Contemporary Percutaneous Coronary Intervention for Complex Lesions: the Treatment of Chronic Total Occlusions and Bifurcations in the Drug-eluting Stent Era

Angela Hoye

ISBN 1-84426-364-9

Printed by Printondemand-worldwide.com

Contemporary Percutaneous Coronary Intervention for Complex Lesions: the Treatment of Chronic Total Occlusions and Bifurcations in the Drug-eluting Stent Era

Hedendaagse Percutane Revascularisatie van Complexe Coronaire Lesies: de Behandeling van Chronische Totale Occlusies en Bifurcatielesies Gebruik Makende van Drug-eluting Stents

Thesis

to obtain the degree of Doctor from the

Erasmus University Rotterdam

by command of the

rector magnificus

Prof.dr. S.W.J. Lamberts

in accordance with the decision of the Doctorate Board

The public defense shall be held on

Wednesday, 22nd March 2006 at 13.45 hrs

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The generous sponsoring by Cordis, a Johnson & Johnson Company is gratefully acknowledged

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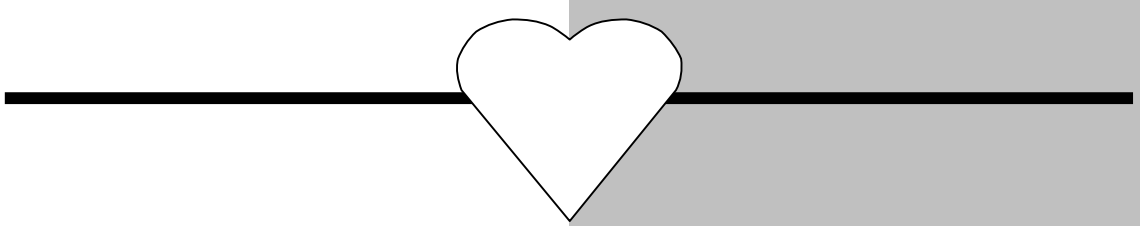
Chapter 1

Introduction and Overview



Percutaneous intervention of coronary stenoses has undergone dramatic evolution in the last 30 years. The utilisation of stents has dramatically increased in the last 10-15 years with stenting becoming applicable in a wide variety of lesion morphologies and clinical settings. Stents provide a scaffold which supports the arterial wall thereby sealing dissections and eliminating elastic recoil which reduces the rate of abrupt vessel closure compared to balloon angioplasty alone. [1,2] Angiographically, stents provide a very pleasing immediate result; however the long-term success is hindered by the development of restenosis which has proven to be extremely difficult to treat effectively. The struts of an expanding stent cause focal deep vascular trauma, and the severity of arterial injury has been shown to directly correlate with inflammation and the development of late neointimal growth and restenosis. [3]

Drug-eluting stents, whilst maintaining the beneficial effect of scaffolding the vessel, have been shown to reduce the rate of subsequent restenosis. Large randomised studies evaluated outcomes in selected populations, and demonstrated efficacy of drug-eluting stents when used to treat relatively simple lesions. [4-7] However, the short- and long-term efficacy of percutaneous coronary intervention is related to the baseline patient and lesion characteristics, and the majority of coronary intervention carried out in current clinical practice involves the therapy of such complex lesions, which were excluded from these studies.

The aim of this thesis was to evaluate contemporary coronary intervention of two of the most complex lesion subtypes: chronic total occlusions (CTOs) and bifurcations. In patients with significant coronary disease, both these lesion subtypes are commonly found on diagnostic angiography. However, both lesions are associated with lower procedural success rates: CTOs because of the difficulty in crossing the lesion with a wire and / or balloon; and bifurcations because of a higher rate of procedural myocardial infarction commonly related to impairment of flow in the side branch. In addition, data with bare metal stents show that both these lesions are subject to a relatively high rate of restenosis. We evaluated the impact of drug-eluting stent implantation on the outcomes of patients treated in the "real world" of interventional cardiology, in particular looking at the impact of these stents in patients treated for chronic total occlusions and bifurcation lesions.

Part 1 of the thesis evaluates chronic total occlusions (CTOs), with an overview described in Chapter 2. In chapter 3, we review the outcomes and trends of all patients treated for a CTO between 1992 and 2002. Prior to drug-eluting stents, intracoronary brachytherapy was the treatment of choice for in-stent restenosis. However, recent data has suggested that this therapy is associated with late recurrence of restenosis including CTO. [8] In chapter 4, we describe the predictors, incidence and prognosis of patients who develop a coronary occlusion following intracoronary beta-radiation therapy.

Despite the development of improved technologies to facilitate CTO recanalization, the overall success rate remains <70% in most catheterization laboratories. In chapter 5 we evaluate the value of pre-procedural multislice CT scanning in order to predict a subsequent successful recanalization attempt. In chapters 6,7 and 8 we evaluate the efficacy of a novel dedicated CTO recanalization technology. The system comprises of a guidewire that combines guidance from optical coherence reflectometry, with power provided by radiofrequency ablation to enable penetration through the occlusion.

