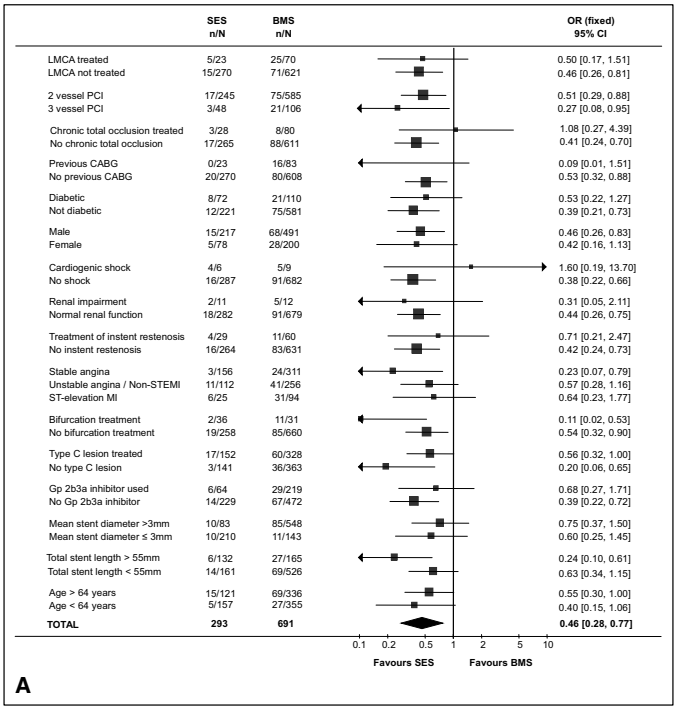

Figure 2. Comparison of the effect of different subgroups on mortality comparing *(A)* SESs versus BMSs, *(B)* PESs versus BMSs, and *(C)* SESs versus PESs. CABG = coronary artery bypass grafting; LMCA = left main coronary artery; OR = odds ratio; PCI = percutaneous coronary intervention.

differences among the 3 stent types. The only independent predictor of definite stent thrombosis was total stent length (per each extra millimeter of stent, adjusted HR 1.02, 95% CI 1.01 to 1.03, p = 0.003).

Multivariate predictors of all-cause mortality and repeated revascularization are listed in Tables 5 and 6. Use of SESs was an independent predictor of lower risk of all-cause mortality (adjusted HR 0.51, 95% CI 0.31 to 0.83). The decrease in mortality with SESs compared with BMSs and PESs was seen across most subgroups, although not always reaching statistical significance (Figure 2). Independent predictors of myocardial infarction were diabetes mellitus (adjusted HR 2.02, 95% CI 1.13 to 3.62, p = 0.02), previous percutaneous coronary intervention (adjusted HR 2.01, 95% CI 1.04 to 3.91, p = 0.04), total stent length (per each extra millimeter of stent, adjusted HR 1.02, 95% CI 1.01 to 1.02, p <0.001), and presentation with stable angina (adjusted HR 0.52, 95% CI 0.30 to 0.93, p = 0.03).

Discussion

The main finding of this single-center observational study was the significant decrease in mortality with SES use. Mortality rates were similar between the PES and BMS cohorts. Both DES types were associated with significant reductions in repeated revascularization with no excess of myocardial infarction or stent thrombosis. These results in unselected patients suggested that DESs could be used safely for multivessel percutaneous coronary intervention with reductions in clinical restenosis compared with BMSs. Furthermore, the reduction in mortality with SESs suggested that multivessel percutaneous coronary intervention with SESs may be a treatment of choice for patients with multivessel disease. Nevertheless, the absence of differences in other hard clinical end points and the relatively small number of patients in the SES group suggested that the possibility that this difference in mortality was caused by chance cannot be excluded. Treatment with BMSs was associated with similar mortality, but an increase in repeated revascularization compared with coronary artery bypass grafting in randomized trials.[2,4] The use of DESs in the setting of randomized trials reduced the need for repeated revascularization, but was not shown to have an effect on mortality.[5,18] The procedural complexity in our patients was similar to patients with BMSs and SESs in the ARTS-I and

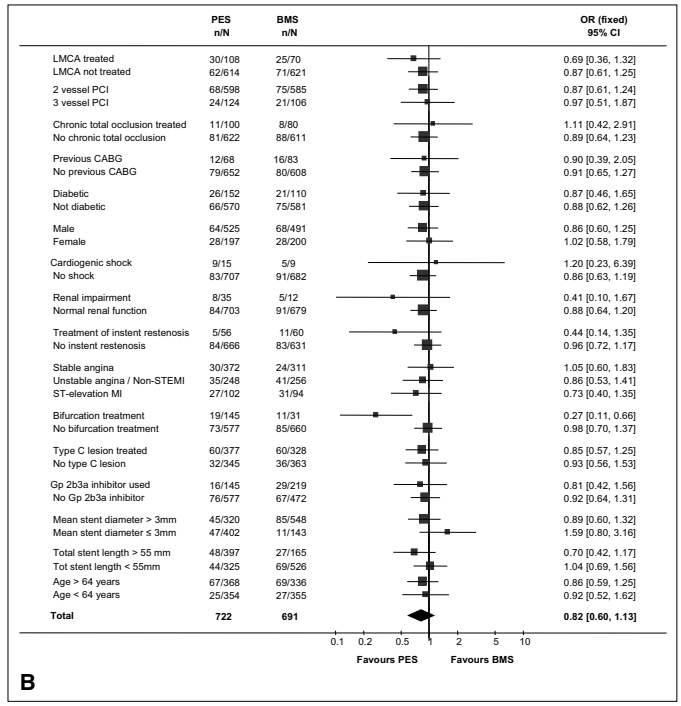

Figure 2. (*continued*)

II (ARTS BMS, 2.8 stents implanted, total stent length 47.6 mm compared with 2.7 stents and 42.3 mm in our BMS group; ARTS-II SES, 3.7 stents implanted, total stent length 72.5 mm compared with SES 3.2 and PES 3.4 stents, total stent length 60.2 mm SES and 66.6 mm PES in our patients). However the ARTS-I and II trials found no difference in mortality between patients treated with SESs and BMSs or coronary artery bypass grafting after 3 years[5] and overall had lower mortality rates (3% in the SES group of ARTS-II) than our patients (6.3% in our patients with SESs). One explanation for this difference is that patients with previous percutaneous coronary intervention, presentation with ST-elevation myocardial infarction, or left main coronary artery disease were excluded from the ARTS-I and II studies.[5] However, the 3-year rate of definite stent thrombosis in ARTS-II was 3.5%, whereas in our patients, rates were 1.4% for SESs and 1.2% for PESs. It was possible that more of our patients with stent thrombosis presented with sudden death, thus precluding them from adjudication as definite stent thrombosis. Nevertheless, we did not find an excess in all-cause mortality with either DES. It was worth noting that our 3 cohorts of patients differed in the recommended duration of clopidogrel therapy as a result of differences in recommendations at the time of implantation. Although the most recent guidelines recommend clopidogrel for 12 months after DES implantation,[19] the initial clopidogrel recommendations were for 3 and 6 months after SES and PES implantation based on the duration given in the pivotal randomized controlled trials,[20,21] respectively.

The overall role of DESs in patients with multivessel disease is currently being investigated in the Synergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) Study, a prospective, multicenter, multinational, randomized clinical trial with an all-comers design recruiting patients with de novo 3-vessel or left main disease.[22]

Previous studies have raised concerns about the suitability of percutaneous coronary intervention in diabetic patients with multivessel disease,[23] and these patients therefore deserve extra attention. More recently, in a single-center observational study of 1,680 patients undergoing either DES implantation or coronary artery bypass grafting for multivessel disease, although the adjusted adverse clinical event rates for the nondiabetic subpopulation were equivalent, the diabetic subgroup had higher event rates compared with coronary artery bypass grafting (2 vessel disease HR 2.29, $p = 0.01$; 3 vessel disease HR 2.9, $p < 0.001$).[9] In our patients, diabetes mellitus was an inde-

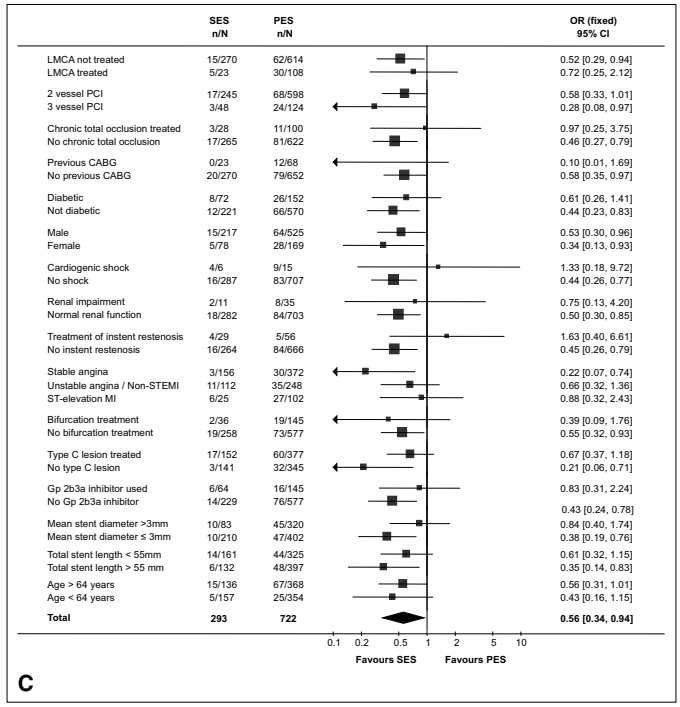

Figure 2. (*continued*)

pendent predictor of mortality and repeated revascularization. Additional information about the optimal treatment for diabetic patients with multivessel disease will be known with the results of 2 ongoing randomized trials comparing DESs with coronary artery bypass grafting in diabetic patients with multivessel disease: the Coronary Artery Revascularization in Diabetes (CARDIA trial, 600 patients) and the Future Revascularization Evaluation in Patients with Diabetes Mellitus; Optimal Management of Multivessel Disease (FREEDOM trial, 2000 patients).[24,25]

In a recent large observational study (n = 17,400) from the New York State registries, at 18 months, coronary artery bypass grafting was reported as being associated with lower mortality rates than treatment with DESs. However, 18-month survival rates for patients with 3-vessel disease (unadjusted 93.7% vs 93.4%, p = NS; adjusted 94.0% vs 92.7%, p = 0.03) and 2-vessel disease (unadjusted 95.0% vs 94.9%, p = NS; adjusted 96.0% vs 94.6%, p = 0.003), actual survival rates were similar.[26] The investigators of this study attempted to adjust for an unadjustable characteristic, the judgment of the treating physician, which is uncorrectable by adjusting for clinical variables. Despite the lack of exclusion criteria, our patients were also selected for multivessel percutaneous coronary intervention based on patient and angiographic factors and after multidisciplinary discussion between interventional cardiologists and cardiac surgeons. This selection poses difficulties for comparison with coronary artery bypass grafting. Nevertheless, although both DESs reduced repeated revascularization, our results suggested a reduction in mortality with SESs, indicating that these might be the preferred stents for patients undergoing multivessel percutaneous coronary intervention.

This was a single-center observational study, and the patients included were not randomly assigned. Nevertheless, these unselected patients represented real-world practice, whereas patients enrolled in clinical trials were carefully selected.[27] Furthermore, although there were significant differences between cohorts, the use of single stent types at any 1 time eliminated some bias, for example, of treating higher risk patients with DESs. There were significant differences between cohorts in a number of baseline and procedural characteristics, including clinical presentation and the incidence of left main disease. We attempted to account for this by using propensity scores, although we acknowledge there was no consensus method for adjusting for these differences.

Acknowledgment: We acknowledge the senior cardiologists involved in the percutaneous coronary intervention procedures: E. McFadden, MD, PhD; P.J. de Feyter, MD, PhD; P.P.T. de Jaegere, MD, PhD; S.H. Hofma, MD, PhD; E.Regar, MD, PhD; G. Sianos, MD, PhD; P.C. Smits, MD, PhD; M.J. van der Ent, MD, PhD; W.J. van der Giessen, MD, PhD; and C.A. van Mieghem, MD.

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CHAPTER 15

Four-year safety and efficacy of the unrestricted use of sirolimus- and paclitaxel-eluting stents in coronary artery bypass grafts

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EuroIntervention. 2008 Nov; 4(3): 311-317.

EuroIntervention

Four-year safety and efficacy of the unrestricted use of sirolimus- and paclitaxel-eluting stents in coronary artery bypass grafts

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The authors have no conflicts of interest to declare.

KEYWORDS
Bypass graft, drug-eluting stent, bare-metal stent, long-term safety

Abstract

Objectives: Recently, concerns were raised about the relative long-term safety and efficacy of drug-eluting stents (DES) in saphenous vein bypass grafts (SVG). Our objective was to assess the 4-year relative safety and efficacy of the unrestricted use of drug-eluting stents (DES) as compared to bare metal stents (BMS) in saphenous vein bypass grafts (SVG).

Methods: Between April 16, 2002 and December 2005 a total of 122 consecutive patients were treated with either sirolimus- or paclitaxel-eluting stents for saphenous vein graft disease. These patients were compared with 128 consecutive patients treated with BMS in the immediate preceding period (January 1, 2000 to April 2002).

Results: At 4-years the cumulative survival rate in the DES group was 77.5% versus 73.0% in the BMS group (adjusted HR 1.09; 95% CI 0.63-1.90, Logrank p=0.65). The cumulative survival free of major adverse cardiac events (MACE: death, myocardial infarction and target vessel revascularisation) was 61.5% vs. 46.8% in the DES and BMS groups respectively (adjusted HR 0.77, 95% CI; 0.51-1.16) due to a higher event free survival of clinically driven target vessel revascularisation in the DES group as compared to the BMS group (81.6% vs. 69.0%; adjusted HR 0.53; 95% CI 0.27-1.05).

Conclusions: In the present study, the use of DES for SVG PCI was associated a similar safety profile and there was a trend towards lower rates of TVR and MACE at four years as compared to BMS.

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Introduction

Saphenous vein grafts are the commonest conduit in coronary artery bypass graft surgery (CABG).[1] However, the lifespan of saphenous vein grafts (SVG) proved to be limited – at 10 years, 50% of such grafts contain at least one significant stenosis with a total occlusion rate of up to 40%.[2,3]

Currently the use of drug eluting stents (DES) for off-label indications is frequent (up to 60 % in our centre) and PCI has surpassed CABG as the treatment of first choice for treating coronary artery bypass graft disease.[4,5] Still, event-free survival after stent implantation remains low due to restenosis at the lesion site.[6-8] The use of DES in SVG lesions has led to a decrease in restenosis and the need for repeat revascularisation at one year as compared to bare metal stents (BMS).[9-11]

Currently there is still scarce evidence about the long-term safety and efficacy of DES when used in coronary artery bypass grafts. The recently published 32-months follow-up of the Delayed Reduction of Restenosis In Saphenous Vein Grafts With Cypher Sirolimus-Eluting Stent (RRISC) trial showed a catch-up in the repeat revascularisation rates in patients treated with sirolimus-eluting stents (SES).[12] Moreover, the authors reported a significant increase in late mortality in patients treated with SES as compared to those treated with bare metal stents (BMS).[12]

The current study was performed to assess the long-term outcome of a consecutive series of patients treated with BMS, sirolimus- or paclitaxel-eluting stents (SES and PES respectively) for lesions in venous bypass grafts.

Methods

Patient selection

Between January 1, 2000 and December 31, 2005 a total of 387 percutaneous interventions were performed in our institution using BMS, SES or PES in coronary bypass-graft lesions (arterial or venous bypass grafts) (Figure 1). A total of 62 procedures were excluded due to treatment restricted to balloon angioplasty (n=35) or the use of (previous) brachytherapy (n=27). Two patients received a Symbiot™ Covered Stent and were also excluded. Out of 323 procedures selected, 298 involved the treatment of saphenous vein grafts and in 25 procedures arterial grafts were treated. From January 2000 until April 16th 2002, 144 PCI procedures in a venous bypass-graft were performed using exclusively BMS, from April 16, until December, 2005, 154 procedures were performed using either sirolimus-eluting stents (Cypher®, Cordis Corp., Johnson & Johnson, Warren, NJ, USA) or using paclitaxel-eluting stents (TAXUS™ Express2™ or Liberté™, Boston Scientific, Natick, MA, USA).

Patients initially enrolled in one of the sequential cohorts (BMS or DES) were maintained for analytical purposes throughout the follow-up period in their original cohort, even if a repeat intervention was performed using a different type of stent at a later stage. Finally, 250 patients fulfilled these criteria.

This study was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

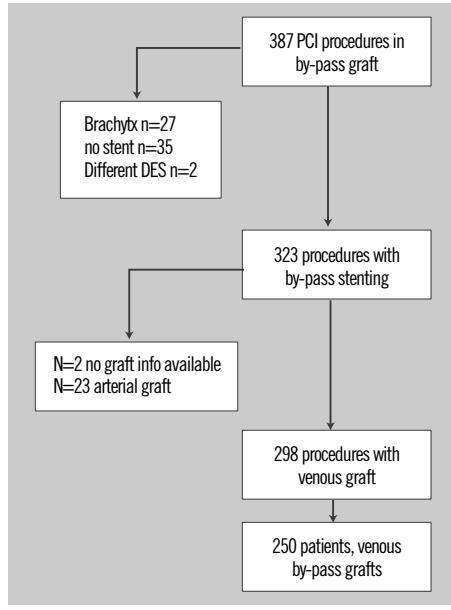


Figure 1. Inclusion flow chart of study population.

Procedural and baseline definitions

All procedures were performed following previously defined current standard procedural guidelines.[13] The use of distal embolisation protection devices and periprocedural glycoprotein IIb/IIIa inhibitors were left to the operator's discretion. Finally, the use of distal protection devices was low (4.7% in the BMS group vs. 1.6% in the DES group; p=0.28).

Patients were prescribed aspirin plus clopidogrel 75 mg/day (after a loading dose of 300 mg) before or during baseline coronary interventions. Patients treated with bare metal stents received at least one month of clopidogrel (median, three months, IQR: 2-6 months). Patients treated with DES received at least three months of clopidogrel (median, six months, IQR: 6-6 months). All patients were advised to remain on aspirin indefinitely.

Hypertension was defined as a blood pressure ≥ 140 systolic or ≥ 90 mm Hg diastolic or based on the current use of antihypertensive treatment. Dyslipidaemia was classified as a total serum cholesterol level of ≥ 6.2 mmol/l or the use of lipid lowering drugs. Diabetes was defined as treatment with either oral hypoglycaemic agent, insulin or through diet. Complete procedural success was defined by the achievement of <50% diameter stenosis (visual assessment) and Thrombolysis in Myocardial Infarction (TIMI) grade flow 3 in all lesions intended to treat. Clinical success was defined as procedural success without death or re-infarction during the index hospitalisation.

Endpoint definitions and clinical follow-up

Our primary endpoint was MACE (major adverse cardiac events; defined as a composite of all-cause death, myocardial infarction [MI] and target vessel revascularisation [TVR]) at 4-years. Secondary endpoints included the itemised outcomes all-cause death, MI and TVR at 4-years. MI was defined as creatinine kinase-MB enzyme elevation ≥ 3 times the upper limit of normal. TVR was defined as a clinically driven (presence of clinical symptoms and/or signs of ischaemia) repeat revascularisation procedure (either percutaneous or surgical) of the index graft. Stent thrombosis (ST) was defined as angiographically defined thrombosis with TIMI grade 0 or 1 flow or the presence of a flow limiting thrombus, accompanied by acute symptoms, resembling the ARC definite criteria.[14,15]

Survival status was obtained from municipal registries. Cause of death was acquired via the Central Bureau of Statistics, The Hague, The Netherlands and classified according to the international Classification of Diseases and Related Health Problems, 10th revision (ICD-10).[16] Questionnaires inquiring about patients current health status, and medication use were subsequently sent to all living patients. Events (MI, TVR) that occurred outside our institution were verified by contacting the peripheral hospital. Finally, follow-up was available for 98.4% of the BMS patients and 95.9% of the DES patients.

Statistical analysis

Summary statistics for all continuous variables are presented as medians together with the interquartile range (IQR). Categorical data are summarised as frequencies and percentages. Continuous variables were compared using the Mann-Whitney U test. Categorical variables were tested for significance using the Chi-square or Fisher's exact test. Survival and event-free survival analysis were presented using Kaplan-Meier survival curves and tested for difference using the log-rank test. Cox proportional hazards regression models were used to control for differences between groups and independent predictors of outcome. First, all baseline, clinical and procedural variables were put in a univariate cox proportional hazards regression model for the different endpoints. Second, all significant predictors of outcome ($p<0.1$) were forced into a second model along with stent type (BMS or DES) and tested for significance. Final results are reported as adjusted Hazard ratios (HR) with their respective 95% confidence intervals (CI). All statistical tests were two-tailed. A value of $p < 0.05$ (unless reported otherwise) was used for all tests to indicate statistical significance. All statistical analyses were performed using SPSS version 12 (SPSS Inc., Chicago, Illinois).

Results

Baseline and procedural characteristics are presented in Tables 1 and 2 respectively. Baseline characteristics were similar between the two groups, except for a significantly higher incidence of family history of coronary artery disease and dyslipidaemia in the DES group as compared to the BMS group. Procedural characteristics differed in terms of a smaller average stent diameter and a longer

Table 1. Baseline characteristics.

	Bare metal stent group n=128	Drug-eluting stent group n=122	P-value
Age (years)			
median	69.3	68.3	0.19
IQR	62.4-77.2	62.4-74.7	
Male gender	80% (102/128)	84% (103/122)	0.33
BMI			0.15
Median	25.8	26.5	
IQR	23.9-28.1	24.5-29.0	
Diabetes mellitus	21% (27/128)	31% (38/122)	0.07
Dyslipidaemia	45% (57/128)	66% (81/122)	0.001
Hypertension	43% (55/128)	49% (60/122)	0.33
Family history of CAD	17% (22/128)	28% (34/122)	0.043
Current smoker	16% (21/128)	8% (10/122)	0.049
Renal impairment	2% (2/128)	5% (6/122)	0.13
Previous MI	46% (59/128)	50% (61/122)	0.23
Previous PCI	27% (34/128)	30% (36/122)	0.77
Enrolment diagnosis			0.37
Stable angina	33% (42/128)	41% (50/121)	
Unstable angina	53% (68/128)	50% (60/121)	
Acute MI	14% (18/128)	8% (10/121)	
Shock	0% (0/128)	1% (1/121)	

Table 2. Lesion and procedural characteristics.

	Bare metal stent group n=128	Drug-eluting stent group n=122	P-value
Revascularisation territory			
LAD	49% (49/127)	33% (37/111)	0.40
LCX	53% (67/127)	49% (54/111)	0.53
RCA	31% (39/127)	34% (38/111)	0.56
Native vessels treated			
LAD	10.9% (14/128)	13.1 (16/122)	0.70
LCX	10.2% (13/128)	12.3% (15/122)	0.43
RCA	12.5% (16/128)	18% (22/122)	0.38
LM	2.3% (3/128)	1.6% (2/122)	1.00
In stent restenosis	8% (10/128)	8% (10/122)	0.91
Lesion type			
A	9% (11/128)	10% (12/122)	0.73
B1	27% (34/128)	25% (30/122)	0.72
B2	37% (47/128)	40% (49/122)	0.58
C	49% (63/128)	59% (72/122)	0.12
Clinical success	97% (124/128)	98% (117/122)	0.46
Number of lesions successfully treated			0.97
Median	1.00	1.00	
IQR	1.0-2.0	1.0-2.0	
Number of treated grafts			0.92
Median	1.0	1.0	
IQR	1.0-1.0	1.0-1.0	
Number of stents per lesion			0.21
Median	2.00	2.00	
IQR	1.0-2.0	1.0-3.0	
Total stent length, mm			0.02
Median	31.9	32.0	
IQR	18.0-40.3	18.0-58.5	
Average stent diameter, mm			<0.001
Median	3.5	3.1	
IQR	3.3-4.0	3.0-3.5	
Distal protection device used	4.7% (6/128)	1.6% (2/120)	0.28
Glycoprotein IIb/IIIa inhibitors	41% (53/128)	21% (26/122)	0.001

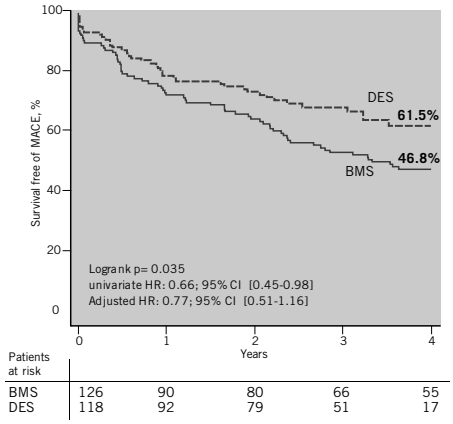


Figure 2. Kaplan Meier event free survival of major adverse cardiac events (MACE, the primary combined endpoints of all-cause mortality, myocardial infarction, and clinically driven target vessel revascularisation). DES stands for drug-eluting stent, BMS for bare metal stent.

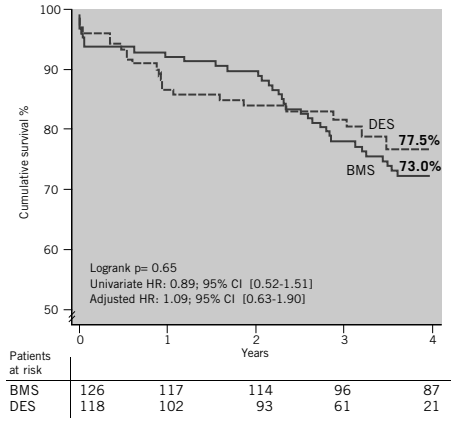


Figure 3. Kaplan Meier event free survival. DES stands for drug-eluting stent, BMS for bare metal stent, TVR for target vessel revascularisation, MI for myocardial infarction and MACE for major adverse cardiac events.

total stented length in the DES group. The use of glycoprotein IIb/IIIa inhibitors decreased over time, from 41% in the BMS group to 21% in the DES group, p=0.001). At 4-years, the cumulative survival free of MACE was 61.5% versus 46.8% in the DES and BMS groups respectively (adjusted HR 0.77, 95% CI; 0.51-1.16). [Figure 2, Table 3] A total of 57 patients died (23 in the DES group and 34 in the BMS group). The cause of death was cardiac in 15/23 (65.2%) in the DES patients and 22/34 (64.7%) in the BMS patients.

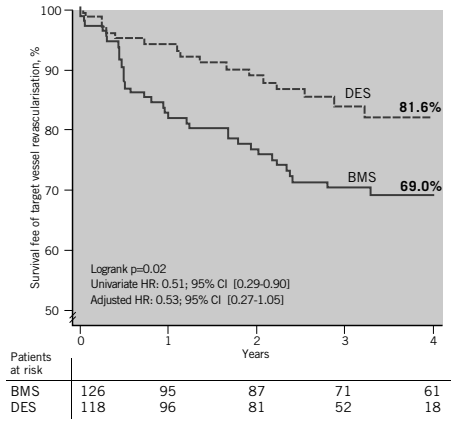
Table 3. Event rates: total, in hospital and after 4 years.

Total population (n=250)	Crude event rates		Kaplan Meier estimates		Hazard rate (95% confidence interval)
Variables	BMS (128 patients)	DES (122 patients)	BMS (128 patients)	DES (122 patients)	
In-hospital events					
Total death	2.3% (3/128)	1.6% (2/122)	2.4%	1.7%	
Cardiac death	2.3% (3/128)	1.6% (2/122)	2.4%	1.7%	
Non-cardiac death	0.0% (0/128)	0.0% (0/122)	–	–	–
Myocardial infarction	3.1% (4/128)	2.6% (3/122)	3.2%	2.5%	
Target vessel revascularisation	1.6% (2/128)	0.0% (0/122)	1.6%	–	–
Major adverse cardiac events	7.0% (9/128)	4.1% (5/122)	7.1%	4.2%	
Events at 4 years					
Death	26.6% (34/128)	18.9% (23/122)	27.0%	22.5%	1.09; 95% CI 0.63-1.90*
Cardiac	17.2% (22/128)	9.0% (15/122)	18.6%	15.1%	1.02; 95% CI 0.52-1.04*
Non-cardiac	9.4% (12/128)	6.6% (8/122)	10.4%	8.6%	1.27; 95% CI 0.50-3.17*
Total myocardial infarction	10.2% (13/128)	5.7% (7/122)	11.1%	7.6%	0.71; 95% CI 0.27-1.82**
Target vessel revascularisation	28.1% (36/128)	13.9% (17/122)	31.0%	18.4%	0.53; 95% CI 0.27-1.05***
Major adverse cardiac events	52.3% (67/128)	33.6% (41/122)	53.2%	38.5%	0.77; 95% CI 0.51-1.16¶

* Adjusted for, diabetes, revascularisation territory LAD, indication acute coronary syndrome, positive family history of coronary artery disease and age
** Adjusted for, hypercholesterolaemia, revascularisation territory LAD
*** Adjusted for, hypertension, average stent diameter, number of treated grafts, number of stents, total stented length, diabetes, age and sex
¶ Adjusted for revascularisation territory LAD, gender, hypercholesterolemia, and indication acute coronary syndrome.

the cumulative survival rate in the DES group was 77.5% versus 73.0% in the BMS group (p=0.65). When adjusting for independent predictors the HR for death in the DES group was 1.09; 95% CI 0.63-1.90). [Figure 3, Table 3] The cumulative event free survival for the combined endpoint death/MI was 70.6 % in the DES group vs. 65.8% in the BMS group (adjusted HR 1.11 95% CI; 0.68-1.81).

Cumulative survival free of clinically driven TVR was higher in the DES group as compared to the BMS group (81.6% vs. 69.0% respectively; adjusted HR 0.53; 95% CI 0.27 - 1.05). [Figure 4, Table 3] A total of five (4.0%) patients treated with BMS suffered from stent thrombosis occurring at a median of 176 days (IQR 134-731) versus only 1 (0.8%) in the DES group occurring at 606 days.



Patients at risk					
BMS	126	95	87	71	61
DES	118	96	81	52	18

Figure 4. Kaplan Meier event free survival of clinically driven target vessel revascularisation. DES stands for drug-eluting stent, BMS for bare metal stent, TVR for target vessel revascularisation.

Discussion

The present study demonstrates that the use of DES in SVG remains safe and effective as compared to BMS up to four years of follow-up, illustrated by similar survival rates and a trend towards significantly lower rates of TVR in patients treated with DES. At four years, the use of DES tended to result in lower MACE rates, mainly caused by lower repeat revascularisation rates in the first year in patients treated with DES – even though definite conclusions cannot be drawn, this is a risk reduction comparable to that observed in both the general PCI population and in SVG stenting.[9,11,17-19]

The 32-months results of the randomised Delayed RRISC trial showed a catch-up in the repeat revascularisation rates in patients treated with SES along with a significant increase in late-mortality as compared to BMS.[12] Unfortunately, the sample size of the latter study was calculated based on in-stent late loss, which explains the sample size of only 75 patients and the highly selected patient population. Patients presenting with MI, with impaired renal function, distal graft lesions, chronic total occlusions were excluded, along with those presenting with aorto-ostial or calcified lesions making the results difficult to apply in real-world clinical practice. Yet, it was difficult to question these findings given the lack of long-term data regarding the safety of DES in SVG and the presence of previously raised concerns about a catch-up in the reintervention rates in diabetics and patients presenting with ST-segment elevation myocardial infarction treated with DES.[20,21] Thus far, individual patient level data meta-analyses of the pivotal randomised Cypher and TAXUS trials were not able to address this issue given the lack of high-risk patients and larger (network) meta-analyses simply precluded subgroup analyses due to the lack of the individual patient data.[17,18,22,23] To date, large-scale registries have not yet reported on the long-term outcome in this specific patient subset.[24,25]

The present study included a total of 250 real world consecutive patients treated for SVG disease of which the vast majority did not undergo routine angiographic follow-up. At four years, both all-cause and cardiac survival were identical between the BMS and DES group and there was no sign of a catch-up in TVR rates following DES use. The importance of detailed analyses of high-risk subgroups can be demonstrated by several recent studies suggesting that DES perform best in high-risk patients, like those presenting with small vessels, long-lesions, diabetes and SVG.[24,26] Thus far, the overall benefit of DES has been widely adopted, but concerns regarding their long-term safety[17,25,27] prompted investigators to further scrutinise their data for cost-effectiveness and heterogeneity of the treatment effect. While thus far, the safety concerns seem to be unfounded, a proper patient selection might become of crucial importance given the unfavourable cost-effectiveness profile of the DES.[26]

The steep drop in the TVR-free survival in the BMS group forced us to scrutinise the indications leading to the re-interventions occurring between 100 and 260 days. Only clinically driven cases of TVR were taken account into the present analysis. Out of the 14 TVR procedures occurring at six months in the BMS group, only two were due to angiographic follow-up and were not counted in the present analysis. Out of the remaining 12 patients who underwent a repeat intervention within this time frame, eight presented with unstable angina, three with stent thrombosis and one patient presented with stable angina and had a positive stress test.

Although patients treated with DES received clopidogrel for a longer period of time, the prescribed duration of clopidogrel did not seem to impact on any of the endpoints, even when adjusting for independent predictors.

The present study has several limitations. Firstly, although the DES and BMS groups in the present study were reasonably well matched in terms of baseline and procedural characteristics, it remains uncertain whether the use of extensive regression analyses was able to fully correct for the dissimilarities between the groups. Nevertheless, the overall risk profile was greater in the DES group. Large-scale randomised trials are needed to prove the long-term benefit advantage of DES over BMS in SVG. Secondly, the drug-

eluting stent cohort contained both patients treated with SES and PES. However, no heterogeneity in the treatment effect was found regarding the use of either SES or PES.

Conclusions

In the present real world patient cohort, the use of DES for SVG lesions appeared safe and effective after 4-years of clinical follow-up. At 4-years, the use of DES tended to results in lower MACE rates as compared to BMS, due to similar survival rates and a trend towards lower rates of TVR.

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CHAPTER 16

Optical coherence tomography for the assessment of pericardium covered stents for the treatment of degenerated saphenous vein grafts

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EuroIntervention. 2010 May;6(1):78-85.

EuroIntervention

Optical coherence tomography for the assessment of pericardium covered stents for the treatment of degenerated saphenous vein grafts

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The authors have no conflict of interest to declare.

KEYWORDS
Angioplasty, stent designs, complex lesions, optical coherence tomography

Abstract

Aims: Pre- and post-interventional optical coherence tomography (OCT) assessment of degenerated saphenous vein grafts (SVG) treated with implantation of pericardium covered stents.

Percutaneous treatment of SVG represents one of the major challenges of current percutaneous coronary interventions (PCI). Artificial membrane-covered stents have failed to show additional benefit over conventional stents.

Methods and results: Six cases of PCI of *de novo* lesions in degenerated SVGs were successfully treated with a novel pericardium covered stent (PCS). Successful deployment was achieved in all cases. Large emboli were retrieved in a distal filter in one case with a long degenerated lesion. Pre- and post-interventional OCT was performed to assess the lesion characteristics and vessel diameter before stenting and the pericardium layer integrity, strut apposition and presence of plaque prolapse after stenting. In order to better understand the OCT images, three PCS of different diameters were deployed in silicone tubes of 700 µm thickness wall with inner tube diameter matching the stent diameter. OCT was repeated after spreading a thin layer of gel inside the tube, mimicking the toothpaste-like plaque observed in SVG. *In vivo* and *in vitro* OCT images excluded the presence of plaque prolapse in all but one case and detected a characteristic pattern with bulging of the pericardium between struts, possibly due to trapping of soft intraluminal plaque (or gel) behind the pericardial layer

Conclusions: These cases offer insight into the mechanism of protection against distal embolisation, elucidated by the appearance of these stents after deployment *in vivo* and *in vitro*.

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Abbreviations

BMS	bare metal stent
CABG	coronary artery bypass graft surgery
CCS	Canadian Cardiovascular Society
CK-MB	Creatine kinase MB isoenzyme
DES	drug eluting stent
EPD	embolic protection devices
LAD	left anterior descending artery
LIMA	left internal mammary artery
MACE	major adverse cardiac event
MI	myocardial infarction
MLCSA	minimal lumen cross section area
MLD	minimal lumen diameter
OCT	optical coherence tomography
OM	obtuse marginal branch
PCI	percutaneous coronary intervention
PCS	pericardium covered stent
PTFE	polytetrafluoroethylene
SES	sirolimus eluting stent
SVG	saphenous vein graft
TIMI	Thrombolysis in Myocardial Infarction
TVR	target vessel revascularisation

Introduction

Within 10 years after coronary artery bypass graft surgery (CABG), saphenous vein graft (SVG) stenosis or occlusion is observed in more than 50% of cases[1]. Percutaneous coronary intervention (PCI) of SVGs carries specific technical challenges and has a 15-20% incidence of major adverse cardiac events (MACE), mainly caused by distal embolisation. Different approaches and adjunctive pharmacological regimens have been studied, but with the exception of distal occlusion balloons and filters[2,3] which nearly halved non-Q-wave myocardial infarction (MI) to approximately 10% of patients, none have shown a clear benefit in reducing the incidence of distal embolisation. Pooled analysis from five randomised trials and one registry evaluating distal embolic protection devices (EPDs) in SVG PCI (3,958 patients) showed that angiographic measurements of the volume and linear extent of filling defects are the most powerful predictors of adverse 30-day outcomes after SVG PCI[4]. In the class with the highest quartile of plaque volume, 30-day MACE rates remained as high as 17.3%, in spite of the use of EPDs. Worse results can be expected when diffusely degenerated or completely occluded SVGs (excluded from the above trials) are treated. Furthermore, distal EPDs can be used only in selected patients without extreme tortuosity or occlusions and with a suitable landing zone for the EPD. A slight reduction of events was observed in a study using proximal balloon occlusion, but the technique is cumbersome and not suitable for ostial or very proximal lesions[5]. Data from American College of Cardiology-National Cardiovascular Data Registry showed that between January 2004 and March 2006 EPDs were used in less than 25% of 19,546 SVG PCI[6], despite class I A recommendations in PCI guidelines[7].

We describe six cases of PCI of *de novo* lesions in degenerated SVG treated with a novel pericardium covered stent (PCS, Over and Under® Pericardium Covered Stent, ITGI Medical Ltd, Or Akiva, Israel), with lesion characteristics before treatment and results after stenting assessed with optical coherence tomography (OCT).

Methods

Patients: Six consecutive patients with degenerated plaques in SVGs with highly irregular contours and intraluminal defects were treated with PCSs. The clinical, angiographic and procedural characteristics of the six patients are reported in Tables 1 and 2. Stent: The PCS consists of a stainless steel stent with 100 µm strut

Table 1. Clinical, angiographic and procedural data of 6 patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	71	65	69	80	75	62
Sex	Male	Male	Male	Male	Male	Male
CCS class	2	3	3	2	4	3
Years after CABG	22	13	15	22	10	12
LIMA-LAD	Yes	No	Yes	Yes	No	Yes
Previous PCI	No	No	No	Yes	Yes	No
Stroke	No	No	Yes, multiple	No	No	No
Diabetes mellitus	Yes	Yes	No	No	No	No
Hypertension	Yes	Yes	Yes	No	Yes	Yes
Smoking	Previous	No	Current	Previous	No	No
Other comorbidities	No	Mitral valve repair	Repair of aortic aneurysm	No	No	No
Previous myocardial infarction	No	No	No	Yes	No	No
Creatinine (µmol/L)	144	125	100	102	–	140
Glycoprotein IIb/IIIa inhibitor	No	No	No	No	No	No
Filter wire	Yes	Yes	Yes	Yes	No	No
Final TIMI flow	3	3	3	3	3	3
Periprocedural non Q-MI	+++	–	–	–	–	–

CCS class: Canadian Cardiovascular Society class; CABG: coronary artery bypass grafting; LIMA-LAD: left internal mammary artery-left anterior descending artery; PCI: percutaneous coronary intervention; TIMI: thrombolysis in myocardial infarction; CK-MB: creatine kinase MB isoenzyme; Non Q-MI: non Q-wave myocardial infarction.

Table 2. Angiographic and OCT measurements before and after PCI.

Patient	Pre-PCI					Post-PCI			
	Angiography		OCT			Angiography		OCT	
	MLD (mm)	Reference diameter (mm)	MLD (mm)	MLCSA (mm^2)	Reference diameter (mm)	MLD (mm)	MLCSA (mm^2)	MLD (mm)
1	0.9	4.8	1.1	3.1	4.6	3.2	8.9	3.3
2	1.7	3.7	1.9	4.4	3.5	3.3	9.8	3.4
3	0.7	4.7		Not done		3.3	9.1	3.4
4	1.6	3.8	1.7	3.6	3.7	3.0	7.4	3.2
5	0.94	3.2		Not done		2.4	5.3	2.5
6	1.1	2.6	1.7	2.8	3.7	2.3	-	2.04

PCI: percutaneous coronary intervention; OCT: optical coherence tomography; MLD: minimal lumen diameter; MLCSA: minimal lumen cross section area

thickness and an uniform 105 µm layer of equine pericardium cylinder made by longitudinal suture. The cylinder is placed over the external body of the stent and under the first and the last elements and then sutured to the edge rows of struts to secure the tissue at both extremities (Figure 1a).

Because of the semi-compliant balloon used for delivery, during deployment both shoulders of the balloon expand first to avoid dislocation of highly friable plaque, which thereby gets jailed between the vessel wall and the pericardium-covered scaffolding (Figure 3c). The delivery system is theoretically compatible with a 6 Fr guide catheter for the smallest diameters and lengths but 7 Fr guides are preferable. Currently, available PCS diameters are: 3.0, 3.5, 4.0 mm and lengths: 13, 18, 23, 27 mm. The PCS is packaged in a tubular container filled with sterile glutaraldehyde solution. Before implanting PCS, the stent must be rinsed in physiological saline for at least two minutes to remove the preservative prior to use. An important difference with conventional metal stents or membrane covered stents using elastic tissue fabrics is that tearing and disruption of the pericardial covering is likely if the operator exceeds the maximal recommended diameter. Since the balloon is

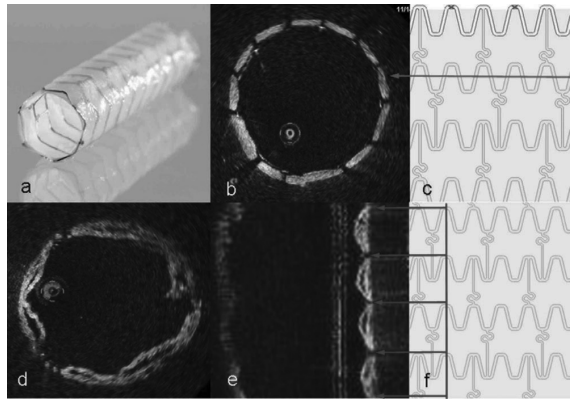

Figure 1. Pericardium covered stent. a. Fully deployed PCS. Please note that the last row of struts is attached to the pericardial membrane and sewn in three points to secure it; b. The OCT image of a 3.0 x 18 mm PCS (across the blue line) deployed within a smooth silicone tube of 3.0 mm diameter shows good apposition of the struts, with the pericardium membrane indistinguishable from the wall of the tube; c. PCS- design features (schematic); d. Same PCS deployed in the 3.0 mm silicone tube after filling it with gel. OCT image showed a hexagonal shape of PCS with bulging of the pericardium into the lumen between struts; e. In the longitudinal view- the gel filled pockets between tube and membrane are more prominent, reaching maximum thickness of 250 µm, a potential useful reservoir for the degenerated friable plaque; f. PCS- design features (schematic).

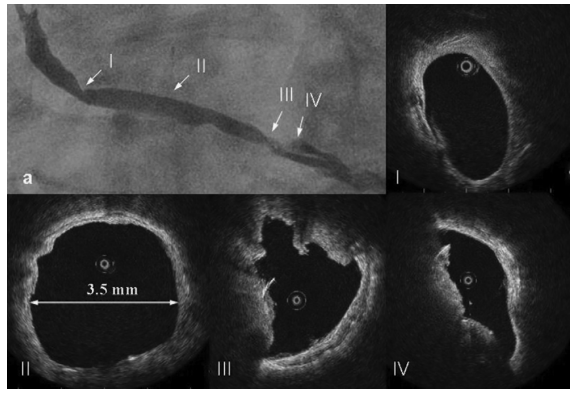

Figure 2. Degenerated SVG lesion. a. Tandem lesion in SVG to OM. The most severe and complex lesion is located in the mid-part of the SVG. OCT images showed: I. Eccentric stenosis with smooth borders of vessel wall; II. Reference segment with mild intimal thickening. The precise measurements of the vessel diameter guide selection of the PCS size[20]; III and IV. Lesion with a smooth contour and intimal thickening only in a small segment of the vessel circumference, extremely irregular, dishomogenous plaque reduces the minimal lumen area. There are no features typical for red or white thrombus and no clear visualisation of cholesterol clefts or macrophages.

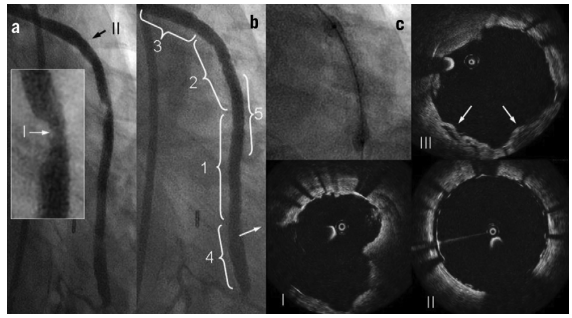

Figure 3. Treatment of SVG. a. Persistent short filling defect in the mid portion of SVG after implantation of 3 PCSs; b. Final angiographic result showing smooth contours after implantation of the 4th PCS; c. Early phase of PCS deployment, with balloon expanded at both extremities, jailing the plaque between the stent and vessel wall; OCT images showed: I. Irregular vessel borders with partially appearing stent struts; II. PCS more proximal to filling defect; III. Pericardium bulging into the vessel lumen, jailing friable plaque behind it (arrows).

semi-compliant, pressures above 8-10 atmospheres should be avoided during deployment.

OCT imaging technique: OCT is a novel imaging tool for coronary arteries characterised by high intravascular resolution (10-15 µm) but with a limited penetration of 1-1.5 mm in tissue and a maximal depth set at 4 mm. The OCT system used in this study (LightLab Imaging Inc., Westford, MA, USA) consists of a 0.006 inch fibre-optic core that rotates within a non-rotating, 0.019 inch transparent sheath. During image acquisition blood clearing is required, because red blood cells scatter the light. OCT examination was performed using a non-occlusive technique[8] with continuous flushing using iodixanol (Visipaque™, GE Healthcare Ltd, Little Chalfont, Buckinghamshire, UK) and motorised pullback at 3 mm/s. Lesion characteristics and vessel diameter before stenting and the pericardium layer integrity, strut apposition and presence of plaque prolapse after stenting were assessed.

In vitro observations: In order to better understand the *in vivo* OCT images, three PCSs of different diameters were deployed in silicone tubes of 700 µm thickness wall with inner diameters matching the stent diameters. OCT evaluation was prepared before (Figure 1b) and after spreading a thin layer of ultrasound gel (Aquasonic 100; Parker Laboratories Inc., Fairfield, NJ, USA) inside the tube. (Figure 1d). The cross section images showed a good apposition of the PCS to the tube and the pericardium bulging into the lumen between struts (Figures 1d,e), an appearance similar to the *in vivo* images (Figure 3, III).

Case 1

Angiography showed a diffusely degenerated SVG to an obtuse marginal branch (OM) with highly irregular contours and multiple intraluminal filling defects in different views, highly suggestive of thrombus (Figure 2a). OCT showed protruding plaque with irregular contours, but no material with the characteristics described by Kume at al[9] as pathognomic for red or white thrombus (Figure 2 III-IV). After insertion of a filter wire (FilterWire EZ™, Boston Scientific, Natick, MA, USA), three PCSs (4 x 23 mm; 3.5 x 18 mm; 3.5 x 23 mm) were directly implanted without predilatation at 14 atmospheres, leaving generous margins beyond the segment of degeneration, while a MGuard™ mesh covered stent (Inspire-MD, Tel Aviv, Israel) was implanted in the more regular, concentric, fibrous lesion near the ostium of SVG. In the mid-portion of the three deployed PCSs, a persistent short filling defect was observed at angiography (Figure 3a) and confirmed with OCT to have the same characteristics of the pre-existing plaque (Figure 3 I). After an unsuccessful attempt to retrieve it using a PRONTO™ thrombectomy catheter (Vascular Solutions, Inc., Minneapolis, MN, USA), a fourth PCS (3.5 x 23 mm) was inserted and slowly deployed, ensuring full expansion of both edges of the balloon before final stent expansion (Figure 3c). There was a good angiographic result with TIMI 3 flow (Figure 3b). The OCT appearance post PCI confirmed good strut apposition without plaque protrusion (Figure 3 II).

Removal of the filter showed multiple yellowish fragments (Figure 4a). Histology of these fragments showed that they were composed mainly of amorphous matrix, fibrin and embedded cholesterol clefts surrounded by macrophages highlighted by immunostaining with CD68 antibodies (Figure 4b-d). Routine postprocedural blood tests revealed a moderate postprocedural rise of myocardial necrosis markers, although the patient did not suffer any chest pain and there were no ECG changes.

Case 2

Angiography was consistent with a complex, irregular lesion with a filling defect in the proximal segment of a SVG to the left anterior descending artery (LAD) (Figure 5a). Pre-interventional OCT showed a smooth eccentric plaque (Figure 5 I). Direct implantation of 4.0 x 23 mm PCS at 8 atmospheres was performed followed by postdilatation with a 4.0 mm short non-compliant balloon at 16 atmospheres. There was a good angiographic result with TIMI 3 flow (Figure 5b). OCT image confirmed good apposition of the PCS with exception at the proximal edge where focal underexpansion was visible (Figure 5 III).

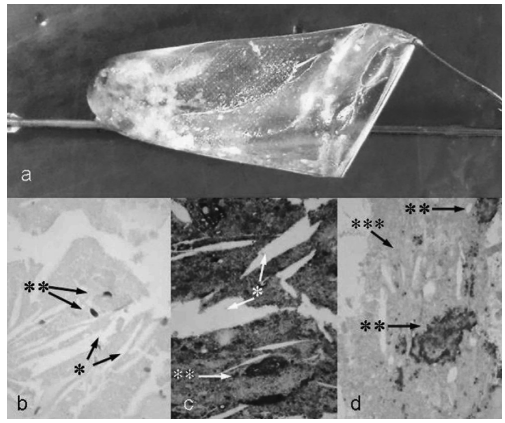

Figure 4. Histological examination. a. Filter wire (FilterWire EZ™, Boston Scientific, Natick, MA, USA) retrieved post-stent deployment, showing multiple yellowish fragments at the end of the procedure; b. Histology showed cholesterol clefts (*) surrounded by macrophages (**) (haematoxylin and eosin staining); c. Immunostaining with antibodies to CD68 delineates better swollen foamy macrophages (**) surrounding the cholesterol clefts (*) embedded in an amorphous, necrotic plaque; d. Immunostaining for fibrinogen highlights fibrin (***) admixed with macrophages (**).

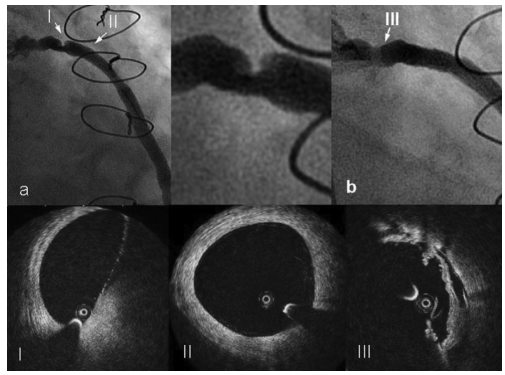

Figure 5. Lesion in SVG. a. Short eccentric lesion with highly irregular contour in proximal segment of SVG to LAD; b. Final angiographic result. Despite aggressive postdilatation up to 16 atm. with non-compliant balloon of 4.0 mm in diameter after PCS deployment focal underexpansion is obvious I. OCT image showed an eccentric lesion; II. Reference vessel segment with a regular lumen 3.5 mm in diameter; III. OCT image confirmed focal underexpansion at the proximal edge of PCS.

Case 3

A proximal complex severe stenosis of a SVG to OM (Figure 6a) was predilated with a 2.0, 2.5 and 3.0 mm non-compliant balloon, advanced over a filter wire (FilterWire EZ™, Boston Scientific, Natick, MA, USA). The balloon expanded well, but because of extreme wall recoil, two attempts of advancing a 4.0 x 27 mm PCS had to be aborted. Despite an 8 Fr Amplatz left 1 guide catheter, two buddy wires including a Choice PT extra support and further predilatation, acute recoil always prevented passage of the PCS. A 4.0 x 27 mm PCS could be advanced only after implantation of a Vision stent (4.0 x 12 mm) to prevent acute recoil. After postdilatation with a 4.0 mm noncompliant balloon, there was a good final angiographic result with TIMI 3 flow (Figure 6b). Final OCT confirmed good strut apposition (Figure 6c).

Case 4

Angiography revealed proximal eccentric lesion in SVG to OM (Figure 7a). Pre-interventional new generation of OCT: Optical frequency-domain imaging (OFDI) showed smooth lesion borders along major part of the circumferential contour and deep fissure. MLA measured 3.6 mm^2 (Figure 7 I). Vessel diameter of healthy looking segment just distal to the lesion measured by OFDI was

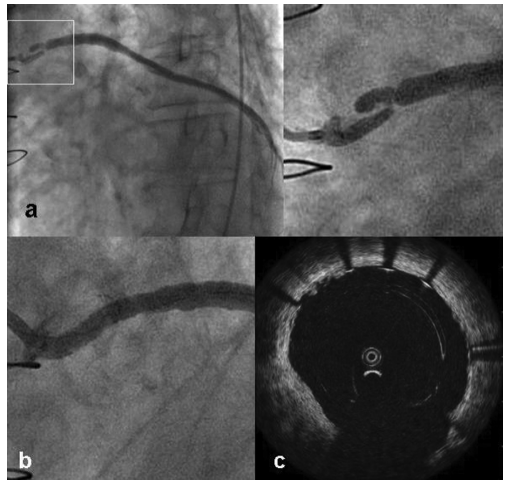

Figure 6. Lesion in SVG. a. Complex severe stenosis at the very proximal part of SVG to OM; b. Final angiographic result; c. Good strut apposition in OCT image.

3.7 mm (Figure 7 II). Direct implantation of 4.0 x 13 mm PCS at 10 atmospheres was performed. During stent deployment there was visible balloon modelling over the resistant lesion (Figure 7b). Postdilatation was performed with a 4.0 mm non-compliant balloon at 19 atmospheres (Figure 7c) with good final angiographic result (Figure 7d). Post-interventional OFDI confirmed good strut apposition (Figure 7 III) with MLA of 7.4 mm^2 and without plaque protrusion.

Case 5

Angiography of a 10-year-old SVG to LAD demonstrated recurrent atherosclerotic disease in the proximal segment of the graft. Two years ago this was treated with drug eluting stent (DES)-TAXUS, but in-stent restenosis occurred. OCT showed a minimal lumen diameter (MLD) of 0.94 mm. After predilatation with a non-compliant 3.0 and 3.5 mm balloon (Mercury NC, Abbott, Abbott Park,

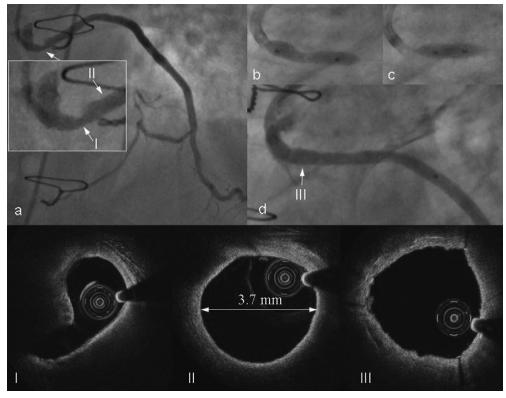

Figure 7. Treatment of SVG to OM. a. Lesion located in the proximal in the proximal segment of the graft; I) OFDI at the level of MLD showed smooth circumferential contour with deep fissure; II) Vessel diameter of healthy looking segment just distal to the lesion measured by OFDI was 3.7 mm; b. Visible modelling of the stent balloon during deployment over the resisting plaque; c. Postdilatation with non-compliant balloon; d. Final angiographic result; III) Well apposed stent struts without protruding plaque.

IL, USA) PCS (3.5 x 20 mm) was implanted at 10 atmospheres. After additional postdilatation with the same 3.5 mm balloon MLD increased to 2.5 mm (by OCT). OCT demonstrated no plaque protrusion but some underdeployment due the multiple layers of stent struts and the inability to maximally dilate with non-compliant balloon to 20 atm.

Case 6

Angiography revealed a significant lesion between the first and second anastomosis of a jump SVG to OM and posterolateral branch. Direct stenting with a 2.5 x 20 mm PCS (deployed at 10 atm) showed a good angiographic result with a residual diameter stenosis of 18%. OCT imaging showed no plaque protrusion. Initial MLD of 0.74 mm increased to 2.3 mm.

There were no further adverse cardiac events after a mean follow-up of three months in four of the six cases. Patient number four suffered from in-stent restenosis after three months and this was treated with implantation of DES (TAXUS). Patient number five, with serious under-expansion due to multiple overlapping stent struts, suffered again from in-segment restenosis after two months, this time treated with a DES (XienceV).

Discussion

Covered stents using polytetrafluoroethylene (PTFE) membranes were designed to entrap friable degenerated plaque against the graft wall. But the promising preliminary observations[10] were not confirmed by large randomised trials[11,12]. The SYMBIOT III randomised multicentre trial compared a self-expanding PTFE-covered stent with commercially available bare metal stents (BMS) in 400 SVG patients. There was no difference in the incidence of MACE between both groups (30.6% Symbiot, 26.6% BMS, P=0.43)[13].

Two covered stents were extensively studied in SVGs. The PTFE-covered stent required very aggressive dilatation pressures (>18 atmospheres) for expansion because the PTFE membrane was thick and sandwiched between two stents. The self-expanding SYMBIOT stent had poor control of positioning due to the cumbersome deployment mechanism which favoured upward displacement of friable plaque during expansion, a possible cause of the frequent proximal edge restenosis.

Because of the negative results of all the randomised studies (RECOVERS, STING, SYMBIOT III), covered stents were withdrawn or their use was limited to the treatment of aneurysms or acute vessel rupture.

These preliminary observations indicate that the PCS are applicable in degenerated SVG lesions. The low pressure expansion required to prevent membrane damage and the uneven initial expansion limited to the edges are beneficial features in the treatment of degenerated SVG lesions, preventing squeezing of debris downstream.

Unlike for most native coronary lesions, there is still no convincing proof of better long term outcome with DES in SVG PCI[14-16]. In the randomised DELAYED RRISC trial with 75 patients undergoing SVG PCI using sirolimus eluting stents (SES) or BMS, the rates of target vessel revascularisation (TVR) at 32 months were not significantly different: 34% for SES vs. 38% after BMS (P=0.74). Periprocedural MIs were more frequent (18 vs. 5%, NS) and mortality significantly higher in the SES group (29 % vs. 0 %, P<0.001), with one death caused by definite very late stent thrombosis and three sudden deaths, possibly because of the higher MI rate[17].

Direct stenting is also possibly beneficial to trap plaques at risks[18], but in our series it was possible only in four lesions, which were not very severe. PCSs have a high profile compared to conventional stents and the difficulties in delivery observed in the third case call for further miniaturisation of the device.

Postdilatation may also cause plaque debris release, but we did not observe flow impairment after postdilatation of PCS. In a small study comparing PTFE-covered stents vs. BMS, Blackman et al reported that in the PTFE group, distal embolisation occurred only in two cases after initial stent implantation; in the remaining seven patients it was seen only after postdilatation (P=0.05)[19], possibly due to squeezing of the plaque from the covered stent. The pockets of elastic pericardium protruding into the lumen (Figure 1d) may represent a reservoir for storage of the incompressible, friable, necrotic plaque. This sequestration of debris in multiple pericardium cells is very different from the situation observed with PTFE covered stents, acting as cylinders lying on the degenerated plaque. Long-term follow-up of the PCS is required to determine whether the more biocompatible equine pericardium also serves as a possible barrier to smooth muscle cell migration, thus reducing restenosis rates.

OCT was instrumental, both *in vivo* and *in vitro*, for elucidating the stent mechanism. OCT was also practically helpful in guiding the procedure, assessing the diameter of the vessel (an essential measurement to select a device with a limited range of expansion), the length of the degenerative lesions, complete apposition and presence of residual plaque protrusion. To our knowledge this is the first report of an OCT study in SVGs, because the traditional method of blood displacement using balloon occlusion was not suitable for use in large vein grafts. The thin OCT imaging wire advanced via an OTW microcatheter has a low risk of plaque displacement and offers excellent visualisation of superficial plaques. OCT ruled out thrombi as the cause of the angiographic intraluminal defects, a diagnosis otherwise impossible with angiography or IVUS.

Limitations

The optimal duration of double antiplatelet therapy after PCS implantation is unknown.

There is also the possibility that the high-profile PCS (0.0669 in.) may lead to significant distal embolisation when crossing the target lesion[5]. Therefore, PCS should be considered not as an alternative to EPD, but an additional device to reduce massive embolisation overloading EPD and to prevent late dislodgement of friable plaques in the first hours after stenting, for which EPDs are of no value, as shown in carotid stenting by the development of strokes and TIAs minutes or hours after deployment.

Currently the largest available PCS is 4.0 mm in diameter, expandable to a maximum of 4.56 mm without risk of membrane rupture. In many venous grafts this may be insufficient. Our aggressive deployment pressure in case one may have damaged the pericardium, which has a limited distensibility and led to the plaque protrusion treated with an additional PCS

Conclusions

These cases of OCT guided PCS for degenerated SVG lesion offer insight into the mechanism of protection against distal embolisation, elucidated by the appearance of these stents after deployment *in vivo* and *in vitro*.

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CHAPTER 17

Optical coherence tomography assessment of a new dedicated bifurcation stent

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Eurointervention 2009 Nov; 5:544-551.

EuroIntervention

Optical coherence tomography assessment of a new dedicated bifurcation stent

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The authors have no conflict of interest to declare.

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KEYWORDS
Bifurcation, percutaneous coronary intervention, optical coherence tomography, Tryton

Abstract

Aims: Dedicated bifurcation stents should facilitate deployment and improve coverage of bifurcational lesions. We used optical coherence tomography (OCT) to assess bifurcation lesions treated with a dedicated stent implanted in the side branch (SB) in conjunction with drug eluting stents in the main vessel (MV) in a culotte-like fashion.

Methods and results: Nine patients treated with the Tryton stent underwent postprocedural OCT examination. Total percent of malapposed struts per patient was 18.1±8.7%. The longitudinal distribution of the percent of malapposed struts per patient showed that the prevalence of malapposed struts was significantly higher at the level of the bifurcation (33.3%), than in both the proximal segment and the distal segment (18.5% and 9.8%, respectively, p=0.011). When the bifurcation was divided into two halves (opposite SB and toward SB), the highest percent of malapposed struts was toward the SB (47.6%). Also the wall-strut distance for malapposed struts was significantly higher in the bifurcation half toward the SB than in the proximal and the distal segment.

Conclusions: Malapposed struts are frequent in bifurcations despite the use of a dedicated stent. The highest frequency and largest vessel wall–stent strut distance are observed in the bifurcation half toward the SB.

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Abbreviation list

DES	drug eluting stent
IQR	interquartile range
IVUS	intravascular ultrasound
KB	kissing balloon
MLA	minimal lumen area
MV	main vessel
OCT	optical coherence tomography
QVA	Quantitative vascular arteriography
SB	side branch
SD	standard deviation
UFH	unfractionated heparin

Introduction

Drug eluting stents (DES) reduce restenosis in coronary bifurcations[1], but concerns remain regarding a higher incidence of stent thrombosis[2] which may be explained by the increased prevalence of malapposed stent struts[3]. When intimal hyperplasia is negated by a powerful antiproliferative coating, malapposition may persist for years after implantation and create an increased risk of late stent thrombosis[4]. In principle, a single stent approach does not provide as good a scaffolding for the whole bifurcation as other techniques of double stenting. However, when universal double stenting has been compared with a single stent approach in randomised trials, results have been neutral or in favour of single stenting[1,5-7].

Intravascular ultrasound (IVUS) analyses have specifically excluded bifurcation segments from the assessment of incomplete stent apposition[8,9], because the prominent artifacts generated by the stent struts and the low resolution of the technique preclude detailed assessment of the complex geometry of a bifurcation. Optical coherence tomography (OCT), due to its high spatial resolution, allows accurate evaluation of strut apposition and assessment of the ostium of the bifurcation during a single pull-back in the main vessel (MV)[10].

The Tryton-Side Branch Stent™ (Tryton Medical, Inc., Newton, MA, USA) is a dedicated bifurcation stent (Figure 1), designed to be implanted in the side branch (SB) of bifurcations in conjunction with a conventional DES in the MV in a culotte-like fashion[11]. Because of large openings in the transition zone, and a proximal segment with few sparse struts designed to fix it in place proximally, the Tryton stent has the potential to reduce malapposition.

The aim of this study was to assess strut apposition by OCT in a bifurcation lesions treated by implantation of a Tryton stent using a modified culotte technique.

Methods

Study population

All consecutive patients, who underwent postprocedural OCT examination after Tryton stent implantation for the treatment of bifurcational lesions between March 2007 and October 2008 were included in the study (n=9).

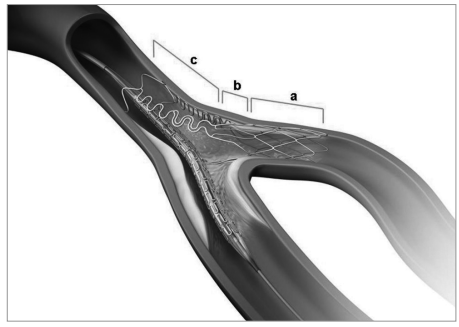

Figure 1. Tryton stent. There are three zones: a- side branch, b- transition, c- main vessel.

Pharmacological treatment and procedural devices

Before the procedure, all patients were pretreated with aspirin and 300 or 600 mg of clopidogrel. During the procedure unfractionated heparin (UFH) or bivalirudin was used: UFH was given to maintain an activated clotting time ≥250 seconds with an initial bolus of 70 IU/kg, whilst bivalirudin was given according to the patient's body weight. Administration of glycoprotein IIb/IIIa inhibitors was at the operator's discretion. In all cases, 6 Fr guiding catheters were used. High pressure or cutting balloon predilatation as well as postdilatation with a high pressure balloon and kissing balloon (KB) postdilatation were performed in all cases.

Stent design and implantation

The Tryton Side-Branch Stent™ is a cobalt-chromium stent designed for bifurcation lesions[11]. It consist of three zones: I-side branch (length: 6 mm), II-transition (length: 4 mm), III-main vessel (length: 8 mm). There are two stent delivery systems. In all the cases except for one we used the stepped balloon system, which has an inflated geometry that corresponds to the three Tryton stent zones with following distal/proximal diameters: 2.5/3.5; 3.0/3.5; 3.0/4.0; 3.5/4.0 mm at nominal inflation pressure[11]. The strut thickness is 0.0033" (84 μm).

The Tryton stent was implanted using a modified culotte technique: two guidewires are advanced into the SB and the MV. The Tryton stent is then introduced into the SB and subsequently aligned using transition zone markers (Figure 2) and deployed. After withdrawal of the stent delivery balloon, the guidewire is switched from the SB into MV without withdrawing it behind the connecting ring in the MV in order to avoid crossing between the connecting ring and MV wall. The second stent (always a drug eluting stent in this series) is then advanced into the distal MV through the wide space between the proximal fronds of the Tryton stent followed by rewiring and final KB. The first successful implantation of this stent with post-procedural OCT examination has recently been reported[12].

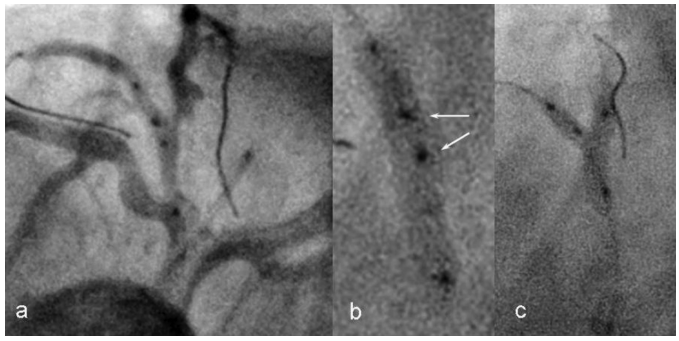

Figure 2. a) Positioning of the Tryton stent. There are two visible points of the transition zone in the middle part of the stent (arrows on Figure b), at the level of the SB ostium, b) Tryton stent during deployment, c) Kissing balloon post-dilatation.

Quantitative angiographic analysis

All bifurcation lesions were classified according to the Medina classification[13].

Quantitative vascular arteriography (QVA) was performed using dedicated software (QAngio XA 7.1, Medis Medical Imaging System, Leiden, The Netherlands), as previously described[14].

Bifurcation angles were measured off-line using the CardiOp-B® software package (Paeion Inc, New York, NY, USA). This system enables 3D reconstruction of coronary arteries using two or three standard angiographic views, provided that they are at least 30° apart (Figure 3c). Bifurcation angle measurement included both the angle between the proximal MV and the SB as well as the angle between the distal MV and the SB and was possible in all nine cases.

OCT imaging technique

In this study, an end-hole microcatheter (0.021" Transit™, Cordis Neurovascular, Miami Lakes, FL, USA) was advanced distal to the lesion in the MV over a conventional guidewire, which was then exchanged for the OCT imaging wire. OCT image acquisition (LightLab Imaging Inc. Westford, MA, USA) was performed using a non-occlusive technique[15] with continuous flushing using a power injector (2-5 ml/sec) of iodixanol (Visipaque™, GE Healthcare, UK)

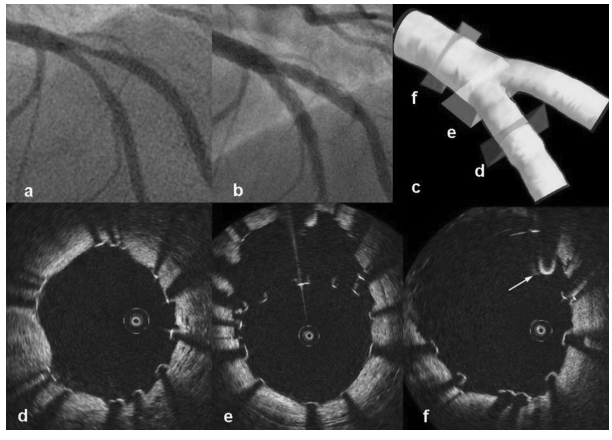

Figure 3. a) Bifurcation lesion involving the left anterior descending artery and diagonal branch (Medina classification: 0,1,1), b) Angiographic result after deployment of a Tryton stent in the SB and DES in the MV, c) Artificial reconstruction of the bifurcation by CardiOp-B® software with corresponding OCT images (d-f). OCT cross sections: d) Distal MV- there are visible single malapposed struts; e) Bifurcation just proximal to carina- malapposed struts creating a metallic neo-carina; f) Proximal MV- there are visible single malapposed struts and guidewire (arrow).

at a pullback speed set at 3 mm/sec. Image acquisition over 30 to 35 mm vessel segments was performed without complication.

OCT image analysis

Cross-sectional images were analysed every 450 microns. Since the strut alloy is opaque to infrared light, stent struts were defined as malapposed if the distance between the luminal surface of the strut and the vessel wall was greater than the thickness of the strut (metal + polymer) plus an additional 15 microns (because the OCT spatial resolution is 10-20 microns)[16]. The thickness of stents used in the study are as follows: Cypher Select 154 μm, Taxus Liberte 127 μm, Endeavor Resolute 95 μm, Xience V 88 μm[16]. Strut apposition was assessed in three segments: proximal MV segment (extending up to 8 mm from the first cross-section when the SB is visible), bifurcation (divided into two 180 degrees halves towards or opposite the origin of the SB) (Figure 4), and distal MV segment (extending up to 4 mm from the last cross-section when the SB is visible) (Figures 3-6). At the level of bifurcation and in the proximal segment there are two different types of stents with different strut thickness- the MV stent and the SB Tryton stent. Since it is impossible to distinguish if malapposed struts (especially at the bifurcation level) are from the MV stent or from the Tryton stent, strut malapposition was calculated on the basis of the MV stent type and strut thickness. The number of fronds of the Tryton stent in the transition zone is minimised and in the proximal part is limited only to three. Secondly, the Tryton stent is the outer stent and the inner stent is the MV stent. That means that the most likely the malapposed struts are from the MV stent. All distances were measured in perpendicular cross-sections from an OCT pullback in the MV.

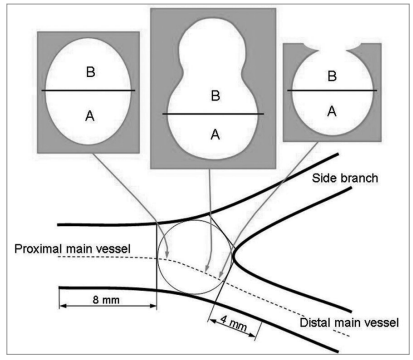

Figure 4. The scheme representing sequential cross sections of the bifurcation divided into two halves: A- the half opposite SB, B- the half toward SB. In the proximal MV strut apposition was assessed up to 8 mm before the bifurcation and in the distal MV up to 4 mm beyond the bifurcation.