The long-term outcomes of CTOs with respect to stent type are assessed in chapters 9 and 10. Consecutive patients treated with sirolimus-eluting, and paclitaxel-eluting stents are compared with an historical cohort treated with bare metal stent implantation, in order to determine the efficacy of drug-eluting stents in this patient subgroup.

In part 2, we assess the treatment of bifurcation lesions, with overviews presented in chapters 12 and 13. The difficulty in this situation relates to the presence of a sizeable side branch (usually defined as ≥2.0mm diameter). Even temporary loss of such a branch may be associated with a significant (≥2x upper limit of normal) release of creatine kinase. This is important as even minor elevations of CK-MB after successful coronary interventions identify a population with a worse long-term prognosis compared with patients with no enzyme release. [9]

In addition, the side branch is at particular risk of subsequent restenosis and the most effective strategy for stenting bifurcation lesions is currently undefined. Studies have evaluated a variety of techniques, however data with bare metal stents demonstrated that stent implantation of both the main vessel and side branch is

associated with a trend towards a higher rate of adverse events compared with use of single stent implantation of the main vessel only. [10-13]

The efficacy of drug-eluting stents for bifurcations is demonstrated in Chapters 14 and 15. The introduction of drug-eluting stents has led to a resurgence of techniques involving elective stent implantation in the side branch. Strategies such as the “crush” technique and Culotte stenting ensure complete lesion coverage, and the results are evaluated in Chapters 16 and 17.

In part 3, the treatment of both chronic total occlusions and bifurcations are put into the context of results of drug-eluting stent implantation in an unselected population. One of the concerns of drug-eluting stents is that by impairing the process of re-endothelialization, these stents might be subject to higher rates of stent thrombosis despite prolongation of the duration of prescribed dual anti-platelet therapy. Such an event is associated with a high rate of mortality and morbidity. [14] In chapter 18, we assess the incidence of stent thrombosis at 30 days following sirolimus- and paclitaxel-eluting stents as compared with previous patients treated with bare metal stents, and evaluate the independent predictors of stent thrombosis.

In chapter 19, we evaluate the clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients, including whether chronic total occlusions and bifurcations are predictors of restenosis. Chapter 20 evaluates the clinical outcomes following the use of paclitaxel-eluting versus sirolimus-eluting stents in unselected populations. Multivariate analysis of the populations determines the independent predictors of both major adverse cardiac events and target vessel revascularization.

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Part 1

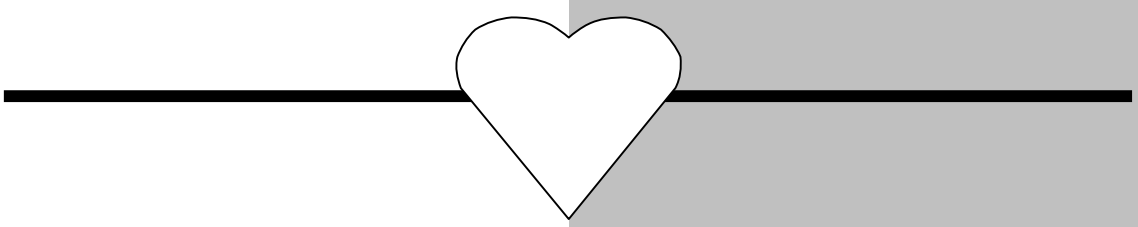
CHRONIC TOTAL OCCLUSIONS

Chapter 2

Chronic Total Occlusions

Angela Hoye

Chapter in A Colour Handbook of Adult Interventional Cardiology
Manson Publishing (in press)



Introduction

A chronic total occlusion (CTO) remains a technical challenge to the interventional cardiologist. Procedural success rates vary in the literature and are very much dependant on patient selection, age of occlusion, and operator experience. Despite technological advances, even in those patients selected to be suitable for percutaneous therapy, published success rates are between 40-80%,[1,2] considerably lower compared to non-occlusive lesions. However, there are several advantages to opening a CTO, with studies demonstrating a reduction in long-term mortality, improvement in anginal symptoms and left ventricular function and a reduction in the need for subsequent coronary artery bypass surgery.[3-8]

Incidence

Recent data suggests that in patients found to have significant coronary disease (defined as ≥70% diameter stenosis) at least one CTO will be found in 52%.[9] However, the presence of a CTO has a significant impact on choice of therapy, with the majority of these patients managed with either medical therapy or referred directly for coronary artery bypass surgery. In most centres, percutaneous intervention for CTO generally comprises ≈10% of angioplasty procedures.

Definition

CTO is commonly defined as a complete occlusion within a coronary artery with TIMI 0 flow, though some studies have also included lesions with TIMI I flow, so-called 'functional occlusions' where late antegrade opacification of the distal vessel is detected though without a discernible luminal continuity.

Determining the duration of occlusion can be difficult without angiographic data, and relies somewhat empirically on the clinical history of onset of angina pain or an episode of prolonged pain which may indicate vessel occlusion. The definition of what is 'chronic' is also variable, many studies have included lesions of more than 15 days duration, though it is generally accepted that to be truly chronic, lesions are of more than 3 months duration.

Pathophysiology

CTO's are thought to either develop after an episode of acute occlusion with plaque rupture and subsequent thrombosis, or relate to progression of a flow-limiting atherosclerotic stenosis. Histology reveals variable amounts of atheroma and thrombus that are increasingly replaced by fibrous tissue and calcification (figure 1).[10] Neointimal channels of 160-230μm in diameter form and are present in 85% lesions older than 1 year (figure 2).[10] There is debate as to whether these channels, which are too small to be visible on angiography, help in providing a route for a guidewire, or hinder angioplasty success due to connection between the vasa vasorum and adventitia thus increasing the likelihood of extra-luminal wire passage.

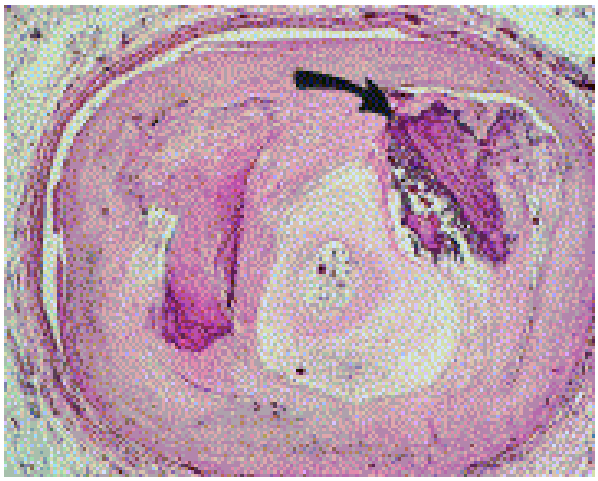


Figure 1: Low power view (hematoxylin-eosin stain) of a hard or fibrocalcific chronic total occlusion with extensive calcification **(arrow)**

Reproduced with permission from Srivatsa SS et al Histologic correlates of angiographic chronic total coronary artery occlusions: influence of occlusion duration on neovascular channel patterns and intimal plaque composition. *J Am Coll Cardiol*. 1997;29:955-63.

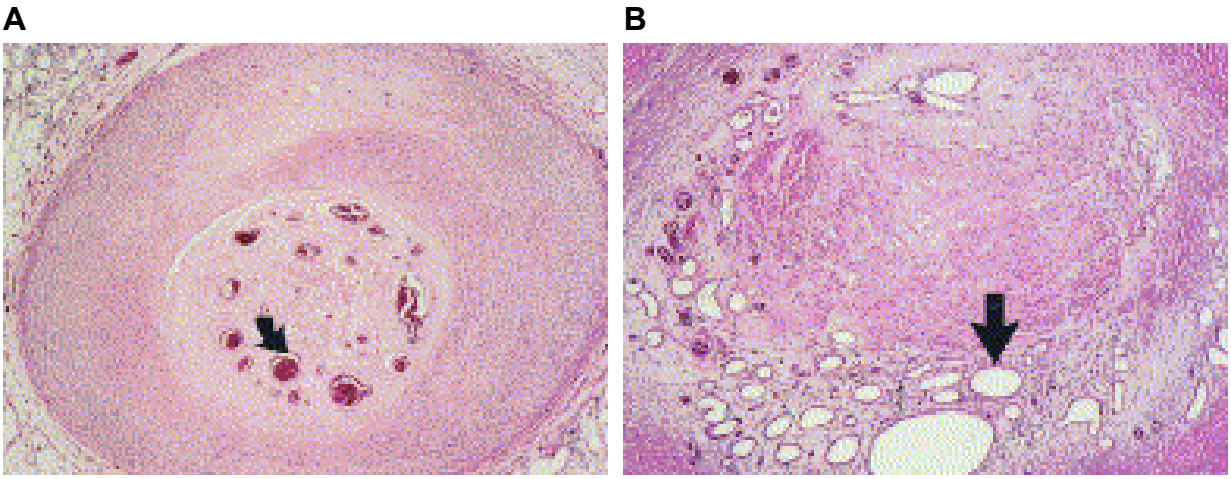


Figure 2: A Low power view (hematoxylin-eosin stain) of a chronic total occlusion lumen recanalization by large central neovascular channels (arrow). **B** High power view (hematoxylin-eosin stain) demonstrating extensive small, medium and large intimal plaque neovascular channels (arrow).

Reproduced with permission from Srivatsa SS et al Histologic correlates of angiographic chronic total coronary artery occlusions: influence of occlusion duration on neovascular channel patterns and intimal plaque composition. *J Am Coll Cardiol*. 1997;29:955-63.