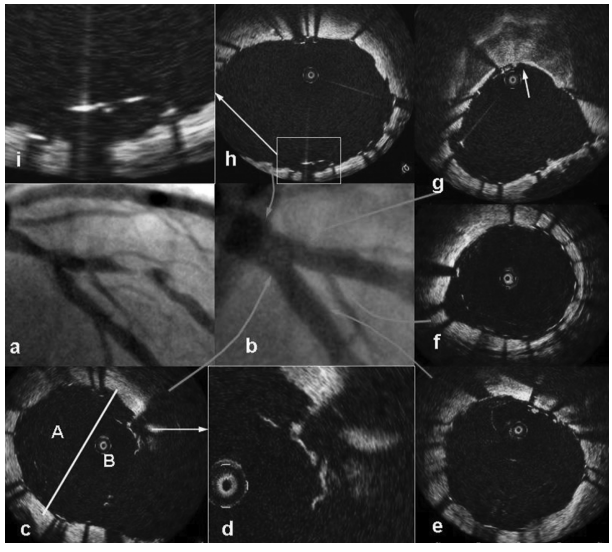

Figure 5. a) Bifurcation lesion involving the left anterior descending artery and diagonal branch, b) Angiographic result after deployment of a Tryton stent in the SB and DES in the MV. Pullback from the MV and from the SB. OCT cross sections: c) Bifurcation- visible malapposed struts in the half facing the SB (A- the half opposite SB; B- the half toward SB), d) Magnification of picture c focused on malapposed struts, e) Distal segment of the MV- well apposed struts, f) Distal segment of the SB- malapposed struts at the level of small branch; g) OCT image immediately distal to SB ostium shows irregular contours of the vessel lumen and confirms the presence of compressed plaque behind struts (arrow), which is typically located opposite the SB, h) Proximal MV- most struts are well apposed and only a few are malapposed, g) Magnification of image h focused on malapposed struts.

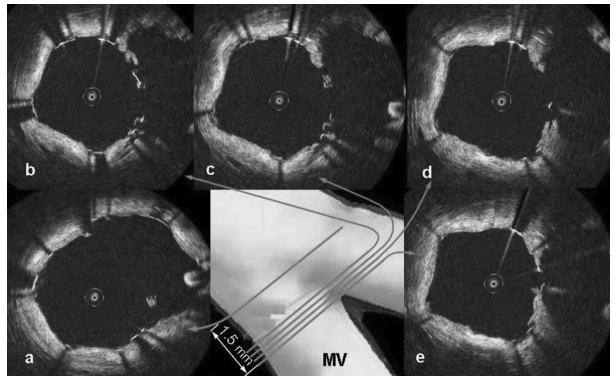

Figure 6. Creation of metallic neo-carina. a) Well apposed struts in proximal part of the bifurcation (arrow- guidewire), b-e) Sequential OCT cross sections show metallic neo-carina.

Cardiac biomarkers

Troponin I was measured routinely 12 to 24 hours after the procedure. Elevation of ≥ 3 times the upper limit of normal (0.04 µg/L) was considered significant and defined as periprocedural MI (with or without pathological Q waves), in the absence of another aetiology.

Statistics

Continuous variables are expressed as mean±standard deviation (SD) or median and interquartile range (IQR). Differences among four segments were assessed with ANOVA or Kruskal-Wallis test. The comparison between two groups was performed with unpaired *t* test or Mann Whitney U-test; Bonferroni's correction was used for multiple comparisons (p value <0.0083, 0.05/6 was the level of statistical significance).

To assess whether the strut location in the bifurcation half toward SB may increase the risk of strut malapposition and may affect the stent strut-vessel separation distance, we performed a multilevel mixed effect logistic regression and multilevel mixed effect linear regression, respectively, fitting a model with three levels. This model accounts for the correlated nature of the data and allows for the heteroscedasticity of the random effects: level 1=the single strut, level 2=the segment (proximal, distal, bifurcation half toward SB and opposite SB), level 3=the patient, adding the presence/absence of malapposed struts toward SB location as random effect at the level 1 and level 2. The statistical significance was a p value <0.05. Statistical calculations were performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA) and STATA 10.1 statistical software (StataCorp LP, College Station, TX, USA).

Results

Sixteen patients were treated with the Tryton culotte technique, nine of whom had additional postprocedural OCT examination. Table 1 summarises demographical and clinical data: 56% of the patients were male with an average age of 66.7±7 years; 44% of patients had two or three vessel disease.

Table 1. Baseline clinical characteristics (patients with OCT sub-analysis).

Number of patient	1	2	3	4	5	6	7	8	9
Sex	F	M	F	M	M	F	F	M	M
Age (years)	57	64	71	60	76	74	71	66	61
Prior MI	y	n	n	n	n	y	n	n	n
Prior PCI	n	y	n	n	n	n	n	n	y
Diabetes mellitus	y	y	n	n	y	y	y	n	y
Hypertension	y	y	y	y	y	y	y	n	y
Current/former smoker	y	y	y	n	n	n	y	n	n
Family history of CAD	n	y	n	n	y	y	y	y	y
Dyslipidaemia*	y	n	y	y	y	y	y	n	y
Renal impairment**	n	y	n	n	n	n	n	n	n
Clinical presentation	SA	UA	UA	UA	UA	SA	SA	SA	SA
Two vessel disease	n	n	y	n	y	y	n	n	n
Three vessel disease	n	n	n	y	n	n	n	n	n

*Total cholesterol ≥5.0mmol/L or treatment with a lipid lowering drug;
**Baseline creatinine above 130 µmol/L; OCT: optical coherence tomography; MI: myocardial infarction; PCI: percutaneous coronary intervention; CAD: coronary artery disease; F; female; M: male; UA: unstable angina pectoris; SA: stable angina pectoris.

Table 2 shows angiographic and procedural details. The target bifurcation lesion was the left anterior descending artery/diagonal branch in seven patients and the left circumflex artery/obtuse marginal branch in two patients. Significant ostial SB stenosis (>50% diameter stenosis) was present in seven lesions. The following DES were implanted into the MV: Cypher Select (n=4), Taxus Liberte (n=2), Endeavor Resolute (n=1) and Xience V (n=2). Final KB was performed in all nine cases. Procedural success by angiography with TIMI 3 flow was achieved in all lesions. In all cases, a mild post-procedural troponin I rise in routine blood tests was noticed (median 0.58 µg/L, IQR 3.41), including one patient with troponin I rise up to 20 µg/L due to occlusion of a small septal branch. No ischaemic ECG changes or pathological Q waves were observed. No other major adverse cardio-vascular events occurred during the in-hospital stay.

The OCT analysis is presented in Table 3 and 4. A total of 2,782 struts were analysed: 1,514 (54.5%) struts in the proximal vessel segment, 449 (16.1%) struts at the bifurcation level and 819 (29.4%) struts in the distal vessel segment. The total number of malapposed struts was 494: 243 in the proximal segment, 133 in the bifurcation and 118 in the distal segment. The overall total percent of malapposed struts was 17.8%, and the mean total percent of malapposed struts per patient was 18.1±8.7%. Per patient analysis of the longitudinal distribution of malapposition showed that the prevalence of malapposed struts was higher in the bifurcation half toward SB (47.6% [35.3-58.6]) than in the distal segment (9.8% [4.5-14.3], p=0.0023), the proximal segment (18.5% [10.5-21.1], p=0.0054), and the bifurcation half opposite SB (14.8% [12.9-19.5], p=0.0054), with no significant difference between proximal and distal segments (p=0.27), bifurcation half opposite SB and proximal segment (p=0.96), bifurcation half opposite SB and distal segment (p=0.35), (p=0.0035 among the four groups). At multilevel mixed effect logistic regression, the location of the struts toward SB carried a significant striking increased risk of malapposition (odds ratio [OR] 5.8, 95% confidence interval [CI] 3.2 -10.7, p<0.001).

Also the strut- vessel wall distance for malapposed struts was higher in the bifurcation half toward the SB (191 µm, [40-371]) compared to the bifurcation half opposite SB (49 µm, [20-80], p=0.0001), the proximal segment (51 µm, [21-98], p<0.0001) and distal segment (37.5 µm [17-90], p<0.0001) with no significant difference between proximal and distal segments (p=0.14), bifurcation half opposite SB and proximal segment (p=0.48), bifurcation half opposite SB and distal segment (0.77), (p=0.0001 for the comparison among the four groups). At multilevel mixed effect linear regression, the location of the struts in the bifurcation half toward SB increased the strut vessel wall separation distance (coefficient 174.8 µm, 95% CI [85.8-263.9], p<0.001).No significant correlation was observed between the percent of malapposed struts (including the analysis of the total number of malapposed struts and the analysis of the individual vessel segments: proximal, bifurcation, distal) and the bifurcation angles (both the angle between the proximal MV and the SB as well as the angle between the distal MV and the SB).

Table 2. Angiographic and procedural data (n=9).

Variable	
Medina classification, n (%)	
1,1,0	2 (22)
0,1,1	3 (33)
1,0,1	1 (11)
1,1,1	3 (33)
Baseline reference vessel diameter, mm±SD	
Proximal MV	2.7±0.4
Distal MV	2.4±0.4
SB	2.1±0.4
Initial diameter stenosis, %±SD	
Proximal MV	59±18
Distal MV	67±22
SB	51±12
Baseline minimal lumen diameter, mm±SD	
Proximal MV	1.1±0.6
Distal MV	0.8±0.5
SB	0.9±0.5
Lesion length, mm±SD	
Proximal MV	9.4±7.9
Distal MV	11.4±5.9
SB	10.8±7.9
Maximal balloon pressure, atm.±SD	
MV	19.6±5.0
SB	17.5±4.6
Total main vessel stent length, mm±SD	38.2±20
Reference vessel diameter after procedure, mm±SD	
Proximal MV	3.0±0.4
Distal MV	2.4±0.4
SB	2.1±0.3
Minimal lumen diameter after procedure, mm±SD	
Proximal MV	2.8±0.4
Distal MV	2.1±0.2
SB	1.8±0.2
Diameter stenosis after procedure, %±SD	
Proximal MV	10.8±10
Distal MV	8.4±8.2
SB	11.4±14
Bifurcation angles, °±SD	
Angle between proximal MV and distal MV	144±19
Angle between distal MV and SB	51±16

MV: main vessel; SB: side branch; SD: standard deviation

Table 3. OCT findings.

	Tryton (n=9)
Final OCT MLA, mm²±SD	
Proximal	9.1±1.5
Bifurcation	9.3±1.6
Distal MV	6.1±1.7
All struts	
Total number of struts, n (% of total number of struts)	2782
Struts in proximal segment, n (%)	1514 (55)
Struts in bifurcation, n (%)	449 (16)
Struts in the half opposite SB, n (%)	264 (9)
Struts in the half toward SB, n (%)	198 (7)
Struts in distal segment, n (%)	819 (29)
Malapposed struts	
Total number of malapposed struts, n (% of malapposed struts in each section)	494 (18)
Malapposed struts proximal, n (%)	243 (16)
Malapposed struts in bifurcation, n (%)	133 (30)
The half opposite SB, n (%)	43 (16)
The half toward SB, n (%)	90 (45)
Malapposed struts distal, n (%)	118 (14)
Percent of malapposed struts per patient, median (IQR)	18.1±8.7
Proximal	18.5 (10.5-21.1)
Bifurcation	33.3 (18.8-37.0)
The half opposite SB	14.8 (12.9-19.5)
The half toward SB	47.6 (35.3-58.6)
Distal	9.8% (4.5-14.3)
Distances between vessel wall and malapposed struts, µm median (IQR)	
Total	57 (101)
Proximal	51 (77)
Bifurcation- total	81 (245.5)
bifurcation-opposite SB	49 (61)
bifurcation-toward SB	191 (331)
Distal	37.5 (73)

OCT: optical coherence tomography; MLA: minimal lumen area; SB: side branch; SD: standard deviation; IQR: interquartile range

Table 4. OCT findings.

Patient	Distances between vessel wall and malapposed struts, µm median (IQR)				
	Proximal	Bifurcation opposite SB	Bifurcation toward SB	Distal	p
1	51 (60)	56 (103)	331 (790)	66 (90)	0.002
2	41 (60)	0	221 (280)	11 (10)	0.012
3	11 (10)	16 (57)	141 (170)	151 (200)	0.003
4	18 (45)	83 (105)	253 (227)	8 (7)	0.000
5	81 (80)	11 (10)	41 (305)	11 (0)	0.26
6	58 (90)	108 (177)	378 (275)	23 (55)	0.000
7	130 (120)	45 (55)	220 (380)	50 (80)	0.002
8	38 (50)	23 (30)	138 (0)	58 (0)	0.29
9	47 (50)	42 (20)	47 (52)	17 (25)	0.06

OCT: optical coherence tomography; IQR: interquartile range; SB: side branch

Discussion

Two theoretical advantages could be expected from using the Tryton stent for the treatment of bifurcation lesions. First, overlapping of struts in the MV, which by itself carries an increased rate of malapposition[16], is minimised by the stent design. Secondly, the large cell size in the transition zone facilitates deployment and optimises alignment of the stent placed in the MV. The results of this study showed that malapposition remained relatively high at the bifurcation level despite routine high pressure postdilatation and KB dilatation with balloons of matching diameter to the distal MV and SB segments. The geometry of a bifurcation is very different from the configuration assumed by two KB, especially when inflated at high pressure: the distal segment of the balloons in the SB and MV, if appropriately sized, are likely to achieve similar apposition to that in straight vessel segments. At the origins of the SB, however, the diameters of the elliptical cross-section of the lumen are larger than the circular diameter of the proximal SB, a phenomenon more evident when the angle between the MV and daughter vessel is acute. This may leave one or more rows of malapposed struts proximal, distal or on both sides dependent on the site at which the wire has crossed the deployed MV stent to re-enter the SB lumen. In the proximal MV, the elliptical geometry of the two balloons may stretch the wall in one direction and generate malapposition in the other (Figure 5h). The ideal method to prevent malapposition in the proximal MV segment is to use a single balloon, the diameter of which is matched to the vessel segment immediately proximal to the SB origin. The highest rate of malapposed struts and the highest distance between malapposed struts and the vessel wall were at the level of the bifurcation, facing the SB. Malapposed struts in this segment often create a metallic neo-carina (Figure 6), which is also observed in other techniques for bifurcation treatment[3]. As the main force vector of expanding KB dilatation is axial and not longitudinal, clustering of malapposed struts in a new carina is almost inevitable. The percent of malapposed struts observed in this study (18.1% in total; 30.1% in bifurcation) must be compared with existing OCT data in bifurcations and overlapping segments. In previous OCT observations, the rate of malapposed struts following the treatment of simple lesions in straight vessel segments was 9%[17], while the rate of malapposed struts in overlapping stents was as high as 41.8%, compared with 20.1% and 9.7% in non-overlapping proximal and distal segments, respectively[16]. It is unclear whether immediate strut malapposition in overlapping segments will remain present at follow-up in the majority of DES. Consistent with previous OCT observations[18], the ODESSA trial showed that the highest rate of strut malapposition observed at six months was in overlapping DES segments as compared to non-overlapping segments (2.6% vs. 0.8%, respectively), and the stents characterised by the highest rates of malapposed struts were Taxus (5.5%) and Cypher (2.9%)[19]. However, the rate of malapposed struts observed immediately after stent implantation may decrease over time and our post-implantation results are consistent with previous post-implantation findings[16,17]. Finally, the clinical presentation of patients could potentially influence the rate of strut malapposition by influencing the decision to use a complex two stent technique[20]. The resistant ostial stenoses of bifurcations (often highly fibrotic or calcific), require high pressure expansion with low compliance short balloons. This is performed before the final kissing, with balloon sizes and pressures higher than the balloons of the final KB as both provisional stenting may cause carina displacement[21] and deployment of stent in a second branch may lead to distortion of the first stent[22]. Final KB, which in this series was performed in 100% of cases, seems to be essential. Better long-term clinical results after KB are supported by previous observations. Adriaenssens et al reported that in their series of 134 bifurcation lesions in 132 patients treated with culotte technique, final KB tended to have a protective effect against stent thrombosis[23]. Also, after the "crush" technique, final KB significantly reduced the SB late lumen loss at nine months angiographic follow-up[24]. In all modern, bifurcation trials (BBC ONE trial[10], CACTUS trial[25]), KB after complex two stent techniques was mandatory.

Limitations

Since we did not compare the Tryton stent to other bifurcation stents or stenting techniques, we are unable to state whether this new stent is better or worse than expected. Furthermore, the limited number of patients meant that the influence of patient and angiographic data could not be correlated to the number of malapposed stent struts. It is also possible that the use of different drug-eluting stents may have affected our findings.

As in any angiographic study, in which a three-dimensional structure is assessed by two-dimensional projection imaging, the results of measurement are influenced by the imaging angle.

Because of the small number of patients included in the study, statistical analysis was calculated with simple parametrical and non-parametrical tests.

Conclusions

OCT assessment of stent apposition after the treatment of bifurcation lesions with a new dedicated bifurcation stent in the SB and DES in the MV in a culotte-like fashion showed non-uniform distribution of malapposed struts. The highest percent of malapposed struts and the largest vessel wall–stent strut distances were observed in the bifurcation half facing the SB. No difference was observed between the rate of malapposed struts in the proximal segment, the bifurcation half opposite the SB and the distal segment.

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CHAPTER 18

Simple versus complex approaches to treating coronary bifurcation lesions: direct assessment of stent strut apposition by optical coherence tomography

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Rev Esp Cardiol 2010 Aug;63(8):904-14.

Simple Versus Complex Approaches to Treating Coronary Bifurcation Lesions: Direct Assessment of Stent Strut Apposition by Optical Coherence Tomography

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Introduction and objectives. Stenting of coronary bifurcation lesions carries an increased risk of stent deformation and malapposition. Anatomical and pathological observations indicate that the high stent thrombosis rate in bifurcations is due to malapposition of stent struts.

Methods. Strut apposition was assessed with optical coherence tomography (OCT) in bifurcation lesions treated either using the simple technique of stent implantation in the main vessel only or a complex technique (i.e. Culotte's). A strut was regarded as malapposed if the gap between its endoluminal surface and the vessel wall was greater than its thickness plus an OCT resolution error margin of 15 μm.

Results. Simple and complex (i.e. Culotte's) approaches were used in 17 and 14 patients, respectively. Strut malapposition was significantly more frequent for the half of the bifurcation on same side as the vessel side branch (median, 46.1%; interquartile range [IQR], 35.3–62.5%) than for the half opposite the side branch (9.1%; IQR, 2.2–21.6%), the distal segment (7.5%; IQR, 2.3–20.2%) or the proximal segment (12.6%; IQR, 7.8–23.1%; *P*<.0001); the gap between strut and vessel wall in malapposed struts was significantly greater in the first segment than the others: 98 μm (IQR, 37–297 μm) vs. 31 μm (IQR, 13–74 μm), 49 μm (IQR, 20–100 μm) and 38 μm (IQR, 17–90 μm), respectively (*P*<.0001). Using the complex technique had no effect on the prevalence of strut malapposition in the four segments relative to the simple technique (*P*=.31) but was associated with a smaller gap in the proximal segment (47 μm vs. 60 μm; *P*=.0008).

Conclusions. In coronary bifurcation lesions, strut malapposition occurred most frequently and was most significant close to the side branch ostium. The use of Culotte's technique did not significantly increase the prevalence of strut malapposition compared with a simple technique.

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Received October 20, 2009.
Accepted for publication March 25, 2010.

Key words: *Bifurcation lesion. Percutaneous coronary intervention. Optical coherence tomography.*

Estrategia simple o compleja para lesiones de bifurcaciones coronarias: evaluación inmediata de la aposición de los *struts* del *stent* mediante tomografía de coherencia óptica

Introducción y objetivos. La implantación de *stents* en lesiones de bifurcaciones coronarias comporta un riesgo elevado de deformación y mala aposición del *stent*. Las observaciones anatomopatológicas han atribuido a la mala aposición de los *struts* un papel causal en la elevada tasa de trombosis de los *stents* que se observa en las bifurcaciones.

Métodos. Se evaluó la aposición de los *struts* en las lesiones de bifurcaciones tratadas con una técnica simple de implantación de *stent* solo en el vaso principal o con una técnica compleja (de *culotte*) mediante el empleo de tomografía de coherencia óptica (OCT). La mala aposición de un *strut* se definió por el hecho de que la distancia entre su superficie intraluminal y la pared vascular fuera superior a su grosor más un margen de error de resolución de la OCT de 15 μm.

Resultados. En 17 pacientes se utilizó la estrategia simple y en 14, la técnica compleja (de *culotte*). Los *struts* con mala aposición fueron significativamente más frecuentes y la distancia entre el *strut* y la pared vascular en los casos de mala aposición fue mayor en la mitad de la bifurcación situada hacia la rama lateral (RL) (46,1% [35,3-62,5]) en comparación con la mitad del lado opuesto (9,1% [2,2-21,6]), el segmento distal (7,5% [2,3-20,2]) y el segmento proximal (12,6% [7,8-23,1]; p < 0,0001) (distancias, 98 μm [37-297] frente a 31 μm [13-74], 49 μm [20-100] y 38 μm [17-90], respectivamente; p < 0,0001). El empleo de la técnica compleja no afectó a la prevalencia de *struts* con mala aposición en los 4 segmentos en comparación con la estrategia simple (p = 0,31) y se asoció a una menor distancia *strut*-pared en el segmento proximal (47 frente a 60 μm; p = 0,0008).

Conclusiones. En las lesiones de bifurcaciones coronarias, la mala aposición de los *struts* se produce con mayor frecuencia y es más importante en la zona de origen de la RL. El empleo de la técnica de *culotte* no au-

ABBREVIATIONS

IVUS: intravascular ultrasound
KB: kissing balloon
MV: main vessel
OCT: optical coherence tomography
PCI: percutaneous coronary intervention
SB: side branch

menta de manera significativa la prevalencia de la mala aposición de los *struts* en comparación con una estrategia simple.

Palabras clave: *Lesión de bifurcación. Intervención coronaria percutánea. Tomografía de coherencia óptica.*

INTRODUCTION

While stenting of coronary bifurcation lesions provides good immediate angiographic results, restenosis (even with drug-eluting stents-DES) and stent thrombosis occur more frequently than in simpler lesions. Bifurcation lesions are still considered off-label procedures because of the potential risk of side branch (SB) jailing and stent deformation and malapposition. Pathology observations have indicated potential correlations between stent strut malapposition and stent thrombosis,[1] which may explain why percutaneous coronary intervention (PCI) for bifurcation lesions is an independent risk factor for stent thrombosis.[2] The incidence and predictors of stent thrombosis using different PCI strategies for bifurcation lesions are controversial. Most studies suggested that stent thrombosis is higher in bifurcations treated with two-stents. In the experience of the Milan and Rotterdam groups Hoye et al. reported a 4.3% rate of stent thrombosis after the "crush" technique.[3] One of the two main randomized trials comparing a simple strategy of stenting the main vessel (MV) only to a complex strategy of stenting both MV and SB, the British Bifurcation Coronary Study: Old, New, and Evolving Strategies (BBC ONE) trial showed higher stent thrombosis in the two vessels strategy group.[4] In the Nordic study however, the 14-month incidence of stent thrombosis was 0.5% in the 2 vessel strategy group arm and 2% in the provisional stenting arm.[5]

Two vessels techniques are expected to induce greater stent deformity and malapposition,[6] but there is no in-vivo confirmation since intravascular ultrasound (IVUS) lacks the ability to precisely detect strut malapposition. Optical coherence tomography (OCT) has higher resolution than IVUS (approximately 10 times), with fewer strut-induced artifacts and offers precise evaluation of strut apposition in a real-life clinical setting.[7] OCT has proved to be useful technique in assessing stent apposition after bifurcation treatment using new dedicated bifurcation stent.[8] Additionally, the results from that study make up a part of the findings in the current complex treatment arm.

The aim of our study was to quantify and compare the apposition of stent struts in bifurcation lesions treated either with a simple technique (MV stenting only) or with a complex technique (stenting of both the MV and the SB using the Culotte technique).[9]

METHODS

Study Population

All consecutive patients, who underwent post-procedural OCT examination after stent implantation in bifurcation lesions from January 2006 to September 2008, were enrolled in the study.

Procedure

Provisional MV stenting and dedicated complex techniques have been described previously.[5,10] Six French guiding catheters were used in all cases. High pressure or cutting balloon pre-dilatation as well as post-dilatation with a high-pressure balloon were performed in all cases. After re-wiring into the SB, final kissing balloon (KB) post-dilatation was performed in all cases of complex strategy, with the balloons diameters matching and SB diameter and MV diameter distal to the bifurcation. The inflation pressure was at the operator's discretion, based on the type of lesion, the compliance of the balloons, etc. The Culotte technique was used for all complex cases. The choice to use a simple or complex technique was at the operator's discretion and it was based on the anatomical scenario of the bifurcation lesion. Procedural success was defined as final diameter stenosis <30% in the MV and <50% in the SB by visual assessment with TIMI 3 flow in both the MV and SB.

Pharmacological Treatment and Procedural Devices

Before the procedure, all patients were pretreated with Aspirin and 300-600 mg of Clopidogrel. During the procedure, either unfractionated heparin (UFH) or bivalirudin were used: UFH was given to maintain an activated clotting time ≥250

seconds with an initial bolus of 70 IU/kg, whilst bivalirudin was given according to the patient's body weight. Intravenous or intracoronary administration of glycoprotein IIb/IIIa inhibitors was at the operator's discretion.

Quantitative Angiographic Analysis

All bifurcation lesions were classified according to the Medina classification depending on the presence or absence of >50% stenosis in the proximal and distal MV and the SB ostium.[11] Quantitative Vascular Arteriography was performed using dedicated 3 segment software (QAngio XA 7.1, Medis Medical Imaging System, Leiden, The Netherlands), as previously described.[12]

OCT Imaging Technique

In this study, an end-hole microcatheter (0.021" Transit™, Cordis Neurovascular, Miami Lakes, FL, USA) was advanced distal to the lesion in the MV over a conventional guide wire, which was then exchanged for the OCT imaging wire. OCT image acquisition (M3 system, LightLab Imaging Inc. Westford, MA, USA) was performed using a non-occlusive technique[13] with continuous flushing of iodixanol (Visipaque™, GE Healthcare, UK) using a power injector (2-5 mL/s) and a pullback speed set at 3 mm/s. Image acquisition over a 30-35 mm vessel segment was performed in each patient without complication.

OCT Image Analyses

Cross-sectional images from the OCT pullback were analyzed every 450 μm (every 3 frames). Since the metallic surface of the strut is opaque to infrared light, the abluminal strut surface cannot be seen; therefore strut malapposition was diagnosed if the distance between the endoluminal surface of even single strut of the stent and the vessel wall was greater than the thickness of the strut (metal+polymer) plus an additional 15 microns margin of error, consistent with the resolution of OCT.[14] The thickness of the stents used in the study was as follows: Cypher Select-154 μm, Taxus Liberté-127 μm, Endeavor Resolute-95 μm, Xience V-88 μm, Antares-88 μm, Costar-89 μm, and Driver-91 μm.[14] Strut apposition was assessed in four segments: proximal MV segment (extending 8 mm proximal to the first cross-section when the SB was visible), bifurcation (divided into two 180 degrees halves towards or opposite the origin of the SB) and distal MV segment (extending 4 mm from the last cross-section when the SB was visible) (Figures 1 and 2). In order to unify the analysis, all distances were measured in perpendicular cross-sections from an OCT pullback in the MV, and not taken from the longitudinal images (this is practically very difficult). The malapposition distance in the half toward the SB of the bifurcation segment was measured as in the straight segments: from an OCT pullback in the MV, the measurement has been taken for the shortest distance between malapposed/floating strut and vessel wall. When using the complex technique, MV and SB stents differed in their strut thickness. The SB stent is the outer stent, the MV stent the inner one, thus malapposed struts are likely to belong to MV stent at the level of bifurcation and in the proximal segment. Strut malapposition was calculated on the basis of the MV stent type and strut thickness.

Cardiac Biomarkers

Peri-procedural myocardial infarction (MI), with or without pathological Q waves was defined as a post-procedural Troponin I elevation of ≥3 times the upper limit of normal (0.04 μg/L).

Statistical Analysis

The presence of normal distribution of continuous variables was assessed by means of visual estimation of their frequency histogram and with the use of Shapiro Wilk test. Continuous variables are expressed as mean (standard deviation [SD]) or median and interquartile range (IQR) if they followed a normal or non normal distribution, respectively. Categorical variables are expressed as frequency and percentage. In the overall population, differences of continuous variables among the four segments within the lesion were assessed with Kruskal-Wallis test, because of the presence of non normal distribution of continuous variables. Comparisons between two groups were performed using Mann Whitney *U* test, as appropriate. A value of 2 tailed $P<.05$ was considered statistically significant. If a significant difference (ie, $P<.05$) was found across the 4 groups we performed 2×2 multiple comparisons with Bonferroni's correction with the level of statistical significance achieved at *P* value <.05/number of comparisons, thus corresponding to $<.05/6$, $P<.0083$. Categorical variables were analyzed using the χ^2 test or Fisher's exact test, as appropriate. The effect of the strategy type (complex vs simple), the different segments expressed as categorical variable and of the interaction between the strategy type and the 4 segments on strut vessel wall separation distance was assessed using mixed effect linear regression analysis, to account for the correlated nature of the data: ie, the presence of segments within lesion, and of multiple struts within segments Briefly, 3 levels were considered: level 1=the single strut, level

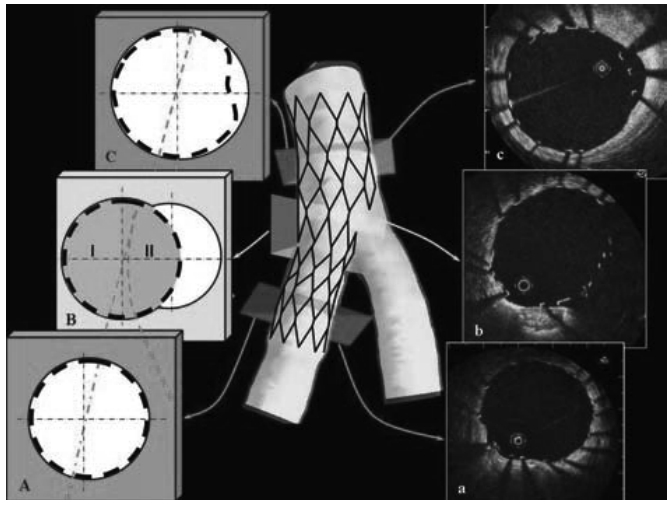

Figure 1. The scheme representing sequential cross-sections of distal segment-A, bifurcation-B and proximal segment-C after bifurcation treatment with simple technique. At the level of bifurcation cross-section has been divided into 2 halves: I-the half opposite side branch, II-half toward side branch. In the proximal main vessel strut apposition was assessed up to 8 mm before the bifurcation and in the distal main vessel up to 4 mm beyond the bifurcation. On the right side there are corresponding optical coherence tomography cross-sections (a-c).

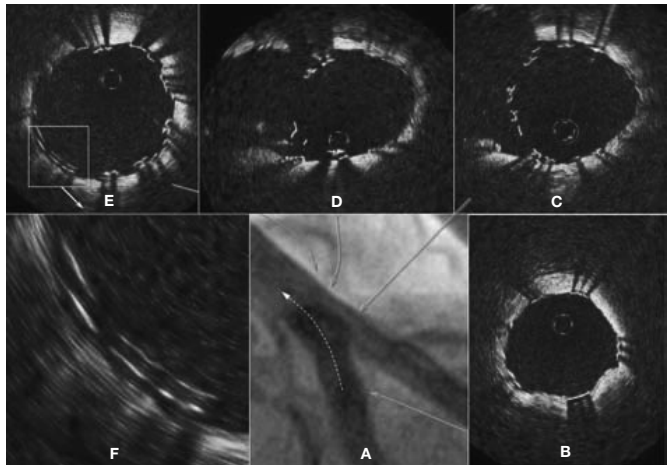

Figure 2. A: angiographic result after implantation of 2 stents into the left anterior descending artery and diagonal branch (Culotte technique). The white arrow indicates the track of the optical coherence tomography imaging wire. Optical coherence tomography images. B: distal segment with well apposed struts. C and D: bifurcation region with malapposed/floating struts in the half facing the side branch. E: well apposed 2 layers of struts in the proximal segment. F: magnification of the 2 layers of struts from the image E.

2=the segment (proximal, distal, bifurcation half toward SB and opposite SB), level 3=the lesion, adding the presence/absence of malapposed struts toward SB location as random effect at the level 1. As the percentage of malapposed struts was not expressed at the strut level, Ancova analysis, with weighted least squares as the estimator to correct for heteroskedasticity, was used for this endpoint, after logarithmic transformation, provided adjusted p values. If a significant effect of the type of strategy or of its interaction with the 4 segments was found on the endpoint, 2×2 multiple comparisons between

TABLE 1. **Baseline Patient Clinical Characteristics**

	Simple Technique (n=13)	Complex Technique (n=14)	*P*
Male, n (%)	12 (92)	8 (57)	.08
Age, mean (SD), y	69 (61-73)	70 (62-75)	.59
Diabetes mellitus, n (%)	3 (23)	6 (43)	.42
Hypertension, n (%)	7 (54)	12 (86)	.10
Current/former smoker, n (%)	8 (62)	10 (71)	.69
Family history of CAD, n (%)	8 (62)	11 (85)	.38
Dyslipidemia,a n (%)	12 (92)	12 (86)	1
Previous MI, n (%)	4 (33)	2 (14)	.37
Previous CABG, n (%)	2 (15)	0 (0)	.22
Previous PCI, n (%)	3 (23)	3 (21)	1
Clinical presentation			.21
Stable angina pectoris, n (%)	11 (85)	8 (57)	
ACS, n (%)	2 (15)	6 (43)	

[a]Total cholesterol ≥5 mmol/L or treatment with a lipid lowering drug.
ACS indicates acute coronary syndrome; CABG, coronary artery by-pass graft surgery; CAD, coronary artery disease; MI, myocardial infarction; NSTEMI, non Q-wave myocardial infarction; SD, standard deviation; PCI, percutaneous coronary intervention.

corresponding segments in the simple and complex group were performed. Bonferroni's correction was applied ($P<.05/10$). All analyses were performed using STATA 10.1 statistical software (Statacorp, Texas, USA).

RESULTS

Baseline Clinical Characteristics

Baseline demographics and clinical data are presented in Table 1. Twenty-seven patients (age 69 [61-73] years) with 31 bifurcation lesions were included in the study. Four patients had 2 bifurcations treated. Most of the patients (70%) presented with stable angina at hospital admission.

Angiographic and Procedural Characteristics

Table 2 summarizes angiographic and procedural data according to the treatment strategy: seventeen lesions (55%) underwent a simple treatment, whilst 14 (45%) underwent complex bifurcation treatment. Overall 26 out of 31 stents (83.9%) implanted in the MV were DES. Nine out 14 SB stents (64.3%) used in the complex technique were dedicated bifurcation stents- Tryton, 3 bare metal stents (21.4%) and 2 DES (14.3%). The bifurcation target lesion was most frequently located at the left anterior descending/diagonal artery (LAD/Dg), n=17 (55%), followed by the circumflex/obtuse marginal artery (LCx/Om), n=13 (42%), with the right coronary artery/posterior descending (RCA/PDA) in 1 case (3%). The location of the target lesion differed between the two treatment arms, with LAD/Dg lesions being more frequent (86% vs 29%) and LCx/Om lesions less frequent (14% vs 65%) in the complex strategy arm compared to the simple strategy arm. The complex technique was more frequently utilized to treat bifurcation lesions with SB disease: SB diameter stenosis ≥50% (79% vs 12%, $P<.001$), larger SB diameter stenosis (63% vs 29%, $P=.001$), SB minimal lumen diameter (0.8 mm vs 1.4 mm; $P=.007$) and SB lesion length (5.6 mm vs 2.9 mm; $P=.04$). There were no differences in treatment strategy with respect to SB reference lumen diameter.

True bifurcation lesions were present in 13 of 31 bifurcation lesions (42%). Eleven of 13 true bifurcation lesions (85%) were treated with complex technique and only 2 true bifurcation lesions (15%) were treated with simple technique ($P<.001$). Significantly higher balloon pressure was applied for SB post-dilatation when a complex technique was used (15 atmospheres vs 11.2 atmospheres; $P=.04$). Procedural success (TIMI 3 flow in both branches and SB residual diameter stenosis <50%) was achieved in all cases. Small procedure-related MI occurred in both groups without significant difference (76.5% v. 100 %; $P=.1$).

Longitudinal Distribution of Malapposed Struts

The OCT analysis is presented in Figures 3 and 4. In total, 8666 struts were evaluated: 4281 (49.4%) in the proximal vessel segment, 1434 (16.5%) at the bifurcation level, and 2951 (34.1%) in the distal vessel segment. The prevalence of malapposed struts was significantly higher at the level of bifurcation half toward SB (46.1% [35.3-62.5]) as compared to the bifurcation half opposite SB (9.1% [2.2-21.6];

TABLE 2. **Angiographic and Procedural Data (per Lesion))**

Variable	Simple Technique (n=17)	Complex Technique (n=14)	*P*
Number of diseased vessels			.021
One vessel, n (%)	6 (35)	8 (57)	
Two vessels, n (%)	2 (12)	5 (36)	
Three vessels, n (%)	9 (53)	1 (7)	
Target vessel bifurcation			.007
LAD/Dg, n (%)	5 (29)	12 (86)	
LCx/OM, n (%)	11 (65)	2 (14)	
RCA/PDA, n (%)	1 (6)	0	
Medina classification, n (%)			.009
0,1,0	9 (53)	1 (7)	
1,0,0	4 (23)	1 (7)	
0,1,1	1 (6)	3 (21)	
1,0,1	1 (6)	3 (21)	
1,1,0	2 (12)	1 (8)	
1,1,1	0 (0)	5 (36)	
True bifurcation, n (%)	2 (12)	11 (79)	<.001
Baseline reference vessel diameter, mean (SD), mm			
Proximal MV	3.1 (0.8)	3.0 (0.9)	.7
Distal MV	2.6 (0.8)	2.2 (0.6)	.2
SB	2.0 (0.6)	2.1 (0.5)	.7
Initial diameter stenosis, mean (SD),%			
Proximal MV	45 (29)	54 (24)	.4
Distal MV	55 (28)	56 (35)	.9
SB	29 (21)	63 (30)	.001
Baseline minimal lumen diameter, mean (SD), mm			
Proximal MV	1.7 (0.9)	1.4 (0.7)	.3
Distal MV	1.1 (0.8)	1.0 (0.9)	.7
SB	1.4 (0.6)	0.8 (0.7)	.007
Lesion length, mean (SD), mm			
Proximal MV	4.6 (4.6)	5.8 (5.5)	.5
Distal MV	6.1 (7.6)	8.6 (8.2)	.4
SB	2.9 (1.5)	5.6 (4.7)	.04
Calcified lesions, n (%)	6 (35)	5 (36)	1
Maximal balloon pressure, mean (SD), atm			
MV	13.9 (5.5)	17.1 (5)	.1
SB	11.2 (4.7)	15.0 (3.4)	.04
Type of stent implanted in the MV, n (%)			.4
Paclitaxel eluting stent (Taxus)	6 (35)	5 (36)	
Paclitaxel eluting stent (Costar)	0	1 (7)	
Rapamycin eluting stent (Cypher)	4 (23)	5 (36)	
Zotarolimus eluting stent (Endeavor Resolute)	1 (6)	1 (7)	
Everolimus eluting stent (Xience V)	1 (6)	2 (14)	
BMS (Antares)	4 (24)	0	
BMS (Driver)	1 (6)	0	
Total MV stent length, mean (SD), mm	31.8 (18.5)	33.8 (19.3)	.8
MLD after procedure, mean (SD), mm			
Proximal MV	3.1 (0.6)	3.2 (0.6)	.8
Distal MV	2.7 (0.5)	2.5 (0.5)	.4
SB	1.9 (1)	2.1 (0.4)	.4
Diameter stenosis after procedure, mean (SD), %			
Proximal MV	7 (6)	7 (9)	.8
Distal MV	8 (6)	7 (8)	.8
SB	20 (22)	9 (11)	.1
Final KB, n (%)	15 (88)	14 (100)	.5
IIb/IIIa inhibitor, n (%)	1 (6)	2 (14)	.4
Post-procedural Troponin I rise, µg/L (SD	1.2 (1.6)	2.4 (5.4)	.6
Post-procedural MI, n (%)	13 (76.5)	14 (100)	.1

BMS indicates bare metal stent; Dg, diagonal branch; KB, kissing balloon; LAD, left anterior descending artery; LCx, left circumflex artery; MI, myocardial infarction; MLD,-minimal lumen diameter; MV, main vessel; OM, obtuse marginal branch; PDA, posterior descending artery; RCA, right coronary artery; SB, side branch; SD, standard deviation.

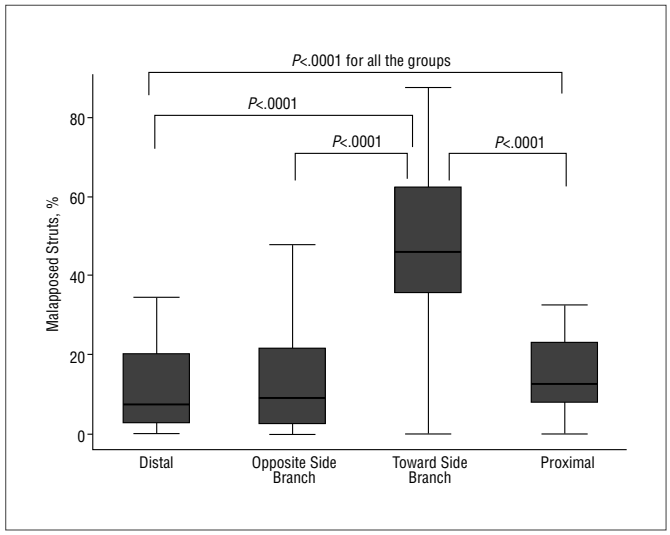

Figure 3. Longitudinal distribution of % of malapposed struts across 4 segments: distal, bifurcation half opposite side branch, bifurcation half toward side branch, proximal. Only significant P values are reported.

P<.0001), the distal segment (7.5% [2.3-20.2]; *P*<.0001, adjusted-*P*), and the proximal segment (12.6 [7.8-23.1]; *P*<.0001), with no significant difference between proximal and distal segments (*P*=.07), bifurcation half opposite SB and proximal segment (*P*=.22), bifurcation half opposite SB and distal segment (*P*=.76) (*P*=.0001 Kruskal Wallis among 4 groups [Figure 3]; Ancova adjusted *P*<.0001). The strut vessel wall distance for malapposed struts was higher toward the SB (98 μm, [37-297]) as compared to the opposite SB (31 μm, [13-74]; *P*<.0001), the proximal segment (49 μm, [20-100]; *P*<.0001) and distal segment (38 μm [17-90]; *P*<.0001]), higher in proximal segment as compared to distal segment (*P*=.0082), and to opposite SB (*P*=.0019), with no significant difference between opposite SB and distal segment (0.23) (*P*=.0001 Kruskal Wallis for the comparison among 4 groups, Figure 4) (20.5 μm, 95% CI, 6.8-34.2; *P*=.003 at mixed effect linear regression analysis).

OCT Analysis: Differences Between Simple and Complex Techniques

Both the overall number of struts per patient and the number of struts in the proximal segment were significantly higher with complex stenting than with a simple technique (323 [97] vs 243 [102]; *P*=.036 and 175 [18] vs 107 [64]; *P*=.015, respectively). The prevalence of malapposed struts and strut vessel wall separation distance, in the 2 groups is shown in Table 3. Regarding the endpoint of the percentage of malapposed struts, Ancova analysis showed that the use of a complex strategy (*P*=.31) and the interaction between complex strategy and the 4 segments (*P*=.75) were not significant. Indeed, no significant difference was found between proximal segments (*P*=.56), distal segments (*P*=.95), segments opposite SB (*P*=.20), and segments toward SB (*P*=.68). Regarding strut vessel wall distance, mixed effect linear regression analysis showed that the interaction between complex strategy and the 4 segments of the lesion was significant (-9.3 μm; 95% CI, -17.9 to 0.7; *P*=.033), while the use of complex strategy was not significant (3.4 μm; 95% CI, -31.3 to 38.1; *P*=.85), indicating that the complex strategy was associated with a lower strut vessel wall distance at specific segments. Indeed, strut vessel wall separation distance was significant lower at the proximal segment in the complex group as compared to the simple group (*P*=.0008), without significant difference between distal segments (*P*=.25), segments opposite SB (*P*=.083), and segments toward SB (*P*=.0878).

DISCUSSION

Angiography evaluates only the vessel lumen and therefore has a very limited ability to recognize the adequacy of stent expansion and wall apposition.

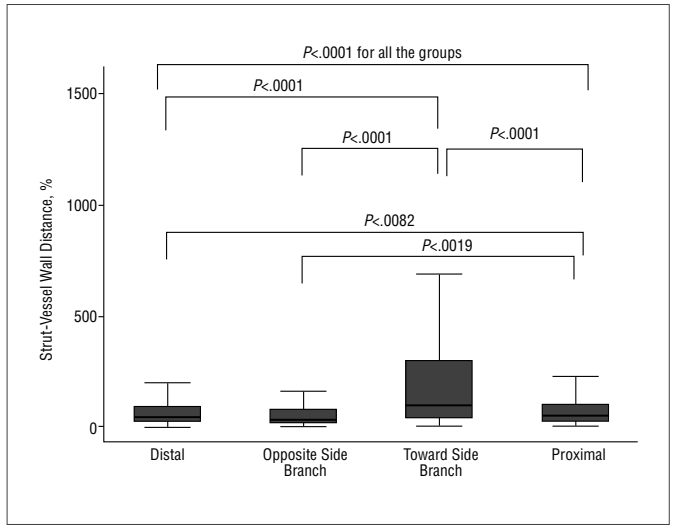

Figure 4. Longitudinal distribution of strut-vessel wall distance across 4 segments: distal, bifurcation half opposite side branch, bifurcation half toward side branch, proximal. Only significant P values are reported.

TABLE 3. **OCT Data According to Simple and Complex Technique**

	Simple Technique (n=17)	Complex Technique (n=14)	*P*
Final OCT MLA, mean (SD), mm²			
Proximal	8.1 (2.6)	9.2 (1.6)	.19
Bifurcation	8.5 (2.4)	9.4 (1.9)	.28
Distal	6.6 (2.3)	6.1 (1.8)	.57
Malapposed struts, %, median (25-75)			
Proximal	11.8 (5.1-23.1)	15.5 (9.4-22.9)	.56
Opposite SB	5.91 (0-17.6)	14.2 (9.1-21.6)	.20
Toward SB	45.4 (35.3-54.5)	50.3(35.3-62.5)	.68
Distal	7.5 (2.3-20.2)	7.9 (2.9-14.3)	.95
Malapposed strut-vessel wall distance, µm, median, (25-75)			
Proximal	60 (20-170)	47 (21-81)	.0008
Opposite SB	21 (8-87)	37 (20-71)	.083
Toward SB	81 (30-267)	123 (41-333)	.088
Distal	38 (17-101)	31 (13-80)	.25

OCT indicates optical coherence tomography; OCT MLA, optical coherence tomography minimal lumen area; SD, standard deviation; SB, side branch.

IVUS allows good assessment of stent expansion but for the detection of stent apposition, its low resolution (about 120 µm) is insufficient to quantify this phenomenon precisely. IVUS data from the Sirolimus-Eluting Stent (SES) in De Novo Coronary Lesions (SIRIUS) trial showed that post-procedural incomplete stent apposition (ISA) was present in 16.2% of 80 SES implantations.[15] A similar incidence of ISA was shown in the IVUS studies by Kimura et al. after implantation of SES in 168 patients (18%)[16] and by Kim et al. after implantation of paclitaxel-eluting stent (PES) and SES in 299 patients (13.9%).[17] However, IVUS may potentially underestimate the prevalence of strut malapposition: in a study comparing IVUS and OCT in 27 patients undergoing PCI, Hou et al. found that IVUS identified stent malapposition in only 10.5% as opposed to 63.2% of cases when

assessed by OCT.[18] Additionally, instead of assessing the prevalence of stent strut malapposition as by OCT, previous IVUS analyses only assessed how many patients had at least one malapposed strut. Finally, previous IVUS analyses have specifically excluded bifurcation segments from the assessment of incomplete stent apposition rightly assuming that malapposition was unavoidable at that level.[15] Indeed only few IVUS analyses have addressed the results of bifurcation stenting and they have focused on poor expansion rather than malapposition. Costa et al. performed post-intervention IVUS assessment in 40 patients treated with the "crush" technique, and found ISA in more than 60% of cases, mainly proximal to the bifurcation where 3 layers of stents were present.[19]

Detailed OCT comparison in the present study showed a much higher incidence of malapposition per lesion. We believe that the prominent artifacts induced by the stent struts with IVUS limit the visualization of the underlying wall, impairing its ability to detect minor degrees of malapposition. The complex 3-dimensional geometry of bifurcation lesions makes it difficult to achieve strut apposition comparable to that observed in a straight segment. In vitro model studies have previously demonstrated the difficulty in achieving good stent apposition at the SB ostium, regardless of which stenting technique is used.[20] Malapposed struts often create a metallic neo-carina both at the proximal and the distal end of often eccentric SB opening (Figure 2). Rewiring the SB in the most distal stent cell close to the carina was consistently attempted, crossing the stent with a looped wire pulled back to the bifurcation. Even when this is achieved, a balloon diameter exactly matching the ostium of the SB inflated at a pressure sufficient to displace all struts is required. In previous OCT observations, the rate of malapposed struts following the treatment of simple lesions in straight vessel segments was 9%,[7] while the rate of malapposed struts in overlapping stents was as high as 41.8%, compared with 20.1% and 9.7% in non-overlapping proximal and distal segments, respectively.[14]

Although pathology studies suggest that stent malapposition is a potential contributor toward adverse events, there are discrepancies when it comes to establishing the prognostic implication of ISA from the only available IVUS studies. Available data are mainly driven from the IVUS sub-studies of the initially highly selected DES studies in straight segments with the exclusion of bifurcation lesions. Similar stent malapposition rates were observed in patients who developed adverse events than in those without adverse events.[21] Others have demonstrated a higher prevalence of abnormal IVUS findings regarding stent apposition and expansion following stent implantation in patients who developed acute stent thrombosis as compared to a control group.[19]

Surprisingly, our study did not show any significant differences between the simple and complex technique with regard to strut malapposition; with a complex technique one could theoretically expect higher rates of malapposed struts simply because of more metal inserted. These findings may be explained by more aggressive KB post-dilatation in two-stents technique than in one-stent strategy, without fear of causing dissection thereby compromising the SB. Also the large usage of a dedicated bifurcation stent in our series may have played a role, although a comparison between different types of stents within the Culotte group cannot be performed given the small sample size.

Pathology studies have shown that arterial branch points are foci of low shear and low flow velocity and are sites predisposed to the development of atherosclerotic plaque and thrombus.[22] The important observation was that the most vulnerable bifurcation area is located opposite the flow divider.[23] Since SB dilatation through the stent struts may cause deformation of the MV stent,[6] it is prudent to focus not only on the carina, (one could expect the worst strut apposition at this site, a finding which we have corroborated) but also careful attention should be paid to strut apposition opposite the flow divider, where lower shear stress might possibly serve as a nidus for restenosis or thrombosis.[24] Our observations did not show an increased rate of malapposed struts in the half opposite SB as compared to non-bifurcation segments (proximal and distal to the bifurcation), although this may be explained by the high rate of KB post-dilatation.

Healing of Malapposed Struts

The prognostic implication of suboptimal acute strut apposition following PCI as assessed by OCT, in patients with satisfactory angiographic images, is unknown.

Final Kissing Balloon Post-Dilatation

Since simple technique may cause SB narrowing via carina displacement[25] whilst dilatation of the SB leads to distortion of the MV stent,[6] final KB is highly recommended when treating bifurcation lesions. The beneficial role of final KB is supported by previous clinical observations.[26] However bench-tests indicate that final KB inflation may decrease, but not necessarily eliminate strut-vessel wall separation.[27]

Limitations

Main limitation is represented by the lack of statistical analysis that could fully account for the correlated OCT data, that presents a hierarchical structure with more lesions clustered in the same patients, 4 segments within a single lesion, more struts within the same segment, for each endpoint analyzed. Formal sample size calculations are difficult in this situation and no power calculation algorithm exists, which is based on generally accepted assumptions regarding intra-cluster correlation design factors. The lack of randomization to a simple or complex technique might have created bias in the study results. Indeed, complex technique tended to be selected for true bifurcations whilst a simple technique was reserved for other bifurcation lesion subtypes. Secondly, we used different stent types (including dedicated bifurantion stents for treatment of a part of the SB lesions in the complex technique) each with a unique geometry and cell size which might also have influenced our findings. Therefore we cannot rule out the existence of a small difference in the prevalence of malapposed struts and stent vessel wall separation distance between the two techniques, due to the lack of statistical power. Thirdly, the findings cannot necessarily be applied to other two-stents techniques for the bifurcation treatment, except from the Culotte stenting. Finally, OCT imaging was acquired only from the MV. This obviously penalizes simple technique since malapposed struts in the SB are not detected. In this study OCT was used only at the end of the angiographically guided optimization of stent deployment.

CONCLUSIONS

In coronary bifurcation lesions, strut malapposition occurs most frequently and is most severe at the level of the SB origin. Our findings suggest that the use of complex technique (Culotte) does not significantly affect the rate of strut malapposition across the four segments of bifurcation lesions and is associated with a lower strut vessel wall separation distance of malapposed struts at the proximal segment as compared to a simple strategy of stenting main vessel only. Whether malapposition may play a role in the high incidence of in-stent restenosis or stent thrombosis affecting bifurcation lesions, needs to be assessed in further studies.

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CHAPTER 19

Long-term outcome after the V stenting technique in de novo bifurcation lesions using drug-eluting stents

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EuroIntervention. 2009 Jun; 5 (2): 197-205

EuroIntervention

Long-term outcome after the V stenting technique in *de novo* bifurcation lesions using drug-eluting stents

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The authors have no conflict of interest to declare.

KEYWORDS
Angioplasty, drug eluting stent, stent thrombosis

Abstract

Aims: To report long-term outcome data on the V technique using drug-eluting stents.

Methods and results: From April 2002 to December 2006, 31 consecutive patients were successfully treated with V stenting of a *de novo* bifurcation lesion. The technique involves the deployment of two stents in the two branches of a bifurcation, the proximal edges of the stents just touching one another. Patients exclusively received either sirolimus- (10), paclitaxel- (20) or biolimus-eluting (one) stents. On average, 1.5±0.8 stents with a total length of 26.6±17.2 mm and 1.1±0.4 stents with a total length of 18.3±7.6 mm were deployed in the distal main vessel and side branch respectively. Mean duration of follow-up was 853±553 days. Within 30 days, three patients died; two other patients had definite stent thrombosis involving the V stents, both requiring re-PCI. Beyond 30 days and within one year, there was one death and three cases of target vessel revascularisation, including one target lesion revascularisation. There were a further three deaths (one cardiac) beyond one year. Eleven patients (35.5%) had angiographic follow-up, exhibiting a binary restenosis rate of 9.1% at 203±33 days.

Conclusions: In this real-world cohort, late clinical events stand in accord with studies on competitive techniques, but early outcome was less encouraging, probably due to the baseline risks.

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Introduction

The optimal technique for treating bifurcation lesions with percutaneous coronary intervention (PCI) has not been clearly established. There is particularly little outcome data on V stenting in the current drug-eluting stent (DES) era. The V stenting technique scaffolds both distal limbs of a bifurcation lesion from the carina onwards and is only suitable when the lesion spares the proximal main vessel (PMV)[1]. In treating bifurcation lesions, optimal coverage without any un-stented gaps is essential for optimal scaffolding and drug delivery to mitigate the restenotic process[2-4]. Recently, various groups have described the Simultaneous Kissing Stents (SKS) technique – the simultaneous deployment of the distal main vessel (DMV) and side branch (SB) stents so that the new apposing struts from the two adjacent stents extended proximally from the carina[5-7] for 8±5 mm[5] or 8.9±2.5 mm[6]. Preliminary angiographic[6] and histologic[7] results showed that a new carinal membrane developed on these struts. While this technique can handle proximal disease close to the carina, the PMV receiving the two stents is often over-dilatated with its attendant risks[5]. A newer approach is to implant in the PMV a conical self-expandable Axxess (Devax, Irvine, CA, USA) stent with a "flared" distal part covering the outer rim of the bifurcation and two stents distally with V technique to scaffold the inner rim. To facilitate progress in this field, noting the possible dreaded complication of late stent thrombosis[8], we reviewed the long-term outcome of V stenting using DES from April 2002[9] to December 2006.

Methods

Study population

On April 16, 2002, our institution began to use sirolimus-eluting stents (SES, Cypher, Cordis Corporation, Warren, NJ, USA) as the default strategy for every PCI, until Feb 16, 2003 when paclitaxel-eluting stents (PES, Taxus, Boston Scientific, Natick, MA, USA) became our default strategy. Data were recorded in the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry[10] and the Taxus Stent Evaluated AT Rotterdam Cardiology Hospital (T-SEARCH) registry[11]. From April 2002 to December 2006, 656 procedures involving treatment of *de novo* bifurcation lesions were performed in 638 patients. Out of this cohort, and after reviewing the angiographic films, we identified 31 consecutive patients, who had one bifurcation lesion successfully treated with V stenting; none of them had a second procedure involving this technique. Written informed consent was obtained from all patients prior to the procedure.

Procedure

V stenting is defined as the delivery and implantation of two stents in the two branches of a bifurcation; one stent is deployed in the DMV and the other one in the SB[12]. The stents can be deployed either concurrently or in a successive mode[13]. The latter is presumably an acceptable alternative, provided that the second stent is deployed concurrently with a balloon inflated in the first stent, to protect this from being crushed; systematic post-dilation with kissing balloons should be performed. To differentiate from the SKS technique, we defined V stenting as the proximal edges of the stents just touching one another without any significant overlap, protruding into the PMV by no more than 5 mm[12] (Figure 1).

All procedures were performed according to current interventional standards at the time. The use of predilation, post-procedure kissing balloon inflation and the use of glycoprotein IIb/IIIa inhibitors was left to the operators' discretion. During the procedure, intravenous heparin was administered, in order to maintain an activated clotting time above 250 seconds. All patients were prescribed 80 mg of aspirin lifelong and were pretreated with 300 mg clopidogrel followed by 75 mg clopidogrel for at least six months.

Clinical definitions and follow-up

Angiographic success was defined as residual stenosis <30% by visual estimation in the presence of Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow. Clinical success was defined as angiographic success without the occurrence of death, myocardial infarction or repeat revascularisation of the target lesion during the hospital stay. Myocardial infarction was diagnosed by an increase in creatine kinase-MB fraction of three times the upper limit of normal, according to American Heart Association / American College of Cardiology guidelines[14]. Target lesion revascularisation (TLR) and target vessel revascularisation (TVR) were defined according to the Academic Research Consortium (ARC) recommendations[15]; they were adjudicated as clinically indicated, only if driven by symptoms/objective signs of ischaemia and a percent diameter stenosis exceeding 50% on follow-up angiography. Clinical events were recorded in two ways: firstly, as composite major adverse cardiac events (MACE), including all-cause death, nonfatal myocardial infarction and TVR and secondly, in the form of the ARC recommended device-oriented composite, including cardiac death, myocardial infarction (not clearly attributable to a non-target vessel) and TLR.

We applied ARC recommendations to adjudicate stent thrombosis. Angiographically defined thrombosis with TIMI grade 0 or 1 flow or the presence of a flow-limiting thrombus accompanied by acute symptoms was considered as definite stent thrombosis. Unexplained death was adjudicated as probable stent thrombosis if occurring within 30 days, and as possible stent thrombosis if after 30 days[15]. Stent thrombosis was further categorised according to the timing of the event into acute (within 24 hours), subacute (24 hours-30 days), late (30 days-1 year) and very late (beyond one year). We retrieved electrocardiographic (ECG) information on patients with myocardial infarction for adjudication.

Data sources for both registries included municipal civil registries for survival status, information from health questionnaires, medical records, and information from local physicians on repeat coronary interventions (surgical or PCI), myocardial infarction and medication usage [10, 11].

Angiographic evaluation

The bifurcation lesions were adjudicated according to the Medina classification[16] after reviewing the pre-procedure images. Quantitative coronary angiographic (QCA) analysis was performed by means of dedicated bifurcation QCA software (CAAS 5.4,

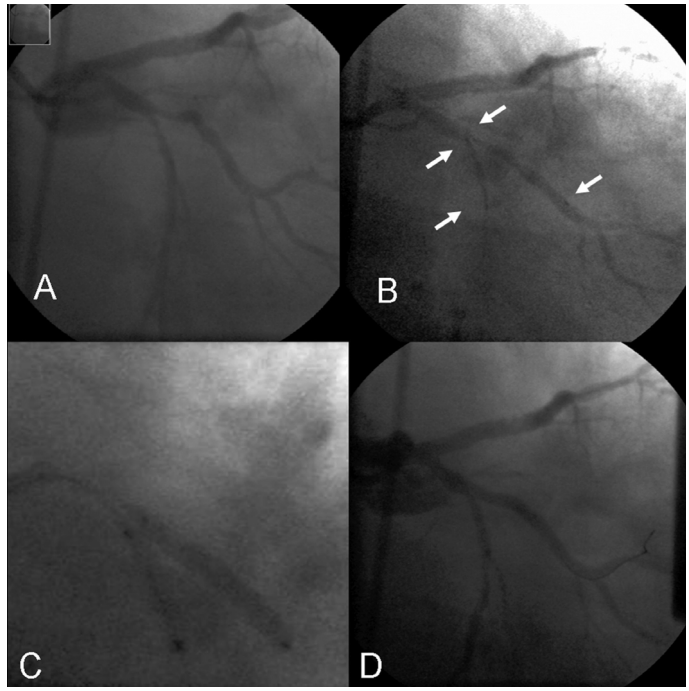

Figure 1. Illustration of V stenting technique. A. Typical 0,1,1 bifurcation lesion involving the left circumflex (LCX) and the obtuse marginal (OM) branch (distal main vessel). B. Two sirolimus-eluting, Cypher, stents have been advanced into position. The 3.0 x 23 mm stent is in the OM, the 2.5 x 13 mm stent is in the LCX. Arrows point at the stents' markers; the proximal markers barely touch each other, not protruding into the proximal main vessel. C. Both stents are simultaneously deployed. D. Final result.

Maastricht, PIE Medical software, The Netherlands) (Figure 2); the relevant methodology employing a ten-segment model for the bifurcation lesion has already been described[17]. Angiographic parameters, namely minimal lumen diameter (MLD), interpolated reference vessel diameter (RVD) and percentage diameter stenosis (DS), were independently determined both within the stent(s) and within the segment(s). These parameters were measured pre-procedure, post-procedure and, when available, at follow-up. In the case of a chronic total occlusion (CTO), the MLD equals 0 mm, %DS equals 100% and RVD cannot be determined. Late lumen loss (LLL) was calculated as the difference in MLD between post-procedure and follow-up. Angles between the PMV and SB (proximal bifurcation angle) and between DMV and SB (distal bifurcation angle) were automatically determined. Binary angiographic restenosis was defined as DS ≥50% at follow-up.

Statistical analysis

Categorical variables are presented as counts and percentages, whereas continuous variables are expressed as mean ± standard deviation. A comparison of angiographic variables both between pre and post and between post and follow-up was performed with a Wilcoxon signed rank test. A p- value of <0.05 was considered significant. Statistical analysis was performed using commercially available software (SPSS 12.0 for Windows, SPSS, Chicago, IL, USA).

Results

The baseline demographics and procedural characteristics in the 31 patients are reported in Tables 1 and 2. PCI was performed in 20 (64.5%) patients for an acute coronary syndrome (22.6% with ST elevation myocardial infarction and 41.9% with unstable angina or non-ST elevation myocardial infarction). Twenty-three patients (74.2%) had multivessel disease and 12 of them (38.7%) had interventions to at least one additional major epicardial vessel beyond the target vessels. All patients received exclusively one type of DES; Taxus and Cypher stents were implanted in 20 and 10 cases respectively. There was a single patient who received exclusively biolimus-eluting stents (BES, Biomatrix, Biosensors, Singapore); he was recruited in a research study and had no clinical event during the follow-up period. The average number of stents was 3.5±1.5 per patient with a total stent length 64.1±32.6 mm. However, regarding

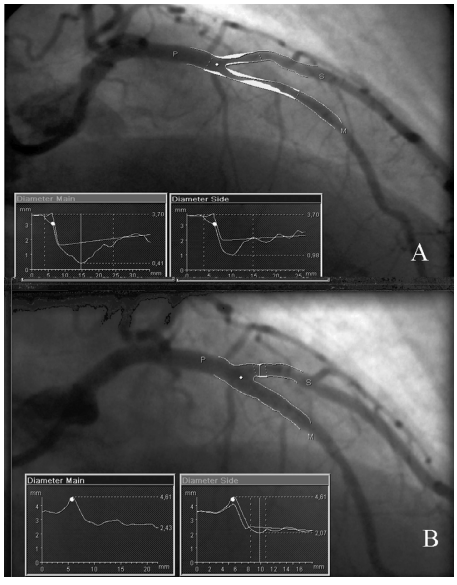

Figure 2. Quantitative coronary angiography of a bifurcation lesion involving the left anterior descending (LAD) and the diagonal branch (side branch). Automatic contour detection pre-procedure (A) and post-procedure (B). Images include the corresponding diameter plots for the main branch and the side branch (CAAS 5.4, Maastricht, PIE Medical software, The Netherlands).

the bifurcation lesion itself, 1.5±0.8 stents with a mean total length of 26.6±17.2 mm and 1.1±0.4 stents with a mean total length of 18.3±7.6 mm were deployed in the DMV and SB respectively. All patients had Medina bifurcation lesion classification of 0,1,1 for the lesion receiving V stenting. The left main bifurcation was the location of the lesion in the majority of the cases (16 cases-51.6%); the lesion involved the left anterior descending (LAD)/diagonal bifurcation in eight cases, the left circumflex (LCX)/obtuse marginal bifurcation in six cases and the distal right coronary artery (RCA) bifurcation in one case. Stents were deployed simultaneously at all times, whereas post-dilation with kissing balloons was performed in 10 cases (32.3%); glycoprotein IIb/IIIa inhibition was employed in 13 cases (41.9%).

Thirty-day outcome

Within 30 days, three patients died (patients 1, 2 and 3 in Table 3). The first death was regarded as non-cardiovascular, since the patient succumbed to hospital acquired pneumonia after a stroke, whereas patient 2 was adjudicated to have probable stent thrombosis. Patient 3 could not be saved despite a rescue procedure for cardiogenic shock after failed thrombolysis, and died of heart failure. Two other patients had definite stent thrombosis and required emergency PCI, one on day 0 and one on Day 5. The latter (patient 4 in Table 3), a 78-year old man suffering a heart attack five days after a prostate operation, had a cerebral haemorrhage on day 4 and therefore aspirin and clopidogrel were discontinued; the stents occluded the very next day. Finally, another patient who had the V stents placed at the left main bifurcation, and also had intervention on a sub-totally occluded venous graft to his right coronary artery, had a myocardial infarction on the same day; ECG changes pointed to the treated graft as the culprit.

Table 1. Patient demographics and clinical characteristics (n = 31).

Age (years)	65.9±11.4
Male gender (%)	22 (70.9)
Diabetes mellitus (%) -all NIDDM	5 (16.1)
Hypertension (%)	10 (32.3)
Hypercholesterolaemia (%)	15 (48.4)
Current smoker (%)	6 (19.4)
Previous myocardial infarction (%)	12 (38.7)
Previous PCI (%)	4 (12.9)
Previous CABG (%)	2 (6.5)
Clinical presentation	
Stable angina (%)	11 (35.5)
Unstable angina or non-ST elevation myocardial infarction (%)	13 (41.9)
ST elevation myocardial infarction (%)	7 (22.6)
Glycoprotein IIb/IIIa inhibitors periprocedural usage (%)	13 (41.9)

NIDDM: non insulin dependent diabetes mellitus; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft surgery

Table 2. Baseline angiographic and procedural characteristics (n = 31).

Multivessel disease (%)	23 (74.2)
Multivessel intervention (%)	21 (67.7)
Angiographic success (%)	31 (100)
Clinical success (%)	25 (80.6)
Target bifurcation lesion location	
LMS (%)	16 (51.6)
LAD / diagonal (%)	8 (25.8)
LCX / obtuse marginal (%)	6 (19.4)
RCA bifurcation (%)	1 (3.2)
CTO within the target bifurcation lesion	5 (16.1)
In the distal main vessel	4 (12.9)
In the side branch	1 (3.2)
Mean number of stents per patient	3.5±1.5
Mean total length of stents (mm)	64.1±32.6
Mean number of stents in the main vessel	1.5±0.8
Mean total length of stents in the main vessel (mm)	26.6±17.2
Mean number of stents in the side branch	1.1±0.4
Mean total length of stents in the side branch (mm)	18.3±7.6
DES implanted	
Patients receiving SES (%)	10 (32.3)
Patients receiving PES (%)	20 (64.5)
Patients receiving BES (%)	1 (3.2)
Post-dilation with kissing balloons (%)	10 (32.3)

LMS: left main stem; LAD: left anterior descending; LCX: left circumflex; RCA: right coronary artery; CTO: chronic total occlusion; DES, SES, PES, BES: drug-, sirolimus, paclitaxel and biolimus- eluting stents respectively

Table 3. All-cause death: patient characteristics and procedural details.

Patient	Gender/Age	Index PCI indication	Treated vessels	V stents location	Stent type	GP IIb/IIIa Inhibitor use	Kissing balloon inflation	Stent thrombosis by ARC definitions	Time to TLR/TVR, days	Time to Death, days	Remarks
1	M/64 yrs	Unstable angina	LCX, intermediate	LCX-intermediate	PES	Yes	Yes	No	No	11	Stroke on day 4, died of hospital acquired pneumonia
2	F/63 yrs	Unstable angina	LAD, LCX	LAD-LCX	PES	Yes	Yes	Probable	No	11	Pulmonary embolism, hence anti-coagulated. Sudden death preceded by generalised convulsion
3	M/78 yrs	ST elevation myocardial infarction	LAD, LCX	LAD-LCX	SES	No	No	No	No	14	Index PCI was rescue procedure for cardiogenic shock. Died of heart failure
4	M/78yrs	ST elevation myocardial infarction	LAD, diagonal	LAD-diagonal	PES	No	No	Definite	LAD stent thrombosis Day 5	42	Cerebral haemorrhage on day 4; cessation of aspirin and clopidogrel on the same day; LAD and LM stented on re-PCI with moderate result Sudden death during recovery
5	F/80yrs	Unstable angina	LAD, LCX, OM	LCX-OM	SES	No	No	No	No	450	Sepsis after amputation
6	M/74yrs	Unstable angina	LAD, LCX	LAD-LCX	SES	No	No	No	Ostial LCX restenosis Day 189	1058	Ischaemia-driven TLR, day 189. Succumbed to end-stage heart failure
7	M/66yrs	Stable angina	LAD, LCX	LAD-LCX	SES	Yes	No	No	No	1206	Sepsis due to pneumonia

PCI: Percutaneous coronary intervention; TLR: Target lesion revascularisation; TVR: Target vessel revascularisation; ARC: Academic Research Consortium; LCX: Left circumflex; LAD: Left anterior descending; OM: Obtuse Marginal branch; LM: Left Main coronary artery; SES/PES: sirolimus-/paclitaxel-eluting stents

Late clinical outcome

Survival status was available in every patient for ≥ 12 months after the initial PCI. The mean duration to the last follow-up or to death was 853±553 days. Beyond 30 days, and within a year, there was one more death (Table 4). Patient number 4 in Table 3 died on day 42 while recovering from the cerebral haemorrhage; this sudden death was adjudicated as possible stent thrombosis. Three patients required a target vessel revascularisation, but in only two were the bifurcation V stents the targets for re-intervention. One patient underwent repeat coronary angiography and subsequently reintervention on day 160 upon referral for unstable angina. He had a mid-LAD in-stent restenosis of 70% and a borderline 50% (by visual estimation) ostial LAD restenosis, involving the V stents implanted at the LAD-LCX bifurcation. The former lesion was deemed the culprit lesion and was re-stented with a DES, whereas the latter was also treated with a DES deployed in the distal left main into the proximal LAD, fenestrated to the LCX; the procedure was completed with a kissing balloon inflation. However, QCA analysis ascribed a 43.9% stenosis to the ostial LAD restenotic lesion; thus this was not adjudicated as an ischaemia-driven revascularisation. Another patient with LAD-LCX V stents, had a re-study on day 189 revealing ostial LCX in-stent restenosis, which was treated with balloon dilatation. No patients had reinfarction beyond 30 days (Table 4). There were a further three deaths on days 450, 1058, 1206; the causes of death were respectively sepsis, end-stage heart failure and sepsis and none was adjudicated as having stent thrombosis (Table 3). The patient who died of heart failure was actually the single ischaemia-driven TLR case. The overall rates of mortality and other clinical endpoints within 30 days and 1-year (cumulative) are summarily reported in Table 4.

Quantitative angiographic analysis

Analysis of the baseline procedure could be done for 30 out of the 31 patients (Table 5); we could not retrieve post-procedure images for one case. Out of the 30 baseline procedures analysed, there were five cases involving a CTO, therefore the preprocedure RVD and the bifurcation angulation parameters could not be determined. In 11 cases, there was minimal stent protrusion into the PMV (2.23±0.72 mm), however never exceeding 5 mm or the respective RVD of the PMV; in three cases the protrusion was actually less than half the respective RVD. Angiographic follow-up (at a period of 203±33 days) was available for 11 patients (35.5%); data are presented in Table 6. Out of this group, eight patients underwent routine control coronary angiography and presented no binary angiographic restenosis of the target bifurcation lesion; out of the three patients who were referred for anginal symptoms (two with stable angina and one with unstable angina), one patient had binary in-stent restenosis. Thus, this cohort exhibited a restenosis rate of 9.1% (1/11). The LLL in the DMV and SB was 0.17±0.53 mm and

Table 4. Clinical outcome over the follow-up period.