The Procedure

The limitation of a successful outcome to angioplasty of a CTO is the inability to cross with a wire / balloon. Adverse predictors of successful recanalisation are documented in the list below, and demonstrated in figures 3 and 4.

- Age of occlusion > 3 months
- Length of occlusion > 15mm
- Presence of calcification
- An abrupt blunt stump as opposed to one which is tapered
- Presence of a side branch at the site of occlusion
- Tortuosity proximal to the occlusion
- Presence of bridging collaterals
- Multivessel disease
- Occlusion in the circumflex

In general, the older the occlusion, the more likely it is to be composed of dense fibrous tissue and calcification, though age alone should not necessarily preclude an attempt to open the artery.

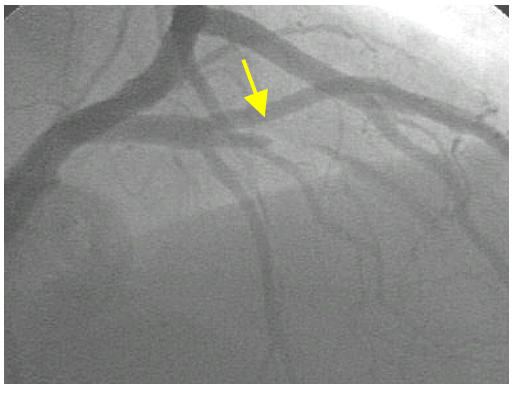
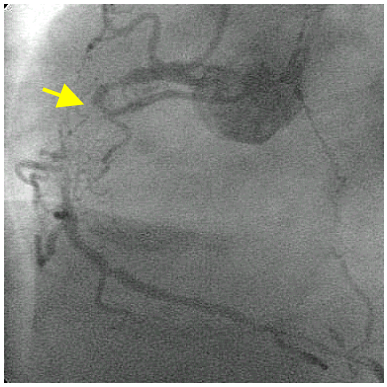


Figure 3: Chronic total occlusion with features consistent of a high chance of recanalization success: short length of 4.2mm, tapered tip (arrow), and central entry point.

Figure 4: Chronic total occlusion with features suggesting it may be difficult to recanalise: long length of occlusion of 18.6mm with bridging collaterals, a blunt / abrupt cut-off, and a side-branch at the site of the stump



The Equipment: choice of guiding catheter

Whichever artery is involved, good support from the guiding catheter is essential. For the right coronary artery, a standard Judkins right curve catheter is usually the first choice, though a left Amplatz will provide additional support and is particularly useful if the proximal part is a “Shepherds crook”. In the left anterior descending artery, a standard Judkins left catheter can be used though a Voda or Extra Backup provides extra support. For the circumflex artery, a left Amplatz may be preferable.

Choice of wire

For non-occlusive stenoses, wires with a floppy tip are used which avoid wall or plaque injury. However in a CTO, the wire needs to penetrate the proximal cap, which may be fibrous, thus one with a stiffer tip is likely to be needed. Commonly an intermediate-strength wire is used initially, progressing, for safety reasons, to stiffer wires in a step-wise fashion. For comparison, it is useful to know the tip load of individual wires. This is defined as the weight needed to be applied to bend / buckle the tip of the guidewire; for intermediate wires this is ≈3g. Some manufacturers make specialized stiffer CTO wires with tip loads of >3g (eg the family of Miracle wires from Asahi-Intecc (Japan) available with tip loads of 3g, 4.5g, 6g, or 12 g).

Hydrophilic wires have a coating, which when wet, makes them extremely slippery. This incurs improved steerability and trackability, though with the disadvantage of a relative lack of feeling resistance by the operator. Most of these wires have a very floppy tip, and unfortunately, if the lesion is particularly tough, have a tendency to “follow the path of least resistance" and take a subintimal route leading to dissection. For CTOs, these wires are most useful in the presence of some antegrade filling of the distal vessel.