	Within 30 days	At one year (cumulative)
All-cause mortality	3 (9.7%)	4 (12.9%)
Cardiac mortality	2 (6.5%)	3 (9.7%)
Non-cardiovascular mortality	1 (3.2%)	1 (3.2%)
Non-fatal myocardial infarction	2 (6.5%)	2 (6.5%)
Target lesion revascularisation (ischaemia driven)	2 (6.5%)	3 (9.7%)
Target vessel revascularisation (ischaemia driven)	2 (6.5%)	5 (16.1%)
MACE-Mortality or non-fatal ST elevation myocardial infarction or target vessel revascularisation	6 (19.4%)	9 (29.0%)
Device oriented composite-cardiac mortality or target vessel related myocardial infarction or target lesion revascularisation	4 (12.9%)	5 (16.1%)
Stent thrombosis according to Academic Research Consortium definitions	Acute	Subacute	Late
Definite	1 (3.2%)	1 (3.2%)	0 (0%)
Probable	0 (0%)	1 (3.2%)	0 (0%)
Possible	0 (0%)	0 (0%)	1 (3.2%)

MACE: Major Adverse Cardiac Events

Table 5. Angiographic parameters for the baseline procedure (n=30).

	Pre	Post	P-value
Proximal main vessel			
MLD (mm)	1.73±0.55	2.45±0.46	<0.01
RVD (mm)	2.69±0.92	2.90±0.65	0.73
%DS	26.2±16.0	13.8±6.8	<0.01
Distal main vessel			
In segment			
MLD (mm)	0.96±0.59	2.13±0.43	<0.01
RVD (mm)*	2.10±0.47	2.69±0.46	<0.01
%DS	54.8±25.9	19.5±10.1	<0.01
In stent			
MLD (mm)	0.96±0.59	2.39±0.37	<0.01
RVD (mm)*	2.10±0.47	2.70±0.45	<0.01
%DS	54.8±25.9	11.0±7.9	<0.01
Side branch			
In segment			
MLD (mm)	0.99±0.41	1.91±0.47	<0.01
RVD (mm)**	2.04±0.49	2.41±0.44	<0.01
%DS	50.3±19.1	21.6±10.5	<0.01
In stent			
MLD (mm)	0.99±0.41	2.10±0.43	<0.01
RVD (mm)**	2.04±0.49	2.45±0.44	<0.01
%DS	50.3±19.1	14.4±6.0	<0.01
Distal bifurcation angle (degrees)	60.7±21.0	51.1±18.3	0.01

MLD: minimal lumen diameter; RVD: reference vessel diameter; DS: diameter stenosis. * 26 patients (4 pre-procedure chronic total occlusions). ** 29 patients (1 pre-procedure chronic total occlusion).

Table 6. Angiographic parameters from the patients having angiographic follow-up (n=11).

	Post	Follow-up	P-value
Proximal main vessel			
MLD (mm)	2.56±0.48	2.29±0.38	0.09
RVD (mm)	3.03±0.53	2.85±0.36	0.16
%DS	15.9±7.1	19.7±8.2	0.42
LLL (mm)		0.27±0.44	
BAR		0	
Distal main vessel			
In segment			
MLD (mm)	2.24±0.46	2.07±0.44	0.35
RVD (mm)	2.74±0.51	2.65±0.41	0.37
%DS	1.6±1.0	23.0±9.5	<0.01
LLL (mm)		0.17±0.53	
BAR		0	
In stent			
MLD (mm)	2.39±0.41	2.08±0.45	0.04
RVD (mm)	2.74±0.54	2.66±0.42	0.45
%DS	12.1±8.4	22.0±10.3	0.03
LLL (mm)		0.31±0.43	
BAR		0	
Side branch			
In segment			
MLD (mm)	1.96±0.46	1.78±0.49	0.33
RVD (mm)	2.42±0.49	2.44±0.59	0.65
%DS	19.0±7.4	27.1±14.0	0.11
LLL (mm)		0.18±0.60	
BAR		0	
In stent			
MLD (mm)	2.12±0.55	1.83±0.49	0.16
RVD (mm)	2.46±0.50	2.46±0.55	0.79
%DS	14.8±5.9	25.9±14.5	0.04
LLL (mm)		0.29±0.57	
BAR		1 (9.1%)	
Distal bifurcation angle (degrees)	45.6±13.2	50.9±17.7	0.29

MLD: minimal lumen diameter; RVD: reference vessel diameter; DS: diameter stenosis; LLL: late lumen loss; BAR: binary angiographic restenosis

0.18±0.60 mm in-segment and 0.31±0.43 mm and 0.29±0.57 mm in-stent respectively. Sixteen cases exhibited a Y anatomical configuration regarding the bifurcation treated, whereas nine were T-shaped; the distal bifurcation angle was smaller than 70 degrees in the former and larger in the latter.

Discussion

This paper reports a real-world experience on V stenting technique using DES. The paucity of outcome data after V stenting reflects that this technique is rarely performed[9]; the current series of 31 patients were collected over nearly five years. A percentage of 13.7% has been reported[18] regarding the frequency of the type 4 bifurcation lesion according to the ICPS classification system, which is the equivalent of the 0,1,1 lesion in the Medina classification. Even if this is per definition, the ideal lesion configuration for the implementation of V stenting, similar techniques such as Simultaneous Kissing Stents claim a great share of those procedures, accounting for the rarity of V stenting.

Many techniques have been described to treat bifurcations, reflecting the lack of a perfect solution. Although the proposed strategy would be stenting the main branch with provisional stenting of the side branch, this would not apply in this setting; a bifurcation lesion involving a large side branch with a long stenosis certainly calls for a two-stent strategy. With the Crush technique, bench studies revealed that stent deployment even after kissing balloon inflation is often suboptimal and associated with malapposition[4,19], findings corroborated by intravascular ultrasound studies[20]. Stent under-expansion could predispose to higher restenosis rate and thrombotic risk[21,22]. Less data has accumulated for Culotte stenting in the current DES era, but this technique has attracted renewed attention[23,24].

Early outcome

The admittedly less than desirable early outcome (MACE rate of 19.4%) should be interpreted in the context of unstable clinical presentation, extensive coronary disease and a multitude of aggravating factors. This series bears the highest rate (64.5%) of acute coronary syndrome as the clinical presentation compared to other relevant studies in the DES era (13.3-62.0%)[2,3,6,7,24,25]; moreover the rates of multivessel disease (74.2%), multivessel intervention (67.7%), intervention on additional major epicardial vessels beyond the target vessels (38.7%) and the rate of left main stem stenting (51.6%) rank high among the corresponding studies. Out of the three deaths occurring within 30 days, none was clearly attributable to the PCI itself, even though two of them were adjudicated as cardiac. One was due to cardiogenic shock, not reversed by a rescue procedure after failed thrombolysis, and the other one had to be adjudicated as probable stent thrombosis, recent pulmonary embolism notwithstanding; an autopsy was not performed.

As to the two definite stent thrombosis cases, both of them presented with ST elevation myocardial infarction; neither of them was treated with glycoprotein IIb/IIIa inhibitors at index procedure, most probably due to old age; cessation of both antiplatelet agents in the second case was undoubtedly the major contributor to the stent thrombosis within 24 hours. Interestingly, in these two cases, stent protrusion by QCA was either trivial on non-existent. The remaining case of myocardial infarction was related to the concomitant intervention on the sub-totally occluded saphenous vein graft. Applying the ARC recommended device-oriented composite, the event rate substantially drops (12.9%), not adjusting however for the aforementioned circumstances.

Late outcome

Contrary to the early outcome, event rates at one year excluding the first 30 days, are close to the corresponding values reported in the vast majority of the relevant literature. As a matter of fact, cumulative 1-year TVR and TLR rates (16.1% and 9.7% respectively) compare favourably to DES studies employing Crush (11.0% TVR and 9.7% TLR at nine months)[25], Culotte (11.1% TVR and 8.9% TLR at nine months)[24], T stenting (TVR and TLR 27.3% at nine months)[24], SKS (TLR 4.0-13.9%)[5,6] and mixed cohorts (TLR 4.3-9.5 at six months)[2,3,9]. Equally amenable are the angiographic features (low LLL in both branches and low binary restenosis rate), despite the increased average number of stents and total stent length implanted. Of note, in the RESEARCH and T-SEARCH registries[10,11], the average stent length was 38.7±23.7 mm and 42.9±31.2 mm respectively. The Nordic Bifurcation Study stands out due to its strikingly low rates of events (3.4% MACE and 1.0% TLR at six months in the two stent arm); however, this is offset by leaving the much higher angiographic restenosis (16.0%) unattended[26]. Over an average of 853 days of follow-up, there was only one case of possible late stent thrombosis.

Unlike the Crush or Culotte techniques, the V stenting technique does not deform conventional tubular stents. It allows the operator to preserve access to both branches throughout the procedure, without the need to rewire. However, this has to be traded against the possibility of using a smaller guiding catheter, since a guiding catheter of at least 7 Fr for the Taxus stent or even 8 Fr for the Cypher stent, is required for simultaneous stent deployment[12]. Moreover, great precision is required for accurate positioning of the stents, in order to avoid geographic miss or protrusion into the PMV. When the PMV is also involved (i.e. Medina classification 1,1,1), usage of dedicated devices such as the Devax stent to deal with the proximal lesion in the main vessel combined with V stenting of the bifurcation should provide full coverage of the lesion with minimal overlapping of the stent struts. The recent multicentre Axxess Plus trial[27] on 139 patients receiving the Axxess (Devax) stent, reported satisfactory outcome at 6-months with a TLR rate of 7.5% and angiographic in-stent LLL of 0.09 mm. However, only 77.7% of patients were regarded as having "true" bifurcation lesions involving both the PMV and SB and only 41.9% had stenting of both DMV and SB[27]. Future studies with V stenting, plus a proximal dedicated device for more challenging bifurcation lesions, are eagerly awaited.

Limitations

An obvious limitation to this analysis is the small number of patients involved. This precluded us from performing any kind of subgroup analysis; we could not compare events in the DMV and the SB or study the influence of variables, such as the type of DES, the clinical indication, the number of stents and total stented length, the location of the bifurcation lesion and last, but not least, the impact of angulation on the short- and long-term outcome. Even more limited was the rate of angiographic follow-up (35.5%), which was not routinely acquired. Regrettably, IVUS images were not available; in this setting they would have verified complete and accurate lesion coverage and adequate stent struts apposition. Finally, this is a retrospective, single-centre study, with no control arm. This does not allow us to favour or discredit the technique at hand.

Conclusions

We provided long-term outcome data on an unselected cohort who had V stenting of *de novo* bifurcation lesions with drug-eluting stents. It is a technique dedicated to a distinct anatomic dataset. Early outcome looks less than encouraging, but on closer scrutiny could appear circumstantial and endpoint-dependent; late outcome, on the other hand, stands in accord with competitive techniques and merits further evaluation.

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CHAPTER 20

Three-year clinical event rates after contemporary percutaneous coronary intervention in different age groups

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In Press, EuroIntervention.

EuroIntervention

Three-year clinical event rates in different age groups after contemporary percutaneous coronary intervention

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The authors have no conflicts of interest to declare.

KEYWORDS

Angioplasty, stent, elderly, clinical events

Abstract

Aims: As the global population ages, elderly patients will form an increasing proportion of those undergoing percutaneous coronary intervention (PCI). We investigated the safety and efficacy of bare metal stents (BMS) and DES in all patients undergoing PCI at our institution, stratified by age.

Methods and results: We investigated three sequential groups of consecutive patients treated exclusively with BMS (n=2,194; January 2000 to April 2002), sirolimus-eluting stents (SES, n=834; April 2002 to February 2003) and paclitaxel-eluting stents (PES, n=2,841; February 2003 to December 2005). The primary endpoint was all-cause mortality. Secondary endpoints included target vessel revascularisation (TVR) and composite major adverse cardiac events (MACE, defined as all-cause death, any nonfatal myocardial infarction or TVR). Patients were followed up for a median of 1,366 days. Patients were stratified into equal quintiles based on age (<51.8, 51.8-58.4, 58.4-65.4, 65.4-73.0 and >73.0 years). All-cause mortality was significantly higher in the eldest two groups, while TVR rates were similar across all age groups. DES were associated with reductions in TVR and MACE and a trend towards reduced mortality in all age groups.

Conclusions: DES are safe and effective when compared to BMS, irrespective of age.

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Introduction

The benefit of percutaneous coronary intervention (PCI) with bare metal stents (BMS) in elderly patients is clearly established, with improvements in quality of life and clinical outcome when compared to medical therapy[1-8]. However, although global life expectancy is rising (projected increase from 77 years to 82 years by 2045-2050 in developed countries)[9] and drug-eluting stents (DES) have been shown to be effective in reducing restenosis in a wide array of patients[10-12], the relative safety and efficacy of DES in the elderly remains less clearly established, with existing data limited to either small cohorts or relatively short-term follow-up[13,14]. The majority of randomised controlled trials of drug-eluting stents had an mean age of 60-65 years[12], and therefore, provide little information for the ever-growing elderly population. As a result, recently the American Heart Association has called for an increase in the recruitment of elderly patients in clinical trials[15,16]. We therefore stratified all patients undergoing PCI in our institution between 2000-2005 for *de novo* coronary stenoses by age, to investigate the long-term safety and efficacy of contemporary PCI with BMS and DES in different age groups.

Methods

Between January 2000 and December 2005, we examined all patients undergoing PCI with a single stent type for *de novo* coronary stenoses in our institution. The only exclusion criteria were the implantation of more than one different stent type during the index procedure or PCI for in-stent restenosis (Figure 1). Initially, all patients were treated with BMS, but on the 16th April 2002, our institution adopted the use of sirolimus-eluting stents (SES: Cypher; Cordis, Warren, NJ, USA) as the default strategy for all coronary interventions as part of the RESEARCH registry[17]. On the 16th of February 2003, SES were replaced by paclitaxel-eluting stents (PES: Taxus; Boston Scientific, Natick, MA, USA) as the default stent as part of the T-SEARCH registry[18]. This single centre registry therefore consists of three sequential groups of consecutive patients: BMS (n=2,194; January 2000 to April 2002), SES (n=834; April 2000 to February 2003) and PES (n=2,841; February 2003 to December 2005). Patients initially enrolled in one of the sequential cohorts (BMS, SES or PES) were maintained for analytical purposes throughout the follow-up period in their original cohort, even if a subsequent intervention of another lesion was performed using a different type of stent. We subsequently stratified the patients into quintiles based on age. The primary endpoint was all-cause mortality. Secondary endpoints included target vessel revascularisation (TVR) and composite major adverse cardiac events (MACE, defined as all-cause death, nonfatal myocardial infarction in any vascular territory or TVR).

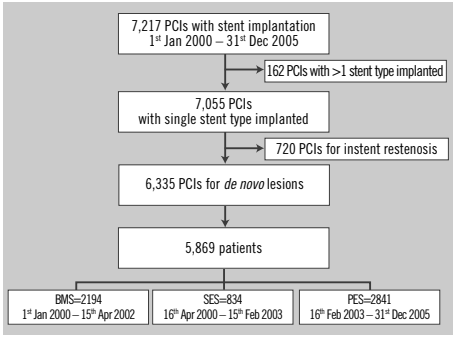

Figure 1. Flowchart of patient recruitment.

All procedures were performed following standard procedural guidelines at the time[19]. The use of glycoprotein IIb/IIIa inhibitors or adjunctive devices was left up to the operator's discretion. Angiographic success was defined as residual stenosis <30% by visual estimation in the presence of Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow. All patients were advised to maintain lifelong aspirin. Hypercholesterolaemia was defined as fasting total cholesterol >5 mmol/l (193 mg/dl) or the use of lipid-lowering therapy. Hypertension was defined as blood pressure greater than 140/90 mmHg or the use of antihypertensive medications. Renal impairment was defined as a serum creatinine >150 µmol/l (1.7 mg/dl).

Annual follow-up survival data were obtained from municipal civil registries for all patients. The causes of death were classified according to the International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). A questionnaire was subsequently sent to all living patients with specific enquiries about repeat hospital admission and adverse events. As the principal regional cardiac referral centre, repeat procedures (percutaneous and surgical) are normally performed at our institution and recorded prospectively in our database. For patients who suffered an adverse event at another centre, medical records or discharge summaries from the other institutions were systematically reviewed. General practitioners, referring cardiologists and patients were contacted as necessary if further information was required. The protocol was approved by the hospital ethics committee and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

Statistical analysis

The patient population was stratified into five groups using the 20th, 40th, 60th and 80th age percentiles as cut-off points. Categorical variables are presented as percentages and were compared by Pearson's chi-square test or Fisher's exact test. Continuous variables are presented as mean ±standard deviation and were compared by means of the F test for analysis of variance. A 2-sided p value of <0.05 was used to indicate statistical significance. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method and curves were compared using the log-rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. To adjust for differences in baseline characteristics between the age groups, each paired age group comparison was forced into separate Cox regression models, using all variables listed in Table 1. To investigate the effects of stent type on outcomes, stent type was forced into separate Cox regression models for each age group,

Table 1. Patient demographics, angiographic and procedural characteristics after stratification by age.

Group	1	2	3	4	5	Overall	*p* for trend
	n=1174	n=1174	n=1175	n=1173	n=1173	n=5869	
Age range (years)	<51.8	51.8-58.4	58.4-65.4	65.4-73.0	>73.0		
Mean age, years	45±5	55±2	62±2	69±2	78±4	62±12	<0.001
Male	81%	83%	74%	67%	57%	72%	<0.001
Hypertension	28%	38%	39%	43%	43%	38%	<0.001
Hypercholesterolaemia	47%	53%	54%	50%	44%	50%	0.03
Family history of coronary artery disease	40%	34%	31%	23%	19%	29%	<0.001
Current smoker	47%	29%	25%	18%	10%	26%	<0.001
Diabetes mellitus	11%	14%	16%	18%	17%	15%	<0.001
Renal impairment	1%	1%	2%	2%	3%	2%	<0.001
Previous myocardial infarction	29%	33%	30%	31%	34%	31%	0.11
Previous coronary artery bypass grafting	3%	5%	9%	12%	16%	9%	<0.001
Previous percutaneous coronary intervention	11%	14%	16%	18%	17%	15%	<0.001
Clinical presentation							
Stable angina	34%	43%	44%	43%	42%	41%	<0.001
Unstable angina / Non-ST-elevation myocardial infarction	28%	30%	29%	32%	39%	32%	<0.001
ST-elevation myocardial infarction	39%	27%	27%	25%	20%	27%	<0.001
Cardiogenic shock	2%	1%	1%	2%	2%	2%	0.20
Number of diseased vessels	1.5±0.7	1.6±0.7	1.8±0.8	1.8±0.8	2.0±0.9	1.8±0.8	<0.001
Multivessel disease	38%	48%	53%	56%	62%	51%	<0.001
Number of vessels treated	1.2±0.5	1.3±0.6	1.3±0.6	1.3±0.6	1.4±0.6	1.3±0.6	<0.001
Multivessel treatment	20%	27%	28%	29%	33%	27%	<0.001
Coronary vessels treated*							
Right coronary	36%	39%	38%	39%	37%	38%	0.80
Left main coronary	3%	3%	4%	5%	7%	4%	<0.001
Left anterior descending	54%	55%	56%	51%	54%	54%	0.25
Circumflex	26%	31%	29%	31%	34%	30%	0.001
Saphenous vein graft	1%	2%	4%	5%	7%	4%	<0.001
Number of lesions treated	1.5±0.9	1.7±0.9	1.7±0.9	1.7±0.9	1.7±1.0	1.6±0.9	<0.001
ACC/AHA lesion classification¶							
Type A	15%	15%	15%	13%	13%	14%	0.07
Type B1	30%	31%	30%	28%	30%	30%	0.40
Type B2	40%	46%	44%	47%	45%	44%	0.007
Type C	39%	37%	37%	38%	41%	38%	0.29
Bifurcation	8%	9%	10%	9%	9%	9%	0.62
Chronic total occlusion	8%	9%	9%	7%	7%	8%	0.02
Bare metal stents	38%	38%	35%	38%	37%	37%	0.51
Sirolimus-eluting stents	15%	16%	14%	13%	13%	14%	0.05
Paclitaxel-eluting stents	47%	46%	50%	50%	49%	48%	0.05
Number of stents implanted	1.8±1.2	2.0±1.3	2.0±1.3	2.1±1.4	2.2±1.5	2.0±1.3	<0.001
Mean stent diameter, mm	3.1±0.6	3.1±0.6	3.1±0.6	3.0±0.6	3.0±0.6	3.1±0.6	0.14
Total stented length, mm	33±26	37±28	37±28	38±28	39±29	37±28	<0.001
Intravascular ultrasound	17%	19%	16%	16%	12%	16%	<0.001
Glycoprotein 2b/3a inhibitor	29%	24%	24%	23%	17%	24%	<0.006
Angiographic success	97%	96%	96%	94%	94%	95%	<0.001
Duration of clopidogrel, months	4.5±2.8	4.6±3.4	4.7±3.9	4.7±3.3	4.6±3.4	4.6±3.4	0.37

*expressed as percentage of patients with each vessel type, hence total >100%; ¶expressed as percentage of patients with each lesion type; ACC: American College of Cardiology; AHA: American Heart Association

again using all variables in Table 1. The final results are presented as adjusted hazard ratios (HR) with 95% confidence intervals (CI).

Results

Complete follow-up was available for 98.6% of patients, with a median duration of follow-up of 1,366 days (interquartile range [IQR]: 962-1,797). The mean age of the total cohort was 61.9±11.6 years. The values for the 20th, 40th, 60th and 80th age percentiles were 51.8, 58.4, 65.4 and 73.0 years, respectively. The patient population was subsequently stratified into five age groups using these cut-off values. There were significant differences in the duration of follow-up between the groups, with a shorter duration for the older groups: Group 1 median follow-up 1,463 days (IQR: 966-2,010), Group 2 median 1,481 days (IQR: 922-2009), Group 3 median 1,379 days (IQR: 887-1,768), Group 4 median 1,332 days (IQR: 833-1,766) and Group 5 median 1,212 days (IQR: 750-1,652).

There were significant differences in risk factor profiles across the groups (Table 1): as the patients became progressively older, there were more women and higher rates of hypertension, diabetes mellitus, renal impairment and the patients more often had undergone previous revascularisation. The eldest groups had lower rates of hypercholesterolaemia and a family history of coronary disease, and were less often current smokers. The older groups were more likely to present with unstable angina or non-ST-elevation-MI, while the younger groups were more likely to present with ST-elevation MI.

Angiographic and procedural variables are also described in Table 1. The older cohorts had more extensive coronary disease and underwent more extensive revascularisation: they were more likely to have treatment of the left main coronary artery or a saphenous vein graft and to undergo multivessel PCI. Glycoprotein IIb/IIIa inhibitors were used less frequently as age increased.

The mortality rates were significantly higher in the eldest two groups (Figure 2A) although there were no differences in TVR rates (Figure 2B). The cumulative rates of composite MACE were also higher in the oldest two cohorts (Figure 2C). Table 2 shows the adjusted hazard ratios for all-cause mortality, TVR and composite MACE between the different age groups. The eldest two cohorts had a trend towards higher TVR rates when compared to the younger three groups (statistically significant when compared to group 2). Mortality rates were higher in the older groups (although not reaching statistical significance when comparing group 1 with group 2, and group 2 with group 3). Although MACE rates also increased in the older groups, the relative excess in risk for MACE compared with younger patients was lower than the risk for death.

When examining clinical endpoints according to stent type, DES were associated with consistent non-significant trends towards lower all-cause mortality in all age groups (Figure 3A). There were no differences in the rates of cardiac death comparing DES with BMS across all five age groups (Figure 3B).TVR was significantly lower with DES in all apart from the oldest group, where the benefit just failed to reach statistical significance (Figure 3C). Overall MACE was lower in all age groups, although not reaching statistical significance in the youngest and oldest (Figure 3D).

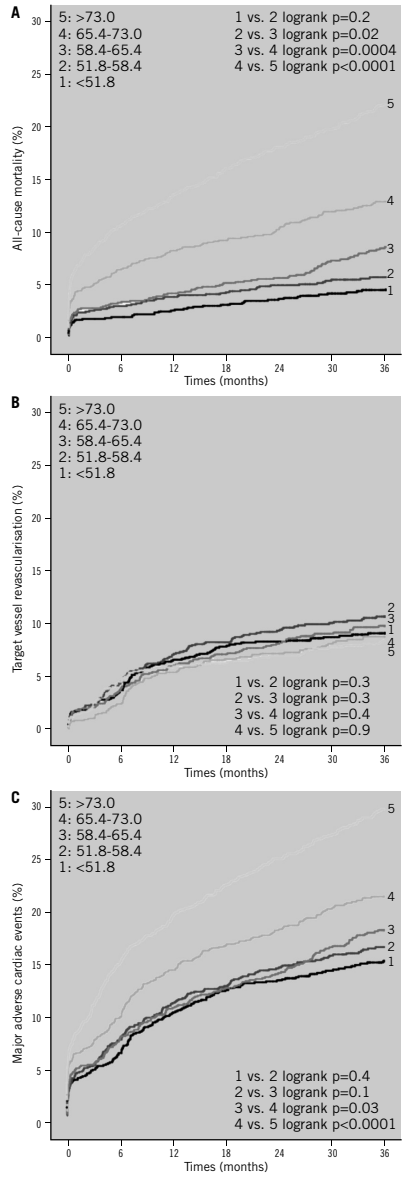

Figure 2. Kaplan-Meier curves for the cumulative incidence of (A) all-cause mortality (B) target vessel revascularisation and (C) composite major adverse cardiac events (all-cause death, nonfatal myocardial infarction or target vessel revascularisation) amongst patients stratified by age.

Table 2. Hazard ratios for 3-year advrse events between different age groups after adjustment for differences in baseline, angiographic and procedural characteristics.

	All-cause mortality Adjusted HR (95% CI)	TVR Adjusted HR (95% CI)	MACE Adjusted HR (95% CI)
Age 51.8-58.4 (Group 2) vs. Age <51.8 (Group 1) (<51.8)	1.30 (0.84-2.03)	1.14 (0.84-1.53)	1.05 (0.83-1.33)
Age 58.4-65.4 (Group 3)	1.61 (1.06-2.43)	1.04 (0.77-1.41)	1.04 (0.83-1.32)
Age 65.4-73.0 (Group 4)	2.77 (1.87-4.09)	0.80 (0.58-1.11)	1.24 (0.99-1.56)
Age >73.0 (Group 5)	5.15 (3.55-7.49)	0.80 (0.56-1.09)	1.93 (1.56-2.40)
Age 58.4-65.4 (Group 3) vs. Age 51.8-58.4 (Group 2)	1.21 (0.83-1.77)	0.95 (0.71-1.27)	1.01 (0.81-1.27)
Age 65.4-73.0 (Group 4)	1.79 (1.25-2.56)	0.74 (0.54-1.00)	1.13 (0.91-1.42)
Age >73.0 (Group 5)	3.73 (2.67-5.20)	0.70 (0.51-0.96)	1.75 (1.41-2.16)
Age 65.4-73.0 (Group 4) vs. Age 58.4-65.4 (Group 3)	1.53 (1.12-2.09)	0.84 (0.62-1.14)	1.16 (0.94-1.43)
Age >73.0 (Group 5)	2.56 (1.93-3.40)	0.81 (0.60-1.11)	1.64 (1.34-2.01)
Age >73.0 (Group 5) vs. Age 65.4-73.0 (Group 4)	1.83 (1.43-2.34)	0.95 (0.69-1.31)	1.39 (1.15-1.69)

TVR: target vessel revascularisation; MACE: major adverse cardiac events defined as all-cause mortality, nonfatal myocardial infarction or target vessel revascularisation; HR: hazard ratio; CI: confidence interval

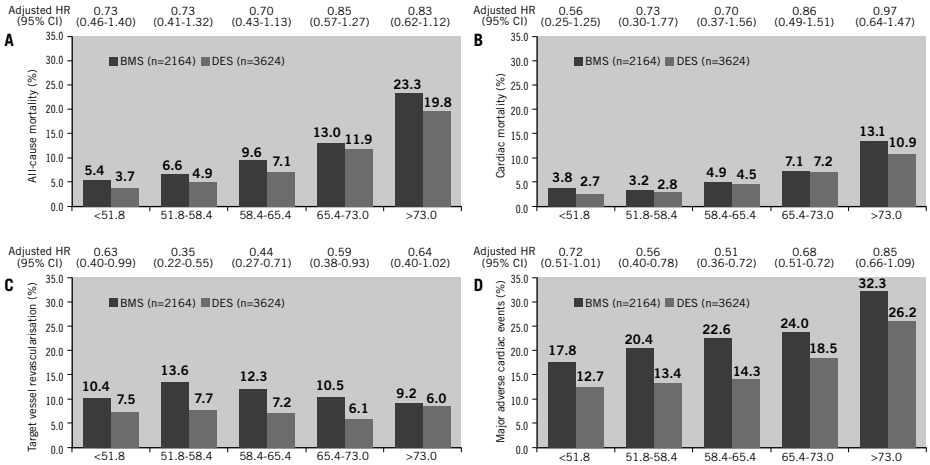

Figure 3. Rates of adverse events in patients according to stent type with Hazard ratios for treatment with drug-eluting vs. bare metal stents after adjustment for differences in baseline characteristics: (A) all-cause mortality (B) cardiac mortality (C) target vessel revascularisation and (D) composite major adverse cardiac events (all-cause death, nonfatal myocardial infarction or target vessel revascularisation). BMS: bare metal stents; DES: drug-eluting stents; HR: hazard ratio; CI: confidence interval

Discussion

The main findings of this study are that DES are safe and effective irrespective of age: they reduce TVR and overall MACE and are associated with non-significant reductions in mortality compared to BMS across all age groups. Although TVR rates were similar between the age groups, MACE and mortality rates increased with age: the oldest group had a five-fold increase in mortality compared with the youngest group within three years of the procedure (adjusted HR 5.15, 95% CI 3.55-7.49).

A recent analysis of Medicare patients in the USA aged 66 or older found a significant reduction in 2-year mortality with DES when compared to contemporary BMS patients (adjusted HR 0.83, 95% CI 0.81-0.86) and historical BMS patients (adjusted HR 0.79, 95% 0.77-0.81)[20]. We found a similar risk reduction amongst our patients groups, although the smaller sample size of our population meant the reduction in mortality across all age groups did not reach statistical significance.

The United Nations department of Economic and Social affairs has estimated that the global life expectancy at birth has risen from 58 years in 1970-1975 to 67 years in 2005-2010, and is expected to keep on rising to reach 75 years in 2045-2050. In developed countries, the projected rise is from 77 years today to 82 years by the

middle of the 21st century, and in the less developed regions, from 65 years in 2005-2010 to 74 years in 2045-2050. In The Netherlands, the current overall life expectancy is 79.8 years (77.5 years for male and 81.9 years for females) which is the 17th highest life expectancy in the world (below Japan but above the USA)[9]. Given this data, and the fact that in our population the age of 80 represented the 95th centile, rather than using an arbitrary cut-off point, we have employed a more recognised statistical methodology by stratifying our patients by age into equal groups by quintiles. The patients in our oldest group (age >73.0 years) had a mean age of 78 years, and therefore represent the very elderly. These patients had significantly higher all-cause mortality than the patients in Group 4 (age 65.4-73.0 [adjusted HR 1.83, 95% CI 1.43-2.34]).

It is already well established that the elderly have more extensive coronary disease and more comorbidities than younger patients. Furthermore, they have greater degrees of coronary artery calcification and a higher risk of bleeding, particularly if glycoprotein IIb/IIIa inhibitors are used[21,22]. Nevertheless, there is evidence that PCI with BMS may improve quality of life[1,2,7] and survival[3,23] in elderly patients, even though their short- and long-term survival remains poor compared to younger patients[24-28]. It is reasonable to assume that provided that DES are safe and effective in reducing restenosis in the elderly, the quality of life benefits may even supersede those provided by BMS. Nevertheless, existing data on revascularisation in elderly patients (irrespective of the definition or cut-off point used) in the DES era are limited either by small numbers or short-term follow-up[13,29]. The randomised trials comparing DES and BMS provide little data on elderly patients[22]. Data from the German Cypher registry found that in 954 patients aged over 75 years, the 6-month unadjusted mortality (3.6%) was three times that of patients under 75, with no difference in TVR (7.3%) or MACE (14.6%)[14]. Our data are therefore unique, since we found a decrease in TVR and overall MACE with DES in all age groups after a median of 1,366 days, despite more advanced coronary disease and more extensive revascularisation in our elderly patients. The similar rates of reduction in TVR across all age groups show that DES are effective, regardless of age. Although the mortality in the eldest group was markedly higher than in younger patients, we found a non-significant trend towards reduced mortality with DES compared to BMS with no increase in cardiac deaths across the board, providing reassuring evidence regarding the safety of DES in elderly patients.

Limitations

This is a single centre observational study. Furthermore, there were significant baseline and procedural differences between the three historical stent groups, together with different lengths of follow-up due to their sequential nature. We have attempted to account for differences between the cohorts in terms of baseline demographics by using Cox regression analysis, although we acknowledge that each statistical method has limitations and there is no consensus method for adjusting for these differences. Nevertheless, the use of a single stent type at any particular time period eliminates bias towards using DES in higher risk patients. Furthermore, very elderly patients (age >90) were not investigated separately in this analysis: further research on this subset of patients is required.

Acknowledgements

We would like to acknowledge the senior cardiologists involved in the PCI procedures: P.J. de Feyter, MD, PhD; P.P.T. de Jaegere, MD, PhD; H.J. Duckers MD,PhD; S.H. Hofma, MD, PhD; E. McFadden, MD, PhD; E.Regar, MD, PhD; G. Sianos, MD, PhD; P.C. Smits, MD, PhD; M.J. van der Ent, MD, PhD; W.J. van der Giessen, MD, PhD; C.A. van Mieghem, MD.

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CHAPTER 21

Impact of sex on 3-year outcome after percutaneous coronary intervention using bare-metal and drug-eluting stents in previously untreated coronary artery disease: insights from the RESEARCH and T-SEARCH Registries

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JACC Cardiovasc Interv. 2009 Jul;2(7):603-10.

Impact of Sex on 3-Year Outcome After Percutaneous Coronary Intervention Using Bare-Metal and Drug-Eluting Stents in Previously Untreated Coronary Artery Disease

Insights From the RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) Registries

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Objectives We investigated the impact of sex on outcomes after percutaneous coronary intervention (PCI) with drug-eluting stent (DES).

Background Women have a higher risk of adverse outcomes after PCI than do men. However, long-term outcomes of women after contemporary PCI with DES have not been fully investigated.

Methods We performed a retrospective cohort study of 4,936 consecutive patients (28.2% women) who underwent PCIs between 2000 and 2004, before and after introduction of DES (bare-metal stent [BMS] group: n = 2,131, DES group: n = 2,805), to assess the impact of sex on long-term PCI outcomes and to compare outcome after PCI of women between the DES and BMS eras.

Results Compared with men, women undergoing PCIs were 5 years older and more frequently have comorbidities such as diabetes mellitus and hypertension. In patients treated throughout the BMS and DES eras, there were no differences by sex for risk of all-cause death, myocardial infarction, or target vessel revascularization 3 years after procedure. The procedural complexity was higher in the DES era, nevertheless, risk for target vessel revascularization and major adverse cardiac event at 3 years were significantly lower in women treated with DES than in women treated with BMS (adjusted hazard ratio [HR] for target vessel revascularization: 0.52 [95% confidence interval (CI): 0.36 to 0.75], adjusted HR for major adverse cardiac event: 0.63 [95% CI: 0.48 to 0.83]).

Conclusions Although women had worse baseline characteristics, no differences in 3-year outcomes were observed between men and women. Compared with BMS use, DES use has decreased revascularization rate equally in women and men. (J Am Coll Cardiol Intv 2009;2:603–10)

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Manuscript received February 9, 2009, accepted March 4, 2009.

Coronary heart disease remains the leading cause of death among men and women in developed countries (1), and in Europe, around 25% of coronary revascularization is performed on women (2). In the early balloon angioplasty era, several studies found that female sex was an independent predictor of in-hospital mortality and that compared with men, women had lower rates of angiographic success, higher incidence of procedural complications and in-hospital death, and worse long-term outcomes after percutaneous

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coronary intervention (PCI) (3–5). In the bare-metal stent (BMS) era, sex-based differences in outcomes have decreased in patients undergoing PCI (6,7). In a large prospective registry study of 4,374 patients treated with BMS, women had lower rates of restenosis at 6-month angiographic follow-up compared with men, and women less frequently required target vessel revascularization (TVR) at 1 year: female sex was an independent predictor of freedom from restenosis (8). Furthermore, a recent study (9) performed in patients treated with BMS demonstrated that female sex conferred a long-term survival advantage after PCI despite the presence of higher risk characteristics.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
MACE = major adverse cardiac event
MI = myocardial infarction
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
TIMI = Thrombolysis In Myocardial Infarction
TVR = target vessel revascularization

Clinical practice of PCI has changed since the introduction of the drug-eluting stent (DES) with a significantly lower rate of restenosis compared with BMS use (10). There is currently a paucity of published data available on the comparison of sex after PCI using DES. Pivotal trials of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) have included only a small number of women and were limited to patients with elective PCI and selective angiographic characteristics. In these low-risk populations, sex was not independently associated with adverse outcomes (11,12). Recently, using the National Heart, Lung, and Blood Institute (NHLBI) dynamic registry including high-risk patients, Abbott et al. (13) reported that adjusted 1-year outcomes in BMS and DES were independent of sex. However, the impact of sex on long-term outcome in unselected patients after PCI has not yet been fully investigated. Therefore, we performed an analysis using the RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) registries' data to assess the impact of sex on long-term PCI outcomes and to compare outcome after PCI of women between the DES and BMS eras.

Methods

Study design and patient population. Between January 1, 2000, and December 31, 2004, 5,358 patients underwent PCI in our institution using BMS, SES, or PES. Initially, all patients were treated with BMS, but on April 16, 2002, our institution adopted the use of SES (Cypher, Cordis, Warren, New Jersey) as the default strategy for all coronary interventions, as part of the RESEARCH registry (14). On February 16, 2003, SES was replaced by PES (TAXUS, Boston Scientific, Natick, Massachusetts) as the default stent, as part of the T-SEARCH registry (15). The exclusion criteria were PCI for a lesion involving a previously implanted stent (n = 287) or patients receiving only BMS (n = 135) in the DES era, because of the unavailability of the adequate size of DES (Fig. 1). In total, 4,936 patients were included in the current study. We defined the BMS group as patients treated in a period before introduction of SES (January 2000 to April 2002, n = 2,131) and the DES group as those treated after introduction of SES (April 2002 to December 2004, n = 2,805).

Procedures and medications. All procedures were performed according to standard clinical guidelines at the time (14,15). During this period of study, primary PCI was the default strategy for all patients with ST-segment elevation myocardial infarction presenting within 6 h of symptom onset. The patients are transferred either directly by the ambulance service or by local emergency departments directly to our catheter laboratory. Angiographic success was

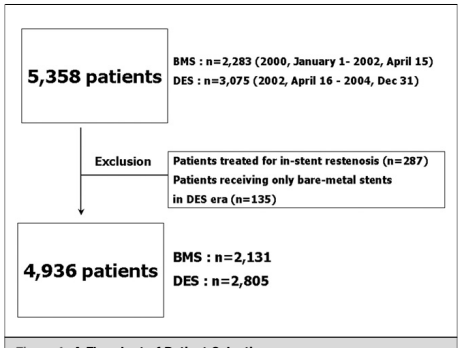

Figure 1. A Flowchart of Patient Selection

Out of 5,358 patients who underwent percutaneous intervention in a single center from 2000 to 2004, 4,936 patients were included in this analysis after exclusion of 422 patients. BMS = bare-metal stent(s); DES = drug-eluting stent(s).

defined as a residual stenosis ≤30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. All patients were pre-treated with 300 mg of clopidogrel. At least 1-month of clopidogrel treatment (75 mg/day) was recommended for patients treated with BMS. Clopidogrel was prescribed for ≥3 or 6 months for patients with SES depending of the complexity of the procedure and for ≥6 months for patients treated with PES. Life-long aspirin therapy was recommended in all patients.

End point definitions and clinical follow-up. The primary end point was major adverse cardiac event (MACE), defined as all-cause death, nonfatal myocardial infarction (MI) irrespective of the stented vessel or TVR. Secondary end points included all-cause mortality, any MI, TVR, target lesion revascularization, definite stent thrombosis, and the composites of all-cause death or nonfatal MI. Myocardial infarction was diagnosed by a rise in creatine kinase-MB >3 times the upper limit of normal (16). Target vessel revascularization was defined as a repeat revascularization of a lesion in the same epicardial vessel treated in the index procedure (17). Target lesion revascularization was defined as a repeat intervention in the stent or in the 5-mm segments proximal or distal to the stent. Hypercholesterolemia was defined as a fasting serum cholesterol level >5.5 mmol/l or use of lipid-lowering therapy at the time of the procedure. Hypertension was defined as blood pressure >140/90 mm Hg or the use of antihypertensive medications. Stent thrombosis was defined as angiographically defined thrombosis with TIMI flow grade 0 or 1 or the presence of a flow-limiting thrombus, accompanied by acute symptoms, irrespective of whether there had been an intervening reintervention (18). The timing of stent thrombosis was categorized as early (within 30 days after implantation), late (between 30 days and 1 year after implantation), or very late (more than 1 year after implantation) (19).

Follow-up data. Survival data for all patients were obtained from municipal civil registries. A questionnaire was subsequently sent to all living patients with specific questions on rehospitalization and MACE year by year. As the principal regional cardiac referral center, repeat revascularizations, either percutaneous or surgical, are normally performed at our institution and recorded prospectively in our database. For patients who suffered an adverse event at another center, medical records or discharge letters from the other institutions were systematically reviewed. General practitioners and referring physicians were contacted for additional information if necessary.

Statistical analysis. Continuous variables are presented as mean ± SD, whereas categorical variables are expressed as percentages. Statistical comparison was made between women and men and stratified by stent type (BMS and DES). Comparisons among the groups were performed by Fisher exact test for categorical variables. All statistical tests were 2-tailed, and a p value of <0.05 was considered statistically significant. The incidence of events over time was studied with the Kaplan-Meier method, and log-rank tests were applied to evaluate the difference. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Cox proportional hazard methods were used to estimate unadjusted and adjusted risk ratios of clinical events at each year in relation to sex and stent type. Models were adjusted for age, cardiogenic shock, presentation with acute MI or unstable angina, hypertension, current smoking, dyslipidemia, diabetes, multivessel disease, family history of coronary artery disease, previous PCI, previous MI, previous coronary artery bypass graft, treatment of chronic total occlusion, bifurcation, bypass graft or left main lesion, American Heart Association classification B2 or C, total stented length, number of implanted stents, and recommended duration of clopidogrel. Cox proportional-hazards models adjusted with the same variables as well as stent type also were used to assess relative risks of 3-year MACE in female sex compared with male sex among patient subgroups. Statistical analysis was performed with SPSS version 12.0 for windows (SPSS Inc., Chicago, Illinois).

Results

Among 4,936 patients included in the analysis, 3,542 (71.8%) were men and 1,394 (28.2%) were women. A total of 2,131 patients received BMS (596 women and 1,535 men), and 2,805 patients were treated with DES (798 women and 2,007 men). Baseline and procedural characteristics stratified by sex and stent type are depicted in Table 1. Among patients treated with BMS, women were on average approximately 5 years older; more often had diabetes, hypertension, current smoking habit, and left main disease, and less often had previous MI. Women more often underwent PCI for unstable angina but less often for an acute MI. Recommended clopidogrel duration was longer than in men, but glycoprotein IIb/IIIa were less frequently used in women.

In demographic and procedural characteristics, differences among men and women receiving DES were similar to differences observed in patients with BMS. However, in the DES era, the rates of left main disease and duration of clopidogrel administration were comparable between men and women. Furthermore, women have lower rates of multivessel disease, bypass graft disease, and smaller diameter of stent used.

Clinical follow-up was available in 4,936 patients (98.9%: male 98.8%, female 99.3%) with a median duration of follow-up of 1,520 days. Cumulative incidences of clinical end points up to 3 years are presented in Table 2. In patients with BMS and DES, there were no differences by sex for rates of all-cause death, MI, TVR, stent thrombosis, and MACE throughout the 3 years after procedure.

Table 1. Patient Baseline Characteristics According to Sex and Stent Type

	BMS (n = 2,131)			DES (n = 2,805)				
	Women (n = 596)	Men (n = 1,535)	p Values	Women (n = 798)	Men (n = 2,007)	p Values	Women (BMS vs. DES) p Values	Men (BMS vs. DES) p Values
Age, yrs	65.5 ± 11.9	59.9 ± 11.3	<0.001	65.4 ± 11.5	60.7 ± 11.0	<0.001	0.82	0.03
Presentation SA	42.3	40.1	0.38	42.5	39.6	0.16	0.96	0.76
Presentation UA	41.6	33.9	0.001	35.5	28.7	0.001	0.02	0.001
Presentation acute MI	16.1	26.0	<0.001	22.1	31.4	<0.001	0.006	<0.001
Cardiogenic shock	1.0	1.1	1.0	2.3	2.2	1.0	0.1	0.01
Diabetes mellitus	16.9	11.4	0.001	20.8	14.8	<0.001	0.07	0.003
Hypertension	41.3	29.1	<0.001	53.4	36.5	<0.001	<0.001	<0.001
Hypercholesterolemia	42.1	43.2	0.66	51.4	54.1	0.21	0.001	<0.001
Family history	23.2	20.9	0.27	34.7	31.6	0.12	<0.001	<0.001
Current smoking	20.6	26.3	0.007	23.7	27.7	0.03	0.19	0.1
Previous PCI	10.2	9.8	0.75	8.3	7.0	0.26	0.22	0.053
Previous CABG	10.4	11.1	0.7	6.8	7.5	0.57	0.02	0.001
Previous MI	28.7	35.8	0.002	23.7	29.9	0.001	0.001	<0.001
Multivessel disease	50.7	54.3	0.13	48.4	55.4	0.001	0.42	0.95
Treated vessels*								
LAD	56.2	54.2	0.41	57.6	56.9	0.74	0.62	0.72
LCX	29.9	30.6	0.75	27.1	33.4	0.001	0.25	0.34
RCA	41.6	38.9	0.26	42.4	37.4	0.016	0.78	0.28
LM	5.2	3.1	0.021	4.0	4.7	0.48	0.3	0.001
Bypass	3.9	5.3	0.18	1.5	3.9	0.001	0.008	0.02
Bifurcation	4.7	2.6	0.02	11.9	12.4	0.75	<0.001	<0.001
Lesion type†								
A	19.6	17.7	0.29	13.4	12.8	0.66	0.002	<0.001
B1	32.9	35.2	0.34	31.2	29.0	0.27	0.52	<0.001
B2	48.2	45.5	0.29	45.0	48.9	0.07	0.25	0.5
C	32.9	36.3	0.14	42.5	45.6	0.14	<0.001	<0.001
Multivessel treatment	32.6	28.7	0.08	28.6	30.5	0.32	0.11	0.89
No. of lesions intended to treat	1.79 ± 0.91	1.74 ± 0.92	0.3	1.76 ± 0.96	1.79 ± 0.97	0.59	0.66	0.47
No. of lesions successfully treated	1.74 ± 9.92	1.70 ± 0.91	0.89	1.72 ± 0.96	1.72 ± 0.98	0.97	0.68	0.31
No. of implanted stents	1.89 ± 1.26	1.83 ± 1.19	0.42	2.22 ± 1.43	2.23 ± 1.43	0.83	<0.001	<0.001
Total stented length per patient	28.8 ± 29.6	28.9 ± 20.3	0.91	41.5 ± 29.3	43.0 ± 30.7	0.22	<0.001	<0.001
Average stent diameter	3.21 ± 0.49	3.33 ± 0.51	0.72	2.85 ± 0.53	2.95 ± 0.55	<0.001	<0.001	<0.001
Chronic total occlusion	8.7	9.2	0.8	8.4	8.6	0.88	0.85	0.15
Glycoprotein IIb/IIIa	27.2	34.7	0.001	17.2	25.1	<0.001	<0.001	<0.001
Clopidogrel prescription duration, months	2.37 ± 2.69	2.25 ± 2.06	0.04	5.50 ± 2.70	5.60 ± 3.10	0.37	<0.001	<0.001
Angiographic success of all lesions	95.5	95.6	0.91	96.1	94.2	0.04	0.59	0.14

Values are expressed as % or mean ± SD.

*Expressed as percentage of patients with each vessel type, hence total >100%. †Expressed as percentage of patients with each lesion type, hence total >100%.

BMS = bare-metal stent(s); CABG = coronary artery bypass graft; DES = drug-eluting stent(s); LAD = left anterior descending artery; LCX = left circumflex artery; LM = left main; MI = myocardial infarction; PCI = percutaneous coronary intervention; RCA = right coronary artery; SA = stable angina; UA = unstable angina.

DES versus BMS in women and men. Among the subgroups of women and men, treatment for acute MI was more frequent in patients with DES than BMS. Risk factors such as hypertension, family history, and current smoking were more frequently observed in patients with DES. The procedural complexity was higher in DES, illustrated by an increase in the treatment of type C lesions and bifurcations. In DES patients, when compared with BMS patients, total stented length and number of stents increased, but the average stent diameter decreased. Rates for TVR and MACE at any time point were significantly lower in women and men treated with DES than in patients of both sexes treated with BMS (Table 2, Fig. 2). At the 3-year follow-up, definite stent thrombosis was higher in men with DES than in men treated with BMS (2.6% vs. 1.5%, log-rank: $p = 0.04$), whereas it was similar in women treated with DES or BMS (2.0% vs. 1.8%, $p = 0.52$).

Table 2. Clinical Outcomes Stratified by Sex and Stent Type

	BMS Era (n = 2,131)			DES Era (n = 2,805)				
	Women (n = 596)	Men (n = 1,535)	p Values	Women (n = 798)	Men (n = 2,007)	p Values	Women (DES vs. BMS) p Values	Men (DES vs. BMS) p Values
At 1 year (cumulative)								
Death	8.0	6.0	0.1	6.8	5.3	0.13	0.39	0.35
Myocardial infarction	3.1	3.3	0.86	2.7	3.2	0.54	0.64	0.77
Target vessel revascularization	11.1	10.0	0.48	6.7	6.2	0.65	**0.005**	**0.0001**
Major adverse cardiac events	19.1	16.5	0.16	14.4	12.2	0.12	**0.02**	**0.0004**
Definite stent thrombosis	1.8	1.3	0.43	1.1	1.7	0.31	0.37	0.34
At 2 years (cumulative)								
Death	9.2	8.4	0.55	8.5	7.5	0.38	0.62	0.32
Myocardial infarction	3.9	4.0	0.94	3.3	3.7	0.56	0.54	0.74
Target vessel revascularization	12.8	12.8	0.96	8.2	8.4	0.88	**0.006**	**<0.0001**
Major adverse cardiac events	22.3	21.3	0.55	17.4	16.4	0.46	**0.02**	**0.0002**
Definite stent thrombosis	1.8	1.5	0.58	1.4	2.3	0.16	0.63	0.07
At 3 years (cumulative)								
Death	11.6	11.0	0.65	10.2	9.5	0.52	0.44	0.18
Myocardial infarction	4.3	4.3	0.95	4.6	4.4	0.96	0.91	0.98
Target vessel revascularization	14.7	13.9	0.63	10.3	9.7	0.72	**0.02**	**0.0001**
Major adverse cardiac events	25.9	24.5	0.45	20.9	19.1	0.27	**0.03**	**0.0001**
Definite stent thrombosis	1.8	1.5	0.66	2.0	2.6	0.62	0.52	**0.04**

Bold values are statistically significant.
Abbreviations as in Table 1.

Multivariate analyses. Unadjusted and adjusted models stratified by stent type showed that female sex did not confer a benefit or risk for any adverse events (Table 3), whereas the use of DES was associated with a lower risk of TVR or MACE in men and women at 1-, 2-, and 3-year follow-ups.

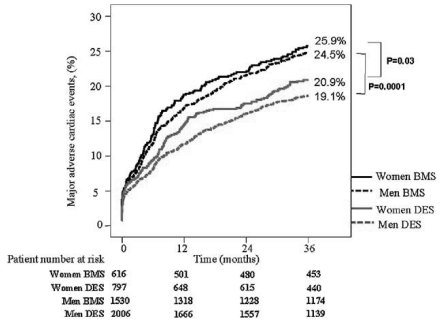

Figure 2. Kaplan-Meier Curve of MACE up to 3 Years After Index Procedure Among 4 Groups

Major adverse cardiac event (MACE) rates were significantly lower in women **(solid red line)** and men **(dotted red line)** treated with DES than in patients of both sexes treated with BMS (**solid black line** for women, **dotted black line** for men). Abbreviations as in Figure 1.

At 3 years, the risk of definite stent thrombosis was higher in men with DES versus BMS in univariate analysis (hazard ratio [HR]: 1.7 [95% confidence interval (CI): 1.03 to 2.81]); this difference was not significant in the adjusted model (adjusted HR: 1.83 [95% CI: 0.93 to 3.59]).

Figure 3 represents the results of subgroup multivariate analysis of the association between sex and the risk of MACE at 3-year follow-up in patients treated with DES. Female sex did not confer a benefit or risk for MACE in any groups except for the subpopulation presenting with acute MI (adjusted HR women vs. men: 1.37 [95% CI: 1.02 to 1.85]).

Discussion

The main findings of the current analysis from the T-SEARCH and RESEARCH registries with respect to sex are as follows: 1) DES use was associated with lower rates of TVR or MACE in both sexes; 2) after stratification for stent type, all clinical end points at any time points up to 3 years were similar between both sexes; and 3) in the subpopulation of patients presenting with acute MI, the risk of MACE at 3 years was higher in women than in men.

Only few data are available regarding sex differences in the DES era. In the TAXUS-IV–2 Year Data (TAXUS-IV) trial, they found that women had more comorbidities and an overall higher rate of repeat PCI than men did (7.6% vs. 3.2%, p = 0.03), but the restenosis rates and late loss

Table 3. Unadjusted and Adjusted HR for Sex (Women vs. Men) in Each Stent Type or for Stent Type (DES vs. BMS) in Each Sex

	HR Women vs. Men		HR DES vs. BMS		
	BMS	DES	Women	Men	p Value for Interaction Between Sex and Stent Type
At 1 year					
Death	1.34 (0.94–1.90)	1.29 (0.93–1.79)	0.84 (0.57–1.25)	0.88 (0.66–1.16)	
Adjusted	1.15 (0.75–1.75)	1.16 (0.78–1.72)	0.68 (0.40–1.15)	0.79 (0.53–1.17)	0.73
Myocardial infarction	0.95 (0.55–1.63)	0.86 (0.53–1.42)	0.86 (0.46–1.61)	0.95 (0.65–1.38)	
Adjusted	0.78 (0.41–1.47)	1.08 (0.64–1.83)	0.70 (0.32–1.53)	0.77 (0.46–1.29)	0.73
Target vessel revascularization	1.11 (0.83–1.50)	1.08 (0.78–1.50)	**0.59 (0.41–0.86)**	**0.61 (0.48–0.78)**	
Adjusted	1.13 (0.83–1.56)	1.16 (0.81–1.64)	**0.44 (0.28–0.69)**	**0.60 (0.44–0.80)**	0.89
Major adverse cardiac events	1.18 (0.94–1.47)	1.19 (0.95–1.49)	**0.74 (0.57–0.95)**	**0.73 (0.61–0.87)**	
Adjusted	1.09 (0.85–1.40)	1.23 (0.96–1.58)	**0.58 (0.42–0.80)**	**0.66 (0.52–0.84)**	0.35
Definite stent thrombosis	1.36 (0.63–2.93)	0.69 (0.33–1.43)	0.66 (0.27–1.63)	1.32 (0.75–2.32)	
Adjusted	1.25 (0.54–2.87)	0.71 (0.33–1.55)	0.50 (0.16–1.58)	1.42 (0.67–3.00)	0.1
At 2 years					
Death	1.10 (0.80–1.52)	1.14 (0.85–1.52)	0.91 (0.64–1.31)	0.89 (0.70–1.12)	
Adjusted	0.90 (0.62–1.31)	1.02 (0.73–1.43)	0.75 (0.45–1.24)	0.88 (0.64–1.21)	0.81
Myocardial infarction	0.98 (0.60-1.61)	0.87 (0.55–1.38)	0.84 (0.47–1.48)	0.94 (0.67–1.33)	
Adjusted	0.88 (0.50–1.54)	1.02 (0.63–1.66)	0.72 (0.35–1.48)	0.85 (0.52–1.38)	0.75
Target vessel revascularization	1.01 (0.77–1.32)	0.98 (0.73–1.31)	**0.63 (0.44–0.88)**	**0.64 (0.52–0.80)**	
Adjusted	1.02 (0.76–1.37)	1.07 (0.78–1.46)	**0.46 (0.31–0.69)**	**0.61 (0.47–0.79)**	0.88
Major adverse cardiac events	1.06 (0.87–1.30)	1.08 (0.88–1.32)	**0.76 (0.60–0.96)**	**0.75 (0.64–0.87)**	
Adjusted	0.98 (0.78–1.23)	1.10 (0.88–1.38)	**0.58 (0.43–0.78)**	**0.70 (0.57–0.86)**	0.42
Definite stent thrombosis	1.24 (0.58–2.62)	0.63 (0.32–1.22)	0.81 (0.34–1.91)	1.59 (0.94–2.68)	
Adjusted	1.18 (0.53–2.66)	0.72 (0.36–1.43)	0.58 (0.20–1.68)	1.70 (0.84–3.44)	0.23
At 3 years					
Death	1.07 (0.80–1.42)	1.09 (0.84–1.42)	0.88 (0.64–1.22)	0.87 (0.70–1.07)	
Adjusted	0.84 (0.61–1.17)	0.92 (0.68–1.25)	0.77 (0.49–1.20)	0.87 (0.66–1.15)	0.92
Myocardial infarction	0.99 (0.62–1.58)	1.01 (0.68–1.51)	1.03 (0.61–1.75)	1.00 (0.72–1.38)	
Adjusted	0.90 (0.53–1.53)	1.22 (0.79–1.87)	0.89 (0.47–1.70)	0.90 (0.57–1.41)	0.76
Target vessel revascularization	1.07 (0.82–1.38)	1.05 (0.80–1.38)	**0.67 (0.49–0.92)**	**0.68 (0.55–0.83)**	
Adjusted	1.08 (0.82–1.43)	1.16 (0.87–1.54)	**0.52 (0.36–0.75)**	**0.65 (0.51–0.83)**	0.87
Major adverse cardiac events	1.08 (0.89–1.30)	1.11 (0.92–1.33)	**0.78 (0.62–0.97)**	**0.75 (0.65–0.87)**	
Adjusted	0.97 (0.79–1.20)	1.11 (0.90–1.37)	**0.63 (0.48–0.83)**	**0.71 (0.59–0.86)**	0.41
Definite stent thrombosis	1.18 (0.56–2.49)	0.87 (0.50–1.51)	1.30 (0.59–2.83)	**1.7 (1.03–2.81)**	
Adjusted	1.15 (0.51–2.55)	1.01 (0.57–1.79)	0.94 (0.37–2.39)	1.83 (0.93–3.59)	0.51

Values are hazard ratio (95% confidence interval) or p value. **Bold** values are statistically significant.
HR = hazard ratio; other abbreviations as in Table 1.

were similar by sex in the DES arm of the study (11). In a pooled analysis of 1,748 patients from 4 randomized SES versus BMS trials, Solinas et al. (12) reported that despite less favorable baseline characteristics in women compared with men, at 1 year, the clinical benefits of SES were independent of sex, with reductions of binary restenosis both in women (6.3% vs. 43.8%) and in men (6.4% vs. 35.6%). Recently, using data from NHLBI dynamic registry, including high-risk patients, Abbott et al. (13) reported that patients with DES had a lower rate of repeat PCI in both sexes (14.1% in women vs. 9.5%, p = 0.02; 12.0% in men vs. 8.8%, p = 0.02) at 1 year. Our findings not only confirm the results of previous studies but also suggest that this superiority of DES to lower revascularization is maintained in both sexes up to 3 years after procedure.

In our analysis, women treated with DES had worse baseline demographics, including older age and higher prevalence of comorbidities, especially diabetes, which is associated with higher rates of restenosis. However, clinical outcomes were independent of sex with the benefit of DES over BMS being almost identical throughout the 3-year clinical follow-up. This is in contrast to previous PCI series that have reported an association between sex and clinical and angiographic restenosis rates (8,20), but it concurs with the data from a recent series on 3,223 patients, in which 1-year clinically driven revascularization was similar for both sexes (13).

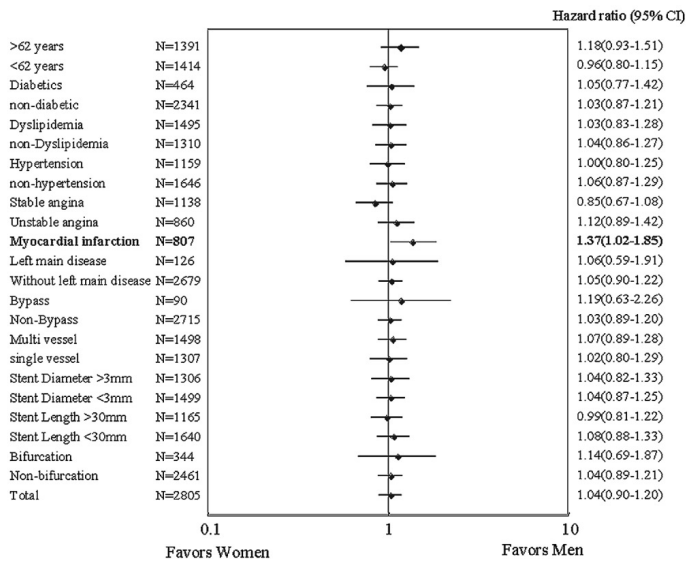

Figure 3. Adjusted Hazard Ratio of Women Versus Men on MACE at Year 3 in Subgroups

Female sex was not associated with differential MACE risk from male sex in any groups except for those presenting with acute myocardial infarction (adjusted HR women vs. men: 1.37 [95% CI: 1.02 to 1.85]). CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 2.

Our subgroup analysis suggests that women presenting with acute MI still have worse outcomes than men do. Because there were substantially fewer females than males (19.5% vs. 29.1%) in this subset, it is plausible that this inequality in proportions could be responsible for the failure to reach statistical significance for the outcomes between sexes and that even matching would have worsened the outcomes of the female cohort. In general, unadjusted comparisons of mortality after acute MI have generally indicated that women have a poorer outcome than men (21,22) and have less favorable short-term outcomes after revascularization procedures (23). In our institution, primary PCI was the default strategy for all patients with acute MI presenting within 6 h of symptom onset. Therefore, our results suggest that despite the use of DES with contemporary PCI techniques, the outcome of women with ST-segment elevation myocardial infarction still needs to be improved. In addition to anatomical differences, the basic biological differences in response to acute MI between men and women have also been suggested (24). Further investigation in this high-risk population is warranted.

Study limitations. The current study suffers from the inherent limitations of a nonrandomized trial. There were significant differences between BMS and DES and between both sexes in terms of baseline demographics. To compensate for these differences, we have performed adjustments employing multivariate analyses, although we cannot adjust confounding factors such as changes in practice during this period using various material, different guidelines, or operator's experiences. Nevertheless, these unselected patients represent real-world practice, whereas patients enrolled in clinical trials are carefully selected. In addition, we only investigated angiographically documented stent thrombosis, using a definition consistent with previous reports on stent thrombosis either after DES or BMS implantation. The latter may have led to an underestimation of the actual incidence of stent thrombosis, particularly, in patients suffering from sudden cardiac death or silent stent occlusion.

Acknowledgments

The authors would like to acknowledge the senior cardiologists involved in the PCI procedures: Drs. E. McFadden,

P. J. de Feyter, P. P. T. de Jaegere, S. H. Hofma, E. Regar, G. Sianos, P. C. Smits, M. J. van der Ent, W. J. van der Giessen, C. A. van Mieghem, R. J. van Geuns, and H. Duckers.

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Key Words: percutaneous coronary intervention ■ bare-metal stent ■ drug-eluting stent ■ major adverse cardiac event ■ myocardial infarction ■ target vessel revascularization ■ target lesion revascularization.

CHAPTER 22

Long-term clinical results following stenting of the left main stem: insights from RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) Registries

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J Am Coll Cardiol Intv, 2010 Jun;3(6):584-94.

FOCUSED UPDATE ON PCI FOR UNPROTECTED LEFT MAIN CAD

Long-Term Clinical Results Following Stenting of the Left Main Stem

Insights From RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) Registries

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Objectives We investigated the long-term clinical outcomes and independent predictors of major cardiac events in unprotected left main coronary artery disease (ULMCA) patients treated by percutaneous coronary intervention with drug-eluting stent (DES).

Background There is limited information on long-term (>3 years) outcomes after DES implantation for ULMCA. Furthermore, bifurcation angle and SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score are emerging as parameters for patient risk stratification, and their prognostic implications have still to be elucidated.

Methods One hundred forty-eight patients with ULMCA treated with DES were analyzed and compared with a historical cohort of 79 patients who received bare-metal stents for the treatment of ULMCA. Patient-oriented composite end point was defined as the occurrence of all-cause death, any myocardial infarction, or any revascularization.

Results The 4-year cumulative incidence of all-cause death, any myocardial infarction, any revascularization, and patient-oriented composite were 35.6%, 3.8%, 25.2%, and 54.4%, respectively. These end points had relatively increased from 1 year to 4 years by Δ70%, Δ5%, Δ50%, and Δ68%, respectively. When compared with a historical cohort who received bare-metal stents for ULMCA treatment, landmark analysis performed after the first 2 years of follow-up demonstrated that the DES cohort had significantly higher patient-oriented composite end point over the last 2 years of follow-up (26% vs. 8%, $p = 0.02$). EuroSCORE (European System for Cardiac Operative Risk Evaluation), cardiogenic shock, and SYNTAX score were identified as independent predictors for the 4-year patient-oriented composite, whereas bifurcation angle was not.

Conclusions Late increase in patient-oriented composite end points after DES implantation for ULMCA warrants careful and long-term follow-up. SYNTAX score and EuroSCORE appear to have a significant prognostic value in long-term patient risk. (J Am Coll Cardiol Intv 2010;3:584–94) © 2010 by the American College of Cardiology Foundation

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Manuscript received February 11, 2010, accepted March 4, 2010.

The prevalence of left main disease in patients with coronary artery atherosclerosis varies from 2.5% to 10% (1). Coronary artery bypass graft (CABG) remains the treatment of choice in patients with unprotected left main coronary artery disease (ULMCA) (2,3). Although percutaneous coronary intervention (PCI) using bare-metal stent (BMS) in patients having 2- or 3-vessel disease is associated with no significant difference in long-term mortality compared with CABG, restenosis and need for repeat revascularization remain major limitations of this mode of revas-

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cularization. These latter limitations have precluded the widespread use of PCI, not only in multivessel disease, but also in LM disease (4). Reduction of restenosis with drug-eluting stents (DES), however, has raised the possibility of their use for multivessel treatment as well as LM treatment. So far, several registries and randomized trials have investigated the short- and mid-term clinical outcomes of PCI using DES for ULMCA treatment (5–14), but little is known about its long-term safety and efficacy beyond 3 years (15). In addition, the rate of potentially fatal consequences of stent thrombosis or in-stent restenosis in this patient subset has not fully been investigated (16,17).

Several clinical and angiographic parameters for risk stratification after PCI are emerging. Recently, EuroSCORE (European System for Cardiac Operative Risk Evaluation), a typically surgical risk stratification score, has been applied to the PCI population (18). As angiographic analysis, the angle between bifurcated branches has been recognized as a significant prognostic factor for immediate procedural outcomes as well as for intermediate-term outcomes (19–21). In addition, a comprehensive, angiographic scoring system, the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score (22,23) based on morphology and location of coronary artery stenoses in the coronary tree has been proven to predict clinical outcomes in high-risk patients (9,24,25).

The main aim of this study was to report the long-term clinical outcomes of patients receiving DES for unprotected LM lesions in a daily practice of a tertiary medical center. In addition, we assessed the prognostic value of recently emerging predictors of adverse outcomes for PCI treatment of multivessel disease and ULMCA, such as EuroSCORE, the bifurcation angle, and SYNTAX score.

Methods

Study design and patient population. Between April 2002 and December 31, 2005, 210 consecutive patients underwent PCI for LM stenting (7,8). Sixty-two patients with a history of CABG were not retained in this analysis. The remaining 148 patients are the subject of the present investigation. On April 16, 2002, our institution adopted the use of sirolimus-eluting stents (Cypher, Cordis, Warren, New Jersey) as the default strategy for all coronary interventions, as part of RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) registry (26). On February 16, 2003, sirolimus-eluting stents were replaced by paclitaxel-eluting stents (Taxus Express2, Boston Scientific, Natick, Massachusetts) as the default stent, as part of the T-SEARCH (Taxus-Stent Evaluated at Rotterdam Cardiology Hospital) registry (27). For evaluation of long-term outcomes, this DES group was compared with a historical cohort who received BMS in the unprotected LM trunk before April 2002 (n = 79).

In this study, the decision to intervene in the patients with PCI was based on a consensus reached during a multidisciplinary medical surgical conference (the so-called heart-team conference) involving surgeon, interventionalist, and referring physician (28), except for patients who presented with ST-segment elevation myocardial infarction (STEMI), considering the emergent character of the clinical presentation. All procedures were performed according to standard clinical guidelines at the time. All patients were pretreated with 300 mg of clopidogrel. At least 1 month of clopidogrel treatment (75 mg/day) was recommended for patients treated with BMS. Clopidogrel was prescribed for at least 3 months for patients with DES. Life-long aspirin therapy was recommended in all patients.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CABG = coronary artery bypass graft
CI = confidence interval
DES = drug-eluting stent(s)
HR = hazard ratio
LM = left main
MACCE = major adverse cerebrovascular cardiac event
MACE = major adverse cardiac events
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiography
STEMI = ST-segment elevation myocardial infarction
TVR = target vessel revascularization
ULMCA = unprotected left main coronary artery disease

QCA analysis. To assess the bifurcation angle between the left anterior descending and left circumflex arteries, 3-dimensional quantitative coronary angiography (QCA) analyses were performed by 2 observers blinded to the patient data and clinical outcomes. A validated program was used to reconstruct 3-dimensional images from 2 different projections at least 30° apart from each other (CardiOp-B system version 2.1.0.151, Paieon Medical Ltd., Park Afek, Israel) (29–31). Separate 3-dimensional angiographic images were constructed for systolic and diastolic phases. The bifurcation angle was defined as the angle between the left anterior descending and left circumflex arteries (32). In cases where the separate projections were not available, 2-dimensional bifurcation software (CAAS version 5.6, Pie Medical, Maastricht, the Netherlands) was used to calculate bifurcation angle (33). In primary PCI cases where TIMI (Thrombolysis In Myocardial

Infarction) flow grade was 0 or 1 pre-procedure, the cineangiography following the first balloon angioplasty was analyzed for the determination of the angle.

SYNTAX score. Two analysts blinded to patient characteristics and clinical outcomes reviewed the angiograms to calculate the SYNTAX score (22,23). In case of disagreement, the opinion of a third observer was obtained and the final decision was made by consensus. Each coronary lesion producing >50% luminal obstruction in vessels >1.5 mm was separately scored and added to provide the overall SYNTAX score. The SYNTAX score was calculated using dedicated software that integrates the following: 1) the number of lesions with their specific weighting factors based on the amount of myocardium distal to the lesion according to the score of Leaman et al. (34); and 2) the morphologic features of each single lesion (35,36). The reproducibility of the SYNTAX score was recently reported (22).

Clinical follow-up. Survival data for all patients were obtained from municipal civil registries on a yearly basis. A questionnaire was subsequently sent to all living patients with specific enquiries on rehospitalization and major adverse cardiac events (MACE). As the principal regional cardiac referral center, most repeat revascularization (either percutaneous or surgical) is normally performed at our institution and recorded prospectively in our database. For patients who suffered an adverse event at another center, medical records or discharge letters from the other institutions were systematically reviewed. General practitioners and referring physicians were contacted for additional information if necessary. Causes of death were obtained from medical records when they happened during hospitalization, and otherwise from the Central Bureau of Statistics, The Hague, the Netherlands (37,38). Causes of death were classified according to the International Classification of Diseases and Related Health Problems-10th Revision. For the present analysis, death from ischemic heart disease (I-20 to I-25), sudden cardiac death (I-46), sudden death undefined (R-96), or death from heart failure (I-50) were considered to be cardiac. Death from cancer was defined as any death from malignant neoplasm (C-009 to C-97). All the remaining deaths were classified as being due to other causes, and no further distinction was made. In this study, there was no mandatory angiographic follow-up.

End point definitions. The primary end point was a patient-oriented composite defined as all-cause death or any myocardial infarction (MI) or any revascularization (all surgical and percutaneous, target lesion, target vessel, and non–target vessel revascularization) according to the Academic Research Consortium definitions (39). The secondary end point was the device-oriented composite end point defined as cardiac death, MI in the target vessel territory, or a target lesion revascularization. In addition, each individual component end point was analyzed in a nonhierarchical way. Definite stent thrombosis was also considered as a separate secondary end point.

Myocardial infarction included periprocedural MI (diagnosed by a rise in creatine kinase-myocardial band fraction of 3 times the upper limit of normal), reinfarction (defined as recurrence of symptoms together with ST-segment elevation or new left bundle branch block and an increase in cardiac enzymes following stable or decreasing values), or spontaneous MI (diagnosed by any rise in creatine kinase-myocardial band fraction above the upper limit of normal) (40). Target lesion revascularization was defined as a repeat revascularization of in-stent or within 5 mm proximal or distal to the stent implanted in the index procedure (41). Target vessel revascularization (TVR) was defined as any revascularization in the same epicardial vessel treated in the index procedure. Definite stent thrombosis was defined as TIMI flow grade 0 or 1 or the presence of a flow-limiting thrombus, accompanied by acute symptoms, irrespective of whether there had been an intervening reintervention (42). The timing of stent thrombosis was categorized as early (within 30 days after implantation), late (between 30 days and 1 year), or very late (more than 1 year) (39).

Statistical analysis. Continuous variables are presented as mean ± SD, whereas categorical variables are expressed as percentages. Comparisons among groups were performed by the independent *t* test for continuous variables and Pearson chi-square test for categorical variables. All statistical tests were 2-tailed, and p value of <0.05 was considered as statistically significant. The incidence of events over time was studied with the use of the Kaplan-Meier method, whereas log-rank tests were applied to evaluate differences between the current cohort and the historical control. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Cox regression models were built to elucidate independent predictors of clinical end points. Significant variables in univariate analysis ($p < 0.1$) were selected to put in the multivariate model. The following pre-procedural variables were included in the initial univariate analysis: gender, diabetes, current smoking habit, hypertension, hypercholesterolemia, age, previous history of myocardial infarction or PCI, SYNTAX score, EuroSCORE, shock at entry, clinical presentation, and bifurcation angle. Clinical presentation (STEMI, unstable angina or non-STEMI, and stable angina) was coded as a categorical variable. Bifurcation angle was partitioned according to tertiles (lowest tertile as a reference). The results are presented as adjusted hazard ratios (HR) with 95% confidence intervals (CI). Statistical analysis was performed with SPSS version 16 for windows (SPSS Inc., Chicago, Illinois).

Results

Baseline and procedural characteristics. The baseline and procedural characteristics of the patients are shown in Table 1.

Table 1. Baseline Characteristics

	Current Cohort With DES (n = 148)	Historical Cohort With BMS (n = 79)	p Value
Demographics			
Age, yrs	64.9 ± 12.1	65.1 ± 11.2	0.96
Men	108 (73)	49 (62)	0.10
Diabetes	24 (16.2)	15 (19)	0.59
Hypertension	61 (41)	34 (43)	0.89
Hypercholesterolemia	80 (54)	34 (43)	0.13
Family history of coronary artery disease	47 (32)	15 (19)	0.04
Current smoking	27 (18)	14 (18)	1.00
Previous PCI	32 (22)	25 (32)	0.11
Previous MI	49 (33)	24 (30)	0.77
Additive EuroSCORE	4.26 ± 3.54	4.37 ± 3.57	0.82
SYNTAX score	39.4 ± 22.9	36.8 ± 24.6	0.96
LVEF, %	45.3 ± 13.6	41.8 ± 16.9	0.48
Presentation			
STEMI	36 (24.3)	22 (27.8)	0.64
Stable angina	60 (40.5)	30 (33.3)	0.78
Unstable angina/non-STEMI	52 (35.1)	27 (34.2)	1.00
Shock at entry	13 (8.8)	6 (7.6)	1.00
Pre-procedural quantitative angiographic analysis			
Bifurcation angle in diastole, °	94.1 ± 25.5	89.5 ± 25.3	0.29
Bifurcation angle in systole, °	84.9 ± 26.6	81.42 ± 23.8	0.42
Minimal lumen diameter, mm	1.09 ± 0.32	1.08 ± 0.27	0.92
Reference vessel diameter, mm	3.35 ± 2.49	3.31 ± 0.36	0.69
Procedural characteristics			
Number of implanted stents	3.08 ± 0.37	2.85 ± 0.47	<0.0001
Total stented length per patient	59.9 ± 40.4	42.4 ± 28.4	<0.0001
Average stent diameter	3.08 ± 0.37	3.52 ± 0.47	<0.0001
Clopidogrel duration in month	7.53 ± 5.32	5.27 ± 4.86	0.01
IVUS use	48 (32)	34 (43)	0.15
Stenting strategy			
Provisional	114 (77)	70 (89)	0.07
Culotte	13 (9)	1 (1)	
T-stenting	15 (10)	8 (10)	
Crush stenting	4 (3)	0	
Kissing technique	2 (1)	0	
Post-procedural bifurcation angle			
Bifurcation angle in diastole, °	85.1 ± 24.8	84.2 ± 25.9	0.83
Bifurcation angle in systole, °	80.0 ± 23.7	76.7 ± 21.2	0.38

Values are expressed as n (%) or mean ± SD.

BMS = bare-metal stents; DES = drug-eluting stents; EuroSCORE = European System for Cardiac Operative Risk Evaluation; IVUS = intravascular ultrasound; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; SYNTAX = Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

The mean age of the patients was 64.9 years old, 16.2% of the patients had diabetes, and 33% had previous history of MI. Approximately one-quarter of patients presented with STEMI, and 8% presented with severe hemodynamic compromise at entry. The average additive EuroSCORE and SYNTAX score was 4.26 and 39.4, respectively.

Clinical outcomes. Clinical follow-up was available in all patients, with a median duration of follow-up of 1,473 days (interquartile range: 1,182 to 1,848 days) for patients alive at follow-up. Hierarchical count of adverse events is shown in Table 2. Patient-oriented composite increases from 32.4% at 1 year to 51.4% at 4 years (Δ58%), which was mainly driven by an increase in all-cause mortality from 19.6% at 1 year to 33.1% at 4 years, a relative increase of 68%. There was 1 case of definite late stent thrombosis at 1 year, and there was 1 case of definite very late stent thrombosis at 4 years.

Kaplan-Meier estimates of clinical end points are presented in Figures 1A to 1C. At 4 years, the cumulative

Table 2. Hierarchical Count of Patient-Oriented Composite After DES Implantation Compared With the Historical Cohort With BMS

	Current Cohort With DES (n = 148)	Historical Cohort With BMS (n = 79)	p Value
1 yr			
All-cause death	29 (19.6)	23 (29.1)	0.14
Any MI	2 (1.4)	1 (1.3)	1.00
Any revascularization	17 (11.5)	10 (12.7)	1.00
Patient-oriented composite	48 (32.4)	34 (43)	0.15
2 yrs			
All-cause death	35 (23.6)	27 (34.2)	0.11
Any MI	3 (2.0)	1 (1.3)	1.00
Any revascularization	19 (12.8)	11 (13.9)	0.84
Patient-oriented composite	57 (38.5)	39 (49.4)	0.12
3 yrs			
All-cause death	41 (27.7)	29 (36.7)	0.18
Any MI	3 (2.0)	1 (1.3)	1.00
Any revascularization	23 (15.5)	11 (13.9)	0.85
Patient-oriented composite	67 (45.3)	41 (51.9)	0.4
4 yrs			
All-cause death	49 (33.1)	30 (38)	0.47
Any MI	3 (2.0)	1 (1.3)	1.00
Any revascularization	24 (16.2)	11 (13.9)	0.7
Patient-oriented composite	76 (51.4)	42 (53.2)	0.9

Event rates were calculated as number of events divided by total number of patients and therefore differ from those in the figures, where event rates were calculated by Kaplan-Meier methods. In this table, comparison was made with the chi-square or Fisher exact test.
Abbreviations as in Table 1.

incidence of all-cause death, MI, any revascularization, and patient-oriented composite were 35.6% (95% CI: 27.3% to 43.8%), 3.8% (95% CI: 0.5% to 7.1%), 25.2% (95% CI: 16.9% to 33.6%), and 54.4% (95% CI: 45.8% to 63.1%), respectively. Cardiac mortality, all-cause mortality, and any revascularization rate relatively increased from 1 year to 4 years by Δ68%, Δ82%, and Δ49%, respectively, whereas the changes in target lesion revascularization and MI was less increased from 1 year to 4 years (Δ5% and Δ28%, respectively) (Figs. 1A and 1B). In summary, the device-oriented and patient-oriented composite increased from 1 year to 4 years by Δ56% and Δ68%, respectively (Fig. 1C). If stratified by the presentation with STEMI versus others (non-STEMI, unstable angina, and stable angina), the patient-oriented composite was higher in STEMI patients (68.6%) than the others (49%, $p < 0.001$), also the device-oriented composite, all-cause death, and cardiac death were higher in the STEMI patients than the others (53% vs. 30%, $p < 0001$; 55% vs. 29%, $p < 0.001$; 48% vs. 16%, $p < 0.001$) (Fig. 2A). With stratification according to the tertiles of EuroSCORE (<2, ≥2 and <5, ≥5), the patient-oriented composite was higher in the high tertile (76.8%) than in the low (41.2%, log-rank $p < 0.001$) or intermediate tertiles (51.8%, log-rank $p < 0.001$) (Fig. 2B). If stratified according to type of DES (Cypher and Taxus), the patient-oriented composite was

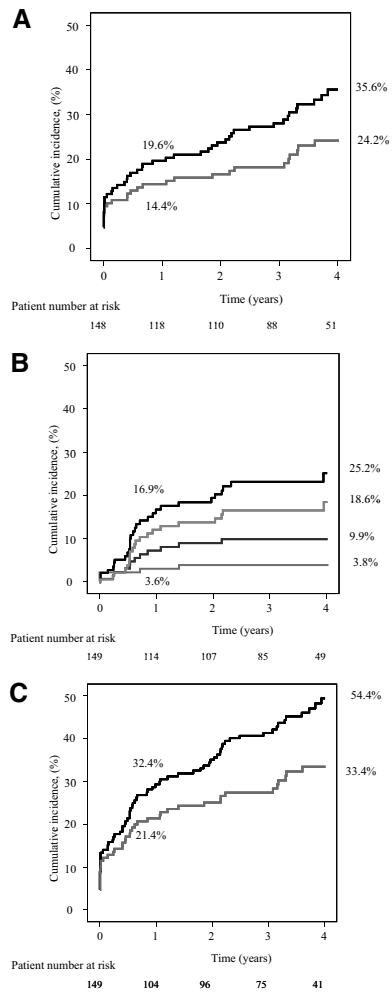

Figure 1. Kaplan-Meier Estimates After Implantation of DES

(A) Kaplan-Meier estimates demonstrate all-cause mortality **(black line)** and cardiac mortality **(red line)**. **(B)** Kaplan-Meier estimates present the end points of any myocardial infarction **(red line)**, target lesion revascularization **(blue line)**, target vessel revascularization **(green)**, and any revascularization including target and non–target vessel revascularization **(black line)**. **(C)** Kaplan-Meier estimates show the composite end point **(red line)** of cardiac mortality, myocardial infarction in the stented vessel territory, or target lesion revascularization and the composite end point **(black line)** of all-cause mortality, any myocardial infarction, or any revascularization. DES = drug-eluting stent.

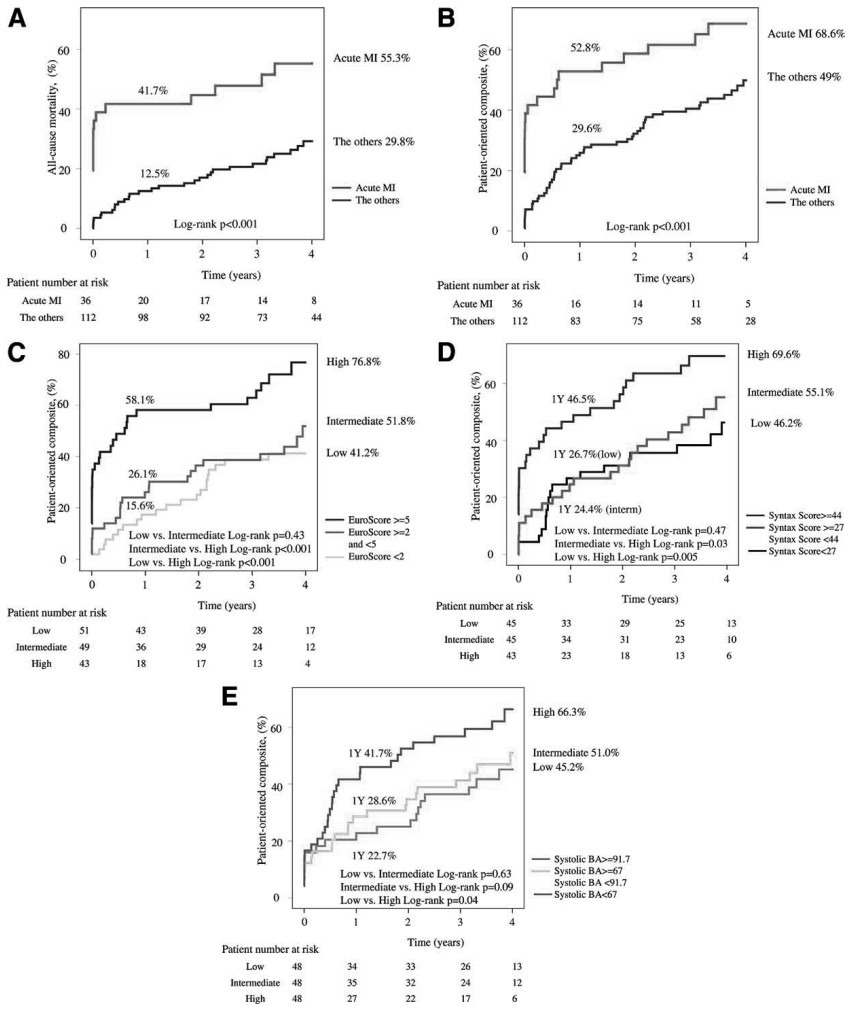

Figure 2. Kaplan-Meier Estimates After Implantation of DES With Stratification of Subgroups

(A) All-cause mortality and **(B)** patient-oriented composite end point (all-cause mortality, any myocardial infarction [MI]), or any revascularization) according to a presentation of ST-segment elevation myocardial infarction or the others (stable angina, non–ST-segment elevation myocardial infarction, or unstable angina). Patient-oriented composite end point stratified by **(C)** tertile division of EuroSCORE (European System for Cardiac Operative Risk Evaluation) with cutoff values of 2 and 5 and **(D)** tertiles of SYNTAX (Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score of the current cohort (cutoff values of 27 and 44). **(E)** The patient-oriented composite end points were classified according to tertiles of bifurcation angle (BA) between the left anterior descending and circumflex arteries (cutoff values of 67 and 91.7). Abbreviations as in Figure 1.

53.8% in Cypher and 54.8% in paclitaxel-eluting stent (p = 0.83), whereas the all-cause mortality was 30.8% versus 36.5%, respectively (p = 0.56).

Comparison with historical cohort. Patient demographics in the historical control (n = 79) were similar to the current cohort except for a lower frequency of family history of coronary artery disease (32% vs. 19%, p = 0.04), reflecting that the changes in clinical practice, number of implanted stents, stent length, stent diameter, and clopidogrel duration are higher in the current cohort than in the historical control group.

Figure 3 shows the Kaplan-Meier estimates of all-cause mortality and the patient-oriented composite end point of the current cohort with DES and the historical control with BMS. At 1 year, the rate of all-cause death (current cohort 19.6% vs. historical cohort 29.1%) and patient-oriented composite (32.4% vs. 43.0%) was lower in the current cohort than in the historical cohort (Figs. 3A and 3B). At 4 years the events rate, however, became comparable between the 2 groups (all-cause mortality: 38.0 vs. 35.6%, p = 0.48; patient-oriented composite: 54.4 vs. 53.2%, p = 0.64) as a result from a late increase of events in the current cohort. Kaplan-Meier estimate before 2 years yielded a numerically higher patient-oriented composite end point in the historical cohort (log-rank p = 0.1), whereas landmark analysis (Fig. 3B) after the second year demonstrated a significantly higher event rate in the current cohort than the historical cohort (log-rank p = 0.02).

SYNTAX score. In the current cohort, the SYNTAX score ranged from 7 to 104 with median of 33.0. If the SYNTAX score is divided into tertiles, the cutoff values were 27.0 and 44.0. The Kaplan-Meier curves of device-oriented composite stratified by these tertiles of SYNTAX score are presented in Figure 2C. The 4-year event rates were 46.2%, 55.1%, and 69.6% in low, intermediate, and high tertile groups, respectively. High tertile group demonstrated significantly higher event rates than intermediate tertile (log-rank p = 0.03) and low tertile (log-rank p = 0.005) groups did.

Three-dimensional QCA analysis. Three-dimensional QCA analysis was feasible in only 50.7% of patients due to the unavailability of 2 separate angiographic views of more than 30° that is a prerequisite for 3-dimensional QCA; in the remaining patients, 2-dimensional QCA was performed. The results are shown in Table 1. In the patient receiving DES, the Kaplan-Meier curves of patient-oriented composite were separated according to the tertiles of systolic bifurcation angle (high >91.7, intermediate ≤91.7 and >67, low ≤67) as shown in Figure 2E. High tertile group demonstrated higher patient-oriented composite at 4 years (66.3%) than the intermediate (51.0%) and the low (45.2%) groups did (log-rank high vs. low: p = 0.04; high vs. intermediate: p = 0.09).

Predictor of adverse events. Table 3 shows the results of the univariate and multivariate analyses to identify the predictors for all-cause mortality and for patient-oriented composite. Bifurcation angle did not remain as a significant predictor of either all-cause mortality or patient-oriented end point in the multivariate analysis.

At 1 year, multivariate analysis demonstrated that EuroSCORE, age, shock at entry, and SYNTAX score were independent predictors for all-cause mortality and patient-

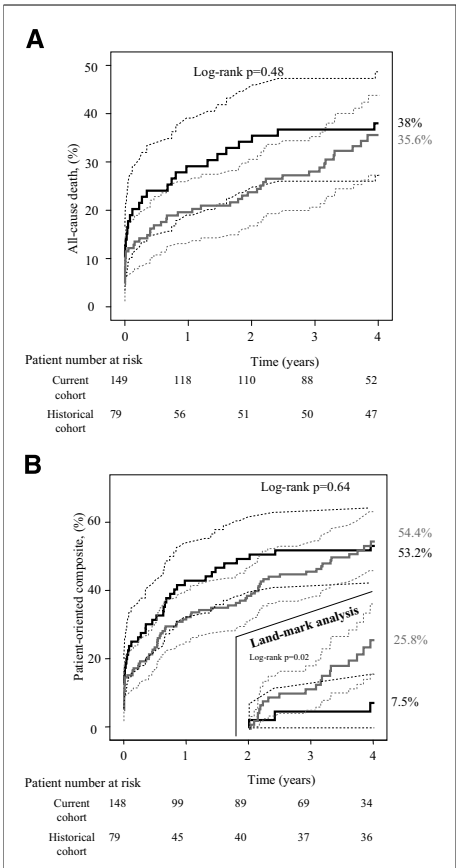

Figure 3. Kaplan-Meier Estimates of DES and BMS Cohorts

Kaplan-Meier estimates of the current cohort treated with drug-eluting stent **(red line)** or historical cohort treated with bare-metal stent **(black line).** All-cause mortality is demonstrated in **(A)**, whereas **(B)** demonstrates patient-oriented composite end point (all-cause mortality, any myocardial infarction, or any revascularization) with a landmark analysis more than 2 years after implantation. **Dotted lines** = 95% confidence interval. BMS = bare-metal stent(s); other abbreviations as in Figure 1.

Table 3. Univariate and Multivariate Analysis for Predictors of All-Cause Mortality and Patient-Oriented Composite After DES Implantation in the Left Main Trunk

	All-Cause Mortality				Patient-Oriented Composite			
	Univariate Hazard Ratio (95% CI)	p Value	Multivariate Hazard Ratio (95% CI)	p Value	Univariate Hazard Ratio (95% CI)	p Value	Multivariate Hazard Ratio (95% CI)	p Value
1-year outcome								
EuroSCORE	1.26 (1.17–1.36)	<0.001	1.24 (1.11–1.39)	<0.001	1.19 (1.12–1.26)	<0.001	1.13 (1.03–1.24)	0.009
Presentation of STEMI*	6.77 (3.56–18.66)	<0.001			4.38 (2.08–9.23)	<0.001		
Age	1.06 (1.02–1.09)	0.003	1.05 (1.01–1.10)	0.03	1.05 (1.03–1.08)	<0.001	1.04 (1.01–1.08)	0.009
Shock at entry	8.56 (3.83–19.1)	<0.001	4.21 (1.50–1.82)	0.006	8.26 (4.09–16.68)	<0.001	5.46 (2.35–12.69)	<0.001
SYNTAX score†	1.35 (1.17–1.56)	<0.001	1.23 (1.06–1.42)	0.006	1.27 (1.13–1.42)	<0.001	1.15 (1.02–1.30)	0.03
Hypercholesterolemia	0.33 (0.15–0.73)	0.006			0.43 (0.24–0.76)	0.004		
Hypertension	0.41 (0.18–0.96)	0.04	0.34 (0.13–0.88)	0.03	0.45 (0.24–0.84)	0.01		
4-year outcome								
EuroSCORE	1.19 (1.12–1.26)	<0.001	1.13 (1.03–1.24)	0.009	1.16 (1.09–1.24)	<0.001	1.09 (1.02–1.16)	0.02
Presentation of STEMI*	4.38 (2.08–9.23)	<0.001			3.42 (1.69–6.94)	0.001		
Age	1.05 (1.03–1.08)	<0.001	1.04 (1.01–1.08)	0.009	1.04 (1.01–1.070)	0.004		
Shock at entry	8.26 (4.09–16.68)	<0.001	5.46 (2.35–12.69)	<0.001	4.61 (2.21–6.61)	<0.001	2.74 (1.30–5.80)	0.008
SYNTAX score†	1.27 (1.13–1.42)	<0.001	1.15 (1.02–1.30)	0.03	1.22 (1.08–1.38)	0.001	1.12 (1.01–1.24)	0.4
High bifurcation angle‡					1.99 (0.93–4.26)	0.075		

Univariate or multivariate hazard ratios were calculated by Cox regression models.
*Stable angina used as a reference. †Each 10-point increase of SYNTAX score. ‡Low tertile bifurcation angle used as a reference.
Abbreviations as in Table 1.

oriented composite. At 4 years, in the final multivariate models, age, shock at entry, the SYNTAX score and EuroSCORE remained as independent predictors for all-cause mortality, whereas EuroSCORE, shock at entry, and SYNTAX score were identified as independent predictors for patient-oriented composite.

Discussion

The main findings of the current study are the following: 1) At 4-year follow-up after DES implantation in ULMCA, patient-oriented composite end point was 51.4% with a 58% relative increase of events from 1 year to 4 years. 2) A landmark analysis of the last 2 years of follow-up indicated a higher composite end point for the current cohort with DES when compared with the historical cohort with BMS (25% vs. 8%, p = 0.02). 3) EuroSCORE and SYNTAX score were independent predictors for both all-cause mortality and the patient-oriented composite end point up to 4 years, whereas pre-procedural bifurcation angle between the left circumflex and left anterior descending arteries was not.

According to the current guidelines of the European Society of Cardiology and the American Heart Association and American College of Cardiology guidelines (40,43), the presence of a stenosis in the LMCA is a class IIB or III indication for PCI unless the patient is not eligible for CABG in presence of extreme comorbidities and STEMI. In the recent U.S. criteria for appropriateness of revascularization, percutaneous treatment of LM disease is considered "inappropriate" (2). In European daily practice, however, 4.6% of patients treated in the catheterization lab have LM stenosis, and 58% of those are treated by percutaneous means (44).

Up to now, 2 randomized trials have been performed to compare CABG and PCI using DES in patients undergoing treatment for LM disease. In the LE MANS (Left Main Coronary Artery Stenting) study by Buszman et al. (10), PCI was associated with a lower 30-day risk of major adverse cerebrovascular cardiac event (MACCE) (p = 0.03) and had comparable 1-year mortality or MACCE to surgery. In the more recent SYNTAX trial (9), which randomized 1,800 patients with 3-vessel or LM coronary artery disease to either CABG or PCI, the use of PCI at 1 year was associated with safety end points (death, cerebrovascular accident, and MI) but a higher rate of MACCE than CABG, due to a significantly higher rate of revascularization. However, in the subgroup of patients with LM disease with an average SYNTAX score of 28.1, PCI and CABG were associated with similar MACCE rates at 1 year (PCI 15.8% vs. CABG 13.6%). In the DES cohort of the present study, the 1-year all-cause mortality and revascularization rate of patients treated with DES (19.6% and 16.9%, respectively) were higher than rates reported in the LM subgroup of the randomized cohort in the SYNTAX trial (4.2% and 12.0%, respectively). This is likely due to the high-risk nature of our all-comers registry (e.g., including 24% STEMI patients with a mean EuroSCORE of 4.26 and an average SYNTAX score of 39.4).

In this analysis, we selected a patient-oriented composite end point as a primary end point, because it represents the most critical clinical approach for a population undergoing a new form of treatment. The Academic Research Consortium defined 2 methodological approaches to report clinical follow-up: 1) the device-oriented composite end point; and 2) the patient-oriented composite end point. The device-oriented approach put the accent on the efficiency and efficacy of a new device, therefore, focusing on the cardiac death, MI, and reintervention related to the device. The patient-oriented end point is a follow-up, which specifically considers the welfare of the patient, and includes all-cause death, any MI, and any revascularization.

In the current analysis, we entered only the pre-procedural parameters in the multivariate analysis and excluded the procedural variables such as angulation after stenting, technique of stenting, number of stent, length of stent, and so forth, because they are factors reflecting the treatment modalities rather than the anticipated prognosis of the treatment. Parameters describing lesion characteristics were also excluded because they were incorporated in the SYNTAX score: for example, Medina classification, chronic total occlusion, American College of Cardiology/American Heart Association lesion classification (45).

Long-term outcomes after PCI in the LM population are limited. Park et al. (46) reported the 3-year safety composite rate (death, Q-wave MI, or stroke) of 9.7% with TVR rate of 12.6%. Vaquerizo et al. (12) demonstrated the device-oriented composite end point at 2 years of 12.6% after UCLMA stenting with paclitaxel-eluting stents in 291 patients from multicenter registry. In these registries, the patients with acute MI or cardiogenic shock were excluded; whereas in our registry, such patients were included and had a negative impact on clinical outcomes. Also, frequent use of intravascular ultrasound might contribute the relatively lower mortality in the Korean registry than in our European registry (46). In one of largest "all-comer" DELFT (Drug-Eluting Stent for Left Main) registries exclusively using DES in ULMCA with 3-year complete follow-up, Meliga et al. (15) demonstrated 3-year MACE rate (a composite of cardiac mortality, MI, and TVR) of 26.5%, cardiac mortality of 9.2%, and TVR of 14.2%. If the same composite definition were applied to the present study, the 3-year MACE rate in our study (26.0%) would be similar to the DELFT registry (26.5%). Wood et al. (47) reported a long-term outcome of 100 patients with high surgical risk after PCI. All-cause mortality at 28 months was 21%; event-free survival was around 65% at 27 months (47).

In the current study, the baseline patient demographics are comparable between the current and the historical cohorts. Although the anatomical complexity reflected by SYNTAX score was comparable between the 2 cohorts (the current cohort 39.4 vs. the historical control 36.8, $p = 0.96$), the cohort with DES was more aggressively treated than the historical cohort with BMS, as indicated by a higher incidence of bifurcation stenting (48% vs. 57%, $p = 0.04$), by a larger number of stents implanted (2.85 ± 0.47 vs. 3.08 ± 0.37), and by on average a longer stented length (42.4 ± 28.4 mm vs. 59.9 ± 40.4 mm).

The source of our concerns is the increase of the patient-oriented composite in the DES group between 2 and 4 years, which was significantly higher than in the historical cohort of BMS, and the long-term safety of DES in the treatment of patients with ULMCA remains an unanswered question. One possible explanation for unfavorable follow-up could be the occurrence of occult stent thrombosis. Occlusion of the LM trunk with thrombus is likely to be lethal. Thus, patients can present with sudden and/or out-of-hospital death rather than with angiographically proven stent thrombosis. The very late stent thrombosis presenting with out-of-hospital death, however, can be undiagnosed and under-reported. The cause of death was obtained from the civil registry, and it is up to the general practitioners to classify the cause of mortality according to International Classification of Diseases and Related Health Problems-10th Revision unless the patient passed away in the hospital. Therefore, no attempt was made to impute death to possible or probable stent thrombosis.

In the large multicenter registry ($n = 731$) by Chieffo et al. (17), the cumulative incidence of stent thrombosis at 29.5 months after LM stenting was reported to be 0.95% for definite stent thrombosis and 2.7% for possible stent thrombosis. In DELFT registry (15) ($n = 358$) at ≥3-year follow-up, the incidence of definite, probable, and possible stent thrombosis were 0.6%, 1.1%, and 4.4%. In ISAR-LEFT MAIN (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions) trial (48) ($n = 607$), the 2-year rate of definite or probable stent thrombosis was about 0.5% to 1.0%. In a series of high surgical risk patients, Wood et al. (47) reported a 5% possible stent thrombosis presenting as sudden death. Taking into account the late increase in mortality shown in our study, follow-up extending beyond 3 years is warranted for patients receiving DES in the setting of ULMCA.

The bifurcation angle has been shown to relate not only to the difficulty level of the procedure but is also associated with intermediate outcomes. Dzavik et al. (19) reported that a bifurcation angle ≥50 was an independent predictor of MACE at 1 year after bifurcation crush stenting in 133 patients. In 132 patients receiving Cypher stents in bifurcations excluding LM lesions, Adriaenssens et al. (49) reported that increasing bifurcation angles is an independent predictor of binary restenosis (HR: 1.53 [95% CI: 1.04 to 2.23] per 10° increase in angulation) after culotte stenting. The worse outcomes in high-angulated bifurcation lesions might be the result of the adjacent presence of low and high shear stress found in bifurcation lesions. High

shear stress possibly stimulates platelet activation and aggregation, and low shear stress might enhance deposition of platelets. This mechanism can be potentially exaggerated in higher bifurcation angles. Furthermore, when bifurcation stenting is performed in high-angle lesions, the stent will likely not appose against the wall of bifurcation (50), especially in the ostium of the left circumflex artery (20). In the present study, however, we observed that the bifurcation angle between the left anterior descending and left circumflex arteries was not an independent predictor for adverse events, although there is a weak statistical association with 4-year composite end points in the univariate analysis (HR: 1.99 [95% CI: 0.93 to 4.26], p = 0.07).

Study limitations. This study has several limitations. This is a single center, observational study that included a modest number of patients. The results of this landmark analysis (reporting a higher event rate in patients treated with DES compared with BMS after 2 years) would need to be confirmed in a larger study. In addition, the low 1-year mortality rate compelled us to include only 2 or 3 independent variables in the Cox regression model, resulting in overfitting of the model. Confounding factors, such as procedural variables, might have been overlooked. Although baseline characteristics were similar in the historical BMS and current DES groups, some procedural variables were in fact different and as a result might have influenced outcomes.

Conclusions

Our study reports a late increase in adverse events up to 4 years, which warrants careful follow-up of the patient receiving DES in the LM trunk. The SYNTAX score and EuroSCORE can be considered important components of risk stratification.

Acknowledgments

The authors would like to acknowledge the senior cardiologists involved in the PCI procedures: E. McFadden, MD, PhD; P. J. de Feyter, MD, PhD; P. P. T. de Jaegere, MD, PhD; S. H. Hofma, MD, PhD; E. Regar, MD, PhD; G. Sianos, MD, PhD; P. C. Smits, MD, PhD; H. Duckers, MD, PhD; M. J. van der Ent, MD, PhD; W. J. van der Giessen, MD, PhD; R. J. van Geuns, MD, PhD; and C. A. van Mieghem, MD, PhD.

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Key Words: coronary disease ■ stents ■ atherosclerosis.

CHAPTER 23

Two-year outcome of the use of paclitaxel-eluting stents in aorto-ostial lesions

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Int J Cardiol. 2008 Oct 13;129(3):348-53.

ELSEVIER

International Journal of Cardiology 129 (2008) 348–353

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Two-year outcome of the use of paclitaxel-eluting stents in aorto-ostial lesions

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Received 10 February 2007; received in revised form 13 June 2007; accepted 10 August 2007
Available online 26 November 2007

Abstract

Background: Percutaneous treatment of stenoses involving aorto-ostial lesions is technically demanding and has been associated with lower procedural success and poorer clinical and angiographic outcomes when compared with non-ostial lesions. This study evaluated the immediate and long-term (2-year) outcome of aorto-ostial stenoses treated with paclitaxel-eluting stents (PES).
Methods: From February 2003 to December 2004, a total of 76 consecutive patients with 76 lesions underwent percutaneous intervention with PES for aorto-ostial lesions (right coronary artery, 37; left main, 26; saphenous vein graft, 13). All patients were clinically followed for the occurrence of major adverse cardiac events (MACE), defined as cardiac death, non-fatal myocardial infarction (MI), target lesion revascularization (TLR) or target vessel revascularization (TVR).
Results: All stents (1.7/lesion) were successfully deployed. Three lesions (3.9%) were pre-treated with debulking devices. Thirty-seven lesions (48.7%) were post-dilated with non-compliant balloons (balloon/artery ratio, 1.2). Stents were positioned protruding into the aortic lumen in 29 lesions (38.2%). Cumulative 2-year event-free survival was 68.4%. There was one angiographically-proven stent thrombosis occurring 427 days after TLR for restenosis after the index procedure. The restenosis rate at 7 months (median) was 20.0% and in-stent late lumen loss was 0.48 mm in 40 patients with angiographic follow-up.
Conclusions: Utilization of PES in this complex lesion subset is feasible and associated with favorable angiographic results at 7 months. However, the gradual increase in later events up to 2 years suggests that aorto-ostial disease remains problematic even in the era of drug-eluting stents.

Keywords: Aorto-ostial lesion; Paclitaxel-eluting stent; Percutaneous coronary intervention; Aorto-ostial lesion; Paclitaxel-eluting stent

1. Introduction

Percutaneous treatment of stenoses involving aorto-ostial lesion is a technically demanding procedure for interventionalists and has been associated with lower procedural success, and poorer clinical and angiographic outcomes when compared with treatment of non-ostial lesion [1,2]. The extremely sclerotic and calcified nature of this lesion site [3–5] has contributed to suboptimal immediate and long-term results after balloon angioplasty as a stand-alone strategy [6]. Debulking strategies with directional coronary atherectomy (DCA) or rotational atherectomy (rotablator) were assumed to alter outcomes for this particular lesion subset, but their efficacies have not been determined. To counter the ostial elasticity resulting in high restenosis rates (enhanced recoil), stent implantation is a reasonable strategy for lesion scaffolding, and bare metal stents have resulted

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doi:10.1016/j.ijcard.2007.08.018

in better outcomes than conventional balloon angioplasty [7–9]. However, in addition to acute and chronic stent recoil, excessive neointimal growth after stenting in this location has been documented [10]. Although drug-eluting stents (DES) have shown even better clinical and angiographic results than bare metal stents, data on the efficacy of DES for ostial lesions are still limited, mostly due to the exclusion of these high risk lesions in the majority of the published randomized trials [11–14]. Percutaneous treatment with sirolimus-eluting stent (SES) for aorto-ostial lesions has already been reported to improve short-term clinical and angiographic outcomes [15]. Polymer-based paclicaxel-eluting stent (PES, TAXUS™ Express2™, Boston Scientific Corp., Natick, MA) is another FDA-approved drug-eluting stent that has been shown to reduce clinical events in simpler lesions [13]. To date, few reports are available on the treatment of ostial stenoses using PES. In addition, little is known about the long-term results of percutaneous treatment of aorto-ostial lesions using DES. This study was made to evaluate both the 7-month angiographic and 2-year clinical outcomes of the use of PES for aorto-ostial narrowings.

2. Methods

From February 2003 to December 2004, a total of 93 consecutive patients underwent percutaneous intervention for 93 aorto-ostial lesions in our institution. All the eligible lesions were primary culprit lesions for each patient and therefore stenting due to dissection, extended stenting from non-ostial lesions, or spasm induced by catheter tip were excluded. Seventeen patients were excluded from this study because of deployment of SES (Cypher™, Cordis/Johnson & Johnson, Warren, NJ) in 7, bare metal stents in 5, angioplasty without stenting in 2, unsuccessful guidewire crossing in 2 (chronic total occlusions), and PES with a different type of platform (Infinium™, Sahajanand Medical Technologies Pvt. Ltd., Gujarat, India) in 1. Thus, the study population consisted of 76 consecutive patients treated with TAXUS™ Express2™ stents. The study population is a constitutive part of Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry of which the design and goals have been described previously [16]. An aorto-ostial lesions were defined as being located less than 3 mm (as measured by quantitative angiographic analysis) of the orifice of the right coronary artery, left main coronary artery, or saphenous venous graft when visualized in an angiographic projection without foreshortening [6]. The study protocol was approved by the local ethics committee and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

2.1. Medications and interventional procedures

Elective patients were all pre-treated with aspirin and clopidogrel. A loading dose of 300 mg of clopidogrel was adopted in emergency cases. Post-interventional prescription of antiplatelet was life-long aspirin and 6-month clopidogrel with daily dose of 75 mg. PESs were available in diameters of 2.25, 2.5, 2.75, 3.0 and 3.5 mm. Usage of debulking devices (DCA or rotablator), distal protection devices and administration of glycoprotein IIb/IIIa inhibitors was left to the discretion of each physician. Slight stent protrusion into the aortic lumen was determined in the least foreshortened angiographic projection. Angiographic success was defined as residual diameter stenosis $<30\%$ in the presence of Thrombolysis in Myocardial Infarction (TIMI) flow grade 3.

2.2. Clinical follow-up and definitions

Adverse events were assessed at 30 days, 1 and 2 years. The primary endpoint was the occurrence of major adverse cardiac events (MACE), defined as a composite of cardiac death, non-fatal myocardial infarction (MI), target lesion revascularization (TLR), and target vessel revascularization (TVR). All deaths were regarded as those of cardiac origin unless a noncardiac origin was proven either clinically or by autopsy. Non-fatal MI was defined as the occurrence of an elevated creatine kinase-MB fraction (CK-MB) >3 times the upper limit of normal [16]. TLR was defined as either surgical or percutaneous reintervention driven by significant ($\geq 50\%$) luminal narrowing either within the stent or the borders 5 mm proximal and distal to the stent that was undertaken in the presence of either anginal symptoms or objective evidence of ischemia. TVR was defined as reintervention in the treated vessel outside the target lesion. Stent thrombosis was defined as angiographically-documented complete occlusion (TIMI flow grade 0 or 1) or flow-limiting thrombus (TIMI flow grade 1 or 2) in a previously treated artery. Stent thrombosis was categorized according to its timing relative to the index procedure as early (within 30 days) or late (>30 days) thrombosis.

All patients were clinically followed for the occurrence of MACE. Information about in-hospital outcomes was obtained from an electronic clinical database maintained at our institution and by review of patients' records. Post-discharge survival status was examined from the Municipal Civil Registries. Occurrence of MI or revascularization at follow-up was collected by consulting our institutional electronic patient database and by contacting referring physicians and institutions.

2.3. Quantitative angiographic analysis

Quantitative angiographic analysis was performed using the computer-based validated QCA system (CAAS II, Pie Medical Imaging, Maastricht, the Netherlands). Quantitative measurements included the diameter of the reference vessel, the minimal luminal diameter, percentage (%) diameter stenosis, and late luminal loss (the difference between the minimal luminal diameter after the procedure and the minimal luminal diameter at follow-up). Binary restenosis was defined as a stenosis of at least 50% of the minimal

Table 1
Baseline clinical and angiographic characteristics ($n=76$)

Age, years	66.0±10.9
Male gender, *n* (%)	51 (67.1)
Smoking:	
current, *n* (%)	15 (19.7)
Former, *n* (%)	14 (18.4)
Diabetes:	
type I, *n* (%)	13 (17.1)
Type II, *n* (%)	4 (5.3)
Hypertension, *n* (%)	31 (40.8)
Hypercholesterolemia, *n* (%)	44 (57.9)
Renal insufficiency, *n* (%)	9 (11.9)
Family history, *n* (%)	28 (36.8)
Prior myocardial infarction, *n* (%)	26 (34.2)
Previous intervention, *n* (%)	18 (23.7)
Previous bypass surgery, *n* (%)	17 (22.4)
Multivessel disease, *n* (%)	55 (72.4)
Stable angina pectoris, *n* (%)	31 (42.1)
Unstable angina pectoris, *n* (%)	32 (42.1)
Acute myocardial infarction, *n* (%)	13 (15.8)
Cardiogenic shock, *n* (%)	4 (5.3)

luminal diameter in the target lesion at angiographic follow-up. In most cases, reference vessel diameter was obtained only from a point distal to the lesion. Angiographic patterns of restenosis were also determined [17].

2.4. Statistical analysis

Values in the text and tables are presented as mean±SD, or frequency (percentage) for descriptive purposes. The cumulative incidence of adverse events was estimated according to the Kaplan–Meier analysis. Statistical analyses were performed with SPSS 12.0.1 for Windows (SPSS Inc., Chicago, IL). A p value <0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Baseline patient, lesion, and procedural characteristics are shown in Tables 1 and 2. Multivessel disease was observed in 72.4% of the patients. More than half of the cases underwent index PCI for an acute coronary syndrome (unstable angina, 42.1%; acute myocardial infarction, 15.8%). There was no documentation of non-atherosclerotic etiologies associated with aorto-ostial disease such as syphilitic cardiovascular disease, Takayasu's arteritis, etc. [18].

The seventy-six target vessels in the present study consisted of 37 right coronary arteries, 26 left main coronary arteries, and 13 venous grafts. These lesions included seven restenotic lesions following bare metal stent implantation (9.2%). Moderate to severe calcification was documented in 19 lesions, presence of thrombus in 13, restenosis of bare metal stent in 7, chronic total occlusion (an occlusion period more than 3 months) in 1.

3.2. Procedural results

Target lesions were treated using 1.69±0.97 stents (total stent length per lesion, 32.11±26.58 mm) that were post-dilated using balloons 3.6±0.44 mm diameter (mean balloon–artery ratio, 1.24). Lesion modification by debulking devices or cutting balloon was made in 7 patients. Stent placement with slight protrusion of the proximal edge into the ascending aorta was performed in 38.2% of the cases. Two patients were complicated by aorto-coronary dissection involving in the sinus of Valsalva, which regressed conservatively over a short period. Thirty-five patients (46.1%) underwent concomitant treatment of non-ostial lesions either in the same or different vessels.

3.3. Clinical outcome up to 2 years

Thirty-day, one-year as well as 2-year outcomes in terms of clinical events are reported in Table 3.

Table 2
Baseline lesion and procedural characteristics ($n=76$)

Lesion characteristics	
Lesion location	
Right coronary artery, *n* (%)	37 (48.7)
Left main coronary artery, *n* (%)	26 (34.2)
Venous graft, *n* (%)	13 (17.1)
In-stent restenosis of bare metal stent, *n* (%)	7 (9.2)
Chronic total occlusion, *n* (%)	1 (1.3)
Thrombus-containing lesion, *n* (%)	13 (17.1)
Moderate to severe calcification, *n* (%)	19 (25.0)
Eccentric lesion, *n* (%)	24 (31.6)
TIMI flow grade ≤2:	
Baseline, *n* (%)	18 (23.7)
After procedure, *n* (%)	3 (3.9)
Procedural characteristics	
Number of stents/lesion, *n*	1.69±0.97
Total stent length/lesion, mm	32.11±26.58
Maximal balloon size, mm	3.64±0.44
Balloon/artery ratio	1.24±0.23
Maximal inflation pressure, atm	20.18±2.65
Debulking, *n* (%)	3 (3.9)
Cutting balloon, *n* (%)	4 (5.3)
Direct stenting, *n* (%)	33 (43.4)
Post-dilatation, *n* (%)	37 (48.7)
Use of glycoprotein IIb/IIIa inhibitors, *n* (%)	10 (13.2)
Distal protection device, *n* (%)	12 (15.8)
Intra-aortic balloon pump, *n* (%)	4 (5.3)
Left ventricular assist device (LVAD), *n* (%)[a]	1 (1.3)
Periprocedural stent thrombosis, *n* (%)	0 (0.0)
Stent protrusion, *n* (%)	29 (38.2)
Aorto-coronary dissection after procedure, *n* (%)	2 (2.6)
Concomitantly treated lesion, *n* (%)	35 (46.1)
Angiographic success, *n* (%)	73 (96.1)

[a] The Impella LVAD Recover LP 2.5 (Impella Cardiotechnik, Aachen, Germany).

Table 3
Major adverse cardiac events

30-day outcome	
Death	6 (7.9)
Non-fatal myocardial infarction	4 (5.3)
Target vessel revascularization	0
Target lesion revascularization	0
MACE	10 (13.2)
Stent thrombosis*	1 (1.3)
1-year outcome	
Death	6 (7.9)
Non-fatal myocardial infarction	4 (5.3)
Target vessel revascularization	8 (10.5)
Target lesion revascularization	3 (3.9)
MACE	18 (23.7)
Stent thrombosis*	1 (1.3)
2-year outcome	
Death	9 (11.8)
Non-fatal myocardial infarction	6 (7.9)
Target vessel revascularization	11 (14.5)
Target lesion revascularization	3 (3.9)
MACE	24 (31.6)
Stent thrombosis†	3 (3.9)

*Subacute stent thrombosis in a concomitantly-treated non-ostial target vessel (left anterior descending) 21 days after the index PCI; †One is subacute thrombosis in a non-ostial target vessel (left anterior descending) 2 days after stenting and the other is late thrombosis in the right coronary ostial lesion 427 days after TLR. MACE = major adverse cardiac events.

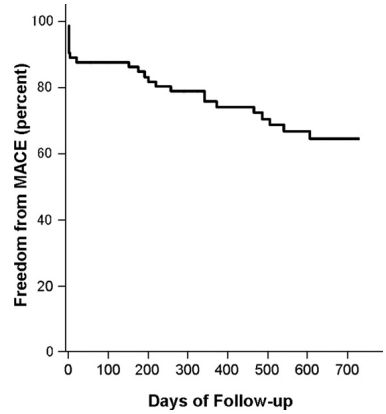

Fig. 1. Kaplan–Meier event-free survival at 2 years for major adverse cardiac events (MACE).

3.3.1. 30-day outcome

In the first month, 6 patients died, four of whom exhibited fatal MI resulting in refractory cardiogenic shock as a baseline clinical presentation, although stents were successfully deployed in each of the target lesions (1 right and 3 left main coronary arteries). One patient with stable angina underwent elective stenting for ostial left main disease, but died due to a rapid hemodynamic collapse resulting from compromised blood flow to the jailed left circumflex artery. One patient died 21 days after concomitant stenting in 2 target lesions (ostial right coronary artery and left anterior descending artery). This case was strongly suspected of having early stent thrombosis either in the territory of the right coronary artery or left anterior descending artery as the cause of sudden death, which was not angiographically-documented.

Out of the 4 MIs, 3 were MIs during the index procedures and the other was a subacute stent thrombosis in a concomitantly-treated different vessel (left anterior descending artery) 21 days after the index procedure. There were no cases of TLR or TVR in the first 30 days.

3.3.2. 1-year outcome

Neither further death nor MI was documented after 30 days up to 1 year. TVR was required in 8 patients (TLR, 3/8), all of which were treated percutaneously.

3.3.3. 2-year outcome

There was a gradual increase in MACE throughout 2 years (Fig. 1). There were 3 more deaths identified between 1 and 2 years. One patient who died 465 days after stenting was strongly suspected of having late stent thrombosis in the territory of the right coronary artery as the cause of sudden

Table 4
Quantitative coronary angiography ($n=76$)

Baseline	
Reference vessel diameter, mm	3.04±0.56
Minimum luminal diameter, mm	0.92±0.51
Diameter stenosis, %	69±16
Lesion length, mm	14.24±15.06
Post procedure	
Reference vessel diameter, mm	3.30±0.51
Minimum luminal diameter, mm	2.73±0.52
Diameter stenosis, %	17±9
Follow-up (n=40) at 7 months[a]	
Reference vessel diameter, mm	3.26±0.54
Minimum luminal diameter, mm	2.23±0.94
Diameter stenosis, %	34±26
In-stent late lumen loss, mm	0.48±0.88
Restenosis, *n* (%)[b]	8 (20%)
Focal — articulation	1
Focal — margin	1
Focal — body	2
Diffuse — intrastent	1
Diffuse — proliferative	1
Diffuse — total occlusion	2

[a]Median of follow-up period.
[b]Restenosis patterns were adopted from the classification by Mehran et al. (Ref. [17]).

death, though this was not angiographically confirmed. Additional 3 clinically-driven TVRs were performed. The 2-year cumulative incidence of MACE was 31.6%. There were two additional stent thromboses (early and late) identified. One occurred 2 days after stenting a non-ostial lesion (left anterior descending) and the other was a late thrombosis 427 days after the index PCI for the right coronary ostial lesion.

3.4. Angiographic results

Quantitative coronary angiographic analysis is summarized in Table 4. The mean reference vessel diameter was 3.04 mm. Angiographic follow-up data were obtained in 40 patients (52.6%) at the median timing of 7 months after the index stenting. Binary in-stent restenosis rate was 20.0% (8/40). Focal patterns of restenosis were found in 50% (4/8). In-stent late lumen loss of PES in this lesion subset was 0.48 mm.

4. Discussion

The present study provides the 7-month angiographic and 2 year clinical outcomes of PES in aorto-ostial lesions in a larger consecutive population than that of earlier studies [1,9,15,19]. The results of the present study suggest the following two main findings: 1) PES utilization is a feasible treatment option in this complex lesion setting by keeping the restenosis rate to 20.0% and thereby TLR rate to 5.3%; 2) The long-term efficacy of PES, however, in overall clinical outcome still remains to be determined due to the subsequent increase in later events.

Aorto-ostial disease can be a critical cause of fatal myocardial infarction or sudden cardiac death due to the relatively large myocardial territory exposed to risk [3]. Lesions in this location are distinctive from branch ostial lesions because of their specific histopathological characteristics such as highly increased fibrous cellularity, calcification and sclerosis [3–5]. Reflecting this lesion background, Tsunoda et al. reported that excessive neointimal growth and chronic stent recoil might be two important etiologic factors for stent restenosis at this particular location [10]. With regards to the former factor, stents coated with antiproliferative agents are reasonable devices of choice and PES demonstrated successful reduction of neointimal growth after stenting (late loss, 0.48 mm),. To overcome another potential factor for restenosis, the combination of debulking and DES may be a particularly optimal approach. Plaque modification prior to stent implantation has been initially embraced as a preferred treatment strategy for this lesion subset [4]. However, since the role of debulking in the era of DES has not been clarified, we performed adjunctive debulking in only 3 patients. Instead of using atherectomy devices, we aggressively post-dilated by adopting a relatively large-sized non-compliant balloon (balloon–artery ratio, 1.24) in order to achieve a satisfactory angiographic result. Because of the delayed healing response of injured vessel wall after implantation of DES [20], it might be speculated that the relatively high mechanical injury resulting from atherectomy further delayed healing process following DES placement. Furthermore, atherectomy of aorto-ostial lesions is technically demanding because of the need to pull the guiding catheter from the coronary ostium while leaving the atherectomy catheter in position for debulking. Additionally, when performing DCA or rotablation for aorto-ostial lesions, great care should be taken to avoid excision of guiding catheter material [21,22].

Slight stent protrusion into the aorta is usually associated with a benign clinical course. However, unapposed protruding stent struts may theoretically promote platelet activation, thrombosis, and/or distal embolization. In addition, protruding stent struts may not only pose an inability to easily re-engage the ostium with either diagnostic or guiding catheters, but also can complicate future interventional as well as surgical procedures [23–26]. We encountered only one angiographically-documented stent thrombosis related to the target vessel and stent protrusion was not implicated in this case. Of the 2 possible stent thrombosis cases, stent placement with slight protrusion was performed in one (465 days after stenting) and not in the other (21 days after stenting). The 2 cases with very late stent thrombosis occurring beyond 1 year suggest that current US Food and Drug Administration-approved indications for 6-month clopidogrel use following TAXUS implantation may not be sufficient to prevent late stent thrombosis. Eisenstein et al. showed that longer-term clopidogrel use may be associated with more favorable clinical outcome for patients receiving DES [27]. However, the small number of patients evaluated in this analysis do not allow for any definitive statement with respect to the safety profile of this stenting technique. So far, it appears that positioning of PES with protrusion of only a short segment of stent into the aorta might instead contribute to lower restenosis by adequately covering the lesion.

Despite the low incidence of TLR at 2 years, the limited role of PES on overall long-term outcome was also indicated because of the gradual increase in TVR rate. Obstruction at the origin of a coronary artery is most often associated with more generalized coronary atherosclerosis and the presence of multivessel coronary artery disease (72.4%). It may be helpful for long-term favorable outcome to prevent and adequately detect the progression of other non-ostial lesions that are not significant at time of treatment of ostial lesions in the same vessel. Long-term evaluation of non-ostial lesions in the target vessels should be considered.

4.1. Study limitations

There were several limitations in this study. First, this was a single-center's experience with implantation of PES in aorto-ostial stenoses. Second, no control group was used to compare the long-term efficacy of PES with other devices. In this regard, direct comparison between PES and bare stent/

SES would have been interesting to address whether a different drug and different stent platform might influence the incidence of restenosis. Third, the rate of follow-up angiography was limited to 52.6% of 76 patients. Finally, since each treatment strategy was not prespecified, the results may reflect our bias toward our treatment technique. However, this study more likely represents "real-life" practice of PES utilization.

5. Conclusions

In conclusion, our findings suggest that PES in aorto-ostial lesions is safe and feasible in light of the low incidence of restenosis at 7 months. However, the increase in later events, especially the TVR rate, may attrite the long-term benefit of PES in patients with this complex lesion subset.

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CHAPTER 24

Greyscale intravascular ultrasound and IVUS-radiofrequency tissue characterisation to improve understanding of the mechanisms of coronary stent thrombosis in drug-eluting stents

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EuroIntervention 2008 Aug; 4 (Suppl C): C33-C38.

EuroIntervention

Greyscale intravascular ultrasound and IVUS-radiofrequency tissue characterisation to improve understanding of the mechanisms of coronary stent thrombosis in drug-eluting stents

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The authors have no conflict of interest to declare.

KEYWORDS
radiofrequency data analysis, incomplete stent apposition, necrotic core

Abstract

Stent thrombosis is one of the major concerns after drug-eluting stent implantation. Multiple mechanical causes (i.e. stent under-expansion, edge dissection, geographic miss, residual stenosis, incomplete stent apposition and aneurysm) have been postulated. These features are easily identifiable by intravascular ultrasound. However, it is uncertain which of them are inextricably related to stent thrombosis, primarily due to the low number of such patients studied by IVUS in case control studies.

Complementary to greyscale IVUS, tissue characterisation by IVUS radiofrequency data (RFD) analysis has the potential to add valuable information on the pathogenesis of stent thrombosis by providing information on plaque composition, specifically on the amount of necrotic core and its location (superficial or deep). However, the clinical utility of IVUS-RFD analysis in this context has yet to be demonstrated.

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Introduction

In current practice, one of the most important concerns for the interventionalist is stent thrombosis, primarily of drug-eluting stents (DES)[1-5]. Among the multiple postulated causes, there is a large group encompassed in so-called mechanical causes (i.e. stent under-expansion, edge dissection, geographic miss, residual stenosis, incomplete stent apposition [ISA] and aneurism [extreme ISA]). These were also formerly related to thrombosis of bare metal stents (BMS). In fact, for this stent type, it has been reported that in 78% of the patients with stent thrombosis at least one mechanical cause is present using greyscale intravascular ultrasound (IVUS)[6]. Furthermore, ISA at long-term follow-up seems to be more frequent after sirolimus-eluting stent (SES) implantation than after BMS implantation[7]. Extreme positive remodelling after DES implantation is one of the main processes involved in cases with late acquired ISA. More importantly, ISA has recently been linked to thrombotic coronary events[4,8].

Complementary to greyscale IVUS, tissue characterisation by IVUS radiofrequency data (RFD) analysis has the potential to add valuable information on the pathogenesis of stent thrombosis by providing information on plaque composition, specifically on the amount of necrotic core (NC) and its location (superficial or deep). Although IVUS-RFD analysis is a new technique and there is a long way ahead to prove its clinical value in the context of stent thrombosis, in this report we describe pathological findings that have been related to stent thrombosis that are identifiable by IVUS-RFD.

We also describe the current evidence that relates greyscale IVUS findings with stent thrombosis.

Definitions of the mechanical causes of stent thrombosis (Figure 1)

Stent under-expansion index, defined as minimum stent cross-sectional area (CSA) ÷ mean of proximal and distal reference areas[4,8].

Significant residual reference segment stenosis, defined as the combination of a reference segment minimum lumen CSA <4 mm^2 plus a plaque burden >70%[9].

Geographical miss, defined as a mismatch of intended lesion and balloon-injured targets with subsequent stent deployment sites[10]. Unlike previous definition, geographical miss also refers to balloon-injured areas left untreated.

Incomplete stent apposition, defined as the lack of contact of at least one stent strut with the vessel wall, not encompassing a side branch. This can be detected immediately after stent implantation (acute or post-stenting ISA) or at follow-up (six months and beyond - late acquired ISA). (Figure 2).

Edge dissection, defined as the presence of a flap in close proximity to stent edges.

Aneurysm, defined as an enlargement of both the external elastic membrane (EEM) and lumen area >50% of the proximal reference segment[11].

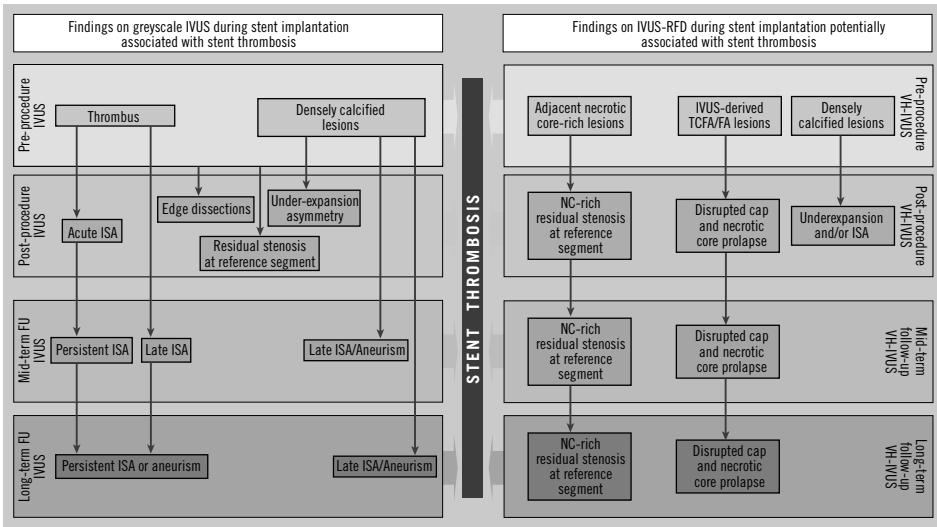

Figure 1. This illustration displays the potential use of greyscale IVUS and IVUS-radiofrequency data (RFD) analysis across the different stages of the interventional procedure and imaging follow-up of the patients. Greyscale IVUS can categorise plaque types and the acute result of the intervention, as well as provide useful information on some characteristics that have been related to stent thrombosis such as incomplete stent apposition (ISA), edge dissection, residual stenosis, under-expansion and thrombus. IVUS-RFD could provide valuable information on the intact plaque, especially on necrotic core (NC) amount and location.

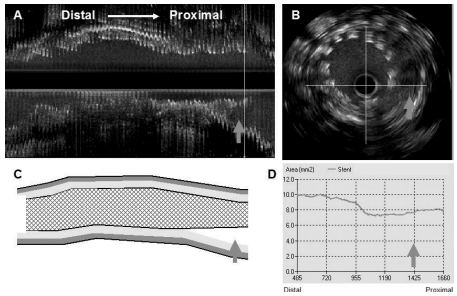

Figure 2. Panel A shows a longitudinal view of an IVUS pullback. The arrow points to a proximal segment that is not apposed to the vessel wall. Panel B is the corresponding cross-sectional area (CSA). The arrow shows multiple stent struts that are not apposed. Panel C is a diagrammatic representation of the longitudinal view. Notice the lack of stent apposition signalled by the arrow. Panel D indicates the stent CSA throughout the segment. An important decrease in stent area is seen at the proximal part.

Greyscale IVUS

Incomplete stent apposition has been postulated to be one of the potential causes of stent thrombosis. Yet, is ISA truly highly prevalent in patients with stent thrombosis after DES implantation? Or is stent thrombosis a rare event among patients with ISA? This is not clear, the reported prevalence of ISA post-stenting among DES studies (sirolimus, paclitaxel ([PES]) and everolimus-eluting stents [EES]) varies from 2.4 to 34.4%[12-18]. On the other hand, although late-acquired ISA has, by definition, the same IVUS appearance as post-stenting ISA, its postulated mechanisms are completely different including progressive expansion of the vessel wall, thrombus resolution and lack of tissue growth around the stent struts[17]. In the literature, the incidence ranges from 0.0 to 16.7%[12-14,16-21]. Possible explanatory reasons for the wide spread of occurrence across all reported stent studies are the following: i) lesion-related (calcified, eccentric, chronic total occlusions or thrombus)[17]; ii) procedure-related (absence of postdilatation and IVUS-guidance); iii) device-related (DES > BMS); and iv) corelab-related (inter-analyst and inter-corelab variability). Of note, no clinical events related to ISA have been reported in these trials.

The STLLR trial documented that geographical miss occurred in 66.5% of implantations and was an additional risk for late acute coronary events following drug-eluting stent implantation[10]. Thus, this suggests that angiographic-guided implantation of DES may be not satisfactory. In this regard, IVUS easily identifies incomplete lesion coverage, stent under expansion and ISA, yet remains infrequently used (approximately 7% of cases in the United States)[22]. Although IVUS-guided stenting could potentially improve stent implantation, the cost-effectiveness of routine IVUS use in this context has yet to be evaluated. More importantly, whether this approach would impact the incidence of late stent-related clinical events is unknown. However, we do not think all cases are suitable for IVUS-guided stenting. In this era of more liberal DES use, interventionalists frequently have to treat vessels with complex anatomy (e.g. severe tortuosity), in which even with IVUS-guided stenting, complete apposition may not be fully ensured. Thus, a careful analysis of the coronary anatomy prior to stent implantation may help operators to select cases in which IVUS imaging is safe and the information useful.

Clinical studies of patients with stent thrombosis and intravascular ultrasound imaging

Fujii et al[9] compared 15 patients treated with SES who experienced early stent thrombosis with 45 patients who had no evidence of SES thrombosis. Incomplete stent apposition was found in 13% of patients with SES thrombosis vs. 16% of controls. The minimum stent CSA was 4.3±1.6 mm^2 in patients with SES thrombosis compared with 6.2±1.9 mm^2 in controls ($p < 0.001$); the stent under-expansion index was smaller in SES thrombosis (0.65±0.18 vs. 0.85±0.14; $p < 0.001$), and the residual reference segment stenosis was 67% in the SES thrombosis group vs. 9% in the controls, $p < 0.001$. In another case control study of 13 patients (14 DES with early thrombosis)[23], the minimum stent CSA was also smaller as compared to controls (4.6±1.1 vs. 5.6±1.7 mm^2; $p < 0.05$), with 11 of 14 stents (79%) having a minimum stent CSAs ≤ 5.0 mm^2 compared with 12 of 30 (40%) in the control group (p=0.04). These authors also found larger residual reference segment stenosis in patients with thrombosis.

Mintz et al[21] reported the comparison of 15 cases of DES with early thrombosis with 45 cases of DES restenosis. In line with the above-mentioned reports, the minimum stent CSA was smaller in DES thrombosis lesions (3.7±0.8 vs. 4.9±1.8 mm^2; p=0.01). Independent predictors of stent thrombosis were diffuse stent under-expansion (odds ratio [OR], 1.5; p=0.03) and proximal location of the site of minimum stent CSA (OR, 12.7; p=0.04).

Siquiera et al[24] reported late-acquired incomplete stent apposition in 10 out of 195 patients (seven with SES, three with PES) studied with IVUS at six months; two out of these 10 patients with late-acquired ISA had stent thrombosis at 331 (PES) and 1,152 days (SES).

A report of two cases with DES thrombosis (one SES and one PES) revealed extensive positive remodelling (increase in vessel volume of 19.7 and 38.6%) leading to large areas of late-acquired incomplete stent apposition in both cases by means of serial angiography and IVUS[25].

More recently, Cook et al[8] reported 11 patients with very late DES thromboses and compared them with 198 controls that had undergone routine IVUS follow-up but did not develop stent thrombosis. Incomplete stent apposition was present at the time of thrombosis in 77% of patients with very late DES thromboses vs. 12% of controls imaged during routine follow-up; $p < 0.0001$. The authors suggested that incomplete stent apposition may play a role in the pathogenesis of this adverse event.

The latest report available in the literature is by Alfonso et al[4] who reported 26 patients with DES thrombosis out of 1,974 patients treated with DES during the same period, resulting in a two-year stent thrombosis incidence of 1.3%. Only 12 were included in the IVUS substudy. Thrombotic occlusion was seen in all patients by IVUS. Severe stent under-expansion and significant residual

reference segment stenosis were again the common denominators in this series. Incomplete stent apposition was detected in 50% of the patients (three subacute, three late thrombosis), and major side branches jailed by the stent were seen in 67% of the patients. According to the Multicentre Ultrasound Stenting in Coronaries Study (MUSIC) criteria[26], deployment of the stents was suboptimal in all patients with stent thrombosis. In contrast with other studies, the minimum stent area was not small (9±3 mm^2). After re-intervention, residual thrombus was present in all patients (17±7% of stent volume post-intervention vs. 51±22% pre-intervention, p= 0.001).

We can therefore conclude that incomplete stent apposition is highly prevalent among patients with DES thrombosis that have been studied by IVUS. In addition, stent under-expansion and residual reference segment stenosis were also constantly associated with DES thrombosis.

Table 1 summarises the IVUS findings that have been reported among patients with stent thrombosis.

Table 1. IVUS findings in patients with stent thrombosis.

EEM CSA, mm^2	28.6	Mean[a]
Increase in EEM volume over time,%	19.7-38.6	Range[b]
ISA,%	50-100	Range[abc]
Maximal ISA CSA, mm^2	2.0-24	Range[a]
Maximal ISA length, mm	6.3	Mean[a]
Calcium arc, °	360	Mean[a]
Stent underexpansion index	0.39-1.00	Range[ac]
Stent asymmetry	0.77-0.90	Range[c]
Minimum stent CSA, mm^2	3.7; 4.3; 4.6	Mean[def]

EEM: external elastic membrane; CSA: cross-sectional area; ISA: incomplete stent apposition; [a]Cook et al; [b]Feres et al; [c]Alfonso et al; [d]Mintz et al; [e]Fujii et al; [f]Okabe et al

IVUS Radiofrequency data analysis

Our knowledge of the pathophysiology of late DES thrombosis is derived from pathologic samples[27-30]. It has been demonstrated that DES cause substantial delayed healing (the most common cause of late DES thrombosis at autopsy) characterised by the lack of complete re-endothelialisation and persistence of fibrin when compared with BMS[31]. This cannot be assessed by any IVUS modality due to its limited axial resolution (100 µm).

Other proposed pathological mechanisms of coronary stent thrombosis are stenting of necrotic core-rich plaques with extensive tissue prolapse and plaque disruption in the proximity of the stented arterial segment[27,31]. (Figure 3). IVUS-RFD is able to characterise necrotic core with high sensitivity and specificity[32]. This technique also provides geometrical analysis of each frame, allowing us to have the combined assessment of necrotic core and plaque size; indeed this relationship has been tested in 25 patients with acute coronary syndromes in whom an increment in plaque size was followed by an increase in the NC[33]. Thus, pre-stenting imaging using IVUS-RFD can give us an insight not only into the extent of plaque but also on the extent of necrotic core within and beyond the intended stenting segment. This latter assessment is important since stenting has been lately performed, under conventional angiography guidance, from "normal to normal" arterial segments;

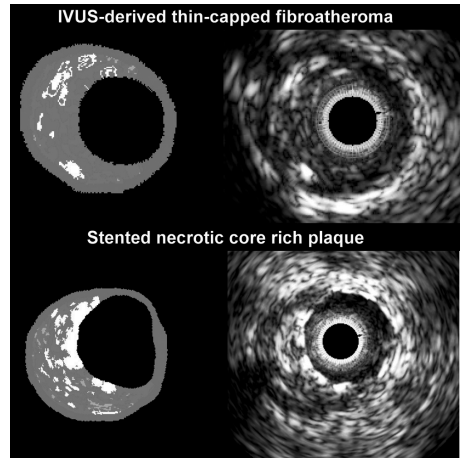

Figure 3. Greyscale IVUS frame and its corresponding IVUS-radiofrequency data frames of an IVUS derived thin cap fibro-atheroma (two upper frames). At the bottom, a stented necrotic core-rich plaque is shown. Notice the presence of stent struts at the lumen in the color picture as "dense calcium" on top of a confluent area of necrotic core. Virtual histology color code: green is fibrous, greenish is fibro-fatty, red is necrotic core and white is dense calcium.

however, disruption of adjacent necrotic core-rich areas that are angiographically disease-free could be avoided by IVUS-RFD pre-stenting investigation. In this context, we studied 24 patients in whom 26 stented segments (by angiography stenting was performed from "normal to normal" coronary segments) using IVUS-RFD were assessed. We observed that necrotic core rich areas were left unstented (5mm-proximal edge mean necrotic core 17.0±13.5% and 5 mm-distal edge 18.5±16.5%); however, no stent thrombosis has been observed in this small cohort of patients at six months follow-up. It has yet to be determined in a larger population whether incomplete coverage of necrotic core-rich coronary plaques or disruption of adjacent necrotic core areas by DES impact on long-term clinical events.

Bifurcation lesions are the preferable location of TCFAs; in clinical studies this subset of lesions has been related to stent thrombosis[4]; we therefore hypothesised that the evaluation of the location and amount of the necrotic core is crucial. Thus, not only may the bifurcation stenting technique change accordingly, mainly by avoiding overlapping segments on these NC-rich areas, but also the stent used to treat these lesions. The desirable objective is a device that offers: a) mechanical stabilisation, b) promotion of vascular healing and c) reduction of inflammation. Nevertheless, it is worth mentioning that although related to a different physiopathological process and other arterial segment – restenosis following carotid stenting – the dissection of a lipid-rich, inflammatory plaque has been recently associated with reduced risk of restenosis.[34]

Theoretically, IVUS-RFD enables us to characterise *in vivo* TCFA - IVUS-derived thin-capped fibro-atheroma (IDTCFA); these lesions

may pose a distinctive high risk of stent thrombosis, due to the fact that they contain large amount of necrotic core located superficially. We have recently developed software to quantify the amount of necrotic core in contact with the lumen, enabling refinement of our analysis. Our current definition of an IDTCFA is a lesion fulfilling the following criteria in at least three CSAs: 1) plaque burden ≥ 40%; 2) confluent necrotic core ≥10% in direct contact with the lumen (i.e., no visible overlying tissue) in the investigated CSA; all consecutive CSAs having the same morphologic characteristics are considered as part of the same IDTCFA lesion[35]. In a recent study, using this refined definition of TCFA as assessed by IVUS-RFD, in patients with ACS who underwent IVUS imaging of all three epicardial coronaries, on average, there were two IDTCFAs per patient, half of which showed outward remodelling[35] (Figure 3).

Post-stenting analysis by IVUS radiofrequency data analysis is limited since this technique lacks proper validation in this respect. An approach to get around this limitation could be to perform pre-stenting and post-stenting IVUS-RFD to assess the acute changes in terms of composition and relate this to the follow-up findings. Thus an IVUS-RFD clinical study that investigates the relationship between plaque composition of the intended stent segment (including its 10 mm proximal and distal segments) and development of stent thrombosis is still to be scheduled.

Conclusions

Although there are several potential mechanical causes of stent thrombosis that can be detected during the index procedure by greyscale IVUS as well as by repeated imaging at follow-up, it is uncertain which of them are inarguably related to stent thrombosis, primarily due to the low number of patients with stent thrombosis studied by IVUS in case control studies where causality is difficult to assess. A longitudinal and prospective study, adequately powered to demonstrate the mechanical factors potentially identifiable by IVUS and related to stent thrombosis is still awaited.

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CHAPTER 25

The risk of stent thrombosis in patients with acute coronary syndromes treated with bare metal and drug-eluting stents

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JACC Cardiovasc Interv. 2009 Jun;2(6):534-41.

The Risk of Stent Thrombosis in Patients With Acute Coronary Syndromes Treated With Bare-Metal and Drug-Eluting Stents

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Objectives We aimed to evaluate the risk of definite stent thrombosis with bare-metal stents (BMS) and drug-eluting stents (DES) in patients treated for acute coronary syndromes.

Background Acute coronary syndromes (ACS) have been reported as increasing the risk for stent thrombosis.

Methods Between January 2000 and December 2005, 5,816 consecutive patients underwent percutaneous coronary intervention for de novo lesions with a single stent type. These patients consisted of 3 sequential groups of BMS (n = 2,248), sirolimus-eluting stents (n = 822) and paclitaxel-eluting stents (n = 2,746). In total, 3,485 patients presented with an ACS.

Results After a median follow-up of 1,394 days, patients with ACS had a definite stent thrombosis rate of 2.5% versus 1.0% in patients with stable angina (propensity score-adjusted hazard ratio [HR]: 2.80, 95% confidence interval [CI]: 1.72 to 4.56). ACS patients had a higher risk of early and late stent thrombosis, although the increased risk of very late stent thrombosis was only present in ACS patients treated with DES. In stable patients, any stent thrombosis resulted in a significant increase in mortality (adjusted HR: 4.0, 95% CI: 1.7 to 9.3), although this was particularly evident for late or very late stent thrombosis; in contrast only early stent thrombosis significantly increased mortality in patients with acute coronary syndrome patients (adjusted HR: 2.0, 95% CI: 1.0 to 4.1).

Conclusions Patients with acute coronary syndromes are at higher risk of early and late stent thrombosis with either BMS or DES, although very late stent thrombosis seems to be uniquely associated with DES. The clinical sequelae of late and very late stent thrombosis are more pronounced in stable patients. (J Am Coll Cardiol Intv 2009;2:534–41)

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Manuscript received August 28, 2008; revised manuscript received March 16, 2009, accepted April 6, 2009.