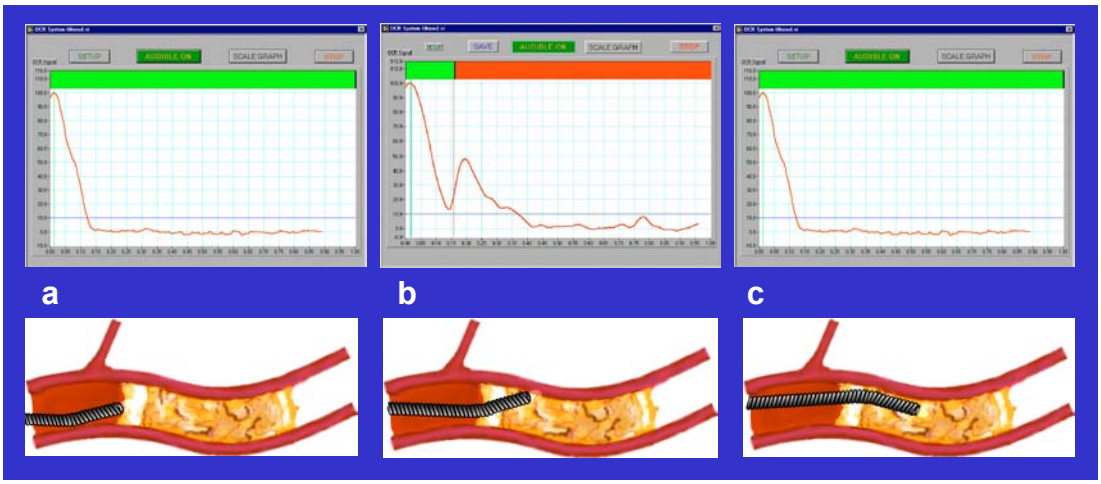
Specialised tapered-tip wires are available which are more able to penetrate dense fibrous tissue. Examples include the family of Cross-it wires from Guidant which have a tip of 0.010”, and are available in a range of tip stiffness, and the Confianza / Conquest wire from Asahi-Intecc, Japan which has a very stiff tip that is 0.009” diameter. The major disadvantage of these wires is the risk of perforation, and they must be advanced across the lesion with care.

Specialised devices

The Intraluminal Wire (figures 5 and 6):

This system combines guidance from optical coherence reflectometry, with the power of radiofrequency ablation to penetrate and cross a CTO. The system emits near infrared light and analysis the backscatter in an A-scan mode, to determine the position of the wire tip in relation to the vessel wall compared with the true vessel lumen. It is therefore a truly forward-looking system, and scans a distance of approximately 5mm. The 0.014” wire is equipped with the capability of radiofrequency ablation with low frequency (250-500 kHz) short duration (100millisecond) pulses.

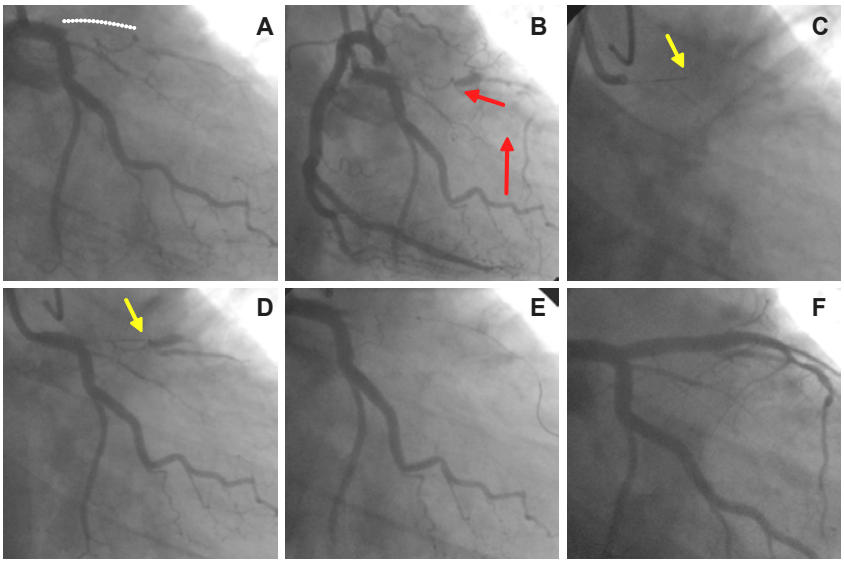
Figure 5: The Safe-Cross system display.



When the Intraluminal wire is within the lumen a green band appears on the monitor and the operator can ablate forwards enabling the wire to advance **(a).** If the wire is directed outside the vessel, a red band appears on the monitor and the ability to ablate is disabled **(b).** Once the wire has been manoeuvred back towards the lumen, the band is again green and ablation is once again permitted **(c)**

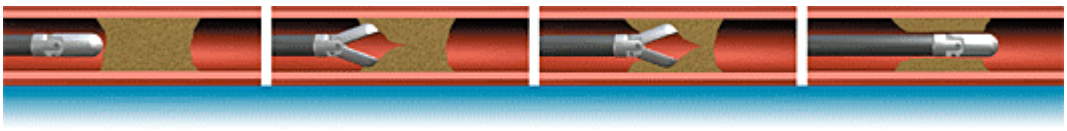
Only when the wire is within the true lumen, is the operator allowed to ablate the tissue ahead advance the wire; when the wire is heading extra-luminal the system does not allow ablation. Preliminary experience suggests that the device facilitates recanalization in an additional 52% of lesions that have been unsuccessful using conventional means.[11] Importantly, use of the device was associated with no procedural major adverse events.

Figure 6: Case example using the Intraluminal™ wire.