Although dug-eluting stents (DES) reduce the rates of repeat revascularization compared with bare-metal stents (BMS) (1–3), there remain concerns about the risk of late and very late stent thrombosis (4–7). Many factors have been found to be associated with the risk of stent thrombosis, including acute coronary syndrome (ACS) at presentation (5,8–10). Mechanical causes such as stent underexpansion, geographical miss, and edge dissections increase the risk of stent thrombosis in both BMS and DES (11–14). Delayed healing and impaired neointimal strut coverage might increase this risk with DES (15–18). In patients with ACS, an additional particular potential problem is the trapping of thrombus between the stent struts and vessel wall, which might contribute to late acquired malapposition after thrombus resolution (14,19,20). Furthermore, stenting of necrotic core-rich plaques might result in stent strut penetration into the necrotic core with ensuing tissue prolapse and plaque disruption that might also contribute to stent thrombosis (21). Nevertheless, a recent meta-analysis of patients with ST-segment elevation myocardial infarction (STEMI) found no difference in mortality between DES and BMS after follow-up ranging between 12 and 24 months, with significant reductions in repeat revascularization with DES (2). However, patients enrolled in randomized trials are carefully selected and might represent only a small fraction of those encountered in everyday clinical practice (22). Therefore we investigated a consecutive series of all-comer patients undergoing percutaneous coronary intervention (PCI) with BMS and DES in our institution to evaluate the effect of clinical presentation on the occurrence of stent thrombosis.

Methods

Between January 2000 and December 2005, of 6,219 consecutive patients undergoing PCI, 5,823 underwent PCI for a de novo lesion with a single stent type (BMS, sirolimus-eluting stents [SES], or paclitaxel-eluting stents [PES]) as their standard treatment in our institution. The only exclusion criteria were the implantation of more than 1 different stent type during the index procedure or PCI for in-stent restenosis. Seven patients without clear documentation of clinical presentation (4 treated with SES, 3 with PES) were also excluded, leaving 5,816 patients whose data were analyzed.

Initially, all patients were treated with BMS, but on April 16, 2002, our institution adopted the use of SES (Cypher; Cordis, Warren, New Jersey) as the default strategy for all coronary interventions. On February 16, 2003, SES was replaced by PES (Taxus; Boston Scientific, Natick, Massachusetts) as the default stent. Therefore this single-center registry consists of 3 sequential groups of consecutive patients: BMS (n = 2,248; January 2000 to April 2002), SES (n = 822; April 2000 to February 2003), and PES (n = 2,746; February 2003 to December 2005). The patients were also categorized according to clinical presentation as either stable angina (SA), unstable angina as defined by the Braunwald (23) classification/non–ST-segment elevation myocardial infarction (UA/NSTEMI), or ST-segment elevation myocardial infarction (STEMI). Acute coronary syndrome refers to either UA/NSTEMI or STEMI (24,25).

All procedures were performed following standard procedural guidelines at the time (26). The use of glycoprotein 2b/3a inhibitors or adjunctive devices was left up to the operator's discretion. Angiographic success was defined as residual stenosis <30% by visual estimation in the presence of Thrombolysis In Myocardial Infarction flow grade 3. All patients were advised to maintain lifelong aspirin. Hypercholesterolemia was defined as fasting total cholesterol >5 mmol/l (193 mg/dl) or the use of lipid-lowering therapy. Hypertension was defined as blood pressure >140/90 mm Hg or the use of antihypertensive medications. Renal impairment was defined as a serum creatinine >150 μmol/l (1.7 mg/dl).

Abbreviations and Acronyms

ACS = acute coronary syndrome
BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
HR = hazard ratio
IQR = interquartile range
MI = myocardial infarction
NSTEMI = non–ST-segment elevation myocardial infarction
PCI = percutaneous coronary intervention
PES = paclitaxel-eluting stent(s)
SA = stable angina
SES = sirolimus-eluting stent(s)
STEMI = ST-segment elevation myocardial infarction
UA = unstable angina

The primary end point was stent thrombosis, defined as angiographically documented thrombus with Thrombolysis In Myocardial Infarction flow grade 0 or 1, accompanied by acute symptoms (consistent with the Academic Research Consortium classification of definite stent thrombosis) (4,27). The timing of stent thrombosis was categorized into early (within 30 days after implantation), late (between 30 days and 1 year), or very late (more than 1 year).

Secondary end points included all-cause mortality, any myocardial infarction (MI), and the composite of all-cause death or nonfatal MI. Myocardial infarction included re-infarction (defined as recurrence of symptoms together with ST-segment elevation or new left bundle branch block and an increase in cardiac enzymes following stable or decreasing values), or spontaneous MI (diagnosed by a rise in creatine kinase-myocardial band fraction of 3 times the upper limit of normal together with symptoms and either the development of ST-segment elevation or new left bundle branch block) (24).

Follow-up survival data for all patients were obtained from municipal civil registries. A questionnaire was subsequently sent to all living patients with specific enquiries about repeat hospital admission and adverse events. Because ours is the principal regional cardiac referral center, repeat

Table 1. Baseline Patient Characteristics

	SA			UA/NSTEMI			STEMI		
	BMS (n = 901)	DES (n = 1,369)	p Value	BMS (n = 824)	DES (n = 1,010)	p Value	BMS (n = 523)	DES (n = 1,189)	p Value
Male	71%	71%	0.9	68%	68%	1.0	81%	77%	0.09
Age (yrs)	62 ± 11	63 ± 11	0.2	63 ± 12	63 ± 12	0.6	58 ± 12	60 ± 12	0.001
Hypertension	39%	50%	<0.001	33%	45%	<0.001	21%	29%	0.001
Hypercholesterolemia	53%	66%	<0.001	43%	58%	<0.001	25%	31%	0.01
Family history of CAD	23%	37%	<0.001	22%	36%	<0.001	21%	27%	0.04
Current smoker	21%	18%	0.06	22%	25%	0.2	36%	40%	0.07
Diabetes mellitus	14%	20%	<0.001	15%	20%	<0.001	10%	10%	0.9
Renal impairment	1%	3%	0.004	1%	3%	<0.001	1%	1%	0.9
Previous myocardial infarction	37%	32%	0.02	41%	37%	0.07	20%	9%	<0.001
Previous CABG	15%	11%	0.001	12%	10%	0.1	3%	2%	0.1
Previous PCI	14%	13%	0.3	10%	9%	0.8	4%	3%	0.3

BMS = bare-metal stent(s); CABG = coronary artery bypass grafting; CAD = coronary artery disease; DES = drug-eluting stent(s); PCI = percutaneous coronary intervention; SA = stable angina; STEMI = ST-segment elevation myocardial infarction; UA/NSTEMI = unstable angina or non–ST-segment elevation myocardial infarction.

procedures (percutaneous and surgical) are normally performed at our institution and recorded prospectively in our database. For patients who suffered an adverse event at another center, medical records or discharge summaries from the other institutions were systematically reviewed. General practitioners, referring cardiologists, and patients were contacted as necessary if further information was required. The protocol was approved by the hospital ethics committee and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

Statistical analysis. Categorical variables are presented as percentages and were compared by Pearson chi-square test or Fisher exact test. Continuous variables are presented as mean ± SD and were compared by means of the independent samples *t* test. A 2-sided p value of <0.05 was used to indicate statistical significance. The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method, and curves were compared with the log-rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Separate Cox multivariate regression analyses were performed for each paired clinical presentation comparison (SA vs. UA/NSTEMI, SA vs. STEMI, and UA/NSTEMI vs. STEMI). To account for baseline differences in the DES and BMS cohorts, propensity scores were calculated by logistic regression with stent type (BMS, SES, or PES) and all significantly different pretreatment variables in Tables 1 and 2 (28). The goodness-of-fit of the propensity score was assessed with the Hosmer-Lemeshow test, which suggested that the models used could explain the variance in dependent variables ($p = 0.13$). Clinical presentation and the propensity scores were then forced into separate forward stepwise Cox multivariate regression analyses with the variables in Tables 1 and 2 as in the preceding text. Variables with a significance of $p < 0.1$ were entered into the next step. The final propensity score-adjusted results are presented as adjusted hazard ratios (HRs) with 95% confidence intervals. Further Cox multivariate analyses with stent type, clinical presentation, and all variables in Tables 1 and 2 were performed to identify independent predictors of stent thrombosis. All statistical analyses were performed with SPSS for windows version 12.0.1 (SPSS, Inc., Chicago, Illinois).

Results

Complete follow-up was available for 97.6% of the patients. The overall median follow-up duration was 1,394 days (interquartile range [IQR] 880 to 1,843). Patients with SA or UA/NSTEMI had a significantly longer duration of follow-up than those with STEMI ($p < 0.001$ for both comparisons): stable median 1,470 days (IQR 958 to 1,930), UA/NSTEMI 1,493 days (IQR 967 to 2057), and STEMI median 1,187 (IQR 746 to 1,657). There were also significant differences ($p < 0.001$) in the duration of follow-up according to stent type: BMS median 2,120 days (IQR 1,673 to 2,374) versus DES median 1,087 days (IQR 801 to 1,454).

Baseline patient characteristics according to clinical presentation and stent type are displayed in Table 1. Renal impairment and diabetes mellitus were more common in the DES patients with SA and UA/NSTEMI compared with their BMS counterparts. Angiographic and procedural details are described in Table 2. Irrespective of clinical presentation, DES patients had more stents implanted, with longer total stented lengths and smaller stent diameters than

Table 2. Angiographic and Procedural Details

	SA			UA/NSTEMI			STEMI		
	BMS (n = 901)	DES (n = 1,369)	p Value	BMS (n = 824)	DES (n = 1,010)	p Value	BMS (n = 523)	DES (n = 1,189)	p Value
Number of diseased vessels	1.8 ± 0.8	1.8 ± 0.8	0.2	1.7 ± 0.8	1.8 ± 0.8	0.02	1.7 ± 0.8	1.6 ± 0.8	0.05
Number of vessels treated	1.4 ± 0.6	1.4 ± 0.6	0.3	1.3 ± 0.6	1.4 ± 0.6	0.08	1.2 ± 0.5	1.1 ± 0.4	0.01
Number of lesions treated	1.8 ± 1.0	1.8 ± 1.0	0.6	1.7 ± 0.9	1.7 ± 1.0	0.8	1.5 ± 0.7	1.3 ± 0.8	0.001
Number of stents implanted	2.0 ± 1.4	2.5 ± 1.6	<0.001	1.8 ± 1.1	2.2 ± 1.5	<0.001	1.6 ± 0.9	1.8 ± 1.1	0.001
Mean stent diameter (mm)	3.2 ± 0.6	2.8 ± 0.6	<0.001	3.3 ± 0.6	2.9 ± 0.5	<0.001	3.5 ± 0.5	3.1 ± 0.4	<0.001
Total implanted stent length (mm)	30 ± 23	49 ± 35	<0.001	28 ± 18	42 ± 32	<0.001	26 ± 16	35 ± 23	<0.001
Left main coronary artery treated	4%	5%	0.1	3%	6%	0.01	4%	3%	0.8
Saphenous vein graft treatment	5%	3%	0.03	8%	5%	0.01	2%	1%	0.05
Type B2 lesion	41%	4%	0.05	56%	49%	0.003	40%	37%	0.1
Type C lesion	39%	41%	0.4	28%	35%	<0.001	41%	47%	0.02
Bifurcation	4%	16%	<0.001	4%	12%	<0.001	3%	7%	<0.001
Intravascular ultrasound	25%	20%	0.003	19%	18%	0.9	2%	6%	0.004
Glycoprotein IIb/IIIa inhibitor use	22%	12%	<0.001	33%	17%	<0.001	48%	36%	<0.001
Angiographic success	95%	94%	0.09	95%	97%	0.2	95%	97%	0.07
Recommended duration of clopidogrel (months)	3 ± 2	6 ± 4	<0.001	2 ± 2	6 ± 3	<0.001	2 ± 1	6 ± 3	<0.001

Abbreviations as in Table 1.

the BMS cohort. The DES patients also underwent bifurcation treatment more frequently. Glycoprotein 2b/3a inhibitors were used less often in DES patients, although clopidogrel was prescribed for longer.

The rates of definite stent thrombosis are presented in Table 3 and Figure 1. Stable patients had lower rates of overall stent thrombosis than STEMI patients, UA/NSTEMI, and overall ACS patients. After adjustment for differences in baseline, angiographic, and procedural characteristics among patients with different clinical presentations, both UA/NSTEMI and STEMI had significantly higher rates of any and early stent thrombosis than stable patients (Table 3). Late stent thrombosis was also more common in these 2 groups but did not reach statistical significance in the STEMI group. There was also a nonsignificant trend toward higher rates of very late stent thrombosis in the UA/NSTEMI and STEMI groups compared with SA. No significant differences could be found between the UA/NSTEMI and STEMI groups.

When examining these groups according to stent type, we found that ACS patients had significantly higher rates of overall stent thrombosis, whether treated with DES or BMS (Fig. 1C). Early and late stent thrombosis rates were higher amongst ACS patients, although for DES this difference did not reach statistical significance. In the DES patients, there was also a nonsignificant trend toward very late stent thrombosis (Fig. 2).

The mortality rates of patients with versus without stent thrombosis were markedly higher for those with SA (Table 4). Although mortality was also increased in both UA/NSTEMI and STEMI patients with stent thrombosis, this

Table 3. Rates of Stent Thrombosis After 3 Years According to Clinical Presentation After Propensity Score Adjustment

Stent Thrombosis	SA (n = 2,252)	UA/NSTEMI (n = 1,819)	STEMI (n = 1,666)	UA/NSTEMI vs. SA Adjusted HR (95% CI)	STEMI vs. SA Adjusted HR (95% CI)	UA/NSTEMI vs. STEMI Adjusted HR (95% CI)
Any	1.0%	2.3%	2.8%	2.58 (1.52–4.39)	3.10 (1.80–5.34)	0.83 (0.53–1.31)
Early	0.5%	1.1%	1.4%	2.52 (1.16–5.49)	3.74 (1.74–8.05)	0.67 (0.35–1.29)
Late	0.2%	0.8%	0.5%	4.18 (1.37–12.74)	2.13 (0.59–7.73)	1.96 (0.73–5.25)
Very late	0.3%	0.4%	0.8%	1.45 (0.52–4.00)	2.06 (0.79–5.35)	0.70 (0.28–1.74)

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

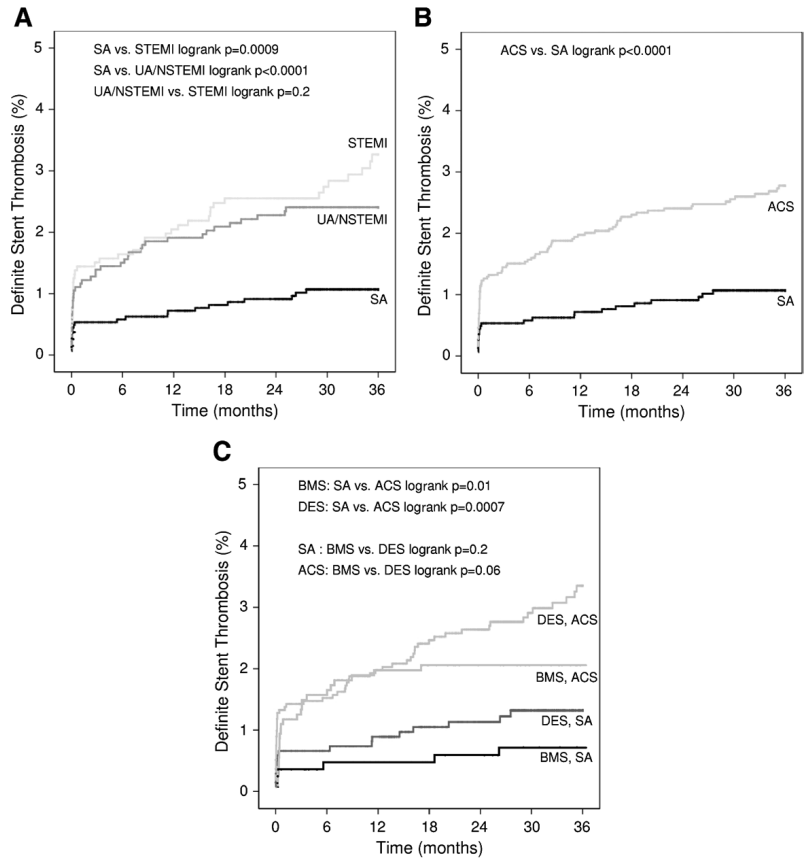

Figure 1. Cumulative Incidence of Stent Thrombosis According to Clinical Presentation, in Stable and Unstable Patients, and According to Presentation and Stent Type

Kaplan-Meier estimates of definite stent thrombosis according to **(A,B)** clinical presentation and **(C)** clinical presentation and stent type. ACS = acute coronary syndromes; BMS = bare-metal stent(s); DES = drug-eluting stent(s); SA = stable angina; STEMI = ST-segment elevation myocardial infarction; UA/NSTEMI = unstable angina or non–ST-segment elevation myocardial infarction.

was only apparent for those with early stent thrombosis, whereas for SA patients, this finding applied regardless of the timing of thrombosis.

Both types of ACS were independent predictors of overall and early stent thrombosis (Table 5). Unstable angina/NSTEMI also predicted late stent thrombosis, whereas the only independent predictor of very late stent thrombosis was DES implantation.

Discussion

Our results confirm the previous findings that presentation with ACS is a risk factor for stent thrombosis (5,8–10). We have found that this excessive risk occurs with both BMS and DES across all time points, with the exception of very late stent thrombosis, which seems to be a unique feature of DES implantation.

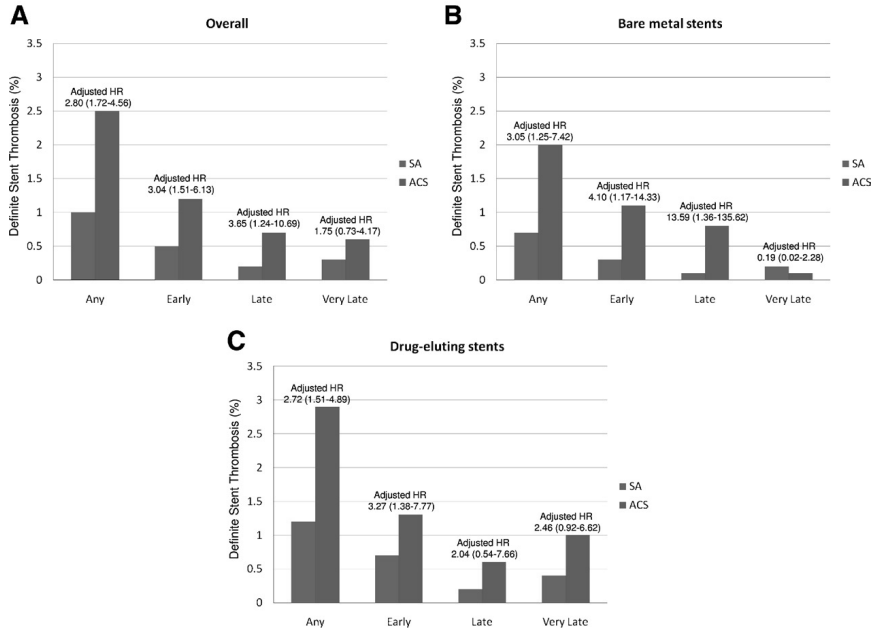

Figure 2. Classification of Stent Thrombosis Timing for All Patients, BMS, and DES

Classification of stent thrombosis timing for **(A)** all patients, **(B)** patients treated with BMS, and **(C)** patients treated with DES. HR = hazard ratio; other abbreviations as in Figure 1.

Although the low risk of stent thrombosis in stable patients (overall 1% over 3 years in both BMS and DES) is encouraging, when it does occur, the consequences can be devastating, with a 4-fold increase in mortality. Unstable patients are at higher risk of stent thrombosis irrespective of the stent type used, but the absolute increase in mortality resulting from late or very late stent thrombosis seems to be less than for stable patients. The mechanisms for this phenomenon are unclear, but the beneficial effects of ischemic preconditioning or the quality of any collateral vessels might provide some protection for unstable patients. It is also possible that patients with ACS might have tighter control of risk factors such as hypercholesterolemia, which might mitigate the potentially devastating effects of stent

Table 4. Propensity Score-Adjusted Mortality Within 3 Years of the Index Procedure in Patients With and Without Definite Stent Thrombosis

	SA (n = 2,252)		Acute Coronary Syndrome (n = 3,485)		Overall	
Stent Thrombosis	Mortality	Adjusted HR (95% CI) vs. No Stent Thrombosis	Mortality	Adjusted HR (95% CI) vs. No Stent Thrombosis	Mortality	Adjusted HR (95% CI) vs. No Stent Thrombosis
None	7%	—	12%	—	10%	—
Any	26%	4.0 (1.7–9.3)	14%	1.5 (0.8–2.8)	16%	2.2 (1.3–3.6)
Early	17%	2.3 (0.6–9.5)	21%	2.0 (1.0–4.1)	20%	2.5 (1.3–4.8)
Late	50%	4.9 (1.1–21.4)	9%	0.9 (0.2–3.7)	15%	1.5 (0.6–4.2)
Very late	29%	7.3 (1.8–30.1)	5%	0.9 (0.1–6.6)	10%	2.5 (0.8–7.8)

Abbreviations as in Tables 1 and 3.

Table 5. Independent Predictors of Stent Thrombosis

Stent Thrombosis		Adjusted HR	95% CI	p Value
Any	STEMI	3.10	1.80–5.34	<0.001
	UA/NSTEMI	2.58	1.52–4.39	<0.001
	Number of stents implanted*	1.18	1.03–1.36	0.01
Early	STEMI	3.74	1.74–8.05	0.001
	UA/NSTEMI	2.52	1.16–5.49	0.02
	Bifurcation treatment	2.70	1.25–5.72	0.008
	Angiographic success	0.16	0.05–0.53	0.003
Late	Saphenous vein graft treatment	5.54	1.85–16.59	0.002
	UA/NSTEMI	2.87	1.23–6.51	0.01
Very late	BMS use	0.11	0.02–0.54	<0.001

*For each extra stent.
Abbreviations as in Tables 1 and 3.

thrombosis. Unfortunately, we do not have data on the control of risk-factors during follow-up and are therefore unable to confirm or refute this hypothesis.

These findings highlight the importance of high-quality interventional techniques aimed at achieving optimal procedural results irrespective of which stent type is implanted. Particularly, care should be taken to avoid potential mechanical factors including stent underexpansion, residual edge dissections, and geographical miss of the target lesion. The use of predilation and intravascular ultrasound might possibly help: a recent report of 12 patients with stent thrombosis found that none of them achieved The MUSIC (Multicenter Ultrasound Stenting in Coronaries) criteria for optimal stent expansion (14,29). The use of thrombectomy devices might also be beneficial, especially in those with a large thrombus burden (30,31).

Although current guidelines recommend 12 months of dual antiplatelet therapy after DES implantation (32), the duration of clopidogrel given to our patients was based upon the protocols from the pivotal DES randomized controlled trials (33,34); therefore initially patients treated with SES were routinely given 3 months clopidogrel, except for complex cases (bifurcations, multiple stents), who were given 6 months. All PES patients were routinely given 6 months. Although the multivariable analysis adjusted for the recommended duration of clopidogrel and this was not found to be an independent predictor of events, it is possible that the differences in dual antiplatelet therapy might have affected the results. We currently recommend, in line with the most recent guidelines (32), dual antiplatelet therapy for 12 months after an ACS unless the patient is at high risk of bleeding and for 12 months after DES implantation.

Recent studies have evaluated the use of prasugrel, a new thienopyridine, in place of clopidogrel. In patients with ACS, prasugrel reduced the rate of stent thrombosis from 2.4% (similar to the rate in our ACS patients) to 1.1% (35). The beneficial effect of prasugrel was found in patients treated with BMS or DES (stent thrombosis HR: 0.36 for DES and HR: 0.52 for BMS) (36). However, major bleeding was more common in patients receiving prasugrel (2.4% vs.1.8%, HR: 1.32; 95% confidence interval: 1.03 to 1.68; $p = 0.03$). This included an increase in fatal bleeding (0.4% vs. 0.1%; $p = 0.002$). Although patients with stent thrombosis have higher mortality than those without stent thrombosis, overall mortality in this report was no different between patients treated with prasugrel and those treated with clopidogrel. This suggests that the increase in bleeding with prasugrel might balance or even outweigh the small absolute excess risk of stent thrombosis in patients with ACS (1.5% over 3 years in our patients). Furthermore, any new antiplatelet regimen should demonstrate cost-effectiveness before it is widely accepted.

In summary, patients presenting with ACS are at higher risk of early and late stent thrombosis with either BMS or DES, although very late stent thrombosis seems to be uniquely associated with DES. There was little difference in this aspect between STEMI and UA/NSTEMI. Stable patients who suffered stent thrombosis had a 4-fold increased risk of mortality.

Study limitations. This is a single-center observational study. Furthermore, there are significant baseline and procedural differences among the 3 historical stent groups, together with different lengths of follow-up due to their sequential nature. Nevertheless, the use of a single stent type at any 1 time period eliminates bias toward using DES in higher-risk patients. Because many of our patients are transferred back to their referring hospital after PCI, we acknowledge that accurate data regarding left ventricular function were not available and therefore not included in the analysis.

Acknowledgments

The authors would like to acknowledge the senior cardiologists involved in the PCI procedures: P.J. de Feyter, MD, PhD; P.P.T. de Jaegere, MD, PhD; H.J. Duckers MD, PhD; S.H. Hofma, MD, PhD; E. McFadden, MD, PhD; E. Regar, MD, PhD; G. Sianos, MD, PhD; P.C. Smits,

MD, PhD; M.J. van der Ent, MD, PhD; W.J. van der Giessen, MD, PhD; and C.A. van Mieghem MD.

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Key Words: acute coronary syndromes ■ drug-eluting stents ■ percutaneous coronary intervention ■ stent thrombosis.

CHAPTER 26

Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study

Daemen J, Wenaweser P, Tsuchida K, Abrecht L, Vaina S, Morger C, Kukreja N, Juni P, Sianos G, Hellige G, van Domburg RT, Hess OM, Boersma E, Meier B, Windecker S, Serruys PW.

Lancet. 2007 Feb 24; 369(9562): 667-78.

Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study

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Summary

Background **Stent thrombosis is a safety concern associated with use of drug-eluting stents. Little is known about occurrence of stent thrombosis more than 1 year after implantation of such stents.**

Methods **Between April, 2002, and Dec, 2005, 8146 patients underwent percutaneous coronary intervention with sirolimus-eluting stents (SES; n=3823) or paclitaxel-eluting stents (PES; n=4323) at two academic hospitals. We assessed data from this group to ascertain the incidence, time course, and correlates of stent thrombosis, and the differences between early (0–30 days) and late (>30 days) stent thrombosis and between SES and PES.**

Findings **Angiographically documented stent thrombosis occurred in 152 patients (incidence density 1·3 per 100 person-years; cumulative incidence at 3 years 2·9%). Early stent thrombosis was noted in 91 (60%) patients, and late stent thrombosis in 61 (40%) patients. Late stent thrombosis occurred steadily at a constant rate of 0·6% per year up to 3 years after stent implantation. Incidence of early stent thrombosis was similar for SES (1·1%) and PES (1·3%), but late stent thrombosis was more frequent with PES (1·8%) than with SES (1·4%; p=0·031). At the time of stent thrombosis, dual antiplatelet therapy was being taken by 87% (early) and 23% (late) of patients (p<0·0001). Independent predictors of overall stent thrombosis were acute coronary syndrome at presentation (hazard ratio 2·28, 95% CI 1·29–4·03) and diabetes (2·03, 1·07–3·83).**

Interpretation **Late stent thrombosis was encountered steadily with no evidence of diminution up to 3 years of follow-up. Early and late stent thrombosis were observed with SES and with PES. Acute coronary syndrome at presentation and diabetes were independent predictors of stent thrombosis.**

Lancet 2007; 369: 667–78

See Comment page 619

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Introduction

Drug-eluting stents significantly reduce rates of restenosis and target lesion revascularisation compared with bare metal stent. Since the publication of pivotal randomised trials on the two DES approved by the US Food and Drug Administration (polymer-based sirolimus-eluting stents [SES] and polymer-based paclitaxel-eluting stents [PES]),[1–4] these devices have been widely used in the percutaneous treatment of coronary artery disease worldwide.[5–8] However, several pre-clinical and clinical safety concerns[9–15] related to the use of drug-eluting stents have been expressed since then. One of the most important issues raised is stent thrombosis, a catastrophic, albeit infrequent, complication that results in abrupt coronary artery closure, which can lead to myocardial infarction or sudden cardiac death. This problem is not restricted to drug-eluting stents, and its incidence does not seem to exceed that seen with bare metal stents up to 1 year of follow-up.[16–22] However, case reports and observational studies have noted that some patients develop stent thrombosis unusually late after implantation of drug-eluting stents.[23–25]

To date, no large-scale study has focused on late stent thrombosis later than 1 year after drug-eluting stent implantation. Although variables such as acute coronary syndromes, bifurcation stenting, diabetes, discontinuation of antiplatelet therapy, renal failure, and stent length seem to be consistently associated with overall stent thrombosis,[19,26–28] predictors specific for late stent thrombosis have not yet been identified. We therefore assessed all angiographically documented stent thrombosis following unrestricted use of SES and PES in routine clinical practice at two academic referral hospitals between April, 2002, and December, 2005. The purposes of this investigation were to: estimate the incidence and time course of stent thrombosis with drug-eluting stents in routine clinical practice; identify predictors of stent thrombosis; identify differences between early and late stent thrombosis; and assess differences between SES and PES.

Methods

Study group and design

Between April 16, 2002, and Dec 31, 2005, a total of 8146 consecutive patients underwent percutaneous coronary intervention with SES or PES at two academic referral hospitals in the Netherlands and Switzerland. 3823 patients were treated with SES (Cypher, Cordis Corporation, Johnson and Johnson, Warren, NJ, USA) and 4323 patients with PES (TAXUS, Express2, or Liberté, Boston Scientific, Natick, MA, USA). In the Dutch

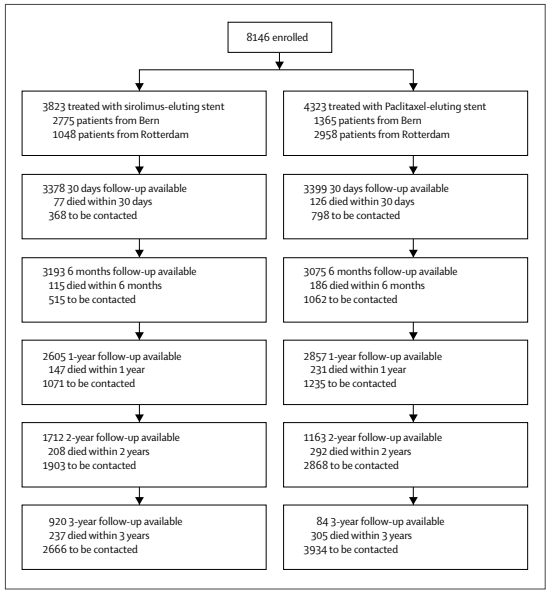


Figure 1: **Study profile**

institution, SES have been used as a default strategy for PCI as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry[7] since April, 2002. From the first quarter of 2003, PES became commercially available and replaced SES as default device for such procedures, as part of the Taxus Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry.[5] In the Swiss institution, SES have been used since April, 2002, and PES since March, 2003. Between April, 2003, and May, 2004, a randomised trial was done to compare the devices.[6] Between June, 2004, and March, 2005, the use of SES and PES was alternated on a daily basis. Since April, 2005, the use of PES has been abandoned and SES have been used as the default device. Patients treated with both types of stents (SES and PES) in one lesion, and lesions previously treated with brachytherapy, were excluded from the study population. The study was designed during a conference between the Bern and Rotterdam investigators. Baseline clinical and angiographic variables, procedural characteristics, and endpoints of interest were identified, and a template with all variables of interest for this study was supplied to the two study sites. Data from both sites were then entered into a database, held at the Thoraxcenter, Rotterdam, The Netherlands, generating all analyses presented in this manuscript.

This study was approved by the local ethics committee at both hospitals and was done in accord with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Procedures

All interventions were done according to current practice guidelines for percutaneous coronary intervention.[29] The operator was responsible for the decision to choose a specific treatment strategy. Patients were prescribed aspirin plus clopidogrel 75 mg per day (after a loading dose of 300 mg or 600 mg) before or during baseline coronary

	Overall (n=8146)	SES (n=3823)	PES (n=4323)	p
Age (years)	62·6 (11·6)	62·5 (11·5)	62·7 (11·6)	0·31
Male	6065/8146 (75%)	2859/3823 (75%)	3206/4323 (74%)	0·53
Hypertension	3745/8144 (46%)	1965/3821 (51%)	1780/4323 (41%)	<0·0001
Family history	2279/8144 (28%)	1112/3821 (29%)	1167/4323 (27%)	0·04
Current smoking	2993/8144 (37%)	1721/3821 (45%)	1272/4323 (29%)	<0·0001
Dyslipidaemia	4079/8144 (50%)	2087/3821 (55%)	1992/4323 (46%)	<0·0001
Diabetes	1315/8144 (16%)	697/3821 (18%)	618/4323 (14%)	<0·0001
Renal failure	134/3309 (4%)	97/2253 (4%)	37/1056 (4%)	0·30
Left ventricular ejection fraction (%)	55 (12)	54 (12)	55 (11)	0·01
Acute coronary syndrome at presentation	2853/4859 (59%)	795/1481 (54%)	2058/3378 (6 1%)	<0·0001
Bifurcation treatment	781/4889 (16%)	267/1488 (18%)	514/3401 (15%)	0·01
Number of stents per patient	1·96 (1·23)	1·87 (1·13)	2·03 (1·31)	<0·0001
Total stent length per patient (mm)	35·9 (25·3)	33·6 (22·6)	37·9 (27·4)	<0·0001
Average stent diameter per patient (mm)	2·93 (1·4)	2·90 (2·1)	2·95 (0·5)	0·11
Duration of clopidogrel prescription (months)*	5·94 (3·1)	4·72 (4·0)	6·36 (2·6)	<0·0001

Data are mean (SD) or n/total with data available (%). *Based on Rotterdam cohort.

Table 1: **Clinical and procedural characteristics of study population stratified by stent type**

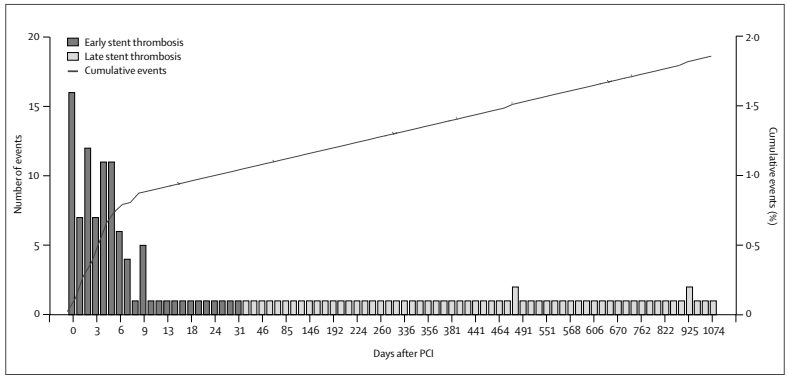


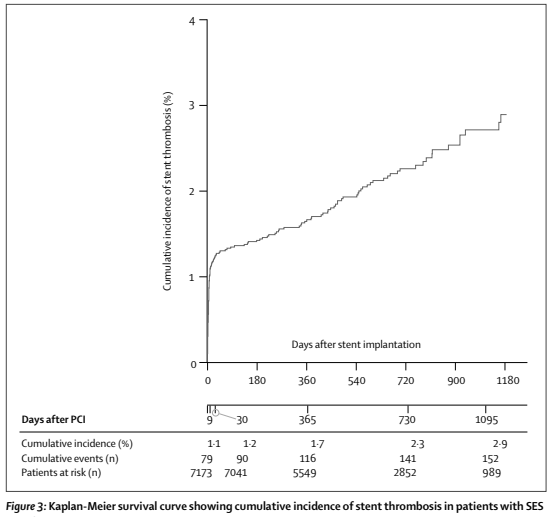
Figure 2: **Occurrence and frequency of stent thrombosis over time**

interventions. After the procedure, all patients were advised to maintain lifelong use of aspirin. In the Dutch institution, patients treated with PES were prescribed at least 6 months of clopidogrel (75 mg per day), on the basis of existing data from a randomised controlled trial.[30] For patients treated with SES, clopidogrel was prescribed for at least 3 months, unless one of the following was present, in which case clopidogrel was maintained for at least 6 months: multiple SES implantation (≥3 stents), total stent length 36 mm or longer, chronic total occlusion, and bifurcations.[5] In the Swiss institution, 12 months of clopidogrel was prescribed irrespective of the stent type used.[6] In a few patients who were on oral anticoagulation therapy, doctors recommended a shorter duration of clopidogrel (eg, 3-month triple therapy with aspirin, clopidogrel, and warfarin).

Patients were contacted according to follow-up schedules specific for each institution for the occurrence of major adverse cardiac events, including all-cause death, myocardial infarction, and repeat revascularisation. Survival data for all patients were obtained from municipal civil registries. A health questionnaire was subsequently sent to all living patients with specific questions on re-admission and major adverse cardiac events. For patients who had an adverse event at another centre, medical records or discharge summaries from other institutions were systematically reviewed. General practitioners, referring cardiologists, and patients were contacted as necessary for additional information. Data were based on a registry at two institutions entered into a database. There was no independent or external monitoring of data entry. However, data were carefully verified and adjudicated by clinicians. Mean follow-up was 1·73 years. Figure 1 shows flow of patients during various follow-up times.

Myocardial infarction was defined as increased creatine kinase by twice the upper limit of normal value and three times the upper limit of normal value of creatine kinase-MB fraction. Repeat revascularisation included target lesion revascularisation (TLR) and non-TLR, irrespective of whether the procedure was clinically or angiographically driven.

Only patients with angiographically proven stent thrombosis were included in the present study. Stent thrombosis was judged to have occurred if thrombolysis



Days after PCI	9	30	365	730	1095
Cumulative incidence (%)	1·1	1·2	1·7	2·3	2·9
Cumulative events (n)	79	90	116	141	152
Patients at risk (n)	7173	7041	5549	2852	989

Figure 3: **Kaplan-Meier survival curve showing cumulative incidence of stent thrombosis in patients with SES or PES**
Slope of linear portion of cumulative incidence curve between 30 days and 3 years was 0·6% per year.

in myocardial infarction (TIMI) flow was grade 0 with occlusion originating in the peri-stent region, or grade 1, 2, or 3 in the presence of a thrombus originating in the peri-stent region. Angiographic evidence of thrombus was defined as a discrete, intraluminal filling defect with defined borders and separated from the vessel wall.[31] Additionally, at least one of the following criteria had to be met: acute ischaemic symptoms (typical chest pain with duration >20 min); ischaemic ECG changes (ST-segment elevation in territory of implanted stent, ST-segment depression or T-wave inversion in territory of implanted stent); typical rise and fall in cardiac biomarkers.[32]

All cases of angiographically proven stent thrombosis were reviewed independently by two experienced interventional cardiologists. In case of disagreement, a consensus was established between the two reviewers, or a third interventional cardiologist was consulted.

Stent thrombosis was categorised dependant on the timing of emergence into early (within 30 days) and late (>30 days).

Risk factors and co-morbidities in each patient were determined as classified by the treating physicians. Acute coronary syndrome was defined as the group of clinical symptoms, electrocardiographic changes, and elevation of cardiac biomarkers that is compatible with acute myocardial ischaemia and encompasses an acute myocardial infarction (ST-segment elevation and non-ST segment elevation myocardial infarction) as well as unstable angina.[32] Hypertension was defined as blood pressure of 140 mm Hg or greater systolic or 90 mm Hg or greater diastolic, or current use of antihypertensive treatment. Dyslipidaemia was classified as a concentration of cholesterol in serum of 6·2 mmol/L or greater, or the use of lipid-lowering drugs.

Angiographic success was defined as: achievement of 30% or less residual diameter stenosis within the stented segment by visual assessment; no evidence of residual dissection; no evidence of thrombus; and achievement of final TIMI flow grade 3. For the quantitative angiographic analysis, in-segment analysis was defined as the stented segment plus the adjacent proximal and distal 5-mm peri-stent regions. Premature discontinuation of antiplatelet therapy was characterised as cessation of either aspirin or clopidogrel before the end of the recommended duration of prescription.

	ST (n=152)	No ST (n=7994)	p
Age (years)	60·3 (12·0)	62·5 (11·5)	0·01
Male	115/152 (76%)	5950/7994 (74%)	0·78
Hypertension	63/152 (41%)	3682/7992 (46%)	0·29
Family history	44/152 (29%)	2235/7992 (28%)	0·79
Current smoking	57/152 (38%)	2936/7992 (37%)	0·87
Dyslipidaemia	74/152 (49%)	4005/7992 (50%)	0·74
Diabetes	29/152 (19%)	1286/7992 (16%)	0·32
Renal failure	9/152 (6%)	132/3242 (4%)	1·00
Left ventricular ejection fraction (%)	52 (12)	55 (12)	0·07
Acute coronary syndrome at presentation	67/95 (71%)	2786/4764 (59%)	0·02
Bifurcation treatment	27/96 (28%)	754/4793 (16%)	0·003
Number of stents per patient	2·35 (1·73)	1·95 (1·22)	<0·0001
Total stent length per patient (mm)	42·3 (34·0)	35·8 (25·1)	0·002
Average stent diameter per patient (mm)	2·83 (0·35)	2·93 (1·44)	0·48

Data are mean (SD) or n/total with data available (%). ST=stent thrombosis.

Table 2: **Comparison of clinical and procedural characteristics between patients with and without stent thrombosis**

	Hazard ratio (95% CI)			
	Bern		Rotterdam	
	Univariate	Multivariate	Univariate	Multivariate
Overall stent thrombosis				
Age	0·99 (0·97–1·00)	0·98 (0·96–1·01)	0·98 (0·96–1·00)	0·97 (0·95–1·00)
Male sex	1·06 (0·63–1·79)	1·32 (0·65–2·66)	1·05 (0·62–1·75)	0·90 (0·51–1·58)
Family history	0·74 (0·44–1·25)	0·67 (0·35–1·28)	1·25 (0·77–2·02)	1·23 (0·74–2·15)
Diabetes	1·04 (0·58–1·85)	1·30 (0·67–2·51)	1·43 (0·81–2·53)	2·03 (1·07–3·83)
Hypertension	0·83 (0·54–1·30)	0·78 (0·45–1·34)	0·72 (0·44–1·19)	0·68 (0·38–1·21)
Smoking	1·05 (0·67–1·63)	0·87 (0·50–1·51)	0·89 (0·51–1·55)	0·78 (0·43–1·44)
Dyslipidaemia	0·77 (0·50–1·20)	0·76 (0·44–1·30)	0·93 (0·58–1·47)	1·07 (0·63–1·82)
Left ventricular ejection fraction	0·98 (0·96–0·99)	*	‡	‡
Renal failure†	1·00 (0·24–4·10)	0·96 (0·23–3·99)	‡	‡
Acute coronary syndrome at presentation	‡	‡	1·80 (1·07–3·05)	2·28 (1·29–4·03)
Bifurcation treatment	‡	‡	1·87 (1·04–3·37)	1·47 (0·79 –2·72)
Paclitaxel-eluting stents	1·26 (0·80–1·97)	1·25 (0·73–2·12)	1·47 (0·86–2·51)	1·38 (0·79–2·44)
Number of stents per patient	1·21 (0·97–1·51)	1·11 (0·74–1·67)	1·27 (1·12–1·43)	1·27 (0·98–1·64)
Total stent length per patient	1·01 (1·00–1·02)	1·01 (0·98–1·03)	1·01 (1·01–1·02)	1·00 (0·99–1·01)
Average stent diameter per patient	0·64 (0·26–1·60)	‡	0·70 (0·46–1·07)	0·72 (0·42–1·22)
Absence of clopidogrel	‡	‡	0·59 (0·77–4·48)	0·77 (0·09–6·24)

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Early stent thrombosis				
Age	1·01 (0·98–1·04)	1·00 (0·97–1·04)	0·98 (0·96–1·01)	0·96 (0·94–0·99)
Male sex	1·02 (0·50–2·08)	1·04 (0·44–2·49)	0·82 (0·45–1·52)	0·70 (0·35–1·39)
Family history	0·50 (0·22–1·12)	0·41 (0·14–1·18)	0·94 (0·50–1·78)	0·83 (0·40–1·70)
Diabetes	1·43 (0·70–2·90)	2·03 (0·91–4·52)	1·94 (1·01–3·73)	2·29 (1·07–4·90)
Hypertension	0·51 (0·28–0·94)	0·40 (0·19–0·86)	0·97 (0·54–1·76)	0·80 (0·39–1·63)
Smoking	0·76 (0·41–1·38)	0·85 (0·41–1·78)	0·40 (0·16–1·01)	0·37 (0·14–0·97)
Dyslipidaemia	0·68 (0·37–1·24)	0·82 (0·39–1·68)	1·03 (0·59–1·82)	1·29 (0·66–2·56)
Left ventricular ejection fraction	0·98 (0·95–1·00)	*	‡	‡
Renal failure†	1·64 (0·39–6·82)	1·23 (0·29–5·28)	‡	‡
Acute coronary syndrome at presentation	‡	‡	1·64 (0·86–3·14)	2·29 (1·16–4·52)
Bifurcation treatment	‡	‡	3·17 (1·66–6·05)	2·52 (1·26–5·02)
Paclitaxel-eluting stents	1·11 (0·60–2·05)	1·28 (0·63–2·59)	0·93 (0·49–1·76)	0·86 (0·44–1·71)
Number of stents per patient	1·32 (1·00–1·74)	1·39 (0·85–2·26)	1·34 (1·17–1·55)	1·18 (0·85–1·63)
Total stent length per patient	1·01 (1·00–1·03)	1·00 (0·98–1·03)	1·02 (1·01–1·02)	1·01 (0·99–1·02)
Average stent diameter per patient	0·63 (0·20–1·95)	‡	0·70 (0·45–1·11)	0·66 (0·35–1·24)
Absence of clopidogrel	‡	‡	¶	*
Late stent thrombosis				
Age	0·96 (0·94–0·99)	0·96 (0·92–0·99)	0·97 (0·94–1·01)	0·99 (0·95–1·03)
Male sex	1·11 (0·50–2·43)	1·93 (0·56–6·63)	1·93 (0·66–5·63)	1·52 (0·51–4·56)
Family history	1·06 (0·51–2·15)	1·04 (0·45–2·43)	2·07 (0·95–4·55)	2·40 (1·03–5·58)
Diabetes	0·61 (0·22–1·73)	0·67 (0·20–2·27)	0·69 (0·20–2·30)	1·22 (0·34–4·34)
Hypertension	1·53 (0·77–3·06)	1·75 (0·75–4·09)	0·36 (0·14–0·98)	0·43 (0·15–1·24)
Smoking	1·52 (0·78–2·97)	0·92 (0·40–2·11)	2·13 (0·97–4·70)	1·70 (0·70–4·11)
Dyslipidaemia	0·88 (0·46–1·70)	0·72 (0·32–1·62)	0·80 (0·37–1·76)	0·89 (0·37–2·04)
Left ventricular ejection fraction	0·98 (0·96–1·01)	*	‡	‡
Renal failure†	..	..	‡	‡
Acute coronary syndrome at presentation	‡	‡	2·34 (0·94–5·87)	2·46 (0·87–7·00)
Bifurcation treatment	‡	‡	0·31 (0·04–2·30)	0·22 (0·03–1·72)
Paclitaxel-eluting stents	1·39 (0·72–2·70)	1·21 (0·54–2·75)	2·43 (0·96–6·17)	2·36 (0·92–6·04)
Number of stents per patient	1·07 (0·75–1·54)	0·73 (0·35–1·56)	1·14 (0·90–1·45)	1·57 (1·00–2·46)
Total stent length per patient	1·00 (0·99–1·02)	1·01 (0·98–1·05)	1·00 (0·99–1·01)	0·99 (0·96–1·01)
Average stent diameter per patient	0·63 (0·13–3·00)	‡	0·85 (0·33–2·15)	0·82 (0·33–2·06)
Absence of clopidogrel	‡	‡	0·74 (0·07–7·42)	1·03 (0·08–13·03)

*Not used for multivariate analysis because of colinearity problems. †Defined as creatinine >150 µmol/L. ‡Not used in analysis, <75% of variables available. ¶Could not be estimated.

Table 3: **Univariate and multivariate Cox proportional hazards analysis**

A creatinine value of 150 µmol per L or chronic haemodialysis qualified for the definition of renal impairment.

Statistical analysis

Continuous variables are described as mean and SD or median values with IQR. Dichotomous variables are described as counts and percentages. Continuous variables were compared between SES and PES and between early and late thrombosis with Student's *t* test (for parametric variables) or Mann-Whitney U test (for non-parametric variables) as appropriate in terms of the clinical, angiographic, and procedural demographics.

The incidence of stent thrombosis was calculated as incidence density and as cumulative incidence. Incidence density was defined as the number of patients with stent thrombosis divided by the total number of patient-years, and expressed as a number per 100 patient-years of observation.[33,34] Cumulative incidence was estimated by the Kaplan Meier method and differences were assessed with the log-rank test. A Cox proportional hazards model was used to identify independent predictors of stent thrombosis, with these variables: age, sex, family history of cardiovascular disease, diabetes, hypertension, current smoking, dyslipidaemia, renal impairment, left ventricular ejection fraction, acute coronary syndrome at presentation, stent type (SES or PES), number of stents, total stent length, average stent diameter, bifurcation treatment, and prescribed duration of clopidogrel. Data

on acute coronary syndrome, bifurcation treatment, and average stent diameter in the Bern cohort, and on left ventricular ejection fraction and renal impairment in the Rotterdam cohort, were available in less than 75% of the patients; therefore, we stratified univariate and multivariate Cox regression analysis by centre. Statistical analyses were done with SPSS 12.0.1 for Windows. All p values were two-sided and values less than 0·05 were judged statistically significant.

Role of the funding source

There was no industry involvement in the study design, data collection, data analysis, or writing of the report. The study was supported by research grants from the two institutions; data from both institutions were entered into a common database held at the Thoraxcenter, Rotterdam, the Netherlands. As principal investigators, PWS and SW had full access to the data and take final responsibility for the data as presented in the manuscript.

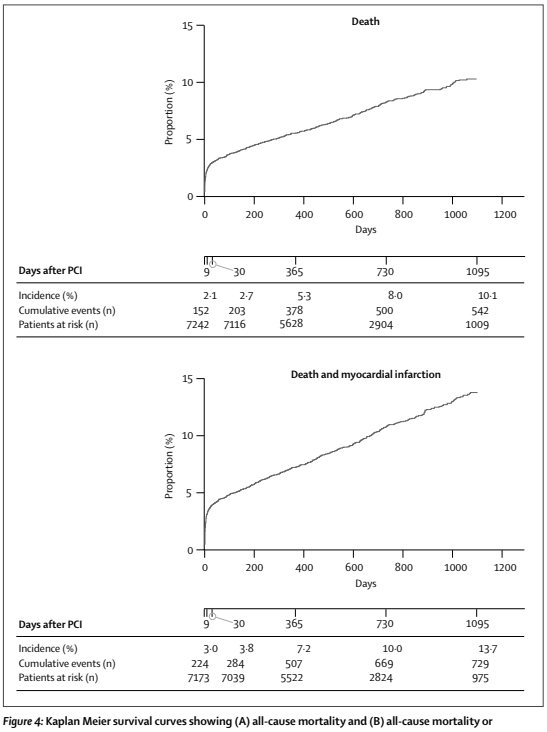

Figure 4: **Kaplan Meier survival curves showing (A) all-cause mortality and (B) all-cause mortality or myocardial infarction in overall population**

	Overall ST (n=152)	Early ST (n=91)	Late ST (n=61)	p
PCI for stent thrombosis	148 (97%)	87 (96%)	61 (100%)	0·51
Additional stenting	59 (39%)	30 (33%)	29 (48%)	0·13
Adjunctive thrombolysis	9 (6%)	5 (6%)	4 (7%)	0·83
Adjunctive thrombectomy	18 (12%)	11 (12%)	7 (12%)	9·85
In-hospital outcome				
Death	11 (7%)	8 (9%)	3 (5%)	0·53
Periprocedural myocardial infarction*	106 (70%)	62 (68%)	44 (72%)	0·99
Reinfarction	2 (1%)	1 (1%)	1 (2%)	0·77
Repeat revascularisation	5 (3%)	3 (3%)	2 (3%)	0·97
Emergency bypass surgery	3 (2%)	2 (2%)	1 (2%)	1·00
Recurrent stent thrombosis	2 (1%)	1 (1%)	1 (2%)	0·77
30-day outcome				
Death	13 (9%)	9 (10%)	4 (7%)	0·40
Reinfarction	3 (2%)	2 (2%)	1 (2%)	1·00
Repeat revascularisation	7 (5%)	4 (4%)	3 (5%)	1·00
Recurrent stent thrombosis	3 (2%)	2 (2%)	1 (2%)	1·00
6-month outcome				
Death	17 (11%)	12 (13%)	5 (8·2%)	0·24
Reinfarction	3 (2%)	2 (2%)	1 (1·6%)	1·00
Repeat revascularisation	10 (7%)	5 (6%)	5 (8·2%)	0·52
Recurrent stent thrombosis	3 (2%)	2 (2%)	1 (1·6%)	1·00
Hierarchical MACE†	117 (76%)	70 (77%)	47 (75·4%)	0·99

PCI=percutaneous coronary intervention. ST=stent thrombosis. MACE=major adverse cardiac events (defined as the composite of death, periprocedural myocardial infarction, reinfarction, and repeat revascularisation). *Myocardial infarction due to stent thrombosis. †Including periprocedural myocardial infarction due to stent thrombosis.

Table 4: **Periprocedural and postprocedural clinical outcomes of patients with stent thrombosis**

Results

Between April, 2002, and December, 2005, 8146 patients underwent percutaneous coronary intervention with SES (3823 patients) or PES (4323 patients) at the two academic hospitals. Table 1 summarises clinical and procedural characteristics of the overall study population. Compared with patients treated with PES, those who received SES were more likely to have hypertension, a family history of coronary heart disease, dyslipidaemia, and diabetes, and were more frequently smokers. Left ventricular ejection fraction was somewhat lower in the SES group than in the PES group. By contrast, patients treated with PES presented more often with an acute coronary syndrome, and received more and longer stents than SES patients.

Angiographically proven stent thrombosis was recorded in 152 of 8146 patients at a median of 9 days (IQR 3–342) after DES implantation during a follow-up period of more than 3 years (mean 1·73 years, SD 0·99). The incidence density of stent thrombosis was 1·3 per 100 person-years. Stent thrombosis occurred early (at 0–30

days) in 91 of 152 (60%) patients, and late (after 30 days) in 61 of 152 (40%) patients. The cumulative incidence of early ST was 1·1% (91 events), whereas late ST occurred at a rate of 0·6 per 100 person-years of observation (61 events). The median time to occurrence of early stent thrombosis was 4 days (IQR 1–6). Of the 61 late ST cases, 36 (59%) patients developed stent thrombosis 1 year or later after stent implantation (median 451 days; IQR 211–665; figure 2). The cumulative incidence of stent thrombosis over time showed an initial steep rise with 50% of cases occurring within 9 days, followed by an almost linear increase in the remaining events up to 3 years. The cumulative incidence of stent thrombosis was 1·2% at 30 days, 1·7% at 1 year, 2·3% at 2 years, and 2·9% at 3 years. The slope of the linear portion of the cumulative incidence curve between 30 days and 3 years was 0·6% per year (figure 3).

Patients with stent thrombosis were younger, presented more often with an acute coronary syndrome, and were treated more frequently for bifurcation lesions, compared with those without stent thrombosis (table 2). The number of stents and total stent length were greater in patients with stent thrombosis than in those without (table 2).

Table 3 summarises the results of Cox proportional hazards analysis. In the Bern group, no independent predictors of overall stent thrombosis emerged. Hypertension was the only independent predictor of early stent thrombosis, and age was the only independent predictor of late stent thrombosis. In the Rotterdam group, acute coronary syndrome at presentation and diabetes were independent predictors of overall stent thrombosis. Age, hypertension, smoking, acute coronary syndrome at presentation, and bifurcation treatment were independently associated with early stent thrombosis. Family history of coronary heart disease was an independent predictor of late stent thrombosis in the Rotterdam group. Absence of clopidogrel treatment did not seem to be associated with an increased risk of total and late stent thrombosis.

In the overall group (n=8146), 3-year cumulative incidences were 10·3% for all-cause mortality, 13·7% for death or myocardial infarction (figure 4), 4·1% for myocardial infarction, 11·7% for target vessel revascularisation, and 22·3% for major adverse cardiac events (ie, death, periprocedural myocardial infarction, reinfarction, and repeat revascularisation). Percutaneous coronary intervention was the initial treatment strategy in almost all patients who developed stent thrombosis (table 4). The majority of patients who presented with stent thrombosis developed myocardial infarction. Notably, recurrent stent thrombosis in two patients and multiple stent thromboses in a different vessel in another patient caused three reinfarctions within 6 months after treatment of stent thrombosis. We noted no differences in clinical outcome between patients with early and late stent thrombosis.

Table 5 shows baseline clinical, angiographic, and procedural characteristics stratified for early or late stent thrombosis. Compared with patients who had late stent thrombosis, patients with early stent thrombosis were slightly younger, more frequently diabetic, less frequently smokers, and had more bifurcation lesions treated, smaller reference vessel diameter, smaller final minimum luminal diameter, and a higher residual diameter stenosis.

Clinical, procedural, and angiographic characteristics of the 152 patients with stent thrombosis are shown in table 6, along with the comparison between SES and PES. More than 70% of stent thrombosis cases occurred in patients who underwent the index percutaneous coronary intervention in the context of acute coronary syndromes. Patients' characteristics, apart from sex and hypertension, were similar for both stent types. The groups were also similar in terms of time course (table 6), 3-year cumulative incidence of total stent thrombosis (SES 2·5%, PES 3·2%, p=0·07; figure 5), and cumulative incidence of early stent thrombosis (SES 1·1%, PES 1·3%, p=0·49). Late stent thrombosis, however, occurred later in the SES group than in the PES group (table 6) and cumulative incidence at 3 years was significantly higher in the PES group (1·9%) than in the SES group (1·4%; p=0.031).

Of patients who had early stent thrombosis, 79 (87%) were on dual antiplatelet therapy, eight (9%) were on a

	Early ST	Late ST	p
Baseline clinical characteristics			
n	91	61	
Age (years)	61·9 (11·7)	58·0 (12·2)	0·05
Male sex	66/91 (73%)	49/61 (80%)	0·34
Clinical presentation			
Stable angina	28/91 (31%)	15/61 (25%)	
Acute myocardial infarction	41/91 (45%)	28/61 (50%)	1·00
Unstable angina	22/91 (24%)	18/61 (30%)	0·57
Cardiogenic shock	8 (9%)	5 (8%)	1·00
Hypertension	35/91 (39%)	28/61 (46%)	0·40
Family history	20/91 (22%)	24/61 (39%)	0·03
Current smoking	25/91 (28%)	32/61 (53%)	0·002
Dyslipidaemia	41/91 (45%)	33/61 (54%)	0·32
Diabetes	25/91 (28%)	5/61 (8%)	0·003
Non-insulin-dependent	18/91 (20%)	4/61 (7%)	0·03
Insulin-dependent	7/91 (7%)	1/61 (2%)	0·15
Renal insufficiency	8/91 (9%)	1/61 (2%)	0·09
Multivessel disease	55/91 (60%)	33/61 (54%)	0·50
Multivessel stenting	31/91 (34%)	17/61 (28%)	0·48
Left ventricular ejection fraction (%)	51 (12)	53 (12)	0·41
Number of stents per patient	2·52 (1·85)	2·08 (1·51)	0·12
Total stent length per patient (mm)	46·4 (37·5)	36·1 (27·2)	0·07
Average stent diameter per patient (mm)	2·82 (0·37)	2·85 (0·32)	0·72
Timing of ST (days)			
Mean (SD)	5·5 (6·5)	459·4 (274·7)	..
Median (IQR)	4·0 (1–6)	442·0 (235–652)	..

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Lesion and procedural characteristics			
n*	98	63	
Pre-procedure			
Treated vessel			
Left main coronary artery	0/98 (0%)	1/63 (2%)	..
Left anterior descending artery	53/98 (54%)	34/63 (54%)	0·989
Left circumflex artery	19/98 (19%)	6/63 (10%)	0·092
Right coronary artery	26/98 (27%)	21/63 (33%)	0·378
Saphenous vein graft	0	1 (2%)	..
ACC/AHA lesion class B2/C	81/89 (91%)	51/63 (81%)	0·089
Bifurcation lesions	34/95 (36%)	8/63 (13%)	0·002
Diameter stenosis (%)	81 (17)	82 (19)	0·740
Lesion length (mm)	20·11 (13·36)	20·30 (13·83)	0·940
MLD (mm)	0·49 (0·41)	0·55 (0·57)	0·465
MLD, excluded total occlusion (mm)	0·68 (0·33)	0·77 (0·53)	0·332
RVD (mm)	2·70 (0·53)	2·87 (0·43)	0·041
Periprocedure or postprocedure			
Number of stents per lesion	1·59 (0·87)	1·63 (1·04)	0·746
Average stent diameter per lesion (mm)	2·95 (0·32)	2·94 (0·29)	0·902
Total stent length per lesion (mm)	32·39 (23·05)	31·08 (23·11)	0·729
Maximum balloon inflation pressure (atm)	16·9 (3·7)	16·2 (3·7)	0·250
Periprocedural bolus heparin (units)	7·4 (3·5)	7·3 (2·9)	0·753
In-stent diameter stenosis (%)	14 (14)	10 (8)	0·046
In-stent MLD (mm)	2·39 (0·52)	2·58 (0·40)	0·024
In-segment diameter stenosis (%)	18 (12)	13 (10)	0·030
In-segment MLD (mm)	2·14 (0·51)	2·38 (0·45)	0·006
Ratio of SES to PES	0·8 (43:55)	0·8 (27:36)	0·899
Direct stenting	29/98 (30%)	17/63 (27%)	0·653
Stent overlap	41/98 (42%)	24/63 (38%)	0·392
Use of glycoprotein IIb/IIIa inhibitors	38/98 (39%)	19/63 (30%)	0·218

Data are mean (SD) or n/total with data available (%), unless otherwise specified. MLD=minimum lumen diameter. PCI=percutaneous coronary intervention. RVD=reference vessel diameter. ACC/AHA=American College of Cardiology/American Heart Association. *Multiple lesions in the same patient counted separately.

Table 5: **Clinical, procedural, and angiographic characteristics for patients with early and late stent thrombosis (ST)**

single antiplatelet drug, and four (4%) were not on antiplatelet therapy. By contrast, late stent thrombosis occurred during dual antiplatelet therapy in 14 (23%) patients, during single-drug therapy in 31 (51%), and in 16 (26%) who were not on antiplatelet therapy (p<0·0001 for the comparison of early *vs* late). Stent thrombosis occurred late in 31 patients on aspirin monotherapy, and 97% (30 of 31) experienced the event after the recommended prescription period of clopidogrel had ended. 23 patients prematurely discontinued one or both of the two antiplatelet drugs (seven of 91 early, 16 of 61 late, p=0·008). The reasons for premature discontinuation were poor compliance in 11 patients (48%), surgery in 7 (30%), bleeding in four (17%), and allergy in one (4%).

Discussion

Our findings from a large cohort of patients with stent thrombosis after implantation of drug-eluting stents add to the evidence about late stent thrombosis[23–28,35] with the following observations: stent thrombosis occurred with an incidence density of 1·3 per 100 person-years and a cumulative incidence of 2·9% at 3 years; the incidence of late stent thrombosis did not diminish, but continued at a steady rate of 0·6% per year during the first 3 years; acute coronary syndrome at presentation and diabetes were independent predictors of overall stent thrombosis; and early and late stent thrombosis occurred with both types of drug-eluting stent, but late stent thrombosis was more frequently observed with PES than with SES.

The principal aim of this study was to assess the incidence of stent thrombosis during a follow-up period of up to 3 years in a large group of patients treated with the unrestricted use of drug-eluting stents. Previous data on stent thrombosis after drug-eluting stent implantation were derived from randomised trials and registries, in which low rates of events were reported and early stent thrombosis seemed to occur with similar frequency in drug-eluting and bare metal stents.[17,19–22,36] Similarly, a recent meta-analysis reported similar event rates for drug-eluting and bare metal stents up to 1 year of follow-up.[18] The incidence of early stent thrombosis (1·2%) and the median time to stent thrombosis (9 days) in the present study were similar to rates previously reported in patients treated with bare metal stents.[16,35]

Of more interest are adverse events during long-term follow-up and the occurrence of late stent thrombosis encountered with drug-eluting stents. Late stent thrombosis has also been shown in the long-term follow-up results of early trials comparing SES and PES with bare metal stents. A pooled analysis of RAVEL, SIRIUS, C-SIRIUS, and E-SIRIUS revealed five cases of late stent thrombosis between 1 year and 4 years of follow-up with SES, but no such case with bare metal stents (survival free from stent thrombosis at 3 years: 98·8% *vs* 99·4%, p=0·20).[37] Similarly, a pooled analysis of TAXUS II, IV, V, and VI showed eight cases of late stent thrombosis between 9 months and 3 years with PES and only one case with bare metal stents (survival free from stent thrombosis at 3 years 98·7% *vs* 99·2%, p=0·36).[22] However, concerns have been raised as to whether these data are truly applicable to everyday clinical practice, because of the small number of patients, and the exclusion of acute coronary syndromes and complex lesions in randomised controlled trials. The complexity of the present population is reflected in the high mortality rates. The cumulative incidence of all-cause mortality was 10·3% in the present study, which is higher than the mortality rates reported in previous studies. However, the results of the present study suggest that late stent thrombosis with drug-eluting stents occurs more frequently than expected[19–22,36] and that rates increase steadily during long-term follow-up. The sustained occurrence over a long-term period might be explained in part by the delayed healing response after implantation of drug-eluting stents, as indicated by delayed re-

	Overall (n=152)	SES (n=69)	PES (n=83)	p
Age (years)	60·3 (12·0)	61·3 (13·4)	59·5 (10·8)	0·37
Male sex	115/152 (76%)	46/69 (67%)	69/83 (83%)	0·02
Hypertension	63/152 (41%)	40/69 (58%)	23/83 (28%)	<0·0001
Family history	44/152 (29%)	23/69 (33%)	21/83 (25%)	0·29
Current smoking	57/152 (38%)	27/69 (39%)	30/83 (36%)	0·74
Dyslipidaemia	74/152 (49%)	33/69 (48%)	41/83 (49%)	0·87
Diabetes	29/152 (19%)	16/69 (23%)	13/83 (16%)	0·30
Renal insufficiency	9/143 (6%)	6/68 (9%)	3/84 (4%)	0·30
Left ventricular ejection fraction (%)	52 (12)	53 (12)	51 (13)	0·61
Acute coronary syndrome at presentation	67/95 (71%)	24/35 (69%)	43/60 (72%)	0·82
Multivessel disease	88/149 (59%)	42/65 (65%)	45/83 (54%)	0·24
Bifurcation treatment	27/96 (28%)	9/36 (25%)	18/60 (30%)	0·65
Timing of early ST (days)				
Mean (SD)	5·5 (6·5)	5·9 (6·3)	5·1 (6·4)	0·58
Median (IQR)	4·0 (1–6)	4·0 (2–8)	4·0 (1–5)	
Timing of late ST (days)				
Mean (SD)	459·4 (274·7)	564·8 (310·1)	375·7 (212·5)	0·007
Median (IQR)	442·0 (235–652)	585 (381–801)	343·5 (214–509)	
Recommended duration of clopidogrel (months)				
Mean (SD)	7·9 (3·5)	8·1 (4·1)	7·9 (3·1)	0·84
Median (IQR)	6·0 (6·0–12·0)	6·5 (3·8–12·0)	6·0 (6·0–12·0)	
Number of stents per patient	2·35 (1·73)	2·20 (1·64)	2·47 (1·80)	0·35
Average stent diameter per patient (mm)	2·83 (0·35)	2·75 (0·28)	2·89 (0·39)	0·051
Total stent length per patient (mm)	42·3 (34·0)	38·5 (28·0)	45·5 (38·2)	0·22

Data are mean (SD) or n/total with data available (%), unless otherwise specified.

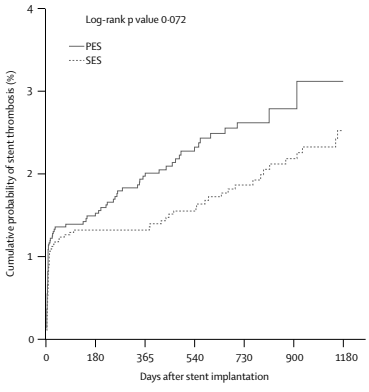
Table 6: **Clinical, procedural, and angiographic characteristics of patients with stent thrombosis (ST) overall and by type of stent**

endothelialisation[38] and hypersensitivity reactions to the antiproliferative drugs or, more probably, to the synthetic polymers.[12,13]

Stent thrombosis is a multifactorial occurrence that has been attributed to a range of angiographic, lesion-related and vessel-related, technical and clinical factors.[39] Acute coronary syndrome, bifurcation treatment, diabetes and premature discontinuation of anti-platelet therapy were the strongest predictors of overall ST in several previous studies.[19,26–28,40] The present study confirms the predictive value of diabetes and acute coronary syndrome at presentation.

Several clinical risk factors were predictive for development of early stent thrombosis. The increased risk in diabetic patients might be related to the more diffuse and aggressive nature of atherosclerosis, accompanied by longer lesion lengths, smaller vessel size, and greater plaque burden, which might incur less optimal procedural results.[41–44] Additionally, the detrimental effects of smoking on endothelial function[45,46] and the long-term impairment of peri-stent vasoreactivity after drug-eluting stent implantation[14,15] are well known. However, the fact that smoking was independently associated with lower rates of early stent thrombosis might be related to the high number of patients with acute coronary syndrome in the present population. Smokers are likely to stop smoking immediately after such an event, which might remove from their risk-factor profile one of the major determinants of atherosclerosis.[47,48] The fact that the use or implementation of an antihypertensive treatment at the time of percutaneous coronary intervention was sufficient to qualify patients as hypertensive might have resulted in the so-called protective predictive value of hypertension for early stent thrombosis and the trend towards a lower risk for late stent thrombosis. However, overall, late stent thrombosis seemed difficult to predict and its cause remains largely unknown.

Although the cumulative incidence of overall and early stent thrombosis was similar for the two types of drug-eluting stent, late stent thrombosis occurred more frequently in patients treated with PES than in those treated with SES during the 3-year observation period. Up to 90% of paclitaxel remains indefinitely sequestered within the polymer, while 10% of the drug is released in a bimodal manner during a 2-week period. In contrast, sirolimus is completely released from the polymer and slowly elutes over a 90-day period. Whether the differences in drug-release kinetics,[49] distribution within the vessel wall, mechanisms of action,[50] or design of the stent platforms[51] affect the incidence and time course of late stent thrombosis remains unclear. PES were implanted in more complex lesions in this study group,



Days after PCI	9	30	365	730	1095
Incidence, SES (%)	1·0	1·1	1·3	1·9	2·5
Cumulative events (n)	36	41	47	60	69
Patients at risk (n)	3535	3508	2671	1710	903
Incidence, PES (%)	1·2	1·3	2·0	2·7	3·2
Cumulative events (n)	43	49	69	81	83
Patients at risk (n)	3626	3493	2667	1131	68

Figure 5: **Kaplan Meier survival curves showing cumulative incidence of stent thrombosis stratified by type of drug-eluting stent**

whereas SES had been used from an earlier time than had PES, and subsequently the length of follow-up differed between the two devices. Only randomised clinical trials will be able to fairly address potential differences in safety between the two stent types.

In this study, 30 of 31 patients who had late stent thrombosis while on single antiplatelet therapy received lifelong aspirin. Although absence of clopidogrel was not associated with a higher risk of stent thrombosis, 80% of patients with late stent thrombosis developed the problem after completion of the recommended duration of clopidogrel treatment. The question of whether extended or indefinite adjunctive clopidogrel treatment, if well tolerated, might be considered for patients who undergo drug-eluting stent implantation remains open. The effect of antiplatelet treatment on the pathophysiology of stent thrombosis is well established. Platelet aggregation studies have shown that an impaired response to antiplatelet treatment[52] and high post-treatment platelet reactivity[53] are associated with stent thrombosis. Furthermore, late stent thrombosis after cessation of clopidogrel has been reported in several studies.[23,25–27,35] In particular, the withdrawal of antiplatelet treatment in patients undergoing non-cardiac procedures seems problematic, because perioperative stress enhances platelet aggregation and thus the risk of thrombotic stent occlusion.[23,54] In this study, seven patients (one early; six late) discontinued both aspirin and clopidogrel before elective dental work or non-cardiac surgery. However, further evidence of the limited ability of clopidogrel to prevent all stent thrombosis is provided in our study, in which 13 of 61 of patients had late stent thrombosis despite dual antiplatelet therapy with aspirin and clopidogrel. Despite the longer duration of clopidogrel prescription (12 months) in the patients from Bern compared with those in Rotterdam (6 months), the incidence of both early and late stent thrombosis was similar in both centres. Additionally, the increased risk of bleeding complications and the economic burden imposed by long-term clopidogrel administration must be carefully weighed in light of these findings.

Effective antiplatelet treatment has a key role in the prevention of stent thrombosis and randomised controlled trials should be appropriately designed to prospectively address the following questions: which drugs are essential and for how long, what is the role of platelet function tests in patients undergoing drug-eluting stent implantation, and what are the therapeutic consequences?

Our study has several limitations. First, this was a non-randomised cohort study, with the decision about stent type and antiplatelet therapy largely determined by local institutional practice. The main purpose of the present study was to investigate the incidence and time course of stent thrombosis in unselected patients treated with drug-eluting stents. A comparison with stent thrombosis after bare metal stent implantation was beyond the scope of the present manuscript. The study was observational in nature and has the same disadvantages as any other observational study, including confounding by indication.[55] SES and PES have been used in both centres at different times, and PES were available for commercial use 1 year later than were SES. This difference in follow up might have biased our results. Nevertheless, results from comparisons of these two stent types should be viewed as hypothesis-generating and have to be confirmed in long-term follow-up of randomised controlled trials directly comparing these devices. Longer-term follow-up of the group of patients we studied will be needed to better understand the time course and incidence of this overall rare problem.