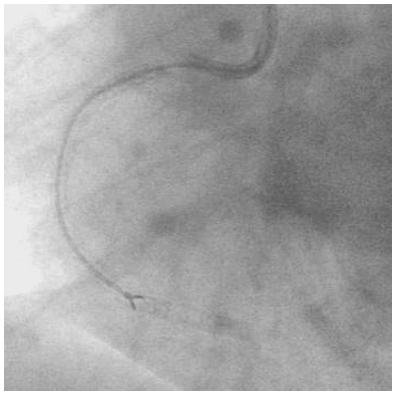
Chronic total occlusion at the ostium of the left anterior descending (LAD), thought, on the clinical history, to be two years old. **A:** By quantitative coronary angiography it was measured to be 21.7mm in length. **B:** The distal LAD is well filled via retrograde collaterals from the right coronary artery (red arrows). These are demonstrated utilizing a dual injection technique with a diagnostic catheter in the right coronary artery. **C/D:** The Intraluminal™ wire, which has a 10mm distal radio-opaque tip, successfully ablates a path forwards (yellow arrow). **E:** Following successful wire passage, the Intraluminal™ wire was exchanged for a conventional floppy tip wire using an over-the-wire balloon. The lesion was pre-dilated and then stented with a 3.5 x 28mm stent. **F:** Final excellent result.

The Frontrunner catheter:



The distal part of this device can be shaped to improve torquability and it has a hydrophilic coating to improve penetrability. The tip itself is blunt and the 'jaws' open allowing controlled blunt dissection and advancement of the device. Preliminary data has shown the device to be successful in 53% lesions with a history of failure using conventional wires.[12] However, in this study of 50 patients, there was a relatively high rate of vessel perforation (18%), leading to tamponade in 2 (4%) patients. The rate of coronary perforation did decrease with time and more experience, but emphasises that care is needed when using this catheter.

Figure 8: Case example using the Frontrunner catheter to open a chronic total occlusion of a long segment of stented vessel



Technique

It is vital to make a detailed coronary angiogram at the start of the procedure to clearly delineate the site of occlusion and stump. With a supportive guiding catheter in position, the tip of the guidewire is shaped in the usual manner with a 30-45˚ angle, though some operators also place a secondary 20-30˚ angle more proximal to the first. Stiff wires have a risk of traumatising the proximal vessel particularly if this is tortuous; this can be avoided by advancing such wires via a support catheter or over-the-wire balloon that has been positioned just proximal to the occlusion. In current practice, wiring technique is to gently rotate the tip (no more than 90˚ clockwise / counter-clockwise) whilst maintaining gentle forward pressure, and aiming the tip towards the distal vessel lumen. It is important to ensure that the wire tip remains 'on track' and it must be visualised in at least two projections. Though not mandatory, the advantage of using biplane is that co-axial views can be evaluated simultaneously, otherwise the operator should change projection at frequent intervals. Unfortunately at times, the "path of least resistance" may lead the wire into the subintima at which point the operator may detect the feeling of some resistance. The wire may be withdrawn and an alternative path sought.

Particularly when the stump is blunt, progression to a relatively stiffer wire may be necessary to penetrate the fibrous cap at the proximal edge. Because of the dangers of artery perforation, some operators may then switch back to a softer wire to traverse the middle part of the occlusion. The distal edge may also be difficult to penetrate due to fibrous tissue and may again require a stiffer wire. Bridging collaterals are relatively fragile vessels; when present, wires must be used with extreme caution because of the increased risk dissection or perforation.

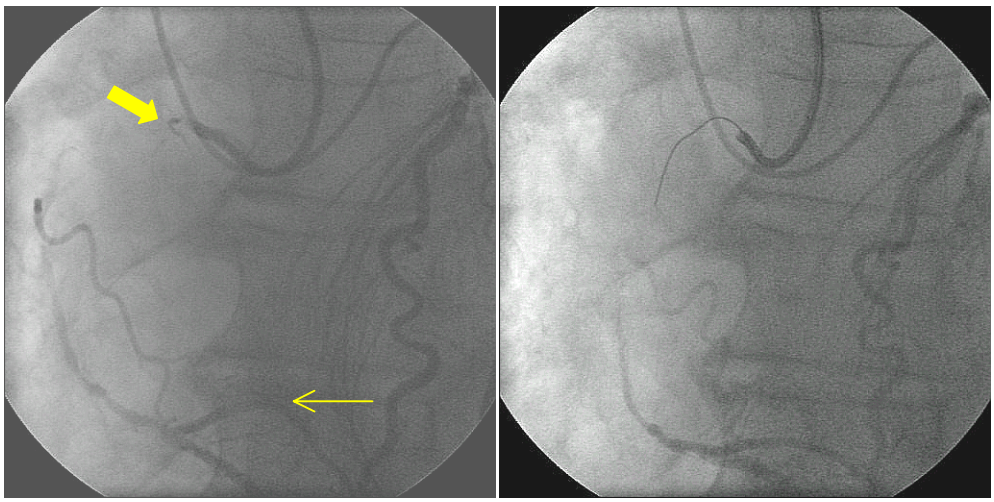
Once the occlusion has been crossed, the operator should have free movement of the tip of the wire, which advances easily. Confirmation of an intraluminal wire position must be made at least two co-axial projections. It is particularly important with both the stiff and hydrophilic wires to ensure that once advanced distally, they remain within the lumen of a large artery and are not at risk of perforating a small branch. After balloon

dilatation of the occlusion, a standard wire with a safer floppy tip may be advanced through to the distal vessel and the stiffer wire removed.

Double injection technique (figure 9):

The presence of collateral filling from the contralateral artery helps to preserve viable myocardium. Such a lesion is liable to be associated with angina, as there remains an insufficient blood supply to meet the increased metabolic needs of physical stress. When antegrade flow is not seen beyond the occlusion, simultaneous injection of contrast into the contralateral artery provides information on the true length of the occlusion and helps direct safe positioning of the guidewire into the distal vessel. In this situation, it is preferable to obtain a second arterial access and position a diagnostic catheter (5F or 6F) at the start of the procedure.

Figure 9: Double injection technique to help with guidance of the wire and facilitate recanalization



The RCA is occluded at the ostium (block arrow) with no antegrade flow. Contrast injection is made via a separate guiding catheter in the left coronary artery ostium to visualise the distal collaterals from the distal LAD to the RCA (open arrow) and help direct the wire.

Guide catheter support and deep engagement

It is important for guide catheters to have a soft and relatively atraumatic tip. However, the shaft of catheters from different manufacturers provide differing degrees of “active” backup support – for a CTO, a more supportive catheter may be an advantage. For this reason, some operators routinely use catheters of 7F or 8F for CTOs. Alternatively, if the lesion is tough and difficult to cross, additional support can be gained from a less supportive guiding catheter by deeply engaging it. A 5F guiding catheter can be particularly useful in this situation, and may even be advanced down the vessel right up to the site of occlusion. In Japan, some 6F guiding catheters have an inner lumen big enough to accommodate a 5F catheter, through which the procedure can be attempted. The combination of both (mother-and-child) catheters provides excellent back-up support.

Balloon support

Support catheters or over the wire (OTW) balloons significantly increase the ‘pushability’ (and thereby the penetration ability) of guidewires. They can be advanced up to the occlusion (using a floppy wire particularly if there is proximal tortuosity), and used to maintain position whilst allowing change of guidewires. For particularly tough lesions which cannot be penetrated with a wire, the system can be stabilised to allow the wire to be pushed with greater penetration force, by inflating a balloon in the proximal vessel. This can either by using a second wire and a balloon in a side branch, or a balloon within the proximal part of the main vessel. In these situations, a compliant balloon is used with the same diameter of the vessel, and inflated to nominal pressure. With the balloon inflated, the wire is advanced in the usual manner.

Multiple wire techniques

It is common for several wires with different properties to be used to achieve a successful result in opening a CTO. However, it may also be useful to use several wires at the same time:

- If a wire takes a subintimal course when it is advanced, it is fixed within the false channel (thus occluding it) and a second wire taken and progressed along a new path (double wire technique).
- If a side-branch originates at the site of occlusion, one wire may be positioned in the branch, sometimes together with a small balloon, to try to block entry into the branch and deflect the tip of a second wire towards the occlusion. Occasionally in this situation an IVUS catheter may be placed in such a side branch and used to image and guide the second wire penetrate and cross the CTO.

The dilation process

Once the lesion is crossed with the wire, most procedures will have a successful outcome with increasing sizes of balloon utilised until a good calibre lumen is achieved. Very occasionally however, it proves impossible to cross the lesion with even the smallest low-profile balloon and the best guide catheter support. If this happens, it can be useful to advance a second wire parallel to the first into the distal lumen. Alternatively, specialized technologies may be considered eg rotational atherectomy, and laser technology (Spectranetics Corporation, Colorado Springs). The Tornus device (Asahi Intecc, Japan) is a novel penetration catheter that is a coreless stainless steel coil consisting of 8 stranded stainless steel wires to cross a severe stenosis by manual rotation. The learning curve for use of the device is relatively short, and preliminary results are encouraging. It is currently under evaluation by the regulators for licensed use.

Stenting

Evidence from several randomised studies demonstrated that long-term results are superior with stenting compared with balloon-only angioplasty. However, the long-term results following bare metal stent implantation suggested a relatively high rate of restenosis of 32-55%. [13-17] However, recent excellent results have been demonstrated following implantation of drug-eluting stents, with restenosis rates for the sirolimus- and paclitaxel-eluting stents of 9% and 8% respectively. [18,19]

Complications

Intervention in CTO's is subject to the same complications as intervention in non-occlusive stenoses, with reported rates of serious complication (death, or myocardial infarction) in 1-2%. There are, however, several complications more specific to the treatment of CTO's:

- Impairment of collateral flow may occur through several mechanisms including distal embolisation of debris or extension of wire-induced dissection. This may be associated with a rise in cardiac enzymes consistent with myocardial infarction.
- Passage of the wire may be associated with varying degrees of dissection and / or perforation of the artery (figure 10) which may lead to pericardial tamponade.