Second, our data provide an estimate of the incidence of stent thrombosis after drug-eluting stent implantation during routine clinical practice at two tertiary care centres. In this study we recorded a high number of stents per patient, small average stent diameter, and overall long total stent length, so our findings might not apply to institutions with more restricted use of drug-eluting stents. Nevertheless, previous randomised trials certainly underestimated the true incidence of stent thrombosis because of their less complex population of patients. Some stent thrombosis might have been undetected in our study despite our attempts at an active surveillance of harms.[56]

Additionally, we only reported angiographically documented cases, using a definition consistent with our previous reports on stent thrombosis after drug-eluting or bare metal stent implantation.[16,17,19–22,36] This practice might have led to an underestimation of the actual incidence of stent thrombosis—for example, if patients had sudden cardiac death or silent stent occlusion. Because of resource limitations it was impossible to ascertain retrospectively characteristics of patients and procedures that were not prospectively collected as part of routine procedures. Therefore, some variables were unavailable. In particular, the actual use of clopidogrel at each time point was not available for a substantial proportion of patients and therefore was not used in the final analysis. By contrast, the duration of clopidogrel prescription was available for all patients in Rotterdam and was included in the final Cox regression models. The value of clopidogrel in preventing stent thrombosis needs to be established in sufficiently powered dedicated trials. Intravascular ultrasound examination was not routinely done and the underlying mechanism contributing to the occurrence of stent thrombosis was not specifically investigated.

In conclusion, our data suggest that late stent thrombosis occurs at a steady rate during follow-up up to 3 years, tends to be more frequent with PES than with SES, and can unpredictably occur at any time point despite antiplatelet therapy. Late stent thrombosis complicating the use of drug-eluting seems to be a distinct entity with pathophysiological factors that differ from those of early stent thrombosis.

Contributors

The first two authors contributed equally to the manuscript. K Tschuchida, P Wenaweser, J Daemen, S Windecker, and P W Serruys were responsible for conception and design of the study, analysis and interpretation of data, and drafting of the manuscript. S Vaina, L Abrecht, C Morger, K Kukreja, P Jüni, G Sianos, G Hellige, R T van Domburg, O M Hess, E Boersma, and B Meier critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript. Statistical expertise was provided by J Daemen, P Jüni, R T van Domburg, and E Boersma. S Windecker, B Meier, and P W Serruys obtained public funding. Administrative, technical, and logistic support were provided by O M Hess, R T van Domburg, B Meier, S Windecker, and P W Serruys. K Tschuchida, P Wenaweser, J Daemen, S Vaina, L Abrecht, C Morger, N Kukreja, G Sianos, and G Hellige acquired data.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

The study was funded by research grants from the University Hospital Bern, Bern, Switzerland, and the Thoraxcenter, Rotterdam, the Netherlands.

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CHAPTER 27

Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice. 4-year results from a large 2-institutional cohort study

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J Am Coll Cardiol. 2008 Sept; 52 (14):1134-40.

Incidence and Correlates of Drug-Eluting Stent Thrombosis in Routine Clinical Practice

4-Year Results From a Large 2-Institutional Cohort Study

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Objectives We sought to determine the risk of late stent thrombosis (ST) during long-term follow-up beyond 3 years, searched for predictors, and assessed the impact of ST on overall mortality.

Background Late ST was reported to occur at an annual rate of 0.6% up to 3 years after drug-eluting stent (DES) implantation.

Methods A total of 8,146 patients underwent percutaneous coronary intervention with a sirolimus-eluting stent (SES) (n = 3,823) or paclitaxel-eluting stent (PES) (n = 4,323) and were followed up to 4 years after stent implantation. Dual antiplatelet treatment was prescribed for 6 to 12 months.

Results Definite ST occurred in 192 of 8,146 patients with an incidence density of 1.0/100 patient-years and a cumulative incidence of 3.3% at 4 years. The hazard of ST continued at a steady rate of 0.53% (95% confidence interval [CI]: 0.44 to 0.64) between 30 days and 4 years. Diabetes was an independent predictor of early ST (hazard ratio [HR]: 1.96; 95% CI: 1.18 to 3.28), and acute coronary syndrome (HR: 2.21; 95% CI: 1.39 to 3.51), younger age (HR: 0.97; 95% CI: 0.95 to 0.99), and use of PES (HR: 1.67; 95% CI: 1.08 to 2.56) were independent predictors of late ST. Rates of death and myocardial infarction at 4 years were 10.6% and 4.6%, respectively.

Conclusions Late ST occurs steadily at an annual rate of 0.4% to 0.6% for up to 4 years. Diabetes is an independent predictor of early ST, whereas acute coronary syndrome, younger age, and PES implantation are associated with late ST. (J Am Coll Cardiol 2008;52:1134–40) © 2008 by the American College of Cardiology Foundation

Drug-eluting stents (DES) reduce angiographic restenosis and the clinical need for repeat revascularization procedures (1,2). Recent systematic reviews and large-scale registries observed similar rates of death and myocardial infarction (MI) for patients treated with either a DES or bare-metal stent (BMS) during long-term 4-year follow-up (3–5). However, very late stent thrombosis (ST) has emerged as a distinct entity overshadowing the use of DES, and concerns persist as to whether this phenomenon might jeopardize the long-term outcome after DES implantation, particularly after discontinuation of dual antiplatelet therapy (6–11).

Drug-eluting stents delay healing and impair endothelialization as evidenced in necropsy studies and clinical investigations (12,13). Vessel remodeling (14) in concert with local drug release enhancing endothelial tissue factor expression (15,16) after DES implantation might result in a prothrombotic milieu predisposing to late ST. Previously, we reported on the frequency and timing of ST after the unrestricted use of DES implantation in a cohort of 8,146 consecutive patients treated at 2 academic institutions (10). Late and very late ST was encountered steadily at an annual rate of 0.6% with no evidence of diminution up to 3 years of follow-up. During extension of the follow-up period to 4 years in the current study, we investigated whether the risk of very late ST would change beyond 3 years, identified

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Manuscript received March 18, 2008; revised manuscript received June 30, 2008, accepted July 1, 2008.

correlates of early as opposed to late ST, and assessed the impact of ST-related mortality after DES implantation on overall mortality in the entire cohort.

Methods

Study cohort, design, and follow-up. Between April 16, 2002, and December 31, 2005, a total of 8,146 consecutive patients underwent percutaneous coronary intervention with the 2 Food and Drug Administration–approved DES at 2 academic referral hospitals in Switzerland and the Netherlands, comprising 3,823 patients treated with sirolimus-eluting stents (SES) (Cypher, Cordis Corp., Johnson & Johnson, Warren, New Jersey) and 4,323 patients treated with paclitaxel-eluting stents (PES) (TAXUS Express2 or Liberté, Boston Scientific, Natick, Massachusetts). The use of the respective stent platforms at the 2 institutions has been reported previously (10). For the present extended 4-year follow-up, patients were again contacted 1 year after the last contact with specific questions addressing repeat hospital stay and major adverse cardiac events (MACE) with a health questionnaire. Patients who did not return the questionnaire were contacted by phone, at which time the questionnaire was completed. Moreover, survival data were obtained from municipal civil registries. If necessary, medical records and discharge summaries from other institutions were systematically reviewed and primary care physicians were contacted for additional or missing information. The median follow-up was 2.53 years/patient, and a complete clinical follow-up was achieved in 96.4% (n = 7,857). The common database was held and analyzed at the Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. There was no industry involvement in the design, conduct, or analysis of the study.

This study was approved by the local ethics committee in both hospitals and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Definitions. Definite ST was defined as follows:

1. Presence of Thrombolysis In Myocardial Infarction (TIMI) flow:
   a. Grade 0 with occlusion originating in the peri-stent region
   b. Grade 1, 2, or 3 in the presence of a thrombus originating in the peri-stent region. Angiographic evidence of thrombus was defined as a discrete, intraluminal filling defect with defined borders and separated from the vessel wall.

And at least 1 of the following criteria had to be met:

1. Acute ischemic symptoms (typical chest pain with duration >20 min)
2. Ischemic electrocardiographic changes
   a. ST-segment elevation in territory of implanted stent
   b. ST-segment depression or T-wave inversion in territory of implanted stent
3. Typical rise and fall in cardiac biomarkers (17).

All cases of definite ST were reviewed independently by 2 experienced interventional cardiologists, and in case of disagreement, a consensus was established between the 2 reviewers or a third interventional cardiologist was consulted. Moreover, ST was categorized into early (within 30 days), late (>30 days and ≤365 days), and very late (>365 days) depending on the timing of occurrence of the event. For the definition of probable ST, the Academic Research Consortium (ARC) criteria were applied (18).

Abbreviations and Acronyms

ACS = acute coronary syndrome
ARC = Academic Research Consortium
ASA = acetylsalicylic acid
BMS = bare-metal stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
MACE = major adverse cardiac event
MI = myocardial infarction
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
ST = stent thrombosis
TIMI = Thrombolysis In Myocardial Infarction

The diagnosis of MI was based on the presence of new Q waves in at least 2 contiguous leads with an elevated creatine kinase-myocardial band fraction. In the absence of pathologic Q waves, the diagnosis of MI was based on an elevation in creatine kinase to more than twice the upper limit of normal with an elevated creatine kinase-myocardial band fraction of more than 3 times the upper limit of normal. Premature discontinuation of antiplatelet therapy was referred to as cessation of acetylsalicylic acid (ASA) or clopidogrel or both before the recommended duration of prescription. A creatinine value ≥150 μmol or chronic hemodialysis qualified as definition of renal impairment.

Interventional procedure and antiplatelet prescription. All interventions were performed according to current practice guidelines for percutaneous coronary intervention. The decision to choose a specific treatment strategy was left to the discretion of the operator. Patients were prescribed ASA 100 mg once daily plus clopidogrel 75 mg/day (after a loading dose of 300 or 600 mg) before or during baseline coronary interventions. After the procedure, all patients were advised to maintain ASA 100 mg once daily lifelong. In the Swiss institution, 12 months of clopidogrel therapy was prescribed irrespective of the stent type used. In the Dutch institution, PES-treated patients received at least 6 months of clopidogrel (75 mg/day), whereas patients treated with SES were prescribed clopidogrel for at least 3 months, unless 1 of the following was present (in which case clopidogrel was maintained for at least 6 months): ≥3 SES implantations, total stent length ≥36 mm, chronic total occlusion, and bifurcations. In a minority of patients under oral anticoagulation therapy, a shorter duration of clopidogrel (e.g.,

3-month triple therapy with ASA, clopidogrel, and warfarin) was recommended.

Statistical analysis. Continuous variables are expressed as mean ± SD or median values with the corresponding interquartile range. Dichotomous variables are expressed as counts and percentages. For comparison of continuous variables between SES and PES as well as early and late thrombosis, a Student *t* test for continuous variables was used.

The incidence of ST was calculated in 2 different ways: 1) incidence density, defined as the number of patients with ST divided by the total number of patient-years under observation (expressed as a number of events/100 patient-years); and 2) cumulative incidence, estimated according to the Kaplan-Meier method and the log-rank test for the differences in survival curve. Univariable and multivariable Cox proportional hazards models were used to assess predictors of ST, with the following variables: age, gender, family history of cardiovascular disease, diabetes, hypertension, current smoking, dyslipidemia, renal impairment, left ventricular ejection fraction, acute coronary syndrome (ACS) at presentation, stent type, number of stents, total stent length, average stent diameter, bifurcation treatment, and prescribed duration of clopidogrel. Statistical analyses were performed with Stata version 9 for Windows (Stata Corp., College Station, Texas). All p values were 2-sided and values <0.05 were considered statistically significant.

Results

Baseline clinical and procedural characteristics of patients with and without ST are summarized in Table 1. Compared with patients without ST, those suffering from definite ST were younger (59.4 ± 12.1 years vs. 62.9 ± 11.5 years, p < 0.001), had a lower left ventricular ejection fraction (52 ± 12% vs. 55 ± 12%, p = 0.035) and more often an ACS (67.7% vs. 54.9%, p < 0.001) at the time of stent implantation, and had received longer (total stent length: 44.0 ± 38.8 mm vs. 36.1 ± 25.5 mm, p < 0.001) and more stents (number of stents: 2.33 ± 1.71 vs. 1.95 ± 1.21, p < 0.001), which were smaller in diameter (2.88 ± 0.32 mm vs. 2.94 ± 0.38 mm, p = 0.048). The status of antiplatelet therapy as recorded during early and late and very late ST is summarized in Figure 1.

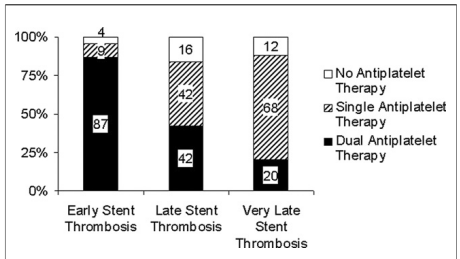


Figure 1 **Status of Antiplatelet Treatment at Time of Definite Stent Thrombosis**

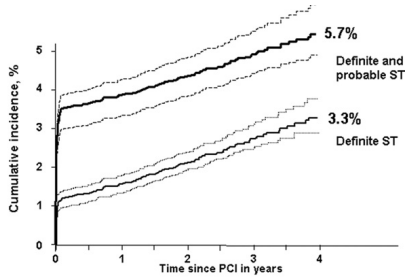
Proportion of patients with early and late stent thrombosis treated with dual, single, or no antiplatelet therapy.

Incidence and time course of ST. During a follow-up period of 4 years, definite ST was encountered in 192 of 8,146 patients after a median of 56 (interquartile range 4 to 593) days (Fig. 2). Early ST was observed in 92 (48%), late ST in 31 (16%), and very late ST in 69 (36%) of 192 patients. Definite ST occurred with an incidence density of 1.0/100 patient-years and a cumulative incidence of 3.3% at 4 years of follow-up. The hazard of late ST (between 30 days and 1 year) amounted to 0.46% (95% confidence interval [CI]: 0.32% to 0.65%), the hazard of very late ST (between 1 and 4 years) to 0.57% (95% CI: 0.45% to

Table 1 **Clinical and Procedural Characteristics of Patients With and Without Definite ST**

	Overall Population (n = 8,146)	ST (n = 192)	No ST (n = 7,954)	p Value
Age (yrs), mean ± SD	62.8 ± 11.5	59.4 ± 12.1	62.9 ± 11.5	<0.001
Male gender, %	74.5	75.0	74.5	0.88
Hypertension, %	46.5	42.2	46.6	0.23
Current smoking, %	36.8	41.7	36.7	0.16
Family history of CAD, %	28.1	29.2	28.1	0.75
Dyslipidemia, %	50.9	50.0	50.9	0.81
Diabetes, %	16.3	20.8	16.2	0.09
Left ventricular ejection fraction (%), mean ± SD	55 ± 12	52 ± 12	55 ± 12	0.035
Renal impairment, %	4.1	2.6	4.2	0.48
ACS at presentation, %	55.2	67.7	54.9	<0.001
Bifurcation treatment, %	11.8	17.9	11.6	0.06
Sirolimus-eluting stent, %	47.9	43.2	48.0	0.19
Total stent length/patient (mm), mean ± SD	36.3 ± 25.9	44.0 ± 38.8	36.1 ± 25.5	<0.001
Number of stents/patient, mean ± SD	1.96 ± 1.23	2.33 ± 1.71	1.95 ± 1.21	<0.001
Average stent diameter/patient (mm), mean ± SD	2.94 ± 0.38	2.88 ± 0.32	2.94 ± 0.38	0.048

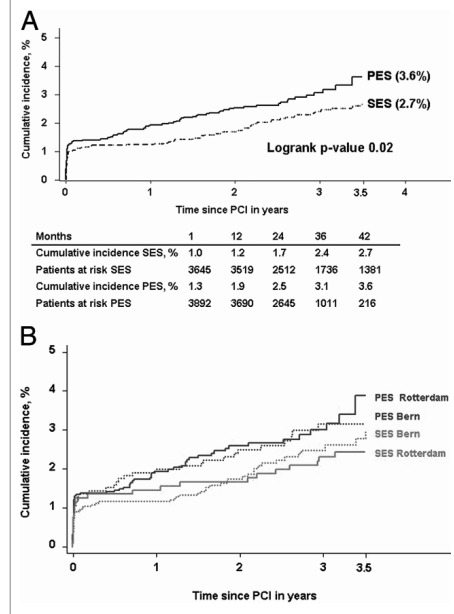
ACS = acute coronary syndrome; CAD = coronary artery disease; ST = stent thrombosis.



Months	1	12	24	36	48
Cumulative incidence definite ST, %	1.2	1.6	2.1	2.7	3.3
Cumulative incidence probable and definite ST, %	3.7	4.1	4.6	5.2	5.7
Patients at risk	7537	7209	5157	2747	1051

Figure 2 Cumulative Incidence of Definite ST in 8,146 Patients During a 4-Year Follow-Up Period

PCI = percutaneous coronary intervention; ST = stent thrombosis.



Months	1	12	24	36	42
Cumulative incidence SES, %	1.0	1.2	1.7	2.4	2.7
Patients at risk SES	3645	3519	2512	1736	1381
Cumulative incidence PES, %	1.3	1.9	2.5	3.1	3.6
Patients at risk PES	3892	3690	2645	1011	216

Figure 3 Cumulative Incidence of Definite ST Stratification

(A) Cumulative incidence of definite stent thrombosis (ST) stratified by stent type. **(B)** Cumulative incidence of definite ST stratified by stent type and treatment site. PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s).

0.72%), and the hazard of the combined rate for late and very late ST (between 30 days and 4 years) was 0.53% (95% CI: 0.44% to 0.64%)/year. The rate of definite and probable ST after 4 years amounted to 5.7% (95% CI: 5.15% to 6.39%) with an incidence of 3.68% (95% CI: 3.29% to 4.12%) after 30 days and 4.09% (95% CI: 3.67% to 4.55%) after 1 year (Fig. 2).

Baseline demographic data for SES- and PES-treated patients differed widely (Table 2). The cumulative incidence of ST up to 3.5 years amounted to 2.7% for SES-treated and 3.6% for PES-treated patients (HR: 0.7; 95% CI: 0.53 to 0.95, p = 0.02) (Fig. 3A). Whereas early ST occurred with similar frequency in SES- (1.0%) and PES-treated

Table 2 Clinical and Procedural Characteristics of Patients Stratified by Stent Type

	SES (n = 3,823)	PES (n = 4,323)	p Value
Age (yrs), mean ± SD	62.6 ± 11.4	63.0 ± 11.5	0.31
Male gender, %	74.9	74.2	0.51
Hypertension, %	41.9	51.6	<0.0001
Current smoking, %	44.9	29.5	<0.0001
Family history of CAD, %	29.0	27.3	0.09
Dyslipidemia, %	55.8	47.3	<0.0001
Diabetes, %	18.3	14.6	<0.0001
Left ventricular ejection fraction (%), mean ± SD	54 ± 12	55 ± 12	0.01
Renal impairment, %	4.3	3.9	0.58
ACS at presentation, %	52.1	58.0	<0.0001
Bifurcation treatment, %	10.3	12.3	0.09
Total stent length/patient (mm), mean ± SD	33.8 ± 23.0	38.6 ± 28.1	<0.0001
Number of stents/patient, mean ± SD	1.87 ± 1.14	2.03 ± 1.30	<0.0001
Average stent diameter/patient (mm), mean ± SD	2.86 ± 0.32	3.00 ± 0.40	<0.0001
Duration of clopidogrel prescription (days), mean ± SD	144 ± 120	194 ± 80	<0.0001

PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s); other abbreviations as in Table 1.

(1.3%) patients (HR: 0.76; 95% CI: 0.50 to 1.15, p = 0.19), late and very late ST occurred with an annual rate of 0.44% (95% CI: 0.33% to 0.59%) after SES and 0.63% (95% CI: 0.49% to 0.83%) after PES implantation (HR: 0.66; 95% CI: 0.44 to 0.99, p = 0.047). A stratified analysis according to treatment site revealed a similar frequency and time course of definite ST after SES (Bern: 2.9% vs. Rotterdam: 2.4%, p = 0.49) and PES (Bern: 3.1% vs. Rotterdam: 3.9%, p = 0.83) implantation at both institutions (Fig. 3B).

Predictors of ST. The results of multivariate analyses to identify overall, early, and late definite ST are summarized in Table 3. Acute coronary syndrome at the time of stent implantation (HR: 1.81; 95% CI: 1.32 to 2.49), diabetes (HR: 1.61; 95% CI: 1.11 to 2.33), younger age (HR: 0.98; 95% CI: 0.96 to 0.99), and use of PES (HR: 1.51; 95% CI: 1.10 to 2.04) were independent predictors of overall ST. Diabetes (HR: 1.96; 95% CI: 1.18 to 3.28) was the only predictor of early ST, whereas ACS at time of stent implantation (HR: 2.21; 95% CI: 1.39 to 3.51), younger age (HR: 0.97; 95% CI: 0.95 to 0.99), and use of PES (HR: 1.67; 95% CI: 1.08 to 2.56) were independently associated with an increased risk of late ST.

Long-term clinical outcome. Mortality after definite ST amounted to 15.6% at 2 years and tended to be higher in patients suffering from early (20.3%) as opposed to late and very late ST (10.4%) (Fig. 4). At 4 years of follow-up, rates of death, MI, and the composite of death or MI were 10.6%, 4.6%, and 14.6%, respectively, in the overall population (Fig. 5). During the entire observation period of 4 years, 27 patients suffering from definite ST subsequently died. Death after the diagnosis of definite ST occurred in 0.4% of the entire population and accounted for 3.9% of all 702 deaths.

Discussion

The results of the present study indicate a continuous hazard of late and very late ST at an annual rate of 0.4% to 0.6% extending to 4 years after DES implantation. The only independent predictor of early ST was diabetes, whereas ACS, younger age, and use of PES were independently associated with an increased risk of late ST. Mortality due to definite ST accounted for only a small fraction of overall mortality.

Autopsy studies and clinical investigations using angioscopy and assessment of endothelial function indicate that DES delay healing and impair endothelialization (12,13, 19–22). Intravascular ultrasound studies demonstrate a higher incidence of stent malapposition and evidence of vessel remodeling after DES implantation in patients with very late ST (14). Furthermore, drugs released from the drug-polymer combination might be thrombogenic on their own, because both sirolimus and paclitaxel enhance endothelial tissue factor expression, the principal activator of the coagulation cascade that activates factors IX and X (15,16). Therefore, it has been suggested that DES might create a prothrombotic milieu predisposing to thrombotic stent occlusion.

Previously, we reported the phenomenon of late ST after DES implantation occurring continuously without diminu-

Table 3 Hazard Ratio and 95% CI for Risk Factors Associated With Definite ST During the Entire Follow-Up Period From Multivariable Cox Regression

Variables	Hazard Ratio	95% CI
ACS at presentation	1.8	1.3–2.5
Diabetes	1.6	1.1–2.3
Number of stents/patient	1.2	0.95–1.4
Current smoking	1.1	0.78–1.5
Family history of CAD	1.0	0.73–1.4
Total stented length/patient	1.0	1.00–1.01
Age	0.98	0.96–0.99
Dyslipidemia	0.95	0.70–1.28
Female	0.89	0.63–1.25
Hypertension	0.85	0.62–1.16
Use of PES	1.67	1.08–2.56

CI = confidence interval; other abbreviations as in Tables 1 and 2.

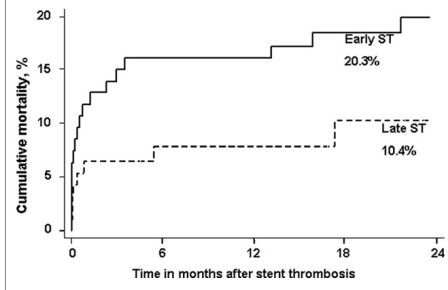


Figure 4 Cumulative Incidence of Death in Patients With Definite ST Stratified According to Early and Late ST

ST = stent thrombosis.

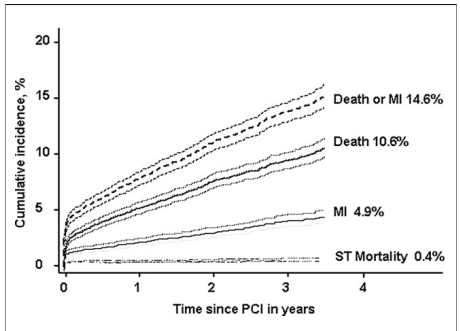


Figure 5 Cumulative Incidence of Ischemic Adverse Events in 8,146 Patients During 4 Years of Follow-Up

MI = myocardial infarction; PCI = percutaneous coronary intervention; ST = stent thrombosis.

tion up to 3 years of follow-up in a large cohort of consecutive patients treated with the unrestricted use of DES (10). The present study extends these findings to a longer-term follow-up and shows that the steady annual rate of 0.4% to 0.6% remains unchanged between 3 and 4 years of follow-up. A continuous linear hazard of late ST comparable to the present study has been corroborated more recently in the extended follow-up of 21,717 DES-treated patients included in the SCAAR (Swedish Coronary Angiography and Angioplasty Registry) with an annual rate of ST of 0.5% during a follow-up of 2 years (23,24). Moreover, several systematic reviews reported a significantly higher rate of very late ST in disfavor of both SES and PES compared with BMS, although the overall rate of ST was not different between the different stent types (3,4,25). Accordingly, very late ST is a distinct entity complicating the use of DES, and arterial healing remains incomplete up to 4 years after DES implantation in humans.

Although late and very late ST complicated the clinical course of both DES types, it was more frequent with PES than SES, and use of PES emerged as independent of late ST. Of note, PES was implanted in more complex lesions in this cohort, whereas SES had been used earlier than PES, and subsequently the length of follow-up was different between the 2 devices, which might have biased the results in disfavor of PES. Yet, Bavry et al. (7) made a similar observation and found the risk of very late ST more pronounced with PES (5.9 of 1,000 patient-years) than SES (3.6 of 1,000 patient-years) in a meta-analysis of 14 trials with 6,675 patients. A meta-analysis directly comparing SES (4,391 patients) with PES (4,304 patients) also reported a higher risk of protocol-defined ST with PES (1.9%) than SES (1.2%; HR: 0.66, 95% CI: 0.46 to 0.94, $p = 0.02$) (26). Finally, a network meta-analysis of 38 trials comparing BMS, SES, and PES reported an increased risk of late ST with PES compared with BMS (HR: 2.11; 95% credibility interval: 1.2 to 4.2, $p = 0.02$), whereas the risk was less pronounced with SES (HR 1.1; 95% credibility interval: 0.6 to 2.3, $p = 0.71$) (5). It can only be speculated whether the different drug-release kinetics, distribution within the vessel wall, mechanisms of action, inhomogeneity of strut coverage, or design of the stent platforms impact on the incidence and time course of late ST.

Previous studies identified clinical characteristics such as premature discontinuation of antiplatelet therapy (27–29), ACS (10,30), diabetes (10,27,30), and renal failure (27,28) as independent risk factors of DES-associated ST. In addition, lesion characteristics including smaller reference vessel diameter, stent length (29), thrombus burden (31), and bifurcation lesions (27,28) were identified as predictive of ST. The present study not only confirms the hazard related to diabetes and ACS in the largest cohort of patients with definite ST to date but also identifies diabetes as a predictor of early ST and ACS as a predictor of late ST. The reasons for a predisposition of diabetic patients to early ST might be related to smaller vessel size (32), longer lesion length, a higher rate of residual dissections, and an increased platelet aggregation (11,33). Conversely, patients with ACS might be predisposed to late and very late ST due to a higher thrombus burden at the time of stent implantation (31), which upon dissolution might result in late acquired stent malapposition and altered flow dynamics around stent struts (14).

The contribution of definite ST to overall mortality was small in the present study (<5%). A similar observation has been made in a pooled analysis of pivotal trials comparing DES with BMS (25), where mortality due to ST accounted for <10% of overall mortality. It might be speculated that the overall outcome regarding death or MI of patients treated by percutaneous coronary interventions might be determined in large part by causes other than target lesion revascularization or ST. Along this line, a pooled analysis of 4 randomized trials comparing SES with BMS in 1,748 patients found that the majority of death or MI in both stent groups was unrelated to either target lesion revascularization or ST, suggesting another etiology, such as disease progression (34). However, it is important to note that the definition of definite ST requiring angiographic or autopsy confirmation of thrombotic stent occlusion leads to a considerable underestimation of the true incidence of ST-related mortality. Because only those patients reaching the catheterization laboratory alive qualify for the diagnosis of definite ST, all deaths before angiographic or autopsy confirmation are missed and not classified as "definite ST"–related. In other words, the presented data only reflect the mortality toll of definite ST after initial survival.

Study limitations. The findings of this study have to be interpreted in light of several limitations. First, the study was nonrandomized, with the decision regarding stent type and antiplatelet therapy largely determined by local institutional practice. The principal purpose was to investigate the incidence and time course of definite ST in unselected patients treated with DES during long-term follow-up rather than a comparison of ST as encountered after BMS implantation. This is an observational study, which suffers from confounding by indication. The SES and PES were used in both centers during different time periods, and PES was available for commercial use 1 year later than SES. This might have resulted in bias due to differences in follow-up. Due to the continuous enrollment of patients into this registry between 2002 and 2005, not all patients had completed the 4-year follow-up. Accordingly, estimates of the risk of ST are less precise during later time points, and the data should be carefully interpreted by considering the corresponding CIs. Second, the data were obtained from a patient population at 2 tertiary care centers with a high number of stents/patient, a small average stent diameter, and an overall long total stent length, which might not apply to institutions with a more restricted DES use. Third, it is possible that some ST went undetected in our study despite our attempts at an active surveillance of harms. In addition, the focus of the present study was on definite ST, which might have led to an underestimation of the actual incidence

of ST as well as mortality related to definite ST. The latter requires angiographic or autopsy confirmation of thrombotic stent occlusion and therefore ignores any death without these prerequisites. However, the definition is in line with previous reports from our group on ST either after DES or BMS implantation and allows for appropriate comparisons. Moreover, the composite of definite and probable ST, suggested as a useful parameter to avoid underestimation and overestimation of ST, is provided in the present study as are the ischemic end points of death and MI. Finally, only the prescribed duration of antiplatelet therapy was available in the present study, whereas the exact duration of dual antiplatelet therapy could not reliably be ascertained in the whole patient population. Therefore, it cannot be excluded that we missed an important relation between the actual duration of thienopyridine therapy and ST.

Conclusions

Late ST is a distinct entity complicating the use of DES and occurs steadily at an annual rate of 0.4% to 0.6% for up to 4 years of follow-up. Diabetes is an independent predictor of early ST, whereas ACS, younger age, and use of PES are associated with late ST.

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Key Words: drug-eluting stent ▪ mortality ▪ stent thrombosis.

CHAPTER 28

Xience V everolimus-eluting coronary stent

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Expert Rev Med Devices. 2009 May;6(3):219-29.

EXPERT REVIEWS

Xience V™ everolimus-eluting coronary stent

Expert Rev. Med. Devices 6(3), 219–229 (2009)

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Drug-eluting stents are widely used for the treatment of coronary artery disease to reduce the risk of restenosis found with bare-metal stents. Nevertheless, there are concerns about device deliverability and safety with the initial generation of drug-eluting stents. The second-generation Xience V™ everolimus-eluting stent incorporates advanced design features such as a cobalt–chromium stent platform coated with an antirestenotic drug, everolimus, incorporated into a biocompatible polymer with a long history of medical use. The efficacy of the stent has been demonstrated with low rates of angiographic restenosis, whilst randomized trials comparing the Xience V everolimus-eluting stent to the first-generation Taxus® paclitaxel-eluting stent have found a reduction in repeat revascularization rates. Further randomized trials, including 'all-comer' patients and registries of unselected patients are currently further evaluating the efficacy and safety of the Xience V stent in high-risk, complex cases.

Keywords: cobalt–chromium • drug-eluting stent • everolimus • percutaneous coronary intervention • Xience V™

Since the first human implant in 1986, intracoronary stents have been successful in reducing the acute complications of percutaneous coronary intervention. By providing a mechanical scaffold, bare-metal stents (BMSs) reduce the rates of emergency bypass surgery to less than 0.5% and restenosis rates from 30–40% with balloon angioplasty to 20–25% [1–3]. However, even with more modern stent designs, restenosis due to neointimal hyperplasia with BMSs still occurs in a significant number of patients and is the major limitation of BMSs. Neointimal hyperplasia is an exaggerated healing response to vessel trauma resulting from the angioplasty and stent procedure and has been the major limitation of percutaneous coronary intervention. The prevention of restenosis has therefore been the pre-eminent focus of recent developments including drug-eluting stents (DESs), which utilize the stent itself as a vehicle for local intracoronary drug delivery.

In 2002–2003, DESs were approved by regulatory bodies in Europe and the USA after initial studies showed a dramatic reduction in rates of restenosis compared with BMSs. However, there have been concerns over the first-generation DESs, which were designed in the late 1990s. The stent platform, polymer and drug have all been the focus for improvement with the aim of maintaining low rates of restenosis whilst improving deliverability and safety. The Xience V™ second-generation DES aims to address these concerns.

First-generation drug-eluting stents

The Cypher™ sirolimus-eluting stent (Cordis, Warren, NJ, USA) consists of a stainless steel platform coated with a permanent polymer (polyethylene-co-vinyl acetate [PEVA] and poly-n-butyl methacrylate [PBMA]) containing the drug. Sirolimus (also known as rapamycin) is a naturally occurring macrolide that is also a potent immunosuppressant licensed for use in transplant recipients (Figure 1) [4]. The lipophilic sirolimus binds to FK506-binding protein-12 and, subsequently, the mTOR and thereby blocks the cell cycle, inhibiting the transition from the G1 to S phase, resulting in inhibition of smooth muscle cell migration and proliferation [5–7]. The initial reports of the sirolimus-eluting stent (SES) demonstrated almost complete abolition of neointimal growth, which was confirmed in the landmark Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with *De Novo* Native Coronary Artery Lesions (RAVEL) trial [8]. This profound effect on restenosis and repeat revascularization has subsequently been confirmed in larger industry-sponsored randomized trials, as well as physician-driven registries including

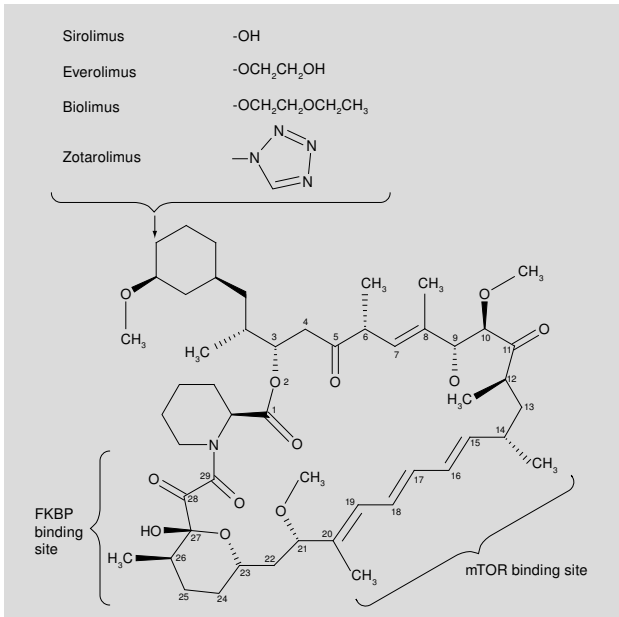

Figure 1. Sirolimus and its analogues everolimus, biolimus and zotarolimus.
FKBP: FK506-binding protein.

more complex lesions [9–18]. The largest meta-analysis to date found that SESs reduced the need for target lesion revascularization (TLR) from 19% with BMSs to approximately 7% with SESs [19]. However, potential adverse biological actions of sirolimus include accelerated senescence of endothelial progenitor cells, the upregulation of tissue factor and an increase in the expression of plasminogen activator inhibitor-1, which can be demonstrated *in vitro* [20–22]. In clinical practice, SESs have been found to unfavorably affect endothelial function with paradoxical vasoconstriction, which may contribute to adverse clinical events [23–26].

The Taxus® (Boston Scientific, Natick, MS, USA) paclitaxel-eluting stent (PES) has also been widely studied in a range of patient and lesion subsets [27–32]. The PES reduces TLR to approximately 9% [19]. This stent also incorporates a stainless steel platform with a permanent polymer coating (poly styrene-b-isobutylene-b-styrene) combined with the drug. The release of paclitaxel is biphasic, with a 48-h early burst followed by low-level release for 2 weeks; however, 90% of the drug remains bound to the polymer [33]. Paclitaxel is an antimitotic microtubule inhibitor, which suppresses cell division in the G0/G1 and G2/M phases, resulting in disruption of smooth muscle cell migration and proliferation. However, paclitaxel also increases expression of tissue factor in endothelial cells and increases the expression of plasminogen activator inhibitor-1 [22,34] and PESs can also result in abnormal vasomotion [35].

One concern with DESs is the risk of stent thrombosis. Although this also occurs with BMSs, DESs have a small excess risk of late (> 30 days) and very late (> 1 year) stent thrombosis [36]. This risk seems to be a combination of patient-related factors (e.g., diabetes mellitus, renal failure, advanced age, low ejection fraction and stenting in acute coronary syndromes), as well as device-related factors: the adverse biological actions of the anti-restenotic drugs, in terms of upregulation of tissue factor, senescence of endothelial progenitor cells, inhibition of endothelial cell proliferation, and migration and vasoconstriction have been suggested as possible contributory mechanisms towards stent thrombosis [36–39]. To permit controlled drug release, both of these stents are coated with a permanent polymer, which persists after drug release. The presence of such a polymer coating may also contribute to stent thrombosis as a result of delayed healing and a hypersensitivity reaction in some cases [40–43]. Since these hypersensitivity reactions can occur more than 4 months after DES implantation (long after the period of drug release), it is possible that these events are due to the polymer coating. The risk of stent thrombosis can be minimized by dual antiplatelet therapy with aspirin and clopidogrel for a minimum of 1 year after DES implantation, although the optimum duration of therapy is unknown [44].

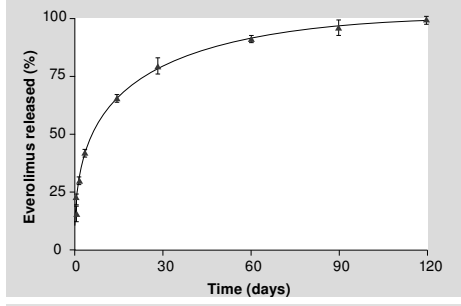

Figure 2. Release kinetics of everolimus from the Xience V™ stent. *In vivo* data in a porcine model.

Additionally, the first-generation drug-eluting stents, designed in the late 1990s, have a strut thickness of greater than 150 µm (Cypher, Taxus Express™) or greater than 100 µm (Taxus Liberte®) when the polymer thickness is added to the metallic strut and lack the flexibility required for the insertion of long stents in distal positions. Despite its excellent results in restenosis prevention, the closed cell design of the Cypher stent limits strut opening in the treatment of bifurcation lesions and confers a small but definite risk of stent fracture when long stents are implanted at flexing points, such as in the right coronary artery or in saphenous vein grafts [45].

Xience V™ everolimus-eluting stent

The Xience V™ everolimus-eluting stent ([EES] Abbott Vascular, Santa Clara, California, USA) consists of the Multi-Link Vision™ cobalt–chromium (CoCr) balloon-mounted stent coated with a nonerodable fluorinated copolymer and 100 µg/cm^2 everolimus (40-O-(2-hydroxyethyl-rapamycin)), an analogue of sirolimus (Figure 1). Preclinical studies indicate that approximately 75% of the drug is released within 30 days (Figure 2) [Data on file, Abbott Vascular]. The device received Conformité Européenne (CE) marking for use in Europe in January 2006 and was commercially released in Europe in October 2006. It is also approved for use in Latin America, Africa, the Middle East and Australasia, and recieved US FDA approval for use in the USA in July 2008. The indications for use in Europe are for use in *de novo* native coronary artery lesions (length ≤ 28 mm) with reference vessel diameters of 2.25–4.25 mm. Currently available stent sizes are 2.25–4.0 mm diameter and 8–28 mm length in Europe; the 2.25-mm stent is not currently available in the USA. The device is currently available in a monorail version in Europe, and both monorail and over-the-wire versions in the USA. The nominal inflation pressure is 8 atmospheres with a rated burst pressure of 16 atmospheres. As with other DESs, dual antiplatelet therapy with aspirin and clopidogrel is recommended for 12 months after implantation [44].

Stent platform

The initial DESs were composed of 316L stainless steel since this material is radio-opaque with adequate radial strength to maintain adequate arterial scaffolding and low degrees of acute recoil.

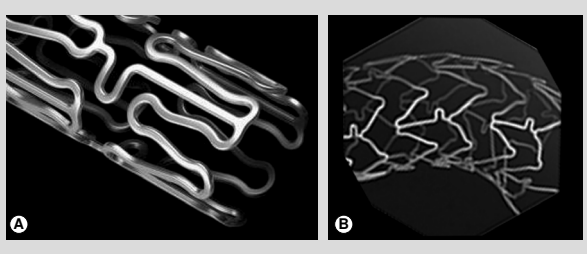

Figure 3. Xience V™ everolimus-eluting stent platform. (A) Appearance when crimped onto the delivery balloon. **(B)** Appearance when fully expanded.

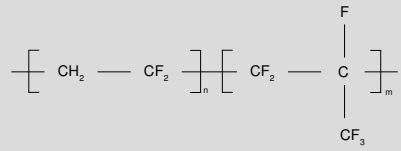

Figure 4. VDF and HFP coating of the Xience V™ stent. HFP: Hexafluoropropylene; VDF: Vinylidene fluoride.

However, CoCr exhibits superior radial strength and improved radiopacity allowing for thinner stent struts, which may reduce restenosis and TLR whilst reducing device profile and, hence, improving its deliverability to the target lesion [46–48]. The Multi-Link Vision stent, consists of serpentine rings connected by links fabricated from a single piece of medical grade L-605 CoCr alloy (Figure 3). The results of a registry of 267 patients treated with the thin strut (0.0032 inches) BMS Multi-Link Vision demonstrated a 6-month binary angiographic restenosis rate of 15.7% and mean late lumen loss of 0.83 ± 0.56 mm. The 6-month rates of mortality, myocardial infarction, target vessel revascularization (TVR) and TLR were 1.2, 0.8, 5.1 and 4.3%, respectively [47].

Polymer

The 7.8-µm polymer coating of the Xience V stent is a fluorinated copolymer consisting of vinylidene fluoride and hexafluoropropylene, compounds that have proven biocompatibility, and are used clinically in permanent surgical sutures (Figure 4). By comparison, the poly-n-butyl methacrylate coating of the Cypher stent and the polystyrene-b-isobutylene-b-styrene coating found on the Taxus stent both induce inflammatory and prothrombotic gene expression in endothelial cells [Data on file, Medtronic].

Everolimus

Everolimus was initially developed for use in transplantation [49] (Figure 1). Everolimus has a similar mode of action to sirolimus: it binds to FK506-binding protein-12 and, subsequently, binds to and inhibits the mTOR. The drug acts as a cytostatic inhibitor of cellular proliferation, by arresting cells in the late G1 phase of the cell cycle and preventing them entering the S phase [49]. Everolimus inhibits cytokine-mediated and growth factor-mediated proliferation of lymphocytes and smooth muscle cells, thereby acting as an immunosuppressant. It has successfully been used in combination with other drugs to prevent rejection in recipients of heart, lung or renal transplants. Furthermore, as a result of its effects on growth factor-stimulated vascular smooth muscle cell proliferation, everolimus also reduces the severity and incidence of cardiac-allograft vasculopathy [50]. Additionally,

Table 1. Histological results at 28 days in porcine coronary arteries.

Parameter	Everolimus-eluting Multi-Link Vision™ stent	Sirolimus-eluting stent	Bare metal Multi-Link Vision stent
Neointimal thickness (mm)	0.13 ± 0.07*	0.13 ± 0.08*	0.20 ± 0.07
Area stenosis (%)	20.8 ± 6.9*	20.8 ± 7.6*	26.9 ± 7.8
Vessel injury score	0.08 ± 0.11	0.15 ± 0.25	0.18 ± 0.25
Struts with fibrin (%)	76.9 ± 31.5‡	88.4 ± 7.7‡	5.4 ± 5.9
Fibrin score	1.36 ± 0.66‡	1.61 ± 0.61‡	0.08 ± 0.15
Inflammation score	0.75 ± 0.29	0.75 ± 0.29	0.89 ± 0.57
Struts with granulomas (%)	0.4 ± 1.3	0	1.9 ± 6.4
Endothelialization (%)	100	99.3	100

*p < 0.05 versus bare-metal stent.
‡p < 0.001 versus bare-metal stent.
Data from [53].

everolimus selectively cleared macrophages in rabbit atherosclerotic plaques by autophagy; an mTOR inhibition-dependent and novel mechanism to induce cell death in mammalian cells. This may be of benefit in tackling vulnerable atherosclerotic plaques not yet significantly stenotic but yet prone to rupture and thrombosis [51]. Although the *in vitro* concentrations required for inhibiting bovine vascular smooth muscle cells are similar, the dose of everolimus used in the EES (88 µg for a 3.0 × 18-mm stent) is lower than the dose of sirolimus in SESs (150 µg for the same size stent).

Preclinical trials

Orally administered everolimus proved to be effective in reducing neointimal hyperplasia in a rabbit iliac artery model. Following balloon injury and implantation of a bare-metal Multi-Link Vision stent, oral everolimus (1.5 mg/kg the day before the procedure followed by 0.75 mg/kg/day for 28 days) reduced the neointimal thickness from 0.12 ± 0.03 mm to 0.07 ± 0.03 mm (p = 0.005) [52]. After 28 days, 86.7 ± 6.8% of the stent surface was endothelialized in the everolimus-treated animals (vs 96.8 ± 5.4% in the control animals; p < 0.006). The results of histological metal assessment in a porcine model, comparing the EES with the bare Multi-Link Vision and the Cypher SES after 28 days are shown in Table 1 [53]. The results were similar for the EES and SES. A further comparison between the bare-metal Multi-Link Vision, Cypher SES, Taxus PES and Endeavor zotarolimus-eluting stent ([ZES] Medtronic Vascular, Santa Rosa, California, USA) in a rabbit iliac artery model has been recently published [54]. After 14 days, the endothelial coverage above the stent struts was significantly higher (p < 0.003) in the EES when compared with other DESs (BMS 79.9 ± 7.4%; EES 64.0 ± 27.5%; ZES 30.2 ± 14.2%; PES 26.8 ± 15.8%; SES 6.4 ± 4.2%) with nonsignificantly higher coverage between the struts (EES 90.4 ± 12.4%; ZES 80.6 ± 9.7%; PES 74.1 ± 16.6%; SES 72.1 ± 9.6%; p = 0.08). After 28 days, they were no longer statistically significant. The integrity of endothelial function was assessed by the measurement of platelet-endothelial cell adhesion molecule-1 and VEGF. The EES exhibited higher expression of platelet-endothelial cell adhesion molecule-1 (after 14 days BMS 55.9 ± 30.2%; EES 45.9 ± 35.6%; PES 21.3 ± 11.8%; ZES 7.4 ± 10.2%; SES 5.8 ± 5.8%) and lower levels of VEGF then the other DESs. All these findings are consistent with improved endothelial function in the EES group, which implies enhanced safety with this stent.

Table 2. Angiographic results of the SPIRIT FIRST first-in-man trial.

Time (months)	Late lumen loss (mm)		Diameter stenosis (%)		Binary angiographic restenosis (%)	
	EES	BMS	EES	BMS	EES	BMS
In-stent						
6	0.10 ± 0.21‡	0.87 ± 0.37	16 ± 8*	39 ± 14	0.0*	25.9
12	0.24 ± 0.27‡	0.84 ± 0.45	18 ± 13‡	37 ± 17	NA	NA
In-segment						
6	0.07 ± 0.19‡	0.61 ± 0.37	22 ± 11‡	41 ± 14	4.3*	33.3
12	0.14 ± 0.24‡	0.59 ± 0.42	22 ± 15‡	40 ± 16	NA	NA

*p < 0.05 versus BMS
‡p < 0.001 versus BMS
BMS: Bare-metal stent; EES: Everolimus-eluting stent; NA: Not applicable.
Data from [58,59].

Clinical trials

FUTURE I & II trials

The effects of everolimus was initially evaluated in a poly-L-lactic acid-coated stainless steel S stent (Biosensors International, Singapore), which was effective in the first-in-man FUTURE I trial of 42 patients randomized 2:1 to EES (27 patients) versus BMS (15 patients). The 6-month in-stent late lumen loss was 0.10 versus 0.85 mm (p < 0.0001) for the BMS and in-stent

Table 3. Cumulative incidence of hierarchical adverse clinical events in the SPIRIT FIRST trial.

Event	6 months		12 months		24 months		36 months		48 months	
	EES (%)	BMS (%)	EES (%)	BMS (%)	EES (%)	BMS (%)	EES (%)	BMS (%)	EES (%)	BMS (%)
Death	0	0	0	0	0	0	0	0	0	0
Myocardial infarction	3.8	0	7.7	0	7.7	0	7.7	0	8.0	0
Target lesion revascularization	3.8	21.4	7.7	21.4	7.7	25.0	7.7	21.4	8.0	21.4
Target vessel failure	7.7	21.4	15.4	21.4	15.4	28.6	NA	NA	NA	NA
Major adverse cardiac events*	7.7	21.4	15.4	21.4	15.4	25.0	15.4	25.0	16.0	25.0

*Death, myocardial infarction or target lesion revascularization.
BMS: Bare-metal stent; EES: Everolimus-eluting stent; NA: Not applicable.
Data from [58,59,60] and Data on file, Abbott Vascular.

binary angiographic restenosis was 0 versus 9.1% (p = not significant) [55,56]. This stent released 70% of the 197 μg/cm^2 everolimus within 30 days and 85% within 90 days. A pooled analysis of 106 randomized patients enrolled in both the FUTURE I and FUTURE II clinical trials demonstrated the beneficial effect of EESs regardless of vessel size [57]. These findings suggested that everolimus was effective in reducing restenosis.

SPIRIT FIRST: first-in-man trial

The first-in-man study of the Xience V stent enrolled 60 patients at nine medical centers in Europe, who were randomized to either the EES (n = 28) or the bare-metal Multi-Link Vision stent (n = 32). The study included patients with stable or unstable angina or silent ischemia with a single *de novo* significant coronary lesion (50–99% stenosis) in a 3.0-mm vessel that could be covered with an 18-mm stent. Patients with an evolving myocardial infarction, unprotected left main stem disease, ostial lesion or within 2 mm of a bifurcation, moderate to heavy calcification, visible thrombus, left ventricular ejection fraction less than 30% or hypersensitivity to aspirin, clopidogrel, heparin, cobalt, chromium, nickel, tungsten, everolimus, polymer coating or contrast were excluded. The angiographic results at 6 months and 1 year are shown in Table 2 and clinical results up to 4 years in Table 3 [58–60]. In summary, this trial found significantly lower late lumen loss, percentage diameter stenosis and rates of binary angiographic restenosis at 6 and 12 months with the EES when compared with the BMS. Since this study was powered for angiographic outcomes (primary outcome: in-stent late lumen loss), any differences in clinical outcomes did not reach statistical significance. There were no cases of stent thrombosis as defined by the Academic Research Consortium criteria [61].

SPIRIT II randomized trial

This was a multicenter trial (28 centers in Europe, India and New Zealand) of 300 patients randomized 3:1 to EES (n = 223) versus PES (n = 77). The primary end point was late lumen loss after 6 months. The trial was powered to demonstrate noninferiority of the EES. More complex patients and lesions were permitted compared with SPIRIT FIRST; the patients could have up to two *de novo* lesions in different arteries, the reference vessel diameter had to be between 2.5 and 4.25 mm, and lesion length of no more than 28 mm. Patients with an acute myocardial infarction within 3 days, left ventricular ejection fraction of less than 30%, aorto-ostial or left main lesion, heavy calcification, visible thrombus or hypersensitivity reaction as defined in SPIRIT FIRST were excluded [62]. The angiographic and clinical results of the SPIRIT II trial are shown in Tables 4 & 5: the EES had lower short-term late lumen loss, percent diameter stenosis and rates of binary angiographic restenosis compared with the PES. Analysis of the 6-month angiographic data confirmed the benefit of the EES across all subgroups (Figure 5) [63]. At 2 years, in-stent angiographic late loss had significantly increased in EES to 0.33 ± 0.37 mm, whereas the late loss in the PES arm remained unchanged (from 0.33 ± 0.32 mm to 0.34 ± 0.34 mm). Nevertheless, after 2 years, despite this increase in late loss in the EES cohort, clinical events were nonsignificantly lower than the PES cohort [64].

SPIRIT III randomized US trial

This US trial recruited 1002 patients who were randomized 2:1 to EES (n = 669) versus PES (n = 333). Patients with a maximum of two *de novo* lesions, each in a different epicardial vessel, were allowed. The lesion criteria for enrollment were a diameter of 2.5–3.75 mm and length of no more than 28 mm. The primary end point was in-segment late lumen loss at 8-month follow-up angiography. The angiographic results confirmed the findings in SPIRIT II (Table 4). Furthermore, EES resulted in a significant reduction in the secondary end point of composite major adverse cardiac events (cardiac death, myocardial infarction or target lesion revascularization) both at 9 months (4.6 vs 8.1%; relative risk: 0.56; 95% CI: 0.34–0.94; p = 0.03) and at 1 year (6.0 vs 10.3%; relative risk: 0.58; 95% CI: 0.37–0.90; p = 0.02) (Table 5) [65]. A pooled analysis of 9-month clinical events in SPIRIT II and III are shown in Figures 6 & 7. Overall, the EES was associated with significant reductions in TLR,

Table 4. Angiographic results from the SPIRIT II and III trials.

Trial	Time	Late lumen loss (mm)		Diameter stenosis (%)		Binary angiographic restenosis (%)	
		EES	*BMS*	*EES*	*BMS*	*EES*	*BMS*
In-stent							
SPIRIT II	6 months	0.12 ± 0.29‡	0.37 ± 0.38	16 ± 10‡	21 ± 12	1.3	3.5
SPIRIT II	24 months	0.33	0.34	19	19	2.1	2.9
SPIRIT III	8 months	0.16 ± 0.41*	0.30 ± 0.53	5.9 ± 16.4*	10.3 ± 21.4	2.3*	5.7
In-segment							
SPIRIT II	6 months	0.07 ± 0.33	0.15 ± 0.38	24 ± 12*	27 ± 13	3.4	5.8
SPIRIT II	24 months	0.21	0.17	NA	NA	5.2	8.6
SPIRIT III	8 months	0.14 ± 0.39*	0.26 ± 0.46	18.8 ± 14.4*	22.8 ± 16.4	4.7	8.9

*$p < 0.05$ versus paclitaxel-eluting stent.
‡$p < 0.001$ versus paclitaxel-eluting stent.
§Analysis per lesion, intent to treat.
BMS: Bare-metal stent; EES: Everolimus-eluting stent; NA: Not applicable.
Data from [62,64,65].

TVR and composite major adverse cardiac events ([MACE]: cardiac death, nonfatal myocardial infarction or TLR) with no difference in safety end points, including death, myocardial infarction and stent thrombosis compared with PES.

Ongoing & future trials

SPIRIT IV

This US randomized trial commenced enrollment in August 2006. Patients with up to three *de novo* lesions (maximum two per vessel) were permitted. In total, 3690 patients have been randomized 2:1 to EES (n = 2640) versus PES (n = 1230). The lesion length had to be no greater than 28 mm and of diameter 2.5–4.25 mm. Enrollment for this trial has now been completed.

SPIRIT V

Starting recruitment in November 2006, this international study consists of two arms. In the diabetic randomized arm, 325 patients were randomized 2:1 to EES versus PES. A further 2700 patients have been recruited into the nonrandomized multinational registry arm, including sites in Europe, Middle East, South Africa, New Zealand, Canada and Asia. The 30-day results have been presented [66]. The registry included 30% diabetics, 42% with multivessel disease and 33% with unstable angina. The mean lesion length was 15.6 mm. Device success was 99%, with procedural success of 98%. After 30 days, all-cause mortality was 0.5% with MACE (all-cause death, MI, or TVR) of 2.6%. Further results will be available after 1 year and then annually to 5 years.

SPIRIT V women

This trial consists of two arms: 450 patients will be randomized 2:1 to EES versus SES. A further 1550 women will be recruited into the nonrandomized registry arm. Patient recruitment started in July 2007 and is ongoing.

Resolute III all-comers trial

This is a randomized European trial comparing the Medtronic Zotarolimus-eluting Endeavor Resolute stent with the Xience V EES. A total of 2300 patients have been randomized 1:1 to the ZES or EES. This 'real-world' trial has broad inclusion criteria, including patients with ST-elevation myocardial infarction and a vessel reference diameter of 2.25–4.0 mm. The only exclusion criteria are pregnancy, a known intolerance or allergy to any of the stent component materials or radiopaque contrast or planned surgery within 6 months of enrollment. In total, 20% of patients are scheduled for angiographic follow-up at 13 months (after the 12-month primary clinical end point) with a further subgroup also undergoing optical coherence tomography follow-up to assess stent strut apposition and coverage in addition to standard volumetric measurements (minimum lumen area, lumen area/volume and stent area/volume). This trial has recently completed recruitment, with 1-year clinical results expected towards the end of 2009.

Xience V stent evaluated at Rotterdam Cardiology Hospital (X-SEARCH) registry

Since 1 March 2007, our institution commenced the use of EES (Xience V; Abbott Vascular) as the default strategy for every percutaneous coronary intervention [67]. Between 1 March and 31 October 2007, 649 consecutive patients presenting with *de novo* lesions were treated exclusively with EES. These patients were compared with three historical cohorts of consecutive patients from the RESEARCH and T-SEARCH registries; 450 patients treated with BMSs between December 2002 and April 2003, 508 with SES treated from April to October 2002 and 576 with PES treated February to September 2003 [29,68].

The patients in the EES cohort were significantly older than the historical controls (64 ± 12 years old for EES patients vs 61 ± 11 BMS, 61 ± 11 SES and 62 ± 11 PES; $p < 0.05$) and more often presented with ST-elevation myocardial infarction (39% EES vs 18% BMS, 18% SES and 21% PES; $p < 0.001$). The

left main stem was also more frequently treated in the EES group (7.4% EES vs 1.7% BMS, 2.2% SES and 3.2% PES; $p < 0.05$) and the total stented length was longer (57 ± 26 mm EES vs 30 ± 20 mm BMS, 39 ± 28 mm SES and 43 ± 31 mm PES; $p < 0.001$). After 1 month, the crude all-cause mortality rate was higher in the EES group (4.2 vs 2.0% BMS, 1.6% SES and 2.1% PES; $p = 0.02$). Multivariable logistic regression to account for differences in baseline and angiographic variables indicated no difference in adjusted mortality between SESs (adjusted hazard ratio [HR]: 1.27; 95% CI: 0.34–4.73) and PESs (adjusted HR: 1.69; 95% CI: 0.58–4.97) when compared with EESs. The BMS group had a higher adjusted mortality (adjusted HR: 4.67; 95% CI: 1.45–15.01). The multivariable analysis suggested a higher incidence of adjusted composite MACE (all-cause death, nonfatal myocardial infarction or target vessel revascularization) rates in the historical cohorts (BMS adjusted HR: 2.52; 95% CI: 1.24–5.10; SES adjusted HR: 1.80; 95% CI: 0.89–3.61; PES adjusted HR: 1.99; 95% CI: 1.07–3.71). Further follow-up is planned at 6 and 12 months, then annually, and will provide essential real-world data on the use of these stents in high-risk complex patients.

Table 5. Cumulative hierarchical incidence of adverse clinical events in the SPIRIT II and III trials.

Event	SPIRIT II (6 months)		SPIRIT III (12 months)		SPIRIT II (24 months)	
	EES (%)	*PES (%)*	*EES (%)*	*PES (%)*	*EES (%)*	*PES (%)*
Cardiac death	0	1.3	0.8	0.9	0.5	1.4
Myocardial infarction	0.9	2.6	2.8	4.1	2.8	4.1
Target lesion revascularization	1.8	2.6	3.4	5.6	3.3	5.5
Major adverse cardiac events*	2.7	6.5	6.0‡	10.3	6.6	11.0
Stent thrombosis (per protocol)	0.5	1.3	0.8	0.6	0.9	1.4
Stent thrombosis (ARC defined definite or probable)	0.0	1.3	1.1	0.6	0.9	1.4

*Death, myocardial infarction or target lesion revascularization.
‡$p < 0.05$ versus PES.
ARC: Academic Research Consortium; EES: Everolimus-eluting stent; PES: Paclitaxel-eluting stent.
Data from [64].

Other second-generation drug-eluting stents

Endeavor™

The Endeavor™ (Medtronic Vascular, Santa Rosa, CA, USA) ZES is also currently commercially available in both Europe and the USA. This uses the CoCr Driver stent platform loaded with a permanent 'biomimetic' phosphorylcholine polymer and the sirolimus analogue, zotarolimus (70% released over 30 days). The 4-year results of the first-in-man trial have been published, with subsequent randomized trials against BMSs and SESs [69–71]. Ongoing trials include the Endeavor IV trial comparing ZESs with PESs. However, there are suggestions that the relatively high late lumen loss with this stent (0.61 ± 0.44 mm in Endeavor I) translates into higher angiographic restenosis and TLR rates [72,73]. This stent is being replaced by the Endeavor Resolute (Medtronic Vascular, Santa Rosa, CA, USA) ZES, which exhibits a much lower late lumen loss (4-month angiographic results with late lumen loss of 0.12 mm in the first-in-man trial) [74]. This stent also uses the Driver CoCr stent platform, but uses the Biolinx polymer: a blend of three different polymers (the hydrophobic C10 polymer to control drug release, the biocompatible and hydrophilic C19 polymer, and polyvinyl pyrrolidone to allow an early burst of drug release). Within 60 days, 85% of the drug is released; the remainder is released within 180 days. Porcine studies demonstrated no difference in inflammation or healing between the Endeavor Resolute and bare-metal Driver stent. This stent is currently being evaluated in comparison with the Xience V EES in the Resolute III trial, as already mentioned.

Biomatrix

The Biomatrix biolimus-eluting stent ([BES] Biosensors International, Singapore) consists of a biolimus a9/biodegradable (PLA) polymer-coated stainless steel stent where approximately

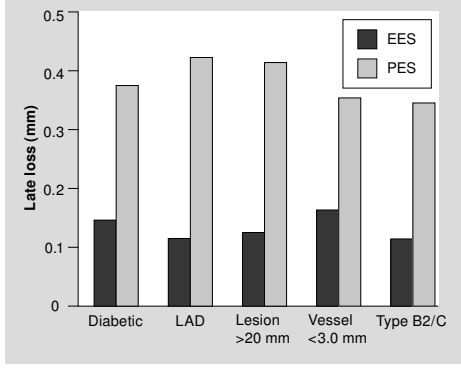

Figure 5. Subgroup analysis from the SPIRIT II trial.
EES: Everolimus-eluting stent; LAD: Left anterior descending artery; PES: Paclitaxel-eluting stent.

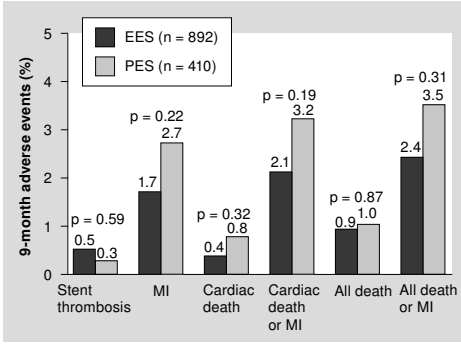

Figure 6. Safety clinical end points from 9-month pooled analysis of SPIRIT II and III. Rates of stent thrombosis, myocardial infarction, cardiac death, cardiac death or myocardial infarction, all-cause death and all-cause death or myocardial infarction. All percentages are based upon an intention-to-treat analysis. p-value based on logrank and not adjusted for multiple comparisons.
EES: Everolimus-eluting stent; MI: Myocardial infarction; PES: Paclitaxel-eluting stent;

70% of the drug is eluted over 30 days followed by sustained release with polymer degradation over several months [75,76]. The drug is applied to the abluminal surface only. The 6-month angiographic results of the Biomatrix First-In-Man study showed a late lumen loss of 0.26 versus 0.74 mm compared with the BMS platform. The all-comer LEADERS trial recently evaluated the outcomes of 1707 patients randomized to the BES or the Cypher SES [77]. This trial uniquely had minimal exclusion criteria (known allergy to stent components or antiplatelet therapy, planed surgery within 6 months, pregnancy, participation in another trial or the inability to give informed consent) thereby reflecting everyday clinical practice: approximately 80% of all patients received a stent for 'off-label' use. There were no significant differences in any of the pre specified end points, including cardiac death, myocardial infarction, clinically driven TVR, stent thrombosis and late lumen loss. The overall rates of the composite clinical end point were 9% for BES versus 11% in SESs. The overall all-cause mortality rates were 2.6 and 2.8% after 9 months, which seem acceptable for the high-risk population studied.

Expert commentary

The Xience V thin strut CoCr EES is a second-generation drug-eluting stent in which all aspects of the stent design are an improvement on the first-generation DESs. The stent platform allows great deliverability to the target lesion, even in tortuous vessels; the polymer is biocompatible with a long history of clinical use in surgical sutures and the drug has proven ability to suppress neointimal formation to an equivalent degree reported with sirolimus and more than paclitaxel, resulting in lower rates of revascularization compared with the Taxus PES. Nevertheless, long-term follow-up data on patients treated with the Xience V stent is currently limited and although the stent appears effective, no firm conclusions regarding improved safety compared with first-generation DESs can be made as yet.

Five-year view

Within 5 years, the results of the large-scale (n = 3690) SPIRIT IV randomized trial will be known. Together with long-term data from SPIRIT FIRST, II and III, we will have data not only on the clinical efficacy but also long-term safety in randomized trial patients. Long-term data from RESOLUTE III and the X-SEARCH registry will complement the pivotal randomized trial data by providing similar information on unselected higher-risk patients. It is very likely that during the next 5 years, we will see more second- and third-generation DESs with ever increasing biocompatibility and safety profiles being investigated and released commercially. Furthermore, a fully biodegradable EES has recently been under investigation; although not currently suitable for everyday use, it is possible that this type of stent may be released commercially [78].

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

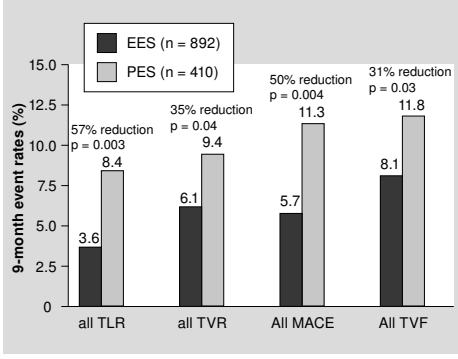

Figure 7. Revascularization end points from the pooled analysis of SPIRIT II and III. Rates of target lesion revascularization, target vessel revascularization, major adverse cardiac events and target vessel failure. End points shown include ischemia-driven and non-ischemia-driven events. All percentages are based upon an intention-to-treat analysis. p-value based on logrank and not adjusted for multiple comparisons.
EES: Everolimus-eluting stent; MACE: Major adverse cardiac events (defined as cardiac death, myocardial infarction or target lesion revascularization); PES: Paclitaxel-eluting stent; TLR: Target lesion revascularization; TVF: Target vessel failure; TVR: Target vessel revascularization.

Key issues

- Concerns have been raised regarding the performance of first-generation drug-eluting stents.
- The Xience V™ everolimus-eluting stent represents a technological improvement over the first-generation drug-eluting stents.
- The Xience V everolimus-eluting stent has proven ability to suppress neointimal hyperplasia to a similar degree to sirolimus and its analogues.
- Compared with the first-generation Taxus™ paclitaxel-eluting stent in the SPIRIT II and III trials, the Xience V everolimus-eluting stent demonstrated angiographic superiority with a decreased need for repeat revascularization, although no difference in safety was demonstrated.
- Registry data on unselected patients confirms the short-term safety of the Xience V stent.
- Results of a large-scale randomized trial (SPIRIT IV) and the all-comers RESOLUTE III trial together with long-term follow-up of SPIRIT FIRST, II and III randomized trials and the X-SEARCH registry will provide further information on the safety and efficacy of the device.

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CHAPTER 29

Randomized comparison of everolimus- and paclitaxel-eluting stents: pooled analysis of the 2-year clinical follow-up from the SPIRIT II and III trials

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Eur Heart J 2010;31:1071-8.

Randomized comparison of everolimus- and paclitaxel-eluting stents: pooled analysis of the 2-year clinical follow-up from the SPIRIT II and III trials

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Received 17 April 2009; revised 27 November 2009; accepted 7 December 2009; online publish-ahead-of-print 29 January 2010

Aims	To investigate the clinical impact of the following observations in the randomized SPIRIT II and III trials: an incremental increase in in-stent neointima between 1 and 2 years with the everolimus-eluting stent (EES) but not with the paclitaxel-eluting stent (PES) in SPIRIT II; a tendency of lower stent thrombosis in EES than in PES among those who first discontinued a thienopyridine after 6 months.
Methods and results	A pooled analysis was performed using the 2-year clinical data from the SPIRIT II and III trials randomizing a total of 1302 patients with *de novo* coronary artery lesions either to EES or to PES. Inclusion and exclusion criteria were comparable between two trials. Major adverse cardiac event (MACE) was defined as cardiac death, myocardial infarction, or ischaemia-driven target lesion revascularization (TLR). At 2 years, MACE rates were 7.1% in EES vs. 12.3% in PES, respectively (log-rank $P = 0.0014$), without late increase in TLR. Among those who first discontinued a thienopyridine after 6 months, Academic Research Consortium (ARC) definite or probable stent thrombosis was 1.1% in EES vs. 1.3% in PES ($P = 1.00$).
Conclusion	The benefits of EES in reducing TLR were robust between 6 months and 2 years. No significant difference in the thrombosis rate among those who first stopped a thienopyridine after 6 months was observed.

Keywords Everolimus-eluting stent • Paclitaxel-eluting stent • Randomized trial

Introduction

Polymer-based sirolimus-eluting stents (SESs) and paclitaxel-eluting stents (PESs) have both been shown to significantly reduce angiographic restenosis and recurrent ischaemia necessitating repeat revascularization, compared with bare-metal stents.[1] However, the occurrence of late stent thrombosis is a concern of this technology.[2–5]

Everolimus is an anti-proliferative agent that inhibits cell proliferation by inducing cell cycle arrest in the late G1 stage of the cell cycle.[6] It is used as immunosuppressive therapy following heart and other solid organ transplantation, and has been shown to delay cardiac allograft vasculopathy.[7] With the goal of further enhancing the safety and efficacy of drug-eluting stent (DES), an everolimus-eluting stent (EES) has been designed in which the anti-proliferative agent is released from a thin (7.8 μm), non-adhesive, durable, biocompatible fluoropolymer coated onto a low profile [0.0032 in. (81.3 μm) strut thickness], flexible cobalt chromium stent. Pre-clinical studies have shown more rapid endothelialization and reduced expression of platelet-endothelial cell adhesion

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molecule-1 and increased secretion and mRNA levels of vascular endothelial growth factor at 14 days with EES compared with both SES and PES.[8]

The clinical efficacy of EES has been tested in the several randomized trials.[9] The SPIRIT II trial ($n = 300$) demonstrated not only non-inferior but also superior in-stent late loss at 6 months with EES compared with PES[10–12] The subsequent SPIRIT III trial ($n = 1002$)[13] demonstrated a significant reduction in the primary angiographic endpoint of in-segment late loss with EES compared with PES at 8 months and non-inferiority to PES for the clinical endpoint of target vessel failure [TVF; cardiac death, myocardial infarction (MI) or ischaemia-driven target vessel revascularization (ID-TVR)] at 1 year and resulted in a significant reduction in major adverse cardiac event (MACE).[14] Nevertheless, certain issues remain unclear. Although angiographic late loss in the diabetic population was less with EES than with PES at 6 and 8 months in the SPIRIT II and III trials, respectively, the TVF or MACE rates were not reduced with EES.[13] Secondly, in the SPIRIT III trial among those who discontinued a thienopyridine after 6 months, the rates of protocol-defined stent thrombosis tended to be lower in EES-treated patients than in PES-treated patients (EES 0.4% vs. PES 2.6%, $P = 0.10$). Thirdly, 2-year follow-up of the SPIRIT II trial suggested late angiographic catch-up of in-stent neointimal hyperplasia or per cent stent volume obstruction (VO) by intravascular ultrasound (IVUS) in EES but not in PES.[15] The impact of these findings on clinical outcome is still uncertain.

To further explore these issues, we performed a pooled analysis of the 2-year clinical data from the SPIRIT II and III trials to examine the comparative long-term outcomes of EES and PES. Poolability was justified on the basis of comparable inclusion and exclusion criteria with similar baseline and angiographic characteristics and endpoint definitions between the two studies.

Methods

Protocol entry criteria

The designs of the SPIRIT II and III trials have been described previously.[10,13] In brief, both were prospective, multicentre, single-blind, randomized controlled clinical trials in which 300 and 1002 patients (in SPIRIT II and III, respectively) were randomized to receive the EES (XIENCE^{TM} V, Abbott Vascular, Santa Clara, CA, USA) or the PES (TAXUS$^{®}$ EXPRESS2^{TM}, Boston Scientific, Natick, MA, USA) (see Supplementary material online, Appendix for site names). In Spirit II, both TAXUS$^{®}$ Express2^{TM} (73% of lesions) and TAXUS$^{®}$ Liberte$^{®}$ (27% of lesions) were used as control. Patients were eligible for the study if they were aged 18 years and above, with a diagnosis of stable or unstable angina or inducible ischaemia. Additional key eligibility criteria were the presence of either one or two *de novo* native coronary artery lesions (maximum one lesion per epicardial coronary artery) with a diameter stenosis of $\geq$50 and $<$100%, with a lesion length of $\leq$28 mm and a reference vessel diameter of 2.5–4.25 and 2.5–3.75 mm in SPIRIT II and III, respectively. Patients were excluded from enrolment if they presented with acute or recent MI, had a left ventricular ejection fraction $<$30%, restenotic lesions or lesions located in the left main coronary artery, were awaiting a heart transplant, or had a known hypersensitivity or contraindication to aspirin, heparin, bivalirudin, clopidogrel or ticlopidine, cobalt, chromium, nickel, tungsten, everolimus, paclitaxel, acrylic, and fluoropolymers. Angiographic exclusion criteria were target lesion(s) in aorto-ostial, left main stem, within 2 mm of the origin of the left anterior descending or left circumflex coronary artery, bifurcation lesions with either the sidebranch $>$50% stenosed or $>$2 mm in diameter or requiring pre-dilatation, lesion located within a bypass graft, lesions with heavy calcification, or a visible thrombus within the target vessel.