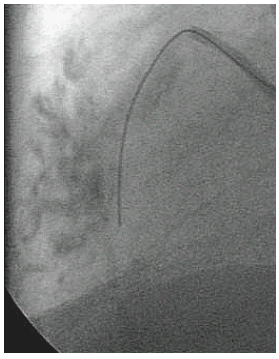


Figure 10: Wire exit has caused this appearance of extraluminal contrast staining. The procedure was stopped; the patient remained asymptomatic with no clinical sequelae.

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Chapter 3

Percutaneous Coronary Intervention for Chronic Total Occlusions: the Thoraxcenter Experience 1992 – 2002

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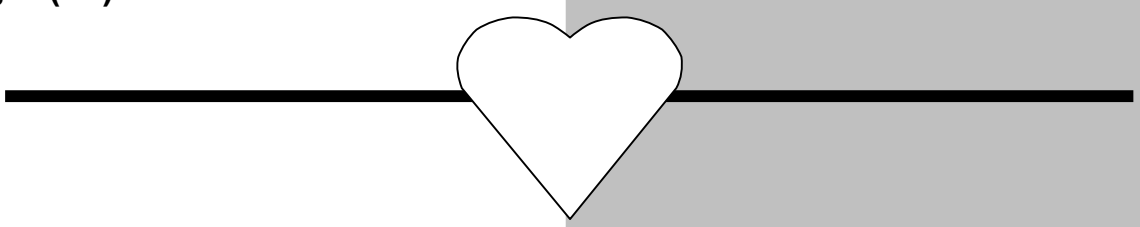
European Heart Journal
2005;26(24):2630-6



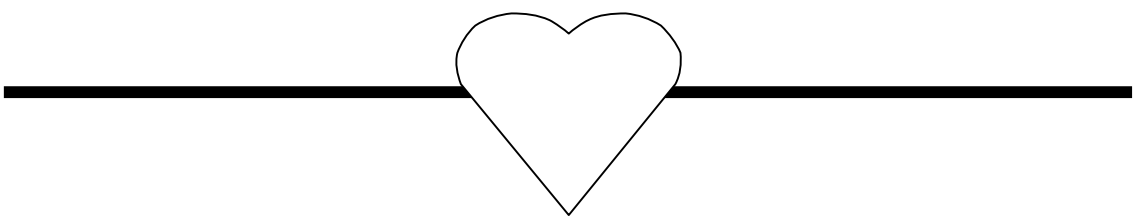
Abstract

Background: Chronic total occlusions are commonly found on diagnostic angiography, and there is some evidence from one study that successful percutaneous revascularization leads to an improvement in long-term survival rates. However, this study included patients treated for unstable angina with short-duration occlusion, and stent implantation was utilized in only 7%. We re-evaluated the long-term outcomes of a large consecutive series of patients with a CTO of >1 months' duration treated at our centre, with stent implantation utilized in the majority.

Methods: All patients treated with PCI between 1992 and 2002 were retrospectively identified from a dedicated database. A total of 874 consecutive patients were treated for 885 CTO lesions. Mean follow-up time was 4.47 ± 2.69 years (median 4.10 years). Patients were evaluated for the occurrence of major adverse events (MACE) comprising death, acute myocardial infarction, and need for repeat revascularization with either CABG or percutaneous coronary intervention (PCI).

Results: Successful revascularization was achieved in 576 lesions (65.1%), in which, stent implantation was used in 81.0%. At 30 days, the overall MACE rate was significantly lower in those patients with a successful recanalization (5.5% versus 14.8%, $p<0.00001$). At 5 years, patient survival was significantly higher in those with successful revascularization (93.5% versus 88.0%, $p=0.02$). In addition, there was a significantly higher survival-free of MACE (63.7% versus 41.7%, $p<0.0001$), with the majority of events reflecting the need for repeat intervention. Independent predictors for survival were successful revascularization, lower age, and the absence of diabetes mellitus and multivessel disease.

Conclusions: Successful percutaneous revascularization of a CTO leads to a significantly improved survival rate, and a reduction in major adverse events at 5 years. Most events relate to the need for repeat re-intervention, and the introduction of drug-eluting stents, with low restenosis rates, encourages the development of technologies to improve recanalization success rates. However, failed recanalization may be associated acutely with an adverse event, and new technologies must focus on a safe approach to successful recanalization.



Introduction

At least one chronic total occlusion (CTO) is found on approximately one-third patients found to have significant coronary disease on angiography. [1] Yet data suggest that percutaneous coronary intervention (PCI) for a CTO accounts for approximately only 10-15% of angioplasty procedures, with the majority of patients treated with either coronary artery bypass surgery (CABG) or medical therapy. Compared with non-occlusive lesions, PCI for a CTO is associated with lower procedural success rates