The studies were approved by the Ethics Committee at each participating institution, and eligible patients gave their written informed consent. Following the confirmation of angiographic criteria, telephone randomization was performed in randomly alternating blocks of four and eight patients in SPIRIT II, or three and six patients in SPIRIT III using an automated voice response system, stratified by the presence of diabetes, planned dual vessel treatment, and study site. Protocol-specified angiographic follow-up was planned in all patients at 6 months for SPIRIT II and at 8 months in a subgroup of 564 SPIRIT III patients. Two-year angiographic follow-up was planned in a predefined subgroup of 152 patients from the SPIRIT II trial and not in the SPIRIT III trial.

Medication administration and clinical follow-up

Patient preparation and pharmaceutical treatment during the procedure were to be in accordance with standard hospital practice.

Table 1 Patient baseline characteristics

	Everolimus-eluting stent	Paclitaxel-eluting stent
Number of patients	892	410
Age in years (mean ± SD)	62.9 ± 10.5	62.6 ± 10.1
Male (%)	70.3	68.2
Diabetes (%)	27.9	27.1
Treated with insulin (%)	7.1	5.7
Hypertension (%)	74.0	72.3
Hypercholesterolaemia (%)	72.8	72.1
Current smoker (%)	25.3	23.8
Prior MI (%)	23.7	19.3
Unstable angina (%)	20.8	26.5
Number of lesions	1032	474
LAD (%)	41.1	43.8
LCX (%)	28.0	26.4
RCA (%)	30.7	29.6
LMCA (%)	0.1	0.2
RVD in mm [median (IQ range)]	2.73 (2.42, 3.05)	2.77 (2.43, 3.04)
MLD in mm [median (IQ range)]	0.87 (0.58, 1.15)	0.89 (0.58, 1.18)
%DS [median (IQ range)]	66.2 (57.0, 77.2)	66.9 (56.2, 77.6)
Lesion length in mm [median (IQ range)]	12.9 (10.0, 17.6)	13.0 (10.5, 17.2)

There were no significant differences between the groups. SD, standard deviation; IQ, inter-quartile; MI, myocardial infarction; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; LMCA, left main coronary artery; RVD, reference vessel diameter; MLD, minimal luminal diameter; %DS, per cent diameter stenosis.

The use of GPIIb/IIIa inhibitors was left to the discretion of the physician. All patients were to receive 75 mg clopidogrel for a minimum of 6 months and ≥75 mg of aspirin daily for a minimum of 1 or 5 years for Spirit II and III, respectively, following the procedure; a longer duration of clopidogrel use was permitted per the discretion of the treating physician. Clinical follow-up was scheduled at 1, 6 (9 months only in SPIRIT III), 12 months, 2 years and then yearly through 5 years.

Data management

Clinical study monitors verified 100% of case report form data on-site. For each study, an independent committee blinded to treatment allocation adjudicated all MACEs after review of the original source documentation. A clinical events committee blinded to randomization performed a *post hoc* adjudication of stent thrombosis using the Academic Research Consortium (ARC) definitions.[16] Angiographic and IVUS analyses were performed by independent core laboratory technicians blinded to treatment assignment and clinical outcomes using validated methods as described previously. A Data Safety and Monitoring Committee periodically reviewed blinded safety data, each time recommending the studies to continue without modification.

Clinical endpoints and definitions

Ischaemia-driven target vessel (or lesion) revascularization [ID-TVR (ID-TLR)] was defined as a revascularization at the target vessel (or lesion) associated with an angiographic diameter stenosis ≥50% by core lab quantitative coronary angiography (QCA) with a positive functional ischaemia study (exercise testing, fractional flow reserve, or coronary flow reserve) or ischaemic symptoms; or a diameter stenosis ≥70% by core lab QCA with or without ischaemic symptoms or a positive functional study. Target vessel failure was defined as the occurrence of either cardiac death, MI, or ID-TVR. Major adverse cardiac event was defined as the occurrence of either cardiac death, MI, or ID-TLR. Myocardial infarction was defined as either the development of new pathologic Q-waves ≥0.4 s in duration in two or more contiguous leads, or an elevation of creatine phosphokinase levels to >2.0 times normal with positive creatine phosphokinase-MB. Stent thrombosis was prospectively defined by the study protocols as an acute coronary syndrome with angiographic evidence of thrombus within or adjacent to a previously treated target lesion, or in the absence of angiography, any unexplained death or acute MI with ST-segment elevation or new Q-waves in the distribution of the target lesion occurring within 30 days post-procedure. Stent thrombosis was also categorized in a *post hoc* analysis according to the definitions proposed by the ARC for definite, probable, and possible stent thrombosis.[16]

Statistical methods

Continuous variables that were normally distributed are presented as mean ± SD and compared using the *t*-test. Continuous variables that did not distribute normally are presented as median (lower and upper quartile range) and compared by the Wilcoxon rank sum test. Categorical variables are presented as percentages and were compared using Fisher's exact test. This pooled analysis of SPIRIT II and III was *post hoc*. All analyses are by intention-to-treat, utilizing all

Table 2 Event rates at 2 years

	EES (%)	PES (%)	Hazard ratio	95% CI	Log-rank *P*-value
MACE (cardiac death, MI, ID-TLR)	7.1	12.3	0.55	0.38–0.80	0.0014
TVF (Cardiac Death, MI, ID-TVR)	10.4	14.7	0.69	0.50–0.96	0.027
Non-hierarchical					
All death	2.4	3.3	0.72	0.36–1.45	0.36
Cardiac death	0.9	1.3	0.72	0.24–2.20	0.56
Any MI	3.1	5.6	0.55	0.31–0.96	0.034
Q-wave MI	0.3	0.5	0.67	0.11–4.03	0.66
Non-Q-wave MI	2.7	5.0	0.54	0.30–0.97	0.037
Any ischaemia-driven TLR	4.1	6.8	0.59	0.36–0.96	0.031
CABG	0.3	0.5	0.67	0.11–4.03	0.66
PCI	3.9	6.3	0.60	0.36–0.99	0.044
All TLR[a]	5.3	10.1	0.51	0.34–0.77	0.0012
CABG	0.3	0.8	0.45	0.09–2.23	0.31
PCI	5.0	9.6	0.52	0.34–0.79	0.0017
Any ischaemia-driven TVR	7.9	9.9	0.77	0.52–1.13	0.18
CABG	1.2	1.3	0.90	0.31–2.63	0.85
PCI	6.9	8.9	0.74	0.50–1.12	0.15
All TVR[b]	9.2	12.7	0.71	0.50–1.01	0.054
CABG	1.5	1.3	1.17	0.42–3.29	0.76
PCI	7.8	12.2	0.63	0.44–0.91	0.012

Event rate was estimated by the Kaplan–Meier method. EES, everolimus-eluting stent; PES, paclitaxel-eluting stent; CI, confidence interval; MACE, major adverse cardiac event; MI, myocardial infarction; ID, ischaemia-driven; TLR, target lesion revascularization; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; TVR, target vessel revascularization.

[a]All TLR includes both ischaemia-driven and non-ischaemia-driven TLR.

[b]All TVR includes both ischaemia-driven and non-ischaemia-driven TVR.

patients randomized in the study, regardless of the treatment actually received. Patients lost to follow-up in whom no event had occurred before the follow-up windows were not included in the denominator for calculations of binary endpoints. Relative risk was calculated as the event rate of EES divided by the event rate of PES arm. The incidence of events over time was studied with the use of the Kaplan–Meier method, whereas log-rank tests were applied to evaluate differences between the treatment groups. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. In addition, a landmark analysis was conducted at 12 months following randomization. Outcomes between 12 and 24 months were then estimated using the Kaplan–Meier method and compared with the log-rank test. Hazard ratios (HRs) of EES vs. PES group were calculated by using Cox's proportional hazard model. To search for the interaction between the subgroup and treatment effect, the logistic regression model was constructed including treatment, subgroup, and treatment*subgroup and *P*-values were calculated by the Wald χ^2 statistics. A two-sided $\alpha = 0.05$ was used for all statistical tests. All statistical analyses were performed by SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

Results

Baseline clinical and angiographic characteristics were comparable between groups as shown in *Table 1*. Of the 892 patients randomized to the EES arm, 854 patients were subsequently treated with EES, whereas 386 of the 410 patients assigned to PES treatment actually received PES. In the SPIRIT II trial, 2-year follow-up was completed in 94.2% (210/223) and 93.5% (72/77) of the EES and PES arms, respectively. In the SPIRIT III trial, 2-year follow-up was completed in 93.6% (626/669) and 89.8% (299/333) of the EES and PES cohorts, respectively. In total, 93.7% (836/892) of the EES patients and 90.5% (371/410) of the PES patients completed the 2-year follow-up. The countries or areas with low follow-up rate (≤85%) have enrolled a relatively small number of patients (≤34 patients).

Clinical outcomes

Kaplan–Meier estimates of TVF, MACE rate, and the components through 758 days are presented in *Table 2*; event rates from 1 to 2 years are shown in *Table 3*. Kaplan–Meier estimates of survival with events are depicted in *Figure 1*. At 2 years, TVF rates were 10.4% for EES vs. 14.7% for PES [HR (95% CI) = 0.69 (0.50, 0.96)]. Major adverse cardiac event rates were 7.1% for EES vs. 12.3% for PES [HR (95% CI) = 0.55 (0.38–0.80)]. The observed reduction in TVF and MACE rates in patients randomized to EES compared with PES were driven by lower rates of non-Q-wave MI (2.7 vs. 5.0%, log-rank $P = 0.037$) and TLR by PCI (3.9 vs. 6.3%, log-rank $P = 0.044$), with no differences in the rates of Q-wave MI (0.3 vs. 0.5%, respectively, log-rank $P = 0.66$) or cardiac death (0.9 vs. 1.3%, respectively, $P = 0.56$). Stent thrombosis rates were comparable by both the pre-specified protocol and

Table 3 Event rate between 1 and 2 years

	EES (%)	PES (%)	Hazard ratio	95% CI	Log-rank *P*-value
MACE (cardiac death, MI, ID-TLR)	2.0	2.6	0.72	0.33–1.56	0.40
TVF (cardiac death, MI, ID-TVR)	3.1	4.2	0.74	0.39–1.39	0.35
Non-hierarchical					
All death	1.2	1.6	0.74	0.27–2.04	0.56
Cardiac death	0.4	0.3	1.33	0.14–12.78	0.80
Any MI	0.8	1.7	0.51	0.17–1.51	0.22
Q-wave MI	0.1	0.3	0.45	0.03–7.12	0.56
Non-Q-wave MI	0.7	1.4	0.52	0.16–1.71	0.28
Any ischaemia-driven TLR	1.1	1.1	0.86	0.29–2.52	0.79
CABG	0.1	0.5	0.22	0.02–2.46	0.18
PCI	1.1	0.6	1.44	0.40–5.23	0.58
All TLR[a]	1.1	0.9	1.01	0.36–2.86	0.99
CABG	0.1	0.5	0.22	0.02–2.45	0.18
PCI	1.1	0.6	1.26	0.41–3.92	0.68
Any ischaemia-driven TVR	2.5	2.6	0.87	0.42–1.79	0.70
CABG	0.4	0.8	0.45	0.09–2.21	0.31
PCI	2.2	1.7	1.08	0.48–2.46	0.85
All TVR[b]	2.6	2.1	1.13	0.53–2.44	0.75
CABG	0.5	0.8	0.60	0.13–2.66	0.49
PCI	2.1	1.8	1.11	0.49–2.50	0.81

Event rates were calculated using the Kaplan–Meier method. EES, everolimus-eluting stent; PES, paclitaxel-eluting stent; CI, confidence interval; MACE, major adverse cardiac event; MI, myocardial infarction; ID, ischaemia-driven; TLR, target lesion revascularization; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; TVR, target vessel revascularization.

[a]All TLR includes both ischaemia-driven and non-ischaemia-driven TLR.

[b]All TVR includes both ischaemia-driven and non-ischaemia-driven TVR.

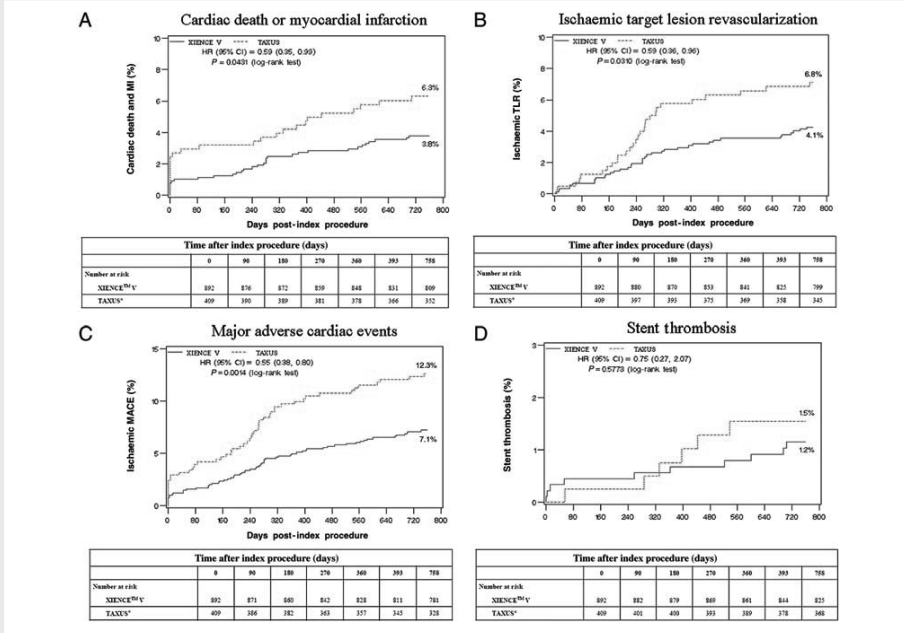

Figure 1 Kaplan–Meier survival curves stratified according to treatment arm of everolimus- or paclitaxel-eluting stent. (*A*) The composite of cardiac death or myocardial infarction, (*B*) ischaemic target lesion revascularization, (*C*) the composite of cardiac death, any myocardial infarction, or ischaemia-driven target lesion revascularization (*D*) stent thrombosis (per-protocol). CI, confidence interval; HR, hazard ratio.

post hoc ARC definitions (*Table 4*). The length of thienopyridine therapy was not different between EES and PES groups (487.4 ± 241.4 vs. 500.0 ± 243.7 days, $P = 0.38$). When stratified by the timing of thienopyridine discontinuation, the incidence of ARC-defined stent thrombosis (definite or probable) did not significantly vary with the two stent types at any time period (discontinuation before 6 months: EES 1.8% vs. PES 3.8%, $P = 0.59$; discontinuation between 180 and 758 days EES 1.1% vs. PES 1.3%, $P = 1.00$; never discontinued 0.8 vs. 0.6%, $P = 1.00$). The *P*-values for interaction of treatment (EES or PES) by first discontinuation of thienopyridine before 180 days (yes or no), treatment by first discontinuation between 180 and 758 days, and treatment by never discontinued were 0.83, 0.88, and 0.48, respectively.

Subgroup analysis

Regression analysis was performed to explore whether or not the reduction of MACE at 2 years with EES compared with PES was consistent across important subgroups. As shown in *Figure 2*, the treatment effect of EES compared with PES was consistent in all subgroups and was mainly in favour of EES, except possibly for patients with diabetes, in whom the frequency of MACE was comparable between EES and PES. Among patients with diabetes mellitus, the 2-year MACE rates were 11.3% with EES compared with 7.2% with PES [RR (95% CI) = 1.56 (0.70–3.46)], whereas in those without diabetes, the 2-year MACE rates were 5.9% with EES compared with 15.5% with PES [RR (95% CI) = 0.38 (0.25–0.58)], with a *P*-value for interaction of 0.002. In diabetic patients, the increased MACE rate in EES is mainly driven by cardiac death (EES 2.1% vs. PES 0%) and ID-TLR (3.8 vs. 1.0%) hierarchically. As the sample size was small for most subgroups, caution should be used in the interpretation of these results and in drawing conclusions.

Discussion

In this pooled analysis of 2-year outcomes from the SPIRIT II and III trials, the use of EES compared with PES resulted in significant reductions in MI and ID-TLR. As seen in the event rate curves (*Figure 1*), the reduction in MI was due to fewer peri-procedural and late events, whereas the reduction in TLR was due to a reduction in restenosis-related events occurring mostly between 4 and 9 months. There were no significant differences between the two stent types in the early or late rates of death and stent thrombosis. Thus, considering composite measures of combined

Table 4 Stent thrombosis rates at 2 years

	EES (n = 892)	PES (n = 410)	Relative risk (95% CI)	P-value
ARC definition				
Acute stent thrombosis (<1 days)				
Definite	0.1% (1/892)	0.0% (0/407)	NC (NC)	1
Probable	0.0% (0/892)	0.0% (0/407)	NC (NC)	NA
Possible	0.0% (0/892)	0.0% (0/407)	NC (NC)	NA
Definite/probable	0.1% (1/892)	0.0% (0/407)	NC (NC)	1
Definite/probable/possible	0.1% (1/892)	0.0% (0/407)	NC (NC)	1
Subacute stent thrombosis (1–30 days)				
Definite	0.2% (2/890)	0.2% (1/407)	0.91 (0.08, 10.06)	1
Probable	0.0% (0/890)	0.0% (0/407)	NC (NC)	NA
Possible	0.0% (0/890)	0.0% (0/407)	NC (NC)	NA
Definite/probable	0.2% (2/890)	0.2% (1/407)	0.91 (0.08, 10.06)	1
Definite/probable/possible	0.2% (2/890)	0.2% (1/407)	0.91 (0.08, 10.06)	1
Late stent thrombosis (31–393 days)				
Definite	0.2% (2/872)	0.3% (1/394)	0.90 (0.08, 9.94)	1
Probable	0.1% (1/872)	0.5% (2/394)	0.23 (0.02, 2.48)	0.2301
Possible	0.5% (4/872)	0.5% (2/394)	0.90 (0.17, 4.91)	1
Definite/probable	0.3% (3/872)	0.8% (3/394)	0.45 (0.09, 2.23)	0.3826
Definite/probable/possible	0.8% (7/872)	1.3% (5/394)	0.63 (0.20, 1.98)	0.5315
Very late stent thrombosis (394–758 days)				
Definite	0.2% (2/841)	0.3% (1/372)	0.88 (0.08, 9.73)	1
Probable	0.2% (2/841)	0.5% (2/372)	0.44 (0.06, 3.13)	0.5906
Possible	0.5% (4/841)	0.3% (1/372)	1.77 (0.20, 15.78)	1
Definite/probable	0.5% (4/841)	0.8% (3/372)	0.59 (0.13, 2.62)	0.4444
Definite/probable/possible	1.0% (8/841)	1.1% (4/372)	0.88 (0.27, 2.92)	0.7643
Overall stent thrombosis (0–758 days)				
Definite	0.8% (7/847)	0.8% (3/376)	1.04 (0.27, 3.98)	1
Probable	0.4% (3/847)	1.1% (4/376)	0.33 (0.07, 1.48)	0.2111
Possible	0.9% (8/847)	0.8% (3/376)	1.18 (0.32, 4.44)	1
Definite/probable	1.2% (10/847)	1.6% (6/376)	0.74 (0.27, 2.02)	0.5889
Definite/probable/possible	2.1% (18/847)	2.4% (9/376)	0.89 (0.40, 1.96)	0.8333
Per-protocol				
Acute (<1 day)	0.1 (1/892)	0 (0/407)	NC	1
Subacute (1–30 days)	0.2 (2/890)	0 (0/407)	NC	1
Late (31–393 days)	0.3 (3/867)	0.8 (3/392)	0.45 (0.09–2.23)	0.38
Very late (394–758 days)	0.5 (4/837)	0.8 (3/372)	0.59 (0.13–2.63)	0.45
Overall stent thrombosis (0–758 days)	1.2 (10/838)	1.6 (6/374)	0.74 (0.27–2.03)	0.59

EES, everolimus-eluting stent; PES, paclitaxel-eluting stent; CI, confidence interval; NC, not calculatable.

safety and efficacy, both TVF and MACE were significantly reduced at 2 years by treatment with EES rather than PES. In addition, the current analysis suggested the following findings: (i) the hypothesis that EES is associated with fewer very late stent thrombosis than PES was not proven; (ii) the late increase in neointima from 6 months to 2 years in EES was not translated into an increase in clinical event rates; (iii) in the diabetic population, EES might have different treatment effects in comparison to PES.

Serial assessment of angiography and IVUS performed at 6 and 24 months in a subgroup of patients in SPIRIT II showed an increase in angiographic late loss and in-stent neointimal volume in the EES group when compared with the PES group.[15] Compared with 6-month QCA, 2-year QCA showed that in-stent late loss had significantly increased in EES from 0.17 ± 0.32 to 0.33 ± 0.37 mm, but was unchanged in the PES group (from 0.33 ± 0.32 to 0.34 ± 0.34 mm). With serial IVUS assessment, neointimal hyperplasia volume and %VO were significantly lower in EES than in PES at 6 months, whereas the differences became no longer significant at 2 years. Despite these results suggesting incremental increase in neointimal hyperplasia noted

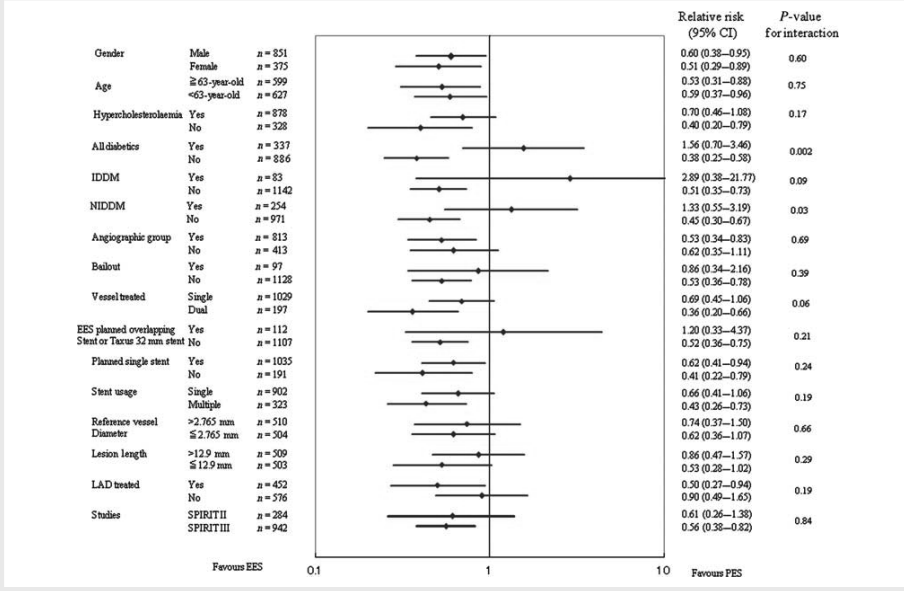

Figure 2 Subgroup analyses of the 2-year rates of major adverse cardiac events among patients randomized to receive the everolimus-eluting stent vs. the paclitaxel-eluting stent. Probability for interaction represents the likelihood for interaction between the variable and the relative treatment effect. CI, confidence interval; LAD, left anterior descending; IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; EES, everolimus eluting stent; PES, paclitaxel-eluting stent.

in EES but not in PES, the present study demonstrates from these two randomized trials that the ID-TLR rates at 2 years with EES are lower than with PES in the non-complex lesions enrolled in these studies.

Subgroup analysis of the combined populations of SPIRIT II and III raise the possibility that there may be a differential treatment effect of stent type according to diabetic status. In non-diabetic patients, a marked reduction in MACE was present with EES compared with PES, whereas in diabetic patients (both insulin-requiring and non-insulin-dependent diabetes mellitus), there were no significant differences in MACE between the two stent types. Of interest, in the SPIRIT II trial, the increase in luminal loss between 6 months and 2 years among EES-treated patients tended to be larger in the diabetic than in the non-diabetic cohort, although this difference did not reach statistical significance (diabetics 0.25 ± 0.43 mm vs. non-diabetics 0.14 ± 0.29 mm, $\Delta + 0.11$ mm, $P = 0.36$). The same trend was observed in %VO with IVUS: Δ %VO in diabetics was 3.76 ± 6.63, whereas Δ %VO in non-diabetics was 2.12 ± 6.22 ($P = 0.44$). Theoretically, the different mechanisms of action of the drugs in terms of inhibition of neointimal proliferation could explain the disparity in outcome of EES and PES in the diabetic patients. Insulin exhibits an up-regulation in the PI3-kinase signal transduction pathway which involves phosphorylation and activation of the mammalian target of rapamycin (mTOR).[17,18] Everolimus, a natural macrocyclic lactone, inhibits mTOR thereby blocking the cell-cycle during the transition from G1 to S phase: inhibiting protein synthesis by blocking mTOR with everolimus (or any other rapamycin analogue) may be less effective in diabetic patients. On the other hand, paclitaxel might exert the same potency in diabetics as in non-diabetics by inhibiting deconstruction of microtubules, independent of insulin resistance.[17]

However, between 6 months and 2 years, there was a non-significant increase in TLR in the EES arm compared with the PES arm [EES 4.6% (11/239) vs. PES 2.1% (2/97), $P = 0.36$). Thus, increased late loss beyond 6 months leading to greater TLR cannot explain the large differences observed in MACE rates between the two stents according to diabetic status. Alternatively, the relatively small size of the diabetic cohort may have falsely led to the noted interaction in this *post hoc* analysis. Specifically, the 2-year MACE rate among patients treated with PES was lower in diabetic compared with non-diabetic patients, an unexpected finding that may have been due to chance. Examination of numerous underpowered subgroups may lead to false-positive as well as false-negative results.[19] Thus, a large, adequately powered randomized trial is required to determine the relative safety and efficacy of EES and PES in patients with diabetes.

The SPIRIT III study suggested that incidence of very late (>1 year) stent thrombosis is less in EES than in PES (0.2 vs. 1.0%,

$P = 0.10$) and that thienopyridine discontinuation after 6 months might be associated with a lower rate of subsequent stent thrombosis with EES than with PES through 2 years of follow-up (0.4 vs. 2.6%), although this difference did not reach statistical significance ($P = 0.10$).[14] In the current analysis, the suggested lower rate of very late stent thrombosis in EES compared with PES was not proven. Between 1 and 2 years, protocol-defined stent thrombosis occurred in 0.5 and 0.8% of the EES and PES patients, respectively, without significant difference ($P = 0.45$). The current analysis also failed to confirm the lower rate of stent thrombosis in the EES than in PES group when thienopyridine was discontinued after 6 months. The rates of stent thrombosis at 2 years were comparable between EES and PES irrespective of the timing of thienopyridine discontinuation, with no difference observed between the two groups at 2 years. Given the low incidence of stent thrombosis, however, larger studies will be necessary to assess the differential effects of DES on stent thrombosis.

In the current analysis, the 2-year follow-up could not be completed for 7.2% of the patients, although it was mandated by protocol. This is a limitation of the current analysis since we cannot exclude occurrence of events in the patients with lost follow-up. Although the completeness of follow-up is similar between EES and PES (93.7 vs. 90.5%), the slight differences could be relevant.

In conclusion, the current analysis reports the largest cohort with the longest follow-up of patients treated with the EES, which is currently the most widely used DES in the USA and Europe. This study has demonstrated that in patients with mostly stable angina and non-complex coronary artery disease, the EES compared with the PES reduces the rates of MI and TLR, with lower overall TVF and MACE. Additional studies are warranted to confirm the long-term safety and efficacy of the EES in diabetic patients, after thienopyridine discontinuation, and in more complex lesions and patients than studied in the SPIRIT trials to date.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

This study was sponsored by Abbott Vascular.

Conflict of interest: S.V., J.D. and S.C. are employees of Abbott Vascular. G.W.S. is a member of advisory board to Abbott Vascular and Boston Scientific.

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CHAPTER 30

The everolimus-eluting stent in real-world patients: 6-month follow-up of the X-SEARCH (Xience V Stent Evaluated at Rotterdam Cardiac Hospital) registry

Onuma Y, Kukreja N, Piazza N, Eindhoven J, Girasis C, Schenkeveld L, van Domburg R, Serruys PW, Interventional Cardiologists of the Thoraxcenter (2000 to 2007).

J Am Coll Cardiol. 2009 Jul 14;54(3):269-76.

EXPEDITED PUBLICATION

The Everolimus-Eluting Stent in Real-World Patients

6-Month Follow-Up of the X-SEARCH (Xience V Stent Evaluated at Rotterdam Cardiac Hospital) Registry

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Objectives The purpose of this study was to investigate the impact of everolimus-eluting stents (EES) in comparison with bare-metal stents (BMS), sirolimus-eluting stents (SES), and paclitaxel-eluting stents (PES) on the 6-month clinical outcomes in an all-comer population.

Background EES have been shown to be effective in the context of randomized trials with selected patients. The effect of EES implantation in more complex, unselected patients cannot be directly extrapolated from these findings.

Methods In total, 649 consecutive unselected patients treated exclusively with EES were enrolled. Six-month clinical end points were compared with 3 historical cohorts (BMS, n = 450; SES, n = 508; and PES, n = 576). Major adverse cardiac events (MACE) were defined as a composite of all-cause mortality, myocardial infarction, or target vessel revascularization (TVR).

Results The patients treated with EES were older, presented more frequently with acute myocardial infarction, and had more complicated lesions than the other groups. The EES group demonstrated a higher incidence of all-cause mortality than the SES group and a lower incidence of TVR than the BMS group. Multivariate adjustment demonstrated that BMS was associated with higher TVR and MACE risk than EES (adjusted hazard ratio [HR] for TVR: 2.02 [95% confidence interval (CI): 1.11 to 3.67]; adjusted HR for MACE: 2.15 [95% CI: 1.36 to 3.42]); that SES had a clinical outcome similar to that of EES, and that PES had a higher risk of MACE than did EES (adjusted HR: 1.57 [95% CI: 1.02 to 2.44]).

Conclusions This study suggests that the use of EES in an unselected population may be as safe as and more effective than BMS, may be as safe and effective as SES, may be as safe as PES, and may be more effective than PES.
(J Am Coll Cardiol 2009;54:269–76)

Compared with bare-metal stents (BMS), polymer-based sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) have been shown to significantly reduce angiographic restenosis and recurrent ischemia necessitating repeat revascularization (1). Stent thrombosis and endothelial dysfunction after both PES and SES implantation, however, remains a concern with this technology. With the goal of further enhancing the safety and efficacy of drug-eluting stents (DES), an everolimus-eluting stent (EES) (Abbott Vascular, Santa Clara, California) has been designed in which the antiproliferative agent is released from a thin (7.8 μm), nonadhesive, durable, biocompatible fluoropolymer coated onto a low-profile (0.0813-mm strut thickness), flexible cobalt chromium stent. Angiographic and clinical noninferiority of the EES to the PES was proven in the SPIRIT II and III randomized studies (2,3).

The clinical trials completed so far, however, have included only elective patients with relatively noncomplex lesions and have excluded high-risk patients such as those presenting with acute myocardial infarction (MI) or those with left main stenosis or calcified lesions (2–4). The effect of EES implantation in complex, unselected patients treated in daily practice still remains unknown and cannot be extrapolated from these randomized controlled trials. We therefore sought to evaluate the impact of this second-generation DES on the clinical outcomes in consecutive patients treated in a real-life, all-comer population. The aim of this study was to report the 6-month outcomes of unrestricted universal use of EES in patients with de novo coronary artery lesions and to compare its efficacy against our historical

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Manuscript received February 26, 2009; revised manuscript received April 6, 2009, accepted May 13, 2009.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
EES = everolimus-eluting stent(s)
HR = hazard ratio
MACE = major adverse cardiac event(s)
MI = myocardial infarction
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization
TVR = target vessel revascularization

BMS, SES, and PES cohort from the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) and T-SEARCH (Taxus-Stent Evaluated At Rotterdam Cardiology Hospital) registries.

Methods

Study design and patient population. The X-SEARCH (Xience Stent Evaluated At Rotterdam Cardiology Hospital) registry is a prospective single-center registry with the main purpose of evaluating the safety and efficacy of EES implantation in consecutive unselected patients treated in daily practice. Its conceptual design and methodology are similar to that of the RESEARCH and T-SEARCH registries (5,6) and follows the dynamic registry design described by Rothman and Greenland (7). Since EES received Conformité Européenne mark approval and became commercially available in Europe in March 2007, it has been our policy to utilize the EES as the device of choice for every percutaneous coronary intervention performed in our institution. All consecutive procedures were included, without any specific anatomical or clinical restriction.

Between March 1, 2007, and October 31, 2007, 649 consecutive patients presenting with de novo lesions were treated exclusively with EES and were included in the present report (EES group) after exclusion of patients treated with EES and other stent types in the same procedure (n = 48), those treated without stent implantation (n = 20), those treated exclusively with BMS or other DES (n = 17), and those treated with EES for in-stent restenosis (n = 44) (Fig. 1). At the initiation of the X-SEARCH registry, EES was available in lengths of 8, 12, 15 and 23 mm and diameters from 2.5 to 4.0 mm. This EES group was compared with a historical cohort from the RESEARCH and T-SEARCH registries that comprised 1) the pre-SES arm of the RESEARCH registry (BMS group, n = 450); 2) the active arm of the RESEARCH registry (SES group, n = 508); and 3) the PES group of the T-SEARCH registry (PES group, n = 576) (Fig. 2).

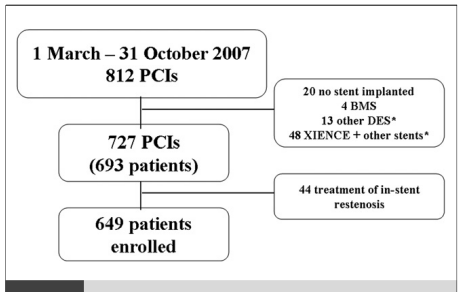

Figure 1 Flowchart of Patient Selection

The flowchart represents patient inclusion and exclusion in the X-SEARCH (Xience Stent Evaluated At Rotterdam Cardiology Hospital) registry. *Occurring in the short transitional period (2 weeks) between paclitaxel-eluting stent/everolimus-eluting stent. BMS = bare-metal stent(s); DES = drug-eluting stent(s); PCI = percutaneous coronary intervention.

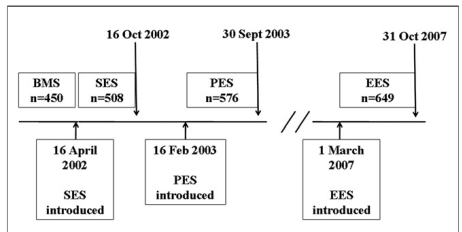

Figure 2 Inclusion Periods of X-SEARCH and Historical Cohorts

Chronological order of 4 cohorts included in analysis: BMS, everolimus-eluting stent (EES), paclitaxel-eluting stent (PES), and SES. X-SEARCH = Xience Stent Evaluated At Rotterdam Cardiology Hospital; other abbreviations as in Figure 1.

Written informed consent was obtained from every patient. All procedures were performed according to standard clinical guidelines at the time of enrollment (8). All patients were pre-treated with 300 mg clopidogrel. At least 1 month of clopidogrel treatment (75 mg/day) was recommended for patients treated with BMS. Clopidogrel was prescribed for ≥3 months for patients with SES, or >6 months for patients with PES, and 12 months for patients with EES, according to the data from the pivotal DES randomized trials (9,10). Life-long aspirin therapy was recommended for all patients.

Definitions. Hypercholesterolemia was defined as fasting total cholesterol >5 mmol/l (193 mg/dl) or the use of lipid-lowering therapy. Hypertension was defined as blood pressure >140/90 mm Hg or the use of antihypertensive medications. Angiographic success was defined as a residual stenosis ≤30% by visual analysis in the presence of TIMI (Thrombolysis In Myocardial Infarction) flow grade 3. The primary end point was major adverse clinical events (MACE), defined as all-cause death, nonfatal MI, or target vessel revascularization (11). Secondary end points included all-cause mortality, MI, target vessel revascularization (TVR), target lesion revascularization (TLR), definite stent thrombosis, and the composites of all-cause death or nonfatal MI. MI included reinfarction (defined as recurrence of symptoms together with ST-segment elevation or new left bundle branch block and an increase in cardiac enzymes after stable or decreasing values) or spontaneous MI (diagnosed by a rise in creatine kinase-MB fraction of 3 times the upper limit of normal together with symptoms and either

Table 1 Patient Characteristics

	BMS (n = 450)	SES (n = 508)	PES (n = 576)	EES (n = 649)	p Value
Age, yrs	61 ± 11	61 ± 11	62 ± 11	64 ± 12	<0.001
Female	28.6	32.1	26.4	28.4	0.22
Current smoker	34.0	30.7	29.0	30.0	0.36
Diabetes mellitus	14.9	17.7	18.4	20.8	0.1
Noninsulin dependent	10.9	11.8	13.2	14.4	0.32
Insulin dependent	4	5.9	5.2	6.4	0.37
Hyperlipidemia	55.3	55.5	62.2	47.6	<0.001
Hypertension	47.6	41.3	41.8	49.3	0.01
Family history of coronary artery disease	28.2	32.5	40.6	45.4	<0.001
Previous MI	39.7	30.2	34.5	25.9	<0.001
Previous CABG	8.0	9.3	6.1	7.3	0.25
Previous PCI	18.0	188	18.2	15.3	0.37
Clinical presentation					
Stable angina	47.6	44.6	45.3	38.8	0.03
Unstable angina/NSTEMI	34.7	37.1	27.0	20.2	<0.001
STEMI	17.8	18.1	28.0	39.3	<0.001
Cardiogenic shock	2.0	1.8	3.8	6.0	<0.001
No. of vessels diseased	1.6 ± 0.7	1.8 ± 0.8	1.8 ± 0.8	1.8 ± 0.9	0.006
Multivessel disease	47.8	54.1	56.1	50.2	0.03
No. of lesions treated	1.8 ± 0.9	2.0 ± 1.0	1.7 ± 0.9	1.8 ± 1.0	<0.001
ACC/AHA lesion classification*					
Type A	19.6	21.9	7.3	6.5	<0.001
Type B1	31.8	30.7	25.0	31.1	0.049
Type B2	49.6	48.6	54.3	51.5	0.25
Type C	29.8	42.5	47.2	38.9	<0.001
Bifurcation	7.8	15.7	15.9	22.2	<0.001
Treated vessels†					
LMS	2.2	2.9	4.3	7.6	<0.001
RCA	34.0	38.5	37.7	33.9	0.25
LAD	59.3	58.5	55.2	38.7	<0.001
LCx	33.1	31.6	33.2	19.1	<0.001
SVG	2.0	3.3	3.3	4.0	0.33
Number of stents	1.9 ± 1.2	2.1 ± 1.4	2.2 ± 1.5	2.1 ± 1.4	<0.001
Average stent diameter, mm	3.1 ± 0.3	2.8 ± 0.2	3.0 ± 0.3	3.1 ± 0.3	<0.001
Total stent length, mm	30 ± 20	39 ± 24	43 ± 31	57 ± 26	<0.001
Clopidogrel duration, months	1.0 ± 0.1	4.0 ± 2.0	6.0 ± 0	11.9 ± 0.7	<0.001
Procedural success	97.3	97.2	97.4	98.3	0.4

Data are presented as % or mean ± SD *Expressed as percentage of patients with each lesion type, hence total >100%. †Expressed as percentage of patients with each vessel type, hence total >100%. BMS = bare-metal stent(s); CABG = coronary artery bypass graft surgery; EES = everolimus-eluting stent(s); LAD = left anterior descending artery; LCx = left circumflex artery; LMS = left main stem; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent(s); RCA = right coronary artery; SES = sirolimus-eluting stent(s); STEMI = ST-segment elevation myocardial infarction; SVG = saphenous vein graft.

the development of ST-segment elevation or new left bundle branch block) (12). TVR was defined as a repeat revascularization of a lesion in the same epicardial vessel treated in the index procedure (13). TLR was defined as a repeat intervention in the stent or within 5 mm proximal or distal to the stent. Stent thrombosis was defined as angiographically defined thrombosis with TIMI flow grade 0 or 1 or the presence of flow-limiting thrombus, accompanied by acute symptoms, irrespective of whether there had been an interceding reintervention (14). The timing of stent thrombosis was categorized as early (within 30 days after implantation), late (between 30 days and 1 year) or very late (>1 year) (11).

Follow-up data. Survival data for all patients were obtained from municipal civil registries at 1 and 6 months after the procedure. A questionnaire was subsequently sent to all living patients with specific queries on rehospitalization and MACE. As the principal regional cardiac referral center, most repeat revascularizations (either percutaneous or surgical) are usually performed at our institution and recorded prospectively in our database. For patients who suffered an adverse event at another center, medical records or discharge letters from the other institutions were systematically reviewed. General practitioners and referring physicians were contacted for additional information if necessary. Over the last 30 years, regular scientific interaction with the referring

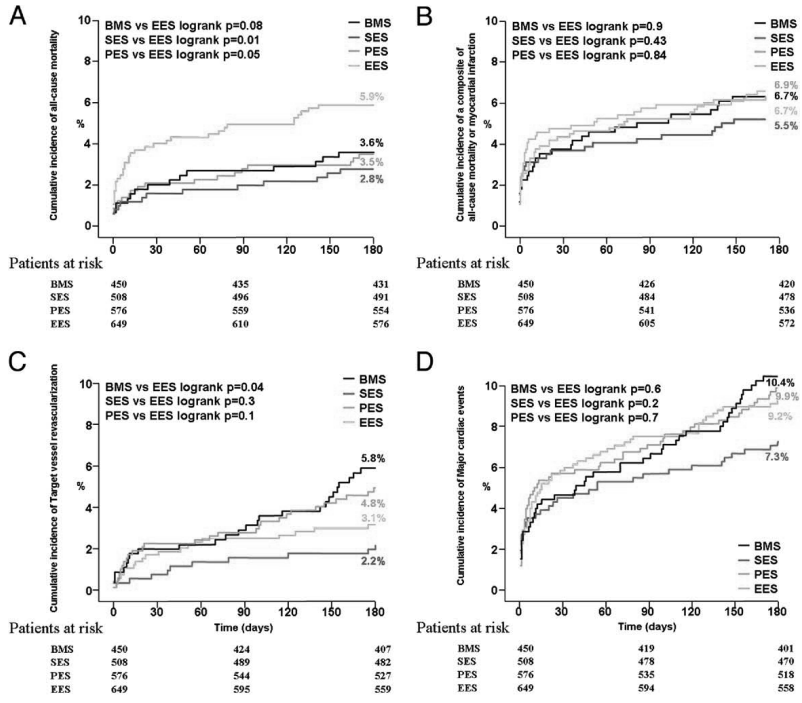

Figure 3 Unadjusted Survival Curves

Kaplan-Meier survival curves stratified according to the stent types: **(A)** all-cause death; **(B)** the composite of death or myocardial infarction; **(C)** target vessel revascularization; and **(D)** the composite of major adverse cardiac events (all-cause mortality, any myocardial infarction, or target vessel revascularization). BMS **(black lines)**; EES **(green lines)**; PES **(yellow lines)**; SES **(red lines)**. Abbreviations as in Figures 1 and 2.

physicians from the local catchment area has encouraged a high level of data collection and source documentation.

Statistical analysis. Continuous variables are presented as mean ± SD, whereas categorical variables are expressed as percentages. Categorical variables were compared using Pearson chi-square test or Fisher exact test, and continuous variables were compared using the F test for analysis of variance. All statistical tests were 2-tailed, and a p value <0.05 was considered as statistically significant. The crude survival curves were constructed with the use of the Kaplan-Meier method to describe the incidence of events over time, and log-rank tests were applied to evaluate differences between the treatment groups. Patients lost to follow-up were considered at risk until the date of last contact, at

Table 2 Cumulative Incidence of Definite Stent Thrombosis

	BMS (n = 450)	SES (n = 508)	PES (n = 576)	EES (n = 649)	p Value
Early (≤30 days)	7 (1.6%)	2 (0.4%)	7 (1.2%)	4 (0.6%)	0.19
Acute (≤24 h)	4 (0.9%)	1 (0.2%)	1 (0.2%)	2 (0.3%)	0.22
Subacute (>1, ≤30 days)	3 (0.7%)	1 (0.2%)	6 (1.0%)	2 (0.3%)	0.21
Late (>30 days)	2 (0.4%)	1 (0.2%)	1 (0.2%)	0 (0%)	0.41
Overall (up to 6 months)	9 (2.0%)	3 (0.6%)	8 (1.4%)	4 (0.6%)	0.09

Abbreviations as in Table 1.

which point they were censored. Adjusted survival curves were calculated using Cox regression models. These models were built to adjust for multiple potential confounders in the baseline characteristics for each paired treatment comparison. Firstly, a univariate analysis was performed to identify significant variables among the following: age, gender, hypertension, type 1 or 2 diabetes mellitus, current smoking, family history, previous coronary artery bypass graft surgery, previous MI, previous percutaneous coronary intervention, clinical presentation of acute MI or unstable angina (stable angina as a reference), presentation with shock, multivessel disease, treated vessel, American Heart Association/American College of Cardiology lesion type, bifurcation treatment, number of lesions treated, number of stents implanted, average stent diameter, and total stented length. Second, a Cox model was built forcing stent type and significant variables in the univariate analysis. The stent type was entered as a categorical variable with EES as the reference. The results are presented as adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). Statistical analysis was performed with SPSS version 16 for Windows (SPSS Inc., Chicago, Illinois).

Results

Baseline characteristics are presented in Table 1. Across the study period, patients became progressively older and were more likely to have hypertension and present with ST-segment elevation myocardial infarction (STEMI) or cardiogenic shock—likely a reflection of changes in disease presentation with time. Bifurcations, left main disease, and the use of longer stents were more common in the DES groups. Fewer EES patients had a history of previous bypass surgery.

6-month clinical outcomes. Clinical follow-up at 6 months was complete in 99% of patients. The cumulative incidences of 6-month clinical end points are presented in Figure 3. The crude all-cause mortality rate was significantly higher in the EES group than in the SES group: 5.9% in the EES group versus 3.6%, 3.5%, and 2.8% in the BMS, PES, and SES groups, respectively (Fig. 3A). The cumulative incidence of all-cause death or any MI was similar in the 4 groups (Fig. 3B). TVR was observed in a significantly lower percentage of EES patients than in BMS patients (3.1% vs. 5.8%, p = 0.04) (Fig. 3C). The composite end point of MACE was observed in 9.2% of the EES patients; comparable event rates were observed in the BMS, SES, and PES groups (Fig. 3D). The cumulative incidences of definite stent thrombosis at various time points are shown in Table 2. The overall rate of definite stent thrombosis was similar across the cohorts (BMS 2.0%, SES 0.6%, PES 1.4%, and EES 0.6%).

Multivariate analyses. Cox multivariable regression models were used to correct for differences across the 4 groups and calculate independent predictors of all-cause mortality. Cardiogenic shock (adjusted HR: 8.1, 95% CI: 4.3 to 15.5), type 1 diabetes (adjusted HR: 3.3, 95% CI: 1.5 to 7.2), presentation with STEMI (adjusted HR: 2.6, 95% CI: 1.4 to 5.0), and multivessel disease (adjusted HR: 2.0, 95% CI: 1.2 to 3.4) were identified as independent predictors of 6-month mortality; in contrast, type A lesion classification was protective (adjusted HR: 0.20, 95% CI: 0.1 to 0.8).

Table 3 Adjusted Hazard Ratios for Pair-Wise Comparisons Between Stents

	Adjusted Hazard Ratio	95% CI
BMS versus EES		
All-cause mortality*	1.98	0.97–4.01
MI or all-cause mortality†	1.92	1.14–3.25
TVR‡	2.02	1.11–3.67
MACE§	2.15	1.36–3.42
SES versus EES		
All-cause mortality*	1.15	0.52–2.55
MI or all-cause mortality†	1.45	0.85–2.47
TVR‡	0.69	0.33–1.45
MACE§	1.18	0.71–1.94
PES versus EES		
All-cause mortality*	1.01	0.53–1.92
MI or all-cause mortality†	1.49	0.89–2.32
TVR‡	1.60	0.89–2.88
MACE§	1.57	1.02–2.44

*The model for all-cause mortality was adjusted for the following variables: age, cardiogenic shock, type 1 diabetes, clinical presentation, multivessel disease, type A lesion characteristics. †The model for MI or all-cause mortality was adjusted for type 1 diabetes, age, multivessel disease, clinical presentation, cardiogenic shock, number of stent and type A lesion characteristics. ‡The Cox model for TVR is adjusted for diabetes, number of stents, number of treated lesions, and type B2 lesion characteristics. §The model for MACE is adjusted for age, cardiogenic shock, clinical presentation, multivessel disease, type 1 or 2 diabetes, smoking, and bifurcation.

MACE = major adverse cardiac events (all-cause death, MI, or TVR); TVR = target vessel revascularization; other abbreviations as in Table 1.

Adjusted hazard ratios of pair-wise comparisons of the EES group to other stent groups are shown in Table 3. The risks of TVR, MACE, and composite of MI or all-cause mortality were significantly higher in the BMS than in the EES group (adjusted HR: 2.02, 2.15, and 1.92, respectively). PES was associated with a higher risk of MACE than EES was (adjusted HR: 1.57, 95% CI: 1.02 to 2.44). SES was similar when compared with EES.

The same Cox regression models were used to draw survival curves adjusted for differences in baseline characteristics, as presented in Figure 4. After adjustment, all-cause mortality was similar among stent types, with a trend toward better survival in the EES group than in the BMS group (1.5% vs. 3.1%, p = 0.059). TVR was significantly lower in the EES group than in the BMS group (2.8% vs. 5.8%, p = 0.02) but was comparable with other DES groups (SES 2.0%, PES 4.6%). The composite end point of MACE was significantly lower in the EES group than in the BMS group (5.5% vs. 11.0%, p = 0.003) and PES group (5.5% vs. 8.6%, p = 0.04); the EES and SES groups had similar MACE rates (5.5% vs. 6.1%, p = 0.6).

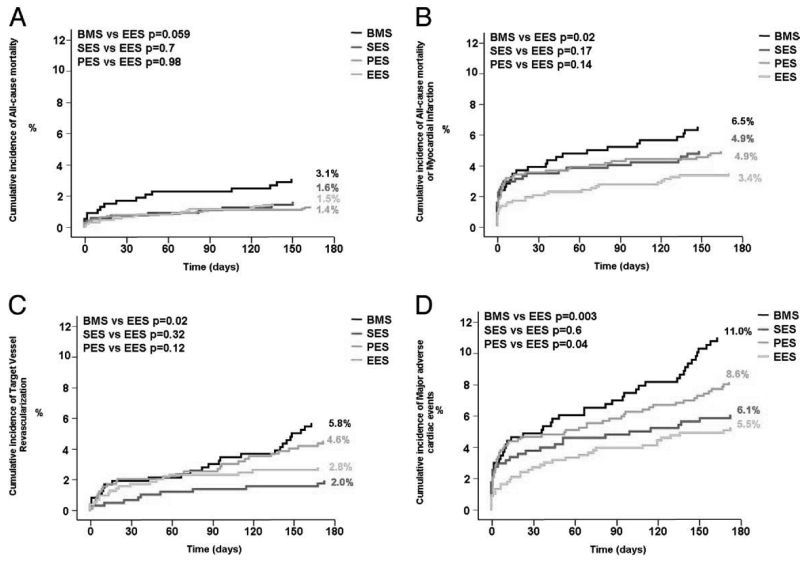

Figure 4 **Adjusted Survival Curves**

Adjusted survival curves stratified according to the stent types using Cox proportional hazard model: **(A)** all-cause death; **(B)** the composite of death or myocardial infarction; **(C)** target vessel revascularization; and **(D)** the composite of major adverse cardiac events (all-cause mortality, any myocardial infarction, or target vessel revascularization). BMS **(black lines)**; EES **(green lines)**; PES **(yellow lines)**; SES **(red lines)**. Abbreviations as in Figures 1 and 2.

Discussion

The X-SEARCH registry, the focus of this report, is a contemporary, all-comer, single-center registry of patients treated with EES. In this registry, patients were older, presented more frequently with STEMI, and had more complicated lesions compared with patients who were treated in the past with BMS, SES (RESEARCH registry) and PES (T-SEARCH registry). At 6-month follow-up, the EES group demonstrated a higher cumulative incidence of all-cause mortality than the SES group, and a lower incidence of TVR than BMS. Taking into account the high-risk patient profile in the X-SEARCH registry, multivariate adjustment with Cox regression model demonstrated that 1) EES was associated with lower TVR and MACE risk than BMS was; 2) EES had a lower MACE rate than PES did; and 3) EES had clinical outcomes similar to SES.

The safety and efficacy of the EES stents have been demonstrated in low-risk profile patients. The randomized SPIRIT II trial, in which 300 patients were enrolled and randomly assigned 3:1 to receive an EES (n = 223) or a PES (n = 77), was performed in Europe, New Zealand, and India. The trial met its primary end point, demonstrating not only noninferiority, but also superiority with respect to in-stent late loss at 6 months with EES (0.11 ± 0.27 mm) compared with PES (0.36 ± 0.39 mm). No significant differences were present, however, in the secondary end points of MACE (cardiac death, MI, or ischemia-driven TLR), presumably because of the small sample size (2,15,16). In the larger SPIRIT III trial performed in the U.S. (3), 1,002 patients with noncomplex coronary artery disease were randomly assigned 2:1 to treatment with EES (n = 669) or PES (n = 333). Angiographic follow-up at 8 months demonstrated a significant reduction in the primary angiographic end point of in-segment late loss with EES compared with PES. At 1 year, EES was noninferior to PES for the co-primary clinical end point of target vessel failure (cardiac death, MI, or ischemia-driven TVR) and resulted in a significant reduction in MACE. The lower MACE risk of EES compared with PES in the current study with all-comer cohorts reconfirms the superiority of EES over PES, not only in low-risk patients but also in the high-risk all-comer populations.

The first-generation DES have been associated with higher rates of late stent thrombosis and thrombosis-related events than BMS (17,18). The cause of late stent throm-

bosis is partly due to the antiproliferative medications retarding the growth of healthy endothelium over stent struts and partly due to chemical features of their durable polymer coating (19–21). The EES, using a novel drug as well as a different polymer, might address this issue. Pre-clinical studies have shown more rapid endothelialization and reduced expression of platelet-endothelial cell adhesion molecule-1 and increased secretion and messenger ribonucleic acid levels of vascular endothelial growth factor at 14 days with EES than with SES or PES (22). The SPIRIT III study suggested that thienopyridine discontinuation after 6 months might be associated with a lower rate of subsequent stent thrombosis with EES than with PES through 2 years of follow-up (0.4% vs. 2.6%), although given the relatively low rates of stent thrombosis, this difference did not reach statistical significance ($p = 0.10$). In the present study, the rate of overall stent thrombosis at 6 months was similar in the EES and other stent groups, although there were no incidences of late stent thromboses with EES up to 6 months. Larger studies with longer follow-up will be necessary to assess the differential effects of EES on late and very late stent thrombosis.

The low incidence of hypercholesterolemia in the EES group might result from the under-diagnosis of hypercholesterolemia in the acute MI population, in which the incidence of hypercholesterolemia was low (24%). Eighty percent of these patients did not have any history related to atherosclerosis, and their cholesterol level was not available at the time of the procedure.

Study limitations. This is a single-center, nonrandomized, observational study. Because we used consecutive but nonsequential patient data from past registries as historical controls, the baseline patient characteristics vary across the cohorts. We used Cox regression analysis to address these differences in baseline characteristics; however, the result can be influenced by the selection of the variables and quality of data. In the current registry, the data in Table 1, which were subsequently used in the Cox regression models, were carefully checked by 2 experienced cardiologists, with review of medical records and cine-angiograms to ensure accurate and complete data entry. In addition, there was no bias in stent selection, because only 1 stent was available in each period of the registries, unlike at other institutions where the penetration of DES has fluctuated after the ESC firestorm in 2006 (23,24). Our study had inadequate statistical power to detect significant differences in adverse outcomes associated with low event rates (e.g., late stent thrombosis). These observations, therefore, can only be used to generate hypotheses when comparing the EES results with those for the other stents.

Conclusions

The current analysis of patients treated with EES compared with SES, PES, and BMS suggests that the use of EES in an unselected population, including high-risk patients, may be as safe as and more effective than BMS, may be as safe and effective as SES, may be as safe as PES, and may be more effective than PES.

Acknowledgments

The authors would like to acknowledge the senior cardiologists involved in the PCI procedures: Eugene McFadden, MD, PhD; Pim J. de Feyter, MD, PhD; Peter P. T. de Jaegere, MD, PhD; Robert Jan van Geuns, MD, PhD; Sjoerd H. Hofma, MD, PhD; Evelyn Regar, MD, PhD; Georgios Sianos, MD, PhD; Pieter C. Smits, MD, PhD; Martin J. van der Ent, MD, PhD; Willem J. van der Giessen, MD, PhD; Carlos A. van Mieghem, MD; and Henricus J. Duckers, MD, PhD. The authors would also like to acknowledge the contribution of the following hospitals for their cooperation in the follow-up of the patients: Maasstad Ziekenhuis, Rotterdam; Albert Schweitzer Ziekenhuis, Dordrecht; Havenziekenhuis, Rotterdam; Vlietland Ziekenhuis, Schiedam; and Amphia Ziekenhuis, Breda, the Netherlands.

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Key Words: everolimus-eluting stent ■ all-comer registry ■ sirolimus-eluting stent ■ paclitaxel-eluting stent.

CHAPTER 31

Biodegradable-polymer-based, sirolimus-eluting Supralimus stent: 6-month angiographic and 30-month clinical follow-up results from the series I prospective study

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Eurointervention. 2008 May; 4(1): 59-63.

EuroIntervention

Biodegradable-polymer-based, sirolimus-eluting Supralimus® stent: 6-month angiographic and 30-month clinical follow-up results from the Series I prospective study

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KEYWORDS
Drug-eluting stent, sirolimus, biodegradable, Percutaneous Coronary Intervention, Coronary Artery Disease

Abstract

Aims: There have been recent concerns regarding the long-term safety of the first generation of drug-eluting stents, which utilised a permanent polymer coating for drug delivery. SERIES I is a prospective, non-randomised, first-in-man open label study with the biodegradable polymer-based Supralimus® sirolimus eluting stent (Sahajanand Medical Technologies Pvt. Ltd, India) for the treatment of patients with coronary artery lesions.

Methods and results: One hundred patients were treated with 126 Supralimus® stents (mean lesion length 10.5±4.3 mm, mean reference vessel diameter 2.66±0.62 mm). The pre-specified primary endpoint was angiographic binary in-stent restenosis at six months. Secondary endpoints were device-orientated major adverse clinical events (MACE; defined as a composite of cardiac death, nonfatal myocardial infarction [Q-wave and Non-Q wave], or clinically-justified target vessel revascularisation) at 30 days, nine months and 30 months. Angiographic follow-up in a pre-specified subgroup of 60 patients at six months showed binary angiographic restenosis rates of 0% (in-stent) and 1.7% (in-segment). The in-stent late loss was 0.09±0.37 mm. MACE rates were 0% after one month, 6% at 9-month follow-up and 7% after 30 months follow-up.

Conclusions: The biodegradable-polymer-based sirolimus-eluting stent (Supralimus®) is effective in inhibiting neointimal hyperplasia.

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Introduction

Although the first generation of drug eluting stents (DES) have drastically reduced rates of restenosis and revascularisation[1-5], concerns persist regarding their long-term safety[6-8]. The presence of a permanent polymer coating may contribute to stent thrombosis as a result of delayed healing and a hypersensitivity reaction in some cases[9-14]. The sirolimus-eluting stent currently approved for clinical practice (Cypher, Cordis, Warren, NJ, USA) uses a non-erodable polymer (polyethylene-co-vinyl acetate [PEVA] and poly n-butyl methacrylate [PBMA]), which may be responsible for the eosinophilic infiltration of the arterial wall seen in animal studies; the hypersensitivity reaction occurs after the complete release of drug, suggesting that the polymer may be the cause[15]. To address this issue, a new generation of DES is currently under development, incorporating biodegradable, biocompatible polymers as vehicles for drug delivery. Full degradation of these polymers into carbon dioxide and water ensures complete drug release, leaving a residual bare metal stent[16-19]. We report on the angiographic and long-term clinical follow-up of a novel biodegradable-polymer-coated sirolimus-eluting stent.

Methods

The Supralimus® stent consists of an established balloon-expandable 316L stainless steel slotted-tube stent platform (Matrix, Sahajanand Medical Technologies Pvt. Ltd., India) with two layers of degradable polymer coating: the base layer consists of 1.4 mcg/mm^2 sirolimus incorporated into a biodegradable polymer matrix consisting of PLLA (Poly L-Lactic acid), PLGA (50/50 Poly DL-Lactide-co-Glycolide) and PVP (Polyvinyl Pyrrolidone), with a drug:polymer ratio of 35:65. The outer protective layer containing only PVP prevents premature drug release and is completely removed within two hours after implantation.

Following removal of this protective layer, an early burst phase releases 50% of the drug within the first seven days to inhibit the inflammatory response and smooth muscle cell migration and proliferation. The remaining 50% of sirolimus is released within 41 days; thus in an average of 48 days, the total drug content is released from the stent surface, as demonstrated in Figure 1.

Porcine studies of the Supralimus® stent have demonstrated partial and complete endothelialisation after eight and 28 weeks respectively, with no evidence of hypersensitivity. The polymer and stent platform have both already been tested in humans, albeit incorporating a different anti-restenotic drug, with no undue concerns regarding safety[17].

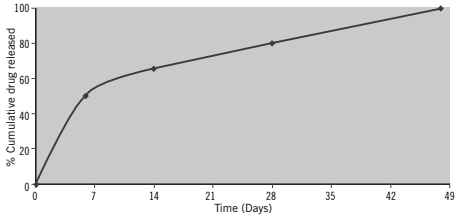

Figure 1. Cumulative in vitro release profiles of sirolimus from Supralimus® stents.

The interventional procedures were performed according to current standard clinical practice[20]. All patients were pretreated with aspirin and either clopidogrel or ticlopidine. Dual antiplatelet therapy was maintained indefinitely after the procedure. Heparin was administered to maintain an activated clotting time of greater than 250 secs.

One hundred patients were enrolled. Inclusion criteria were stable or unstable angina; a reference vessel diameter between 2.5 and 4.0 mm and lesion length: < 25 mm, which could be covered by a single Supralimus® stent (available stent sizes were from 2.5-4.0 mm diameter and 11-33 mm in length). Exclusion criteria included a platelet count < 100,000 cells/mm^3 or > 700,000 cells/mm^3; WBC of < 3,000 cells/mm^3; documented or suspected liver disease (including laboratory evidence of hepatitis); recipients of heart transplants; known allergy to aspirin, clopidogrel, ticlopidine, heparin or stainless steel; ST elevation myocardial infarction within past 24 hours; presence of chronic renal failure (creatinine > 2.5 mg/dl); advanced malignancy; scheduled for major non-cardiac surgery within six months of PCI.

The pre-specified primary endpoint was binary angiographic in-stent restenosis. Secondary endpoints were composite major adverse clinical events (MACE), defined as a composite of cardiac death, non-fatal myocardial infarction (Q-wave and Non-Q wave), or clinically justified target vessel revascularisation at 30 days, nine months and 30 months.

Angiographic follow up was proposed to all patients, but was carried out only on those consecutive patients who consented, numbering 60 in total.

Quantitative coronary angiography (QCA) was performed by an independent core laboratory (Cardialysis BV, Rotterdam, The Netherlands) using the CAAS II analysis software (Pie Medical BV, Maastricht, The Netherlands). The stented segment refers to the stent and 5 mm proximal and distal to the stent edges. The following data were obtained: minimum lumen diameter (MLD), interpolated reference vessel diameter and percentage diameter stenosis (DS). Binary restenosis was defined as a DS ≥50% at follow-up angiography. Late loss was defined as the difference between MLD post-procedure and MLD at follow-up. Video-densitometric QCA was also performed to obtain the reference vessel area (RVA), minimum lumen area (MLA) and percentage area stenosis[21-23].

Results

On hundred and twenty-six Supralimus® stents (diameter range 2.5-4.0 mm, length range 11-33 mm) were implanted in 100 patients (mean 1.26 stents per patient). The PCI procedure was successful in all cases. The baseline patient and lesion characteristics are shown in Tables 1 and 2.

The mean lesion length was 10.5±4.30 mm. The mean stent length and diameter were 18.95±7.58 mm and 2.95±0.44 mm respectively. Angiographic follow-up after six months was available in 59 out of 60 scheduled patients. These results are shown in Table 3; the rates of angiographic binary in-stent and in-segment restenosis were 0% and 1.7% respectively.

All the patients were clinically followed up at 30 days, six, nine, 24 and 30 months. Follow-up data was available in all the living

Table 1. Baseline patient characteristics (n=100).

Variable	
Diabetes mellitus	29%
Hypertension	57%
Hyperlipidaemia	38%
Smoker	22%
Previous myocardial infarction	56%
Heart failure	7%
Previous PCI	6%
Number of diseased vessels	
One	73%
Two	22%
Three	6%
Clinical presentation	
Stable angina	59%
Unstable angina	41%

Table 2. Lesion characteristics (n=126).

Variable	
Vessel treated	
LAD	56%
RCA	25%
Lcx	16%
LMS	1%
Other	2%
ACC / AHA lesion classification	
Type A	18%
Type B1	42%
Type B2	24%
Type C	16%
Chronic occlusion	17 (12%)
In stent restenosis	1 (1%)
Ostial lesion	8 (5%)
Bifurcation	5 (3%)

ACC: American College of Cardiology; AHA: American Heart Association

patients, up to the pre-specified trial end point of 30 months. There were no in-hospital complications and no adverse clinical events at 30 days follow-up. After nine months, the composite MACE rate was 6%. The long-term clinical follow-up is shown in Table 3 and Figure 2. The event-free survival rate was 93% after 30 months follow-up. Four patients underwent TVR. Out of the three deaths, one patient died five months after the PCI of unknown causes; another died seven months after stent implantation due to progressive heart failure; the third patient died from a myocardial infarction after 24 months; all deaths were classified as cardiac according to Academic Research Consortium definitions (ARC)[24].

Table 3. Quantitative coronary angiographic analysis (n=59).

	Baseline	Post-procedure	6 months
Reference vessel diameter, mm			
In stent	2.66±0.62	2.86±0.45	2.85±0.46
In segment		2.80±0.47	2.77±0.48
Minimum lumen diameter, mm			
In stent	0.73±0.61	2.53±0.43	2.44±0.48
In segment		2.14±0.49	2.11±0.51
Late loss, mm			
In stent			0.09±0.28
In segment			0.02±0.37
Diameter stenosis,%			
In stent	72.4±21.7	11.5±6.6	14.2±9.9
In segment		24.0±9.3	23.9±12.7
Binary angiographic restenosis, n (%)			
In stent			0 (0)
In segment			1 (1.7)
Reference vessel area, mm^2			
In stent	5.85±2.78	7.05±3.41	6.84±2.83
In segment		6.41±2.54	6.51±2.42
Minimum lumen area, mm^2			
In stent	0.91±1.08	6.24±2.99	5.63±2.67
In segment		4.28±2.45	4.30±2.24
Area stenosis,%			
In stent	84.4±15.9	10.1±21.8	18.0±19.8
In segment		34.0±20.5	34.8±20.7

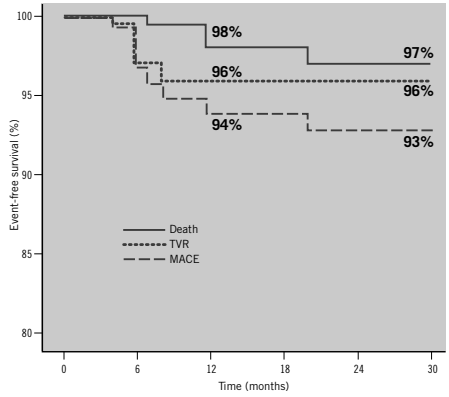

Figure 2. Kaplan-Meier estimates of clinical events.

Table 4. Major adverse clinical events (n=100).

Variables	1 Month	6 Months	9 Months	24 Months	30 Months
Death (%)	0	1	2	3	3
Non-fatal myocardial infarction (%)	0	0	0	0	0
Death or nonfatal MI (%)	0	1	2	3	3
TVR (%)	0	2	4	4	4
Death or nonfatal MI or TVR (%)	0	3	6	7	7
Freedom from MACE (%)	100	97	94	93	93

MI: myocardial infarction; TVR: target vessel revascularisation; MACE: major adverse clinical events, defined as death, non-fatal myocardial infarction or target vessel revascularisation

Using the ARC guidelines, the device orientated composite endpoint (cardiac death, myocardial infarction [not clearly attributable to non-target vessel], TLR), was reached in 6% and 7% of patients after one and two years respectively. There were no cases of definite stent thrombosis. The classification of stent thrombosis according to ARC criteria is shown in Table 5.

Table 5. Occurrence of stent thrombosis* after 30 months (n=100).

Stent thrombosis classification	Incidence	Timing	
Definite	0%		
Probable	1%	207 days	Late
Possible	1%	606 days	Very late

* as defined by the Academic Research Consortium

Discussion

The initial enthusiasm following the introduction of the first-generation of DES has since been somewhat cooled by long-term safety concerns, particularly regarding stent thrombosis and the clinical sequelae of myocardial infarction and death. The exact causes of these complications remains unclear, but both the drug and the permanent polymer coating have been implicated[9-11,25]. One potential modification of the next generation of DES is the use of a biodegradable polymer to reduce adverse interactions whilst allowing controlled drug release.

Polymer-based sirolimus-eluting stents have already been evaluated with mixed results: the CURA stent (Orbus Neich, Fort Lauderdale, FL, USA) consisting of a stainless steel stent with a PLA / PLGA / sirolimus matrix had angiographic restenosis rates of 22% and a late loss of 0.74 mm when used in patients presenting with acute myocardial infarction[26]. This compares poorly to the late loss with the first generation sirolimus-eluting stent (late loss of 0.17 in the SIRIUS trial[1]). The Excel stent (JW Medical Systems, China), a stainless steel stent with abluminal PLA / sirolimus performed much better, with a late loss of 0.07 mm[27,28].

When comparing the angiographic efficacy for the Supralimus stent to the first generation sirolimus-eluting stent (Cypher: Cordis, Warren, NJ, USA), both the in-stent (late loss 0.09 mm for Supralimus vs. 0.17 mm for Cypher, angiographic restenosis 0% for Supralimus vs. 3.2% for Cypher) and in-segment (late loss 0.02 mm for Supralimus vs. 0.24 mm for Cypher, angiographic restenosis 1.7% for Supralimus vs. 8.9% for Cypher) results appear favourable[1]. The video-densitometric QCA results from the Supralimus stent (a decrease in in-stent minimum lumen area from 6.24±2.99 mm^2 post-procedure to 5.63±2.67 mm^2 after 6 months) also appear favourable when compared with the commercially available paclitaxel-eluting stent (Taxus: Boston Scientific, Natick, MA, USA) which had a corresponding decrease from 6.42±2.45 mm^2 post-procedure to 4.51±2.42 m^2 after six months[29]. In the Randomised Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with *de Novo* Native Coronary Artery Lesions (RAVEL) study, an 18 mm stent was used to treat a mean lesion length of 9.56±3.33 mm^2. In SERIES-1 we also ensured complete lesion coverage by using a mean stent length of 18.95±7.58 mm to treat a mean lesion length of 10.5±4.30 mm.

The clinical and safety profile of the Supralimus stent gives comparable results across all the clinical endpoints when scrutinised next to the two year meta-analysis of the pivotal US, European and Canadian randomised controlled trials of the Cypher stent (mortality 2.1%, TLR 5.7%, overall MACE 10.6% compared to 3%, 4% and 7% respectively for the Supralimus stent)[30].

Beyond efficacy and safety, a further issue with DES is the high cost compared to bare metal stents, which may limit their use worldwide[31,32]. Hopefully the advent of drug-eluting stents developed and manufactured in South Asia will prove beneficial, since these stents are likely to be cheaper than those produced in the USA or Europe. The cost difference between Cypher and Supralimus is approximately 700 USD.

This study is a first-in-man single-centre clinical evaluation and therefore is limited by small patient numbers and the treatment of less complex patients than some of the available registries[33]. The long-term safety and efficacy of the biodegradable polymer-based Supralimus® stent needs to be established by future large-scale clinical trials. Nonetheless, the long term MACE-free survival and angiographic late loss appear to be comparable to other available DES.

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CHAPTER 32

MAHOROBA, first-in-man study: 6-month results of a biodegradable polymer sustained release tacrolimus-eluting stent in de novo coronary stenoses

Onuma Y, Serruys PW, den Heijer P, Joesoef KS, Duckers H, Regar E, Kukreja N, Tanimoto S, Garcia-Garcia HM, van Beusekom H, van der Giessen WJ, Nishide T.

Eur Heart J. 2009 Jun;30(12):1477-85.

MAHOROBA, first-in-man study: 6-month results of a biodegradable polymer sustained release tacrolimus-eluting stent in *de novo* coronary stenoses

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Received 8 September 2008; revised 5 February 2009; accepted 11 March 2009; online publish-ahead-of-print 30 April 2009

Aims	To report the 4-month angiographic and 6-month clinical follow-up in first-in-man study using the tacrolimus-eluting bioabsorbable polymer-coated cobalt–chromium MAHOROBA™ stent.
Methods and results	A total of 47 patients with either stable angina or unstable angina, or silent myocardial ischaemia, based on a *de novo* coronary stenosis that could be covered by a single 18 mm stent in a native coronary artery with a diameter between 3.0 and 3.5 mm were enrolled at three sites. The primary endpoint was in-stent late loss at 4 months. The secondary endpoints include %volume obstruction of the stents assessed by intravascular ultrasound (IVUS) at 4 months and major adverse cardiac events (MACE) at 6 months. Forty-seven patients were enrolled. Procedural success was achieved in 97.9%. At 4-month follow-up, in-stent late loss was 0.99 $\pm$ 0.46 mm, whereas in-stent %volume obstruction in IVUS was 34.8 $\pm$ 15.8%. At 6 months, there were no deaths, but 2 patients suffered from a myocardial infarction and 11 patients required ischaemia-driven repeat revascularization. The composite MACE rate was 23.4%.
Conclusion	This tacrolimus-eluting stent failed to prevent neointimal hyperplasia, despite the theoretical advantages of the tacrolimus, which has less inhibitory effects on endothelial cells than smooth muscle cells.

Keywords Tacrolimus-eluting stent • First-in-man study • Drug-eluting stent • Coronary artery disease

Introduction

Sirolimus-eluting stents (SESs) and paclitaxel-eluting stents (PESs) have markedly reduced the rate of in-stent restenosis and late lumen loss compared with bare-metal stents (BMSs),[1] resulting in a significant reduction in repeat revascularizations. Accordingly, percutaneous coronary intervention (PCI) using drug-eluting stents (DESs) has been accepted as the most effective treatment option for *de novo* coronary artery disease.

However, enthusiasm for this technology has recently been dampened by concerns about late stent thrombosis, an event often associated with lethal consequences. Delayed re-endothelialization after DES has been suggested as one of the plausible causes of late stent thrombosis.[2–4] Pathological autopsy studies also support the hypothesis of delayed endothelialization, showing an association between lack of neointimal strut coverage after DES implantation and stent thrombosis. Localized hypersensitivity reactions to the durable polymer coating and/or to the drug

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itself may also theoretically add to stent thrombosis.[5] Furthermore, endothelial dysfunction after DES has lately attracted considerable attention. Recent reports suggest that DES may impair endothelial responses to acetylcholine or exercise-mediated vasodilation in humans.[6,7]

Tacrolimus is a macrolide immunosuppressant drug licensed for prophylaxis of rejection in recipients of organ transplantation.[8] The intracellular receptors are the FK binding proteins (FKBP, including FKBP12): the tacrolimus–FKBP complex binds to inhibit the calcineurin–calmodulin complex,[8] which suppresses proliferation of T-cells, smooth muscle cells (SMCs), and endothelial cells (ECs). Tacrolimus has a much less inhibitory effect on SMC and EC than sirolimus, but tacrolimus depresses EC less than SMC.[9–11] These results suggest that tacrolimus may allow better re-endothelialization than sirolimus if proper concentrations for suppressing SMC proliferation are used. Furthermore, unlike sirolimus or paclitaxel, tacrolimus does not affect the tissue factor and e-NOS expression, which might attenuate the risk of stent thrombosis.[12,13]

A poly D, L-lactide-co-glycolide (PLGA) polymer with sustained drug release for several months was employed to maintain high tissue concentration of tacrolimus. This polymer coating is fully absorbable and theoretically minimizes adverse effect, such as possible hypersensitivity reactions, caused by the permanent presence of a durable polymer. In a porcine model, the MAHOROBA stent (Kaneka, Osaka, Japan) demonstrated early re-endothelialization and reduction of neointimal thickening up to 90 days after the implantation.[14] Conversely, it has yet to be demonstrated that the biodegradation of the polymer in human atherosclerotic vessels does not in itself induce an inflammatory and proliferative response.

The objective of the MAHOROBA I, first-in-man (FIM) study was to test the safety and feasibility of the MAHOROBA™ stent to treat *de novo* coronary lesions.

Methods

Study design and patient selection

The study enrolled 47 patients at three participating sites in The Netherlands. The local Ethics Committee approved the protocol for each study site, and all patients gave written informed consent before the procedure. Patients over 18 years of age were eligible, provided they had stable angina, unstable angina, or silent myocardial ischaemia with a *de novo* coronary artery lesion with >50 and 100% stenosis of a length that could be covered by a single 18 mm stent with a diameter between 3.0 and 3.5 mm in one or two major epicardial arteries. The second lesion should fit with inclusion/exclusion criteria and be treated with the same study stent. Patients were not eligible for enrolments if they had an evolving acute myocardial infarction (MI) within 72 h, renal dysfunction (serum creatinine >2.0 mg/dL), a total occlusion with a TIMI flow of 0 or 1, low left ventricular ejection fraction (<30%), a platelet count of <100 000 cells/mm^3 or >700 000 cells/mm^3, a white blood cell count of <3000 cells/mm^3, previous drug-eluting or BMS implantation in the target vessel, a target lesion supplied by an arterial or venous bypass graft, a heavily calcified lesion, a bifurcation lesion involving a side branch >2.0 mm in diameter with an ostial disease, unprotected left-main disease, planned PCI within 60 days after trial stent implantation, planned surgery within 6 months after stent implantation, stroke or transient ischaemic attack within the prior 6 months, a known allergy to aspirin, clopidogrel, cobalt–chromium alloy, heparin, tacrolimus (or similar drugs), or contrast agents that cannot be adequately premedicated.

The MAHOROBA stent

The MAHOROBA tacrolimus-eluting stent (TES) comprises a drug-eluting PLGA coating and a cobalt–chromium (CoCr) stent with a strut thickness of 75 μm, as previously described.[15] The stent has an open-cellular balloon-expandable design and consists of two helical coils inter-crossed with two phase-different links on each turn, in which each link deviates diagonally along the longitudinal axis (*Figure 1*). The entire abluminal surface of the stent is coated with a fully biodegradable PLGA polymer matrix. The molecular weight of the PLGA polymer was 84 000 Da. The mass ratio of the drug and polymer was 20.6 and 79.4 wt%, respectively. The dose density of tacrolimus and the polymer was 0.94 and 3.58 μg/mm^2, respectively. The purity of the polymer was over 99.9%. The PLGA polymer was proven by compliance with the ISO 10093s. In the porcine artery model, the PLGA degrades and disappears completely in 6 months.[16] Tacrolimus is released continually for several months and completely resolves with PLGA degradation.

Study procedure

Lesions were treated using standard interventional techniques with mandatory pre-dilatation prior to stent implantation. The following sizes of MAHOROBA stent were used in the study: 18 mm length and either 3.0 or 3.5 mm diameter. Intravascular ultrasound (IVUS) was performed after angiographically optimal stent placement and was repeated if additional post-dilatation was required. Treatment

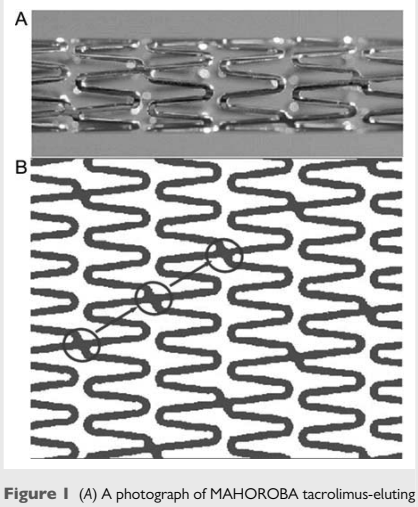

Figure 1 (*A*) A photograph of MAHOROBA tacrolimus-eluting stent. (*B*) A schematic view of the stent structure. Two helical coils inter-cross with two phase-different links. Blue circles and arrows indicate that each link deviates diagonally along the longitudinal axis.

with aspirin, at a minimal dose of 100 mg per day, was started prior to procedure and continued indefinitely. A loading dose of 300 mg of clopidogrel was administered at least 6 h before the procedure, followed by 75 mg daily for at least 13 months.

Follow-up

Patients were evaluated clinically at 30 days and 4 months with further evaluation scheduled at 9 and 12 months followed by annual evaluation out to 5 years: patients were asked specific questions about major cardiac adverse events and the interim development of angina according to the Canadian Cardiovascular Society classification of stable angina. Angiographic and IVUS evaluations were performed at 4 months.

Quantitative coronary angiography

Quantitative coronary angiography (QCA) analyses were performed by a corelab (Cardialysis B.V., Rotterdam, The Netherlands) with the CAAS II analysis software (Pie Medical B.V., Maastricht, The Netherlands). In each patient, the stented segment and the peri-stent segments defined by a length of 5 mm proximal and distal to the stent edge were analysed. The following QCA parameters were computed: minimal luminal diameter (MLD), reference diameter obtained by an interpolated method, and percentage diameter stenosis. Binary restenosis was defined in every segment (proximal, distal, and stent) as diameter stenosis $\geq$50% at follow-up. Stent-to-artery ratio was calculated as a mean diameter of the last balloon at the highest pressure divided by the baseline reference vessel diameter. Late loss was defined as the difference between MLD post-procedure and MLD at follow-up. Results are presented as means using matched pair of angiographic views using multiple X-ray views.

For the assessment of acute stent recoil, two sequential angiographic images were analysed: first an image of the complete expansion of the largest balloon at the highest pressure, whereas the second was an image immediately after the final balloon deflation. These two images were analysed in the same angiographic projection. When the stent delivery balloon was used for stent expansion, QCA measurements were performed between the markers of the stent delivery balloon and within the deployed stent markers. Acute stent recoil was calculated as previously described.[17–19]

Intravascular ultrasound

All cases were imaged with a 2.5 F Atlantis SR pro imaging 40 MHz catheter (Boston Scientific, Santa Clara, CA, USA). Post-procedure and at follow-up, stented culprit vessel segments were examined with mechanical IVUS using automated pullback at 0.5 mm per second. The coronary segment was examined by IVUS beginning 5 mm distal to and extending 5 mm proximal to the stented segment. A validated offline quantitative computer-based IVUS software was used for semi-automated three-dimensional reconstruction and analysis (CURAD Vessel analysis, Wijk bij Duurstede, The Netherlands).[20] The lumen, stent boundaries, and the external elastic membrane were detected in longitudinal reconstructed views. In order to obtain a smooth appearance of the vessel wall structures in the longitudinal views, a retrospective image-based gating method was applied (e.g. Intelligate^{TM}).[21]

The volumetric parameters of the stent, lumen, and obstruction [e.g. neointima hyperplasia (NIH)] volume and percentages were calculated as:

$$\text{Stent\_Volume} = \sum_{i=1}^{n} (\text{Stent\_Area}(i)) \times H,$$

where Stent_Area(i) is the stent area in one of the cross-sections of the stent, n the number of cross-sections, and H the distance between two consecutive cross-sections.

$$\text{Lumen\_Volume} = \sum_{i=1}^{n} (\text{Lumen\_Area}(i)) \times H,$$

where Lumen_Area(i) is the lumen area in one of the cross-sections of the stent. The other parameters are similar as described in the above formula.

$$\text{NIH\_Volume} = \sum_{i=1}^{n} (\text{Stent\_Area}(i) - \text{Lumen\_Area}(i)) \times H,$$

where Stent_Area(i) is the stent area in one of the cross-sections of the stent, Lumen_Area(i) the lumen area in the same, and the other parameters are similar as described in the above formula.

$$\%\text{NIH\_Obstruction} = \frac{\text{NIH\_Volume}}{\text{Stent\_Volume}} \times 100\%.$$

Incomplete apposition was defined as one or more stent struts separated from the vessel wall with evidence of blood speckles behind the strut by ultrasound, whereas late acquired incomplete apposition was defined as incomplete apposition of the stent at 4-month follow-up which was not present at post-procedure.

Clinical endoint definitions

Target vessel (or lesion) revascularization was considered to be ischaemia-driven if the target vessel (or lesion) diameter stenosis $\geq$50% by core laboratory quantitative analysis with ischaemic symptoms or with objective signs of ischaemia at rest or during exercise test, or a target vessel (or lesion) diameter stenosis $\geq$70% with or without documented ischaemia. Major adverse cardiac events (MACE) was defined as the composite of cardiac death, any MI, or ischaemia-driven target lesion revascularization (TLR). Spontaneous MI was defined as either a typical rise and gradual fall (Troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with ischaemic symptoms, development of new pathological Q-waves on the ECG or ECG changes indicative of ischaemia, or pathological findings of an acute MI, or development of new pathological Q-waves on follow-up ECG in the absence of cardiac biomarker assessment during the acute event.[22] Stent thrombosis was prospectively adjudicated using the Academic Research Consortium definitions.[23] Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation of thrombosis.

Study endpoints

The primary study endpoint was in-stent late loss at 4 months as measured by QCA. Angiographic secondary endpoints include in-segment late loss, binary restenosis rate, percentage diameter stenosis, and proximal and distal late loss at 4 months. Secondary IVUS endpoints at 4 months include minimal lumen area, stent volume, luminal volume, intrastent neointimal volume, %volume obstruction, incomplete stent apposition, and plaque volume behind the stent struts. Secondary clinical endpoints at 6 months included all-cause death, MI, coronary artery bypass surgery, TLR, definite stent thrombosis, and MACE.[23]

Statistical analysis

Continuous variables are presented as means $\pm$ standard deviation, and categorical variables are presented as counts and percentages. Paired comparisons between post-procedure and 4-month follow-up

were done by a Wilcoxon's signed rank test. All statistical tests were two-tailed and a *P*-value of <0.05 was considered as statistically significant. The current study is a FIM and single-arm study, and was designed to provide preliminary hypothesis-generating observations for further studies. The sample size was not defined on the basis of an endpoint hypothesis but rather to provide some information about the device efficacy and safety. The sample size requirement was established by the assessment of the minimum number of patients needed to provide reliable and non-trivial results, but is in range of the test group of the FIM trials of the SES ($n = 45$).[24,25] Statistical analysis was performed with SAS 8.2 (SAS Institute Inc., NC, USA).

The role of funding source

The study was sponsored by Kaneka (Osaka, Japan). In collaboration with the investigators, the sponsor designed the study. Data collection and data analysis were done by an independent clinical research organization (Cardialysis B.V.). The sponsor had no role in data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Patient characteristics

Forty-seven patients were included between May 2007 and November 2007. The baseline clinical characteristics are presented in *Table 1*. The average age of the patients was 61.1 ± 9.4 years, whereas 19.1% were diabetic and 66.0% were male. Procedure success was 97.9% since, in one patient, the MAHOROBA stent did not cross the lesion due to severe calcification. Since the follow-up is planned up to 5 years, the follow-up will be accomplished in November 2012.

Table 1 Baseline clinical, lesion, and procedural characteristics

Patient (*n*)	47
Male [*n* (%)]	31 (66)
Age (years ± SD)	61.1 ± 9.4
BMI (kg/m^2 ± SD)	28.2 ± 3.5
Cardiovascular risk	
Diabetes mellitus [*n* (%)]	9 (19.1)
Current smoker [*n* (%)]	14 (29.8)
Hypercholesterolaemia [*n* (%)]	34 (72.3)
Family history of CAD [*n* (%)]	27 (57.4)
Hypertensive [*n* (%)]	24 (51.1)
Previous MI [*n* (%)]	12 (25.5)
Previous CABG [*n* (%)]	2 (4.3)
Prior PCI [*n* (%)]	5 (10.6)
Anginal status [*n* (%)]	
Silent ischaemia	3 (6.4)
Stable angina	38 (80.9)
Unstable angina	6 (12.8)
Target vessel [*n* (%)]	
Left anterior descending artery	20 (40.8)
Left circumflex artery	12 (24.5)
Right coronary artery	16 (32.7)
AHA/ACC lesion classification [*n* (%)]	
A	1 (2.1)
B1	23 (48.9)
B2	22 (46.8)
C	1 (2.1)
Reference vessel diameter (mm ± SD)	2.76 ± 0.46
Lesion length (mm ± SD)	11.69 ± 5.36
Minimal lumen diameter (mm ± SD)	1.09 ± 0.36
Stent/artery ratio (mean ± SD)	1.17 ± 0.15
Maximal inflation pressure (atm ± SD)	16.3 ± 3.00

SD, standard deviation; BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

Quantitative coronary angiography analysis

Angiographic follow-up at 4 months was achieved in 41 patients (*Figure 2*). The angiographic parameters with matched pair analysis for phase and projection at baseline, post-procedural, and follow-up angiography ($n = 37$) are presented in *Table 2*. *Table 3* presents the results of QCA parameters related to acute stent recoil assessment. Acute absolute recoil was 0.22 ± 0.20 mm. At 4 months, the mean in-stent late loss, in-stent percentage diameter stenosis, and the rate of binary angiographic restenosis were 0.99 ± 0.46 mm, 38.66 ± 20.79%, and 26.7%, respectively. *Figure 3* demonstrates the cumulative frequency of in-stent MLD immediately after the index procedure and after 4 months.

Intravascular ultrasound evaluation

At 4 months, IVUS evaluation was performed in 40 patients. The results are tabulated in *Table 4*. A significant reduction of luminal volume was observed (187.4 ± 93.4 mm^3 at post-procedure vs. 123.5 ± 67.2 mm^3 at follow-up, $P < 0.0001$) with %volumetric obstruction of 34.78 ± 15.76%.

Incomplete stent strut apposition at baseline was reported in 16 of 46 (34.8%) patients, and this was resolved in 10 and persisted in 7 patients at 4-month. There were three cases of late acquired incomplete apposition based on the IVUS definition of malapposition of at least one stent strut separated from the vessel wall. According to a methodology, previously reported by our group, the malapposed volume at follow-up was 3.99 mm^3 in median (inter-quartile range 1.88–7.39).[26]

Major adverse cardiac events

Major adverse cardiac events are listed in *Table 5*. There were two cases of MI: one patient suffered a non-Q-wave MI at 64 days after the implantation of one MAHOROBA stent in the proximal left anterior descending artery, whereas the other experienced a non-Q-wave MI at 4 days after the procedure with angiographically proven definite stent thrombosis in the proximal left circumflex. Both patients were taking dual antiplatelet therapy at the time of MI. The latter patient experienced second TLR at 124 days due to restenosis of the MAHOROBA stent. There were other nine

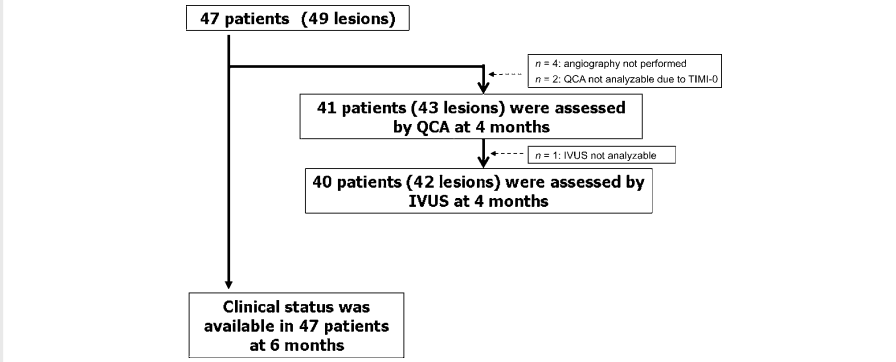

Figure 2 Study profile.

Table 2 Results of quantitative coronary angiographic analysis in matched pairs ($n = 37$)

Variables	In-stent	In-segment
Reference vessel diameter (mm)		
After procedure	2.94 ± 0.41	2.90 ± 0.43
At 4 months	2.57 ± 0.48	2.57 ± 0.48
Minimal luminal diameter (mm)		
After procedure	2.57 ± 0.36	2.27 ± 0.46
At 4 months	1.58 ± 0.63	1.55 ± 0.62
P-value	<0.0001	<0.0001
Late loss (mm)	0.99 ± 0.46	0.72 ± 0.51
Diameter stenosis (%)		
After procedure	12.50 ± 5.73	21.54 ± 8.75
At 4 months	38.66 ± 20.79	40.00 ± 20.29
P-value	<0.0001	<0.0001
Binary restenosis rate at 4 months[a] (%)	26.7	26.7

[a]Binary restenosis was calculated based on the unmatched data.

Table 3 Angiographic parameters related to acute stent recoil assessment ($n = 40$)

Variables	
Mean diameter of balloon at the highest pressure (mm)	3.17 ± 0.32
Mean diameter of stent immediately after balloon inflation (mm)	2.95 ± 0.37
Acute absolute recoil (mm)	0.22 ± 0.20
Acute per cent recoil (%)	7.11 ± 6.18

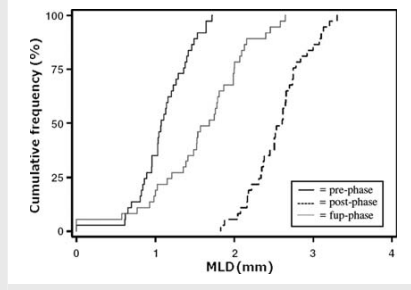

Figure 3 Cumulative frequency distribution curves of % minimal luminal diameter at pre-procedure, post-procedure, and follow-up.

cases of ischaemia-driven TLR (ID-TLR). In total, MACE rate (cardiac death, target-vessel MI, or ID-TLR) at 6 months is 23.4% (11/47).

Discussion

The efficacy of tacrolimus in inhibiting neointimal proliferation has been demonstrated in preclinical studies. Wieneke *et al.*[27] in an *in vivo* study using rabbit iliac artery model demonstrated that TESs coated with a nanoporous layer of aluminium oxide resulted in a significant reduction of neointimal thickness (NIT) by 50% with a total dose of 60 μg of tacrolimus and 56% for a dose of 120 μg of tacrolimus, when compared with BMS. In the *in vivo* study by Kollum *et al.*[28] using a swine model of restenosis, TES (JOMED, Rangendingen, Germany) with a nanoporous ceramic aluminium

Table 4 Intravascular ultrasound measurements in matched pairs at post-procedural and 4 months follow-up ($n = 42$)

	Post	Follow-up	*P*-value
Vessel volume (mm^3) (mean ± SD)	350.1 ± 170.7	377.2 ± 175.9	0.0002
Stent volume (mm^3) (mean ± SD)	188.6 ± 98.7	190.7 ± 100.7	0.316
Luminal volume (mm^3) (mean ± SD)	187.4 ± 93.4	123.5 ± 67.2	<0.0001
Plaque volume behind stents (mm^3) (mean ± SD)	165.1 ± 75.9	186.48 ± 81.87	<0.0001
Intimal hyperplasia volume (mm^3) (mean ± SD)		67.23 ± 48.36	
In-stent volume obstruction (%) (mean ± SD)		34.78 ± 15.76	
Frequency of ISA (%)[a]	34.8	21.4	
Resolved ISA at follow-up [*n* (%)]		10 (50)	
Persisting ISA at follow-up [*n* (%)]		7 (35)	
Late acquired ISA at follow-up [*n* (%)]		3 (15)	
ISA volume (mm^3) [median (inter-quartile range)]	2.69 (2.12–7.03)	3.99 (1.88–7.39)	

SD, standard deviation; ISA, incomplete stent apposition.
[a]Frequency of ISA was calculated as number of patients with at least one strut with incomplete stent apposition divided by the total number of patients.

Table 5 Adverse cardiac events at 6 months (per-patient analysis)

Event	*n*	%
All-cause death	0	0
Cardiac death	0	0
Stroke	0	0
Myocardial infarction	2	4.3
Target vessel	2	4.3
Non-target vessel	0	0
Cardiac death, stroke, or myocardial infarction	2	4.3
Repeat PCI–ID-TLR[a]	11	23.4
Repeat PCI–non-ID-TLR[b]	1	1
Repeat PCI–TVR	0	0
CABG	0	0
MACE (cardiac death, target-vessel myocardial infarction, or ID-TLR)	11	23.4
Definite stent thrombosis	1	2.1

MACE, major adverse cardiac events; ID-TLR, ischaemia-driven target lesion revascularization; Non-ID-TLR, non-ischaemia-driven target lesion revascularization; TVR, target vessel revascularization; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.
[a]One patient experienced ID-TLR twice, but counted as one.
[b]One patient experienced both ID-TLR and non-ID-TLR.

oxide coating at a dose of 180 μg demonstrated a significant inhibitory effect on neointimal proliferation. However, the inhibitory effect on restenosis was counteracted by inflammatory reaction due to major particle debris as a result of cracking of the ceramic coating.

After these preclinical studies, two clinical trials were performed using a TES with a biocompatible and non-thrombogenic carbofilm™ coating (Janus; Sorin Biomedica Cardio, Italy). In the 'FIM' study using the Janus stent loaded with a 1.5 $\mu g/mm^2$ of tacrolimus, TES was associated with a 3.8% binary restenosis rate at the 6-month follow-up in non-diabetics and 16.9% in diabetics.[29] After increasing the dose of TES from 1.5 to 2.3 $\mu g/mm^2$, the investigators performed a randomized trial including 332 patients to compare the performance of the TES with that of the BMS. The free drug—not incorporated in polymer or excipient—was released from wells carved in the abluminal side of the stent. No differences in angiographic results were observed at 6-month (in-stent late luminal loss; TES 0.65 ± 0.47 vs. BMS 0.66 ± 0.53 mm), and the 12-month MACE rates of TES were not lower than BMS (19.5 vs. 16.1%).[30]

The MAHOROBA strut has its own design with no previous clinical use and its mechanical performances were evaluated in this FIM study. Acute recoil analysis by QCA suggests that the MAHOROBA stent may have a relatively weaker radial strength than contemporary metallic DESs; the absolute recoil of MAHOROBA was 0.22 ± 0.20 mm, whereas % relative recoil was 7.11 ± 6.18%. Different methodologies of recoil assessment render comparison between different stents difficult. However, recent analysis by an independent clinical research organization (Cardialysis B.V.) provides us with comparative recoil analysis of a CoCr everolimus-eluting stent and the MAHOROBA stent employing the same methodology. According to the results, the acute recoil of the MAHOROBA seems to be higher, although stent oversizing can affect the results.[15]

The MAHOROBA stent is characterized by a biodegradable polylactic-co-glycolic acid coating with a bioabsorption time of about 6 months, resulting in a long-term sustained release of the drug. Although the MAHOROBA stent was used in patients with favourable characteristics and simple lesion, angiographic follow-up at 4 months demonstrated a mean in-stent late loss of 0.99 mm, which is equivalent or even slightly higher than the late loss observed in historical series with BMSs.

The reason for the absence of neointimal inhibition in MAHOROBA may be multifactorial: first of all, contrary to the mode of action of sirolimus and its analogues that inhibit mTOR and subsequently up-regulate p27, tacrolimus acts through different

pathways and involves the calcineurin–calmodulin complex. Therefore, its mode of inhibition of SMC proliferation is fundamentally different from sirolimus, and redundancy of signalling pathways for cell growth may supersede the specific inhibitory effect of tacrolimus. Pimecrolimus, a tacrolimus analogue might not only fail to inhibit but might also even promote further neointimal hyperplasia. In the recent prospective, three-arm, GENESIS study randomizing patients with *de novo* coronary artery disease either to paclitaxel-eluting (10 μg) or pimecrolimus/paclitaxel dual-eluting (162.5/10 μg) or pimecrolimus-eluting stent (325 μg), the pimecrolimus-eluting stent demonstrated the highest in-stent late loss (paclitaxel 0.58 ± 0.58 vs. paclitaxel/pimecrolimus 0.96 ± 0.73 vs. pimecrolimus 1.40 ± 0.67 mm) with the highest target vessel revascularization rate (2.0 vs. 14.4 vs. 35.0%) at 6-month.[31] Therefore, the GENESIS study was suspended before complete enrolment was achieved. Taking these results into consideration, tacrolimus and its analogue might not be a suitable drug to prevent the restenosis even though efficacy in neointimal inhibition of neointima had been demonstrated in the animal studies. Secondly, the relatively low intra-parietal concentration during elution may be insufficient to effectively inhibit neointimal hyperplasia. Matter *et al.*[11] demonstrated that in human saphenous vein cells, the IC50 of sirolimus to inhibit proliferation of vascular SMC was 4.1×10^{-9} mol/L, whereas the IC of tacrolimus was 0.38×10^{-6} mol/L. In the study by Mohacsi *et al.*[10] using human thoracic aorta, IC50 of sirolimus and tacrolimus was $1–10 \times 10^{-9}$ and 1×10^{-6}, respectively. These results suggest that a100- to 1000-fold higher tissue concentration of tacrolimus is necessary to exert the same neointimal inhibition as a SES. The MAHOROBA stent has a tissue concentration with a peak value of around 130 ng/mg artery (*Figure 4*), whereas Cypher is around 6 ng/mg artery[32] in animal models. The concentration of tacrolimus may therefore still be too low to achieve sufficient neointimal inhibition, although it is about 20 times higher than the SES. Recently, in a porcine coronary study, van Beusekom *et al.* assessed neointimal thickening after the implantation of a BMS, polymer-coated stent (Pol) without drug, a slow degrading low dose (1 μg/mm^2) TES, and a fast degrading high-dose (2 μg/mm^2) TES. The low-dose TES is similar to the MAHOROBA stent. Morphometry indicated that NIT in both TES was significantly reduced when compared with BMS and Pol up to 90 days (BMS: 335 ± 148; pol: 381 ± 186; low-dose TES: 226 ± 52; and high-dose TES: 262 ± 80 μm). However, at 180 days, only the high-dose TES showed significantly lower NIT when compared with BMS or Pol stent because the slow degrading low-dose TES demonstrated catch-up of NIT between 90 and 180 days. Therefore, the inhibitory effect of low-dose TES (equal to MAHOROBA stent) on neointimal hyperplasia was somewhat suboptimal in the animal study, and high-dose TES might be optimal for DES. Thirdly, remnant polymer after complete elution of the drug could to some extent continue to stimulate neointimal growth in the stent. In a porcine model, the polymer of the MAHOROBA stent continues to be degraded up to 110 days but possibly without sufficient tacrolimus beyond 90 days to dampen the tissue response.[30] Fourthly, the rate of incomplete stent apposition appears high at 35% in this study, although it is still in the range of previous study.[33] The lack of proper elution of the drug at the abluminal side might be a potential explanation for the large presence of neointimal hyperplasia observed in this study.

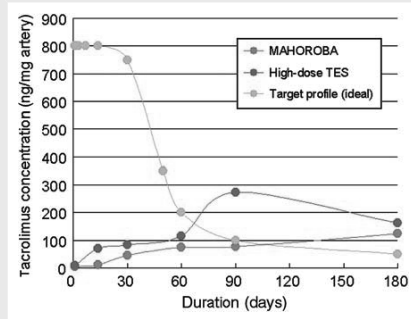

Figure 4 Comparison of release curves in MAHOROBA stent (1 μg/mm^2, orange), high-dose tacrolimus-eluting stent (2 μg/mm^2, pink), and ideal curve (light blue).

Modification in the dose and release of tacrolimus might be mandatory to create an effective TES. *Figure 4* shows the tissue concentration of tacrolimus in TES with different doses. Conversely, the MAHOROBA demonstrates the ability to maintain tissue concentrations for longer periods, but in the first 2 weeks is unable to attain sufficient concentration that are considered adequate for neointimal inhibition after stenting. Theoretically, a biphasic-release TES with a burst phase in the first 2 weeks followed by sustained release could have the ability to inhibit neointimal proliferation. A dual polymeric coating with rapid and slow drug-eluting profiles might be necessary to achieve biphasic release. An increased amount of polymer is indispensable to contain higher dose of drug than current, which could result in a thicker profile of the stent struts and a longer duration of absorption. It will be a technological challenge to develop a dual-coated stent with thin struts and an improved polymer degradation profile synchronized with drug release.

Intravascular ultrasound analysis in the current study demonstrated a significant increase in the plaque behind the stent (PBS) 4 months after the procedure. In the PISCES study using PESs with a durable PGLA polymer coating, specially designed for drug delivery with programmable pharmacokinetics, a significant increase in PBS at 4-month was reported in paclitaxel-loaded stents with equal or longer elution than 10 days, but not in-stents with a short elution of 5 days.[34] These results suggest that the long-term presence of either drugs or PGLA polymer might cause extensive remodelling after stent implantation, presumably resulting from vessel inflammation. Also in the study using PESs,[35] a significantly increased peri-stent area was observed at 6 months. However, sirolimus[36] or everolimus-eluting stents[26] with durable polymers, this effect on positive vascular remodelling has not been reported.

The current study has several limitations. The angiographic and IVUS follow-up were only performed at 4 months, which might be

too short to assess the full extent of neointimal hyperplasia after DES implantation. At the time of the study design, further invasive imaging with angiography and IVUS was planned in the protocol at 12 months to assess the full process of neointimal hyperplasia. However, after evidencing high amounts of neointimal hyperplasia with high rates of ischaemic TLR events at 4 months, the protocol was amended by the data safety monitoring board for safety reasons. It was decided to monitor patients more carefully with non-invasive stress ECG testing at 6 months and 9 months. Since the scientific goal had not been achieved, the invasive angiography originally planned at 12 months for scientific purposes was abandoned, and angiographic follow-up after 4 months was only performed for clinical reasons. Frequency of incomplete stent apposition was as high as 34.5%. The rate of malapposition, however, was calculated as the number of patients with at least one strut with incomplete stent apposition divided by the total number of patients and does not reflect the number of malapposed strut or the malapposed volume. This study did not mandate IVUS-guided stenting, so that post-dilation was completely left to the operators' discretion. In addition, given the relatively high stent malapposition rate and % acute recoil, it is difficult to know how much each component of the stent (i.e. polymer, stent platform and drug) could contribute to the failure of this DES.

Despite the conceptual advantages of using tacrolimus with a biodegradable polymer, this FIM study has failed to establish the effectiveness of this stent. Taking the multifactorial reasons of failure into consideration, tacrolimus formulation of the current stent seems unsuitable to prevent restenosis. Technical improvements enable us to construct TES with a higher drug content and improved polymer degradation profile in synchronization with drug release.

Funding

The study was sponsored by Kaneka (Osaka, Japan).

Conflict of interest: T.N. is an employee of Kaneka corporation.

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CHAPTER 33

Assessment of the absorption process following bioabsorbable everolimus-eluting stent implantation: temporal changes in strain values and tissue composition using intravascular ultrasound radiofrequency data analysis. A substudy of the ABSORB clinical trial

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EuroIntervention. 2009 Jan; 4(4): 443-448.

EuroIntervention

Assessment of the absorption process following bioabsorbable everolimus-eluting stent implantation: temporal changes in strain values and tissue composition using intravascular ultrasound radiofrequency data analysis A substudy of the ABSORB clinical trial

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None of the authors have a conflict of interest to declare.

KEYWORDS
Bioabsorbable stent, palpography, IVUS-VH

Abstract

Aims: The main objective was to use IVUS-backscatter radiofrequency (IVUS-RF) to assess the degradation of a bioabsorbable stent by measuring serial changes in dense calcium (DC) and necrotic core (NC) as assessed by intravascular ultrasound-Virtual Histology™ (IVUS-VH) and in the strain as assessed by palpography.

Methods and results: In the ABSORB trial, 27 patients treated with a single bioabsorbable everolimus-eluting stent (BVS, Abbott Vascular, Santa Clara, CA, USA) were all imaged with IVUS-RF post-stenting and at 6-month follow-up, and 13 and 12 patients were also investigated pre-stenting with IVUS-VH and palpography respectively.

From pre- to post-stenting, with VH (n=13), there was an increase in mean "DC" (9.8 vs. 25.4%, p=0.0002) and "NC" (15.5 vs. 30.5%, p=0.0002). In palpography (n=12), the mean number of frames with Rotterdam Classification (ROC) III/IV per cm decreased from 1.22±1.91 to 0.12±0.31 (p= 0.0781) and the mean cumulative strain values (all frames with ROC I-IV scores) changed from 0.50±0.27 to 0.20±0.10% (p= 0.0034).

Comparing post-stenting with follow-up (n=27), VH showed a decrease in "DC" (29.7% vs. 21.1%, p=0.0001). "NC" also decreased (26.9 vs. 21.5%, p=0.0027). For palpography (n=25 patients), an increase in the mean number of frames with ROC III/IV per cm was observed from 0.09±0.26 to 0.22±0.36 (p=0.1563) while the mean cumulative strain values (all frames with ROC I-IV scores) changed from 0.15±0.10 to 0.26±0.12% (p<0.0001).

Conclusions: IVUS-VH changes at 6 months suggest alteration of the BVS with reduction of RF backscattering by polymeric struts. Strained plaques on the palpograms were almost abolished following stent implantation. However, strain values reappeared within 6 months suggesting an increase in endoluminal deformability of the stented vessel.

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Introduction

Metal stent use has been one of the major breakthroughs in the treatment of patients with coronary artery disease.[1] However, the many advantages are somewhat counterbalanced by associated pitfalls such as restenosis, the persistent metal presence that may preclude late surgical revascularisation of the treated vessel, and jailing of side branches.[2-9] The advent of a new bioabsorbable everolimus-eluting stent[10] promises to overcome some of these disadvantages. The *in vivo* serial changes in its structural conformation (polymer degradation profile) were established in a porcine coronary artery model. Mass loss was approximately 30% at 12 months with a further reduction to 60% mass loss by 18 months after implantation[10]. However, in human coronary arteries the bio-absorption process has never been explored. Hence in the ABSORB trial all clinically available and potentially useful invasive coronary imaging techniques to assess bio-absorption of polymeric struts were used (i.e. echogenicity, intravascular ultrasound [IVUS] – radiofrequency [RF] data analysis: Virtual Histology™ [VH] and palpography and optical coherence tomography). Nevertheless, none of these techniques have been specifically designed to assess bio-absorption. Specifically, IVUS-VH[11,12] is a tool developed to assess the tissue composition of intact native coronary arteries. The analysis of the actual stent area and its surroundings by IVUS-VH identified the stent struts as "dense calcium" and "necrotic core" (white and red colour in the VH colour-code), which correspond to a specific backscattered radiofrequency of the polymeric strut structures (highly echogenic). Palpography is an IVUS-based technique that assesses the local mechanical deformation of the vessel wall by measuring the relative alteration of backscattered radiofrequency signals at two different blood pressure levels. For instance, lipid-rich vulnerable plaques ha ve greater deformation and higher strain values compared to calcific or fibrous plaques.[13] The main objective was twofold: i) to use IVUS-VH to follow-up the degradation of a bio-absorbable everolimus-eluting stent by measuring the temporal changes in IVUS-VH characteristics at pre-, post-stenting and at 6 months; and ii) to evaluate the temporal changes in palpographic strain values in the stented segment.

Methods

Study design

The study design for the prospective, open label ABSORB trial has already been published elsewhere.[10] Briefly, this was a single arm study that enrolled 30 patients at 4 participating sites between March and July 2006. Patients were older than 18 years, with a diagnosis of stable, unstable or silent ischaemia. All treated lesions were single, *de novo* in a native coronary artery of 3.0 mm, shorter than 8 mm for the 12 mm stent or ≤14 mm for the 18 mm stent (only two patients received an 18 mm stent), with a % diameter stenosis ≥50% and <100% and a thrombolysis in myocardial infarction (TIMI) flow grade of ≥1. Major exclusion criteria were patients presenting with an acute myocardial infarction, unstable arrhythmias or patients who had left ventricular ejection fraction <30%, restenotic lesions, lesions located in the left main coronary artery, lesions involving a side branch >2 mm in diameter, and the presence of thrombus or another clinically significant stenosis in the target vessel.

The study was approved by the ethics committee at each participating institution and each patient gave written informed consent before inclusion.

Study device

The BVS stent has a polymer backbone of Poly-L (racemic)-lactic Acid (PLLA) coated with a Poly-D (racemic), L-lactic acid (PDLLA) polymer that contains and controls the release of the anti-proliferative drug everolimus. Both PLLA and PDLLA are fully absorbable. The absorption process occurs via hydrolysis: the long chains of PLLA/PDLLA become shorter as bonds between the repeating units are hydrolysed, producing lactic acid which is metabolised via the Krebs cycle, and small particles <2 microns diameter that are phagocytosed by macrophages. The time for complete absorption of the polymer backbone is predicted from preclinical studies to be about 2-3 years whereas the polymer coating is absorbed in approximately 9 months.

Stenting procedure

Lesions were treated with routine interventional techniques that included mandatory pre-dilatation using a balloon shorter than the study device and 0.5 mm less in diameter. The BVS stent was implanted at a pressure not exceeding the rated burst pressure (16 atm). All patients were pretreated with aspirin and a loading dose of at least 300 mg of clopidogrel was administered according to local hospital practice. After the procedure, all patients were to receive aspirin ≥75 mg daily for the study duration (5 years) and clopidogrel 75 mg daily for a minimum of 6 months. Anticoagulation and glycoprotein IIb/IIIa inhibitor use was according to local hospital practice.

Imaging procedure

Pre-stenting IVUS-VH (n=13) and pre-stenting palpography (n=12) imaging were obtained in a subgroup of patients treated at the Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands. The purpose of these analyses was to observe the acute changes after the implantation of the BVS stent. Subsequently, in the entire population IVUS-RF was obtained post-stenting and at follow-up. Both imaging techniques were acquired simultaneously with a phased array 20 MHz intravascular ultrasound catheter (EagleEye™; Volcano Corporation, Rancho Cordova, CA, USA) using automated pullback at 0.5 mm per second. Four tissue components (necrotic core – red; dense calcium – white; fibrous – green; and fibro-fatty – light green) were identified with autoregressive classification systems.[11,14] Each individual tissue component was quantified and colour coded in all IVUS cross sections as previously described. In a previous post-mortem validation study, RF analysis demonstrated sensitivity and specificity for detection of necrotic core of 92% and 97%, respectively.[14] All IVUS- VH analyses were performed offline using pcVH 2.1 (Volcano Corporation, Rancho Cordova, CA, USA) by an independent clinical research organisation (Cardialysis, Rotterdam, The Netherlands). For each cross section, polymeric stent struts were detected as areas of apparent "dense calcium" and "necrotic core". We used the change in quantitative analyses of these characteristics between implantation and follow-up as a surrogate assessment of the polymer bio-absorption process. IVUS-based palpography assesses deformability of the plaque. The underlying principle is that softer tissue is more readily deformed

compared with harder tissue when force (eg, pulsatile arterial pressure) is applied.[13] The deformability of coronary plaque is quantified using the analysis of radiofrequency signals at different diastolic pressure levels. The strain is normalised to a pressure difference of 2.5 mm Hg per frame. This allows the construction of a 'strain' image in which harder (low strain) and softer (high strain) regions of the coronary arteries can be identified, with radial strain values ranging between 0% and 2%.[13] In post-mortem coronary arteries that were investigated with histology and IVUS palpography, the sensitivity and specificity of palpography to detect high strain values were 88% and 89%, respectively.[13]

Plaque strain values were assigned a Rotterdam Classification (ROC) score ranging from I to IV (ROC I: 0% to 0.6%; ROC II: 0.6% to <0.9%; ROC III: 0.9% to <1.2%; ROC IV: >1.2%) as previously described.[15] All IVUS- palpography analyses were performed by an independent clinical research organisation (Cardialysis, Rotterdam, The Netherlands).

The clinical and geometrical analysis in the ABSORB study has already been reported.[10] Thus, in this paper, we exclusively report changes in tissue composition and plaque deformability.

Statistical analysis

As stated in the main ABSORB Study, the sample size was not defined on the basis of an endpoint hypothesis but rather to provide information about device efficacy and safety. Therefore, the present substudy should be seen as hypothesis-generating.

Discrete variables are presented as counts and percentages. Continuous variables are presented as means ± SD, quartiles and ranges. A two-sided p-value of less than 0.05 indicated statistical significance. Due to the exploratory nature of these analyses, p values were unadjusted for multiple comparisons in this manuscript.

The density of high-strain spots per 10 mm was defined as the number of cross-sections with strain values ≥0.9% (i.e. ROC III or IV) divided by the number of all analysable cross sections in the region of interest and normalised for 10 mm.

Paired comparisons between pre-procedure, post-procedure and follow-up were done by the Wilcoxon signed rank test. Statistical analyses were performed with use of SAS 9.1.

Results

Overall, 30 patients were included in the ABSORB study. The mean age was 62±9 years, most being male patients (60.0%), while 70.0% of the patients presented with stable angina, 26.7% and 3.3% had unstable angina and silent ischaemia respectively. The studied vessel was the left anterior descending in 46.7%, the left circumflex in 30.0% and the right coronary artery in 23.3% of the patients.

Intravascular ultrasound Virtual Histology™

Changes between pre- and post-stenting

In 13 patients, IVUS-VH was performed pre- and post-stenting (Table 1 and Figure 1). The mean percentage of "dense calcium" increased from 9.8% to 25.4% (p=0.0002) and "necrotic core" went from 15.5% to 30.5% (p=0.0002). Fibrous tissue, the major component of the vessel wall when expressed as mean area did not demonstrate statistically significant changes post-stenting, however its

Table 1. Acute changes in IVUS-VH in 13 patients.

	Pre stenting	Post stenting	p value
Dense calcium (mm²)			0.0002
Mean ± SD (N)	0.42±0.44 (13)	1.23±0.68 (13)	
Median	0.27	1.12	
(Q1-Q3)	(0.06, 0.89)	(0.87, 1.51)	
Range (min, max)	(0.01, 1.14)	(0.39, 2.90)	
Dense Calcium (%)			0.0002
Mean±SD (N)	9.83±9.64 (13)	25.42±11.27 (13)	
Median	6.19	27.09	
(Q1-Q3)	(4.26, 15.06)	(16.79, 31.78)	
Range (min, max)	(0.25, 34.66)	(9.91, 46.87)	
Fibrous (mm²)			0.1099
Mean±SD (N)	2.52±1.37 (13)	2.12±1.17 (13)	
Median	2.43	2.37	
(Q1-Q3)	(1.40, 3.62)	(1.05, 2.88)	
Range (min, max)	(0.17, 4.40)	(0.32, 4.08)	
Fibrous (%)			0.0002
Mean±SD (N)	60.75±13.06 (13)	38.98±10.47 (13)	
Median	64.40	37.14	
(Q1-Q3)	(52.32, 72.71)	(31.73, 45.35)	
Range (min, max)	(35.31, 76.90)	(24.88, 58.28)	
Fibrofatty (mm²)			0.0034
Mean±SD (N)	0.63±0.46 (13)	0.29±0.25 (13)	
Median	0.67	0.19	
(Q1-Q3)	(0.32, 0.94)	(0.10, 0.43)	
Range (min, max)	(0.01, 1.50)	(0.01, 0.81)	
Fibrofatty (%)			0.0002
Mean±SD (N)	13.89±8.31 (13)	5.07±3.92 (13)	
Median	13.22	3.76	
(Q1-Q3)	(8.76, 14.47)	(2.45, 5.48)	
Range (min, max)	(4.50, 34.16)	(1.44, 14.31)	
Necrotic Core (mm²)			0.0002
Mean±SD (N)	0.74±0.62 (13)	1.66±0.86 (13)	
Median	0.60	1.70	
(Q1-Q3)	(0.28, 1.24)	(0.89, 2.28)	
Range (min, max)	(0.03, 1.92)	(0.29, 2.88)	
Necrotic Core (%)			0.0002
Mean±SD (N)	15.53±8.43 (13)	30.54±6.16 (13)	
Median	14.10	31.56	
(Q1-Q3)	(9.86, 21.31)	(28.39, 33.62)	
Range (min, max)	(1.19, 33.01)	(17.50, 41.82)	

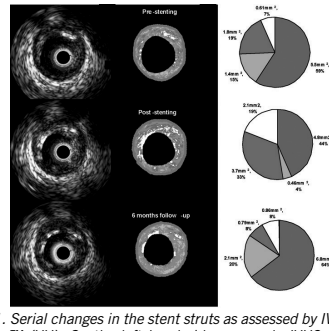

Figure 1. Serial changes in the stent struts as assessed by IVUS Virtual Histology™ (VH). On the left hand side, greyscale IVUS images are shown at pre-, post-stenting and follow-up. In the central part, their corresponding colour code VH images are depicted. On the right hand side, per-cross section quantification in absolute and relative terms is shown. Of note, increases in "dense calcium" (white) and "necrotic core" (red) are noted after stenting. At follow-up, a change in the stent strut appearance in greyscale IVUS is noted and decreases in the "dense calcium" and "necrotic core" contents in IVUS- VH are detected. Fibrous - green; and fibro-fatty - light green.

relative contribution to the stented vessel wall decreased significantly (60.8% vs. 39.0%, p=0.0002). In a similar fashion the percentage of fibro-fatty tissue decreased (13.9% vs. 5.1%, p=0.0002).

Changes from post-stenting to follow-up

Overall, in patients (n=27) with post-stenting and follow-up VH, a significant decrease in "dense calcium" (29.7% vs. 21.1%, p=0.0001) was shown. In 21 out of 27 patients, there was a regression in the "calcified" pattern (Table 2 and Figure 2). The content of "necrotic core" also decreased (26.9% vs. 21.5%, p=0.0027). In turn, both fibro-fatty and fibrous tissue increased in terms of both mean areas and percentages (Table 2 and Figure 1).

Intravascular ultrasound palpography

CHANGES FROM PRE- TO POST-STENTING

In 12 patients, IVUS-palpography was performed pre- and post-stenting (Figure 3 and 4). The mean number of frames with ROC III/IV per cm decreased from 1.22±1.91 to 0.12±0.31 (p=0.0781). The mean cumulative strain values in all frames with ROC I-IV scores changed from 0.50±0.27 to 0.20±0.10% (p= 0.0034).

CHANGES FROM POST-STENTING TO FOLLOW-UP

In patients (n=25) with post-stenting and follow-up palpography, a slight increase in the mean number frames with ROC III/IV per cm from 0.09±0.26 to 0.22±0.36 (p=0.1563) was observed, while the mean cumulative strain values in all frames with ROC I-IV scores increased significantly from 0.15±0.10 to 0.26±0.12% (p<0.0001) (Figure 3 and 4).

Discussion

In this substudy of the ABSORB clinical trial the main findings in IVUS-VH were an important increase in "dense calcium" and "necrotic core" immediately after stent implantation and a subsequent decrease of these tissue surrogates at 6 months follow-up; this decrease potentially reflects echogenic alteration of the BVS stent struts. On the palpograms, the almost complete initial abolition of the high strain regions was decreased six months following stent implantation: presumably after partial stent absorption the mean strain values increased again.

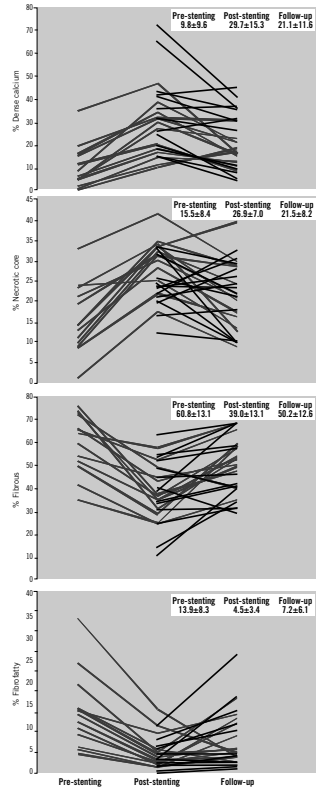

Figure 2. Temporal changes in virtual histology tissue types. From top to bottom, the mean percentage of "dense calcium", "necrotic core", fibrous tissue and fibro-fatty tissue is reported. Thirteen patients were imaged at pre-, post-stenting and follow-up (red solid lines). A further 14 patients were only imaged at post-stenting and follow-up (black dotted lines).

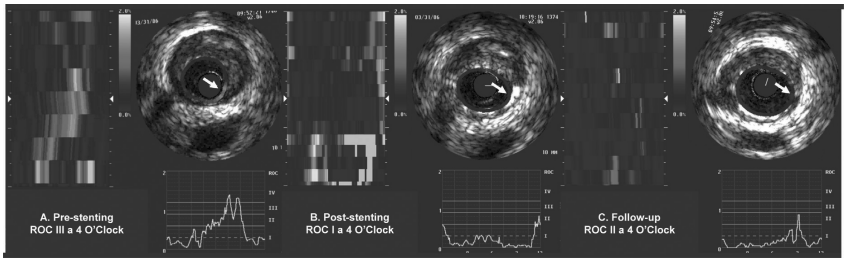

Figure 3. Sequential changes in high-strain values as assessed by IVUS-palpography. Panel A shows an intact plaque with a ROC III spot at 4 o'clock (white arrow). Panel B depicts abolition of this high strain spot following stenting (ROC I). In panel C a slight increase in plaque deformability was documented (ROC II).

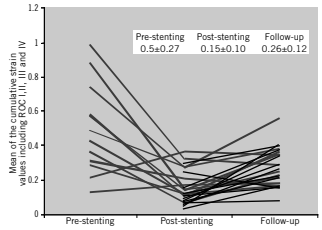

Figure 4. Temporal changes in strain values. The mean cumulative strain values in all frames with ROC I-IV scores are shown. Twelve patients were imaged at pre-, post-stenting and follow-up (red solid lines). Another 13 patients were only imaged at post-stenting and follow-up (black dotted lines). After stenting, abolition of the strain values was noted; however a higher level of plaque deformability was present at follow-up.

Table 2. Changes from post -procedure to 6-months.

	Post stenting	Follow-up	p value
Dense Calcium (mm^2)			0.6065
Mean±SD (N)	0.97±0.59 (27)	0.88±0.61 (27)	
Median	0.89	0.86	
(Q1-Q3)	(0.49, 1.25)	(0.31, 1.22)	
Range (min, max)	(0.28, 2.90)	(0.17, 2.82)	
Dense Calcium (%)			0.0001
Mean±SD (N)	29.66±15.25 (27)	21.13±11.58 (27)	
Median	27.09	18.49	
(Q1-Q3)	(18.22, 38.44)	(10.86, 30.80)	
Range (min, max)	(9.91, 72.10)	(4.66, 44.91)	
Fibrous (mm^2)			<0.0001
Mean±SD (N)	1.65±1.23 (27)	2.42±1.37 (27)	
Median	1.47	2.53	
(Q1-Q3)	(0.69, 2.57)	(1.19, 3.36)	
Range (min, max)	(0.06, 4.08)	(0.17, 4.93)	
Fibrous (%)			<0.0001
Mean±SD (N)	39.02±13.07 (27)	50.20±12.55 (27)	
Median	37.79	50.71	
(Q1-Q3)	(30.70, 49.81)	(40.26, 59.24)	
Range (min, max)	(10.85, 63.69)	(29.26, 68.95)	
Fibro-fatty (mm^2)			0.0040
Mean±SD (N)	0.21±0.23 (27)	0.38±0.42 (27)	
Median	0.11	0.22	
(Q1-Q3)	(0.04, 0.33)	(0.12, 0.48)	
Range (min, max)	(0.00, 0.81)	(0.01, 1.72)	
Fibro-fatty (%)			0.0096
Mean±SD (N)	4.47±3.36 (27)	7.22±6.12 (27)	
Median	3.32	4.72	
(Q1-Q3)	(2.45, 5.65)	(2.57, 11.16)	
Range (min, max)	(0.54, 14.31)	(1.21, 26.18)	
Necrotic core (mm^2)			0.4815
Mean±SD (N)	1.14±0.86 (27)	1.01±0.73 (27)	
Median	0.89	0.90	
(Q1-Q3)	(0.33, 1.77)	(0.58, 1.23)	
Range (min, max)	(0.10, 2.88)	(0.13, 3.07)	
Necrotic core (%)			0.0027
Mean±SD (N)	26.85±6.97 (27)	21.45±8.17 (27)	
Median	25.53	21.80	
(Q1-Q3)	(21.85, 33.11)	(13.61, 28.59)	
Range (min, max)	(12.30, 41.82)	(8.87, 39.70)	

In a previous study by Tamai et al,[16] PLLA stents analysed by greyscale IVUS at 6 months seemed to maintain their scaffolding properties and apparently did not exhibit changes in echogenicity as a sign of biodegradation. In the ABSORB trial, a reduction of the stent area was observed suggesting a mild recoil of the polymeric stent structures.[10] Implantation of polymeric struts resulted in the appearance in the vessel wall of highly echogenic structures with radiofrequency backscattering similar to calcific structures (Figure 1). Indeed, in this study using IVUS-VH, an increase in absolute "dense calcium" (Δ0.82 mm^2, p=0.0002) from pre- to post-stenting was observed. This dramatic and sudden change in "DC" may be attributed to the introduction of polymeric struts and might correspond to the VH fingerprint of the polymeric struts.

Following BVS stent implantation, the mean fibrous tissue area showed a slight decrease that failed to reach statistical significance (from 2.5 to 2.1 mm^2, p=0.1099). The mean fibro-fatty tissue area decreased significantly, although the change is numerically very small, and might be an artefact. From the ultrasonic point of view, the introduction of these highly echogenic structures might affect ultrasound penetration and therefore the backscattering of other tissue components located behind the struts, since potentially less acoustic signals are reaching the tissue.

Although we acknowledge that the classification tree of the IVUS radiofrequency analysis has not been validated for polymeric stent struts, the radiofrequency backscattering is expected to increase with the reduction in the echogenicity of the implanted stent. It is reasonable to assume that the hydrolysis of the polymer which affects its molecular weight and mass, will also alter its acoustic properties. The BVS stent is constituted of PLLA (backbone) and PDLLA (coating) which are both fully bio-absorbable. During bio-absorption, the long chains of PLLA and PDLLA are progressively shortened and ultimately phagocytosed by macrophages.[10] At follow-up, these pseudo-dense calcific structures shrink by nearly 30% (in absolute terms, an 8.6 % reduction in "dense calcium" from 29.7% to 21.1%), which is consistent with the reduction in mass of the BVS polymeric struts observed in animals. These observations are at variance with the previous report by Tamai et al where no signs of biodegradation were observed.[16] A possible explanation is that the speed of bioabsorption of a polylactic polymer is greatly influenced by its purity, crystallinity and relative composition of L and D isomers.

The changes in the physical properties of an artery can be described in terms of stiffness, ability to distend and compliance. These characteristics are dependent on the composition of the vascular wall.[17] Deployment of a stent against the vessel wall undoubtedly modifies the physical properties of the endoluminal surface. The near-abolition of the high strain values (ROC III/IV) immediately post-stenting reflects major changes in deformability of the plaque and the observed reductions in high strain values may be due to a real decrease in deformability of the scaffolded vessel wall. Alternatively, it may also reflect an ultrasonic artefact, namely the incapability of palpography to measure intrinsic changes in strain of the vessel due to the acoustic properties of the stent struts preventing a proper propagation of radiofrequency signal behind them. The loss of mass observed over time in the porcine model may cause the reappearance of high strain values on the endoluminal surface of the vessel wall. All these observations are indirect indicators of the modifications in strut structure. Although

IVUS-VH and palpography have not been validated to detect change in the integrity of polymeric stents, they seem to change acutely and chronically with the introduction and subsequent bio-absorption of the polymeric struts.

These new imaging techniques allow a better understanding of the effect of different therapeutic modalities.

Among the many clinical implications of the use of a biobasorbable stent, the most relevant pertains to the possibility to avoid potentially deadly events such as late stent thrombosis, providing the stent is fully absorbed in a reasonable period of time. Ideally, bio-absorption must occur after neointimal growth has been modulated. Knowing that this occurs mainly during the first 6 months after stent implantation, we have assessed bio-absorption using IVUS radiofrequency data analysis over this period of time. The results of the present substudy are unique findings since the *in vivo* bio-absorption rate in diseased human arteries is not known.

Limitations

In the context of stent studies, IVUS radiofrequency data analysis faces the following issues: i) misclassification of the stent struts as "dense calcium" and "necrotic core" in VH; ii) with both techniques – VH and palpography – the lack of proper validation to assess polymeric stents and; iii) the potential interference of the superficial stent struts on the backscattering from the tissue behind them. However, these techniques have corroborated other observations of polymer alteration documented with light transmission. In other words, changes in optical coherence of the struts reported elsewhere confirm the ultrasonic modifications reported here.

Conclusions

The quantitative assessment of the IVUS-VH changes at 6 months suggests early strut alteration of the BVS stent with reduction of radiofrequency backscattering. High-strain plaques seen on the palpograms were almost abolished following stent implantation. However, strain values reappeared at 6 months in some patients also suggesting an increase in deformability on the luminal surface of the stented vessel.

Acknowledgements

Authors are grateful to Jurgen Ligthart, Senior IVUS technician in Thoraxcenter, Erasmus MC and Monique Schuijer, ABSORB trial project manager at Cardialysis NL. Authors also thank Susan Veldhof from Abbott Vascular.

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Summary and Conclusions

SUMMARY AND CONCLUSIONS

We have seen huge technological strides since the first introduction of DES into clinical practice. The concerns regarding stent thrombosis have driven investigators across the globe to carefully scrutinize the outcomes of patients treated with drug-eluting stents. This holds true particularly for patients with complex co-morbidities or complex coronary anatomy: such cases account for two thirds of patients treated in the real world, but these patients have historically been excluded from randomized controlled trials. In this thesis, the long-term results from the 1st generation of DES are investigated. The data gained from this is unique and invaluable since all patients undergoing PCI were treated with DES without any selection bias since their commercial availability.

Long-term follow-up of 1st generation drug-eluting stents

Both SES and PES reduce the need for target vessel revascularization (adjusted HR 0.69, 95% CI 0.58-0.82) compared with BMS even after 4 years of clinical follow-up. Stent thrombosis rates were non-significantly higher with DES (adjusted HR 1.26, 95%CI 0.82-1.95), but this did not translate into higher rates of myocardial infarction or death.

ST-elevation myocardial infarction

Implanting a DES in the presence of a thrombus-laden acutely occluded vessel has caused concern for many interventional cardiologists. In this primary PCI environment, with an increased potential for late stent malapposition as the thrombus resorbs, the safety issues have been heightened. There have been randomized trials showing the benefit of DES in this setting, but even these trials have had exclusion criteria. We followed-up 1738 consecutive patients for a mean duration of 1185 days. We found a strong trend towards a reduction in major adverse cardiac events (all-cause death, nonfatal myocardial infarction or target vessel revascularization) with SES compared with BMS (adjusted HR 0.66, 95%CI 0.43-1.01, logrank p=0.04). There were no differences between PES and BMS (adjusted HR 0.97, 95% CI 0.75-1.26, logrank p=0.4). Overall, DES were not associated with increased overall 3-year adverse events when used for primary PCI. However, given the cost difference compared with BMS, our results do not support the use of PES in patients with STEMI as these stents conferred no clinical benefit over BMS. SES, however, were associated with a trend toward improved mortality compared with PES and BMS, although this did not reach statistical significance.

Diabetics

Patients with type II diabetes exhibit a breakdown in the PI3-kinase insulin signal transduction pathway, the pathway in which mammalian target of rapamycin (mTOR) is involved. It has been hypothesized that in this situation, inhibiting protein synthesis by

blocking mTOR with rapamycin may be less effective. In Part 4 of this thesis, we found that Target vessel revascularization was 19.5% in the BMS group, vs. 15.3% in the SES group and 9.7% in the PES group. PES (21.2%), but not SES (28.9%), were superior to BMS (29.7%) in reducing major adverse cardiac events in diabetics.

Chronic total occlusions

The treatment of patients with chronic occlusions remains a challenge: dedicated guidewires and special devices are required, and even with a complete arsenal, success rates remain far lower than for other coronary lesions. Patients undergoing successful PCI of a chronic occlusion often require multiple overlapping stents and demonstrate higher rates of restenosis than for simpler lesions. In Part 5 of the thesis, a description of techniques is given. We found that after 3 years, there was no longer any benefit of SES in these patients; the rates of major adverse events had caught up those for BMS (15.8% vs. 18.3%, p=0.7).

Patients with multivessel disease

Previously thought to be the domain of cardiac surgeons, PCI is now performed for many patients with multivessel disease. Patients with multivessel disease including involvement of the proximal LAD treated with SES in the ARTS-II trial were compared to patients treated with coronary artery bypass grafting or bare metal stents in the ARTS-I trial. They had better survival than both ARTS-I groups (ARTS-II 98.6% vs. ARTS-I BMS 95.7%, p=0.05 and vs. ARTS-I CABG 94.7%, p=0.01) and lower rates of the hard clinical composite endpoint of death or non-fatal myocardial infarction (ARTS-II 3.1% vs. ARTS-I BMS 9.6%, p=0.002 and vs. ARTS-I CABG 9.7%, p=0.002). Although the ARTS-I CABG patients had a lower need for repeat revascularisation than ARTS-II (5.3% vs. 13.1%, p=0.002), the overall composite adverse event rates (death, myocardial infarction, stroke or any repeat revascularisation) were not significantly different between the ARTS-I CABG and ARTS-II patients

(15.0% vs. 18.0%, p=0.4), suggesting that treatment with SES is a safe and effective alternative to CABG in patients with multivessel disease involving the proximal LAD in selected patients. However, these results are not applicable to patients with more complex coronary artery disease since in the ARTS-II trial, the average Syntax score was only 22.9±9.7: the Syntax trial has demonstrated that patients with more complex disease (as assessed by the Syntax Score) benefit from CABG rather than stenting (Figure 1).

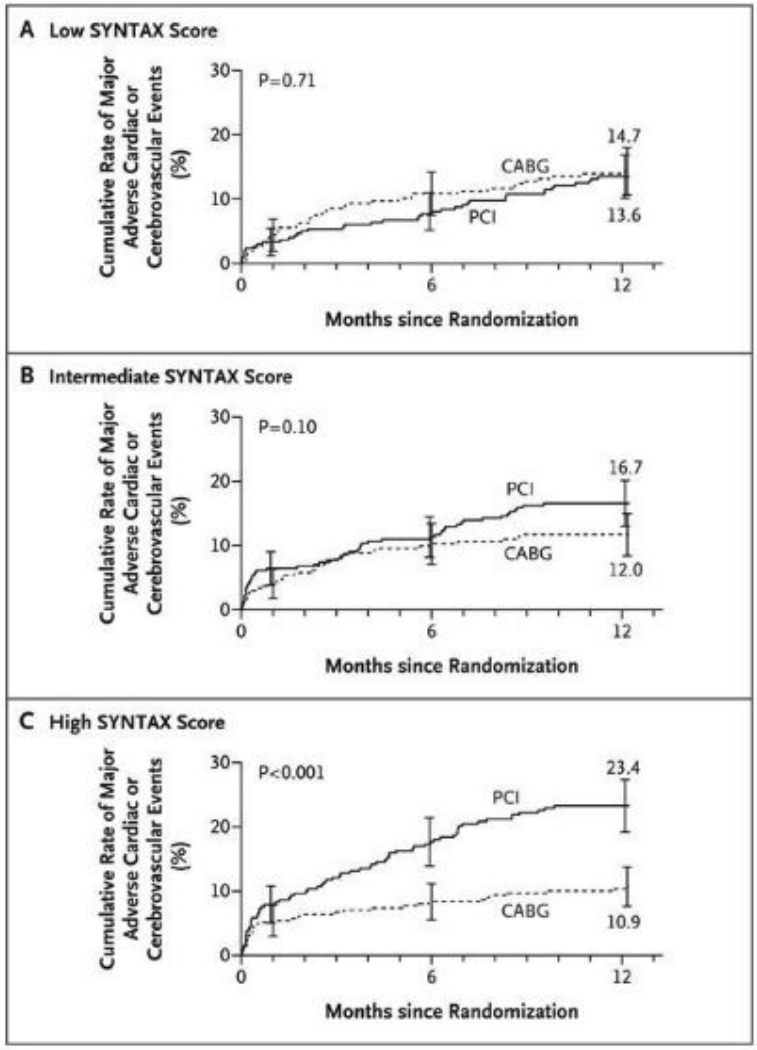

Figure 1. The 12-month event rates were similar between the two treatment groups for patients with low SYNTAX scores (0 to 22) (Panel A) or intermediate SYNTAX scores (23 to 32) (Panel B). Among patients with high SYNTAX scores (≥33, indicating the most complex disease), those in the PCI group had a significantly higher event rate at 12 months than those in the CABG group

When comparing different stent types used for multivessel treatment (Chapter 14), there was improved 3-year survival in the SES group (93.7%) compared with both the BMS (86.1%) and PES groups (87.3%), which remained significant after propensity score adjustment for differences in baseline and procedural characteristics. There was

no difference in mortality between the PES and BMS groups, although both DES types significantly reduced the need for clinically driven target-vessel and target-lesion revascularization without an excess in myocardial infarction or stent thrombosis. These findings support the validity of treating multi-vessel disease patients with PCI, particularly with SES.

Saphenous vein grafts

PCI for lesions in saphenous vein grafts has remained a challenge. Examining the long-term data for DES use in these patients (Chapter 15), TVR rates were lower with DES, but with no differences in mortality. Distal embolisation may occur with either stent type, thereby increasing the risk of peri-procedural adverse events: Chapter 16 describes a new pericardium-covered stent which is not drug-eluting but may reduce distal embolisation by trapping friable debris behind the pericardial layer.

Bifurcation Lesions

Treatment of bifurcation lesions with PCI is another technical challenge where there is often a complex interplay between complete scaffolding, homogenous stent strut distribution and adequate local drug delivery. Dedicated bifurcation stents have been designed to help overcome these challenges. The assessment of the Tryton stent is explored in Chapter 17, and a comparison made between the 2-stent Culotte technique in Chapter 18. Finally, a less common 2-stent technique, V-stenting is evaluated in Chapter 19, but these high risk patients had a high risk of early mortality. The number of patients is too few to be certain if this was due to limitations of the technique or to the high risk nature of the patients (a high proportion were patients with left main disease presenting with ST-elevation MI).

Other high risk groups

There are a number of other high-risk patient subgroups which historically have been excluded from randomized trials. This includes patients with left main disease and the very elderly. In addition, women tend to be under-represented in clinical trials. In Part 9, the long-term outcomes in these subgroups are systematically reviewed: reassuringly, all these patient populations (even those in the eldest quintile) benefit from DES without any excess in adverse events.

Stent thrombosis

Although stent thrombosis rates have been reduced to acceptable levels with dual antiplatelet therapy with BMS, late and very late stent thrombosis has emerged as the Achilles heel for DES. Mechanical issues (such as stent underexpansion, incomplete apposition, geographical miss and edge dissections) play a role as described in Chapter 24.

DES patients are at higher risk, since the drugs used in DES also delay endothelialisation, whilst some patients may experience reactions to the polymer coating. When stent thrombosis occurs, the clinical consequences are often severe, with a significant mortality rate as described in Chapter 25. In Chapters 26 and 27, we see that this risk of stent thrombosis continues with an annual rate of 0.4-0.6% per year up to 4 years of follow-up. The use of PES (HR: 1.67; 95% CI: 1.08 to 2.56) was an independent predictor of late ST. These findings, which are clearly of concern, have spurred on research into safer DES, with less toxic drugs and polymer coatings: these are the 2nd generation DES.

2nd generation drug-eluting stents

The Xience V everolimus-eluting stent (EES) has a biocompatible polymer coating and a thin strut Cobalt Chromium backbone to facilitate delivery. In randomized trials and in the real world, the EES has lower rates of major adverse events than PES and BMS. Other stents, using biodegradable polymers have been developed to try to improve long-term safety. One such stent is described in Chapter 31. Chapter 32 reminds us all that not every new stent is a success. The tacrolimus-eluting stent, despite the hypothetically favorable properties of coupling a biodegradable polymer with a drug whose predominant action is on smooth muscle cells rather than endothelial cells, had high rates of restenosis. This failure to prevent restenosis has been attributed to inadequate drug concentration and pharmacokinetics, which are key factors in the efficacy of DES.

Conclusion

The data on the long-term safety of the 1st generation DES in high-risk patients with complex lesions is indeed reassuring. Nevertheless, the risk of stent thrombosis remains, although interventional cardiologists should be encouraged that the safety concerns have been rapidly addressed. We are now seeing the clinical results from new generations of DES, incorporating biocompatible or biodegradable polymer coatings: these devices are now the most commonly used in Europe. The future for DES is bright, with further exciting developments, including completely biodegradable stents on the horizon.

Acknowledgements

ACKNOWLEDGEMENTS

There are many people who I met and worked with during my time in Rotterdam, who have integral to completing this thesis. I would like to give my thanks to all of you.

I think the first mention should go to Jurgen Lightart, one of the first people I met when I initially visited Rotterdam and again one of the first I met when I actually started as a fellow. Jurgen, thank you for all your kindness and help. You remain one of the Thoraxcenter's key assets and it was a pleasure to benefit from your vast experience and to share an office with you.

There were many others who helped me to settle in Rotterdam, and none are more important than Hector Manual Garcia-Garcia. Your guidance and assistance throughout my time in Rotterdam and in completing this thesis was invaluable and without you I would have achieved very little. Thank you for always finding time to provide help and advice. I hope that one day you will actually come and visit me in London!

Yoshinobu Onuma, my friend and colleague with whom I had a very productive partnership. Many of the publications would not have possible without you. I very much enjoyed our collaboration in terms of writing manuscripts, eating sushi and drinking sake.

Amongst the other fellows, I have made some lifelong friends, including Anne-Louise Gaster, the Danish fellow with a keen interest in the orchestra, Niccolo Piazza, the pseudo-Italian, pseudo-Canadian and now perhaps also pseudo-German and Emanuele Meliga, another key fellow and a international expert in eating tuna handrolls.

I would also like to thanks the other fellows of the Thoraxcenter for their friendship and support: Nieves Gonzalo-Lopez, Shuzou Tanimoto, Sophia Vaina, Joost Daemen, Keiichi Tsuchida, Chrisafios Girasis and Carl Schulz.

I am also indebted to the experience and knowledge of the senior cardiologists of the Thoraxcenter: Eric Duckers, Robert-Jan van Geuns, Carlos van Mieghem, Martin van der Ent, George Sianos, Evelyn Regar, Peter de Jaegere and Pim de Feijter. I must give a special mention to the late Wim van der Giessen, who will be sorely missed.

A great deal of credit must go to my co-promotor, Ron van Domburg, who helped guide me through many manuscripts and through the preparation of the thesis, and has been a pillar of support for me and many others.

Of course, I owe most to Patrick Serruys, the reason I went to Rotterdam. He has been and continues to be an inspiration to me as he has for numerous other fellows over the years. Patrick, I hope you will continue to push the boundaries of interventional cardiology and continue to inspire not just your fellows, but all other interventional cardiologists across the globe. Please don't take it personally though if you don't collect any more prestigious awards – I think you have all of them already and there are no more for you to collect!

Finally, I would like to thank my parents, without whose support none of this would have been possible.

Curriculum Vitae

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Publication List

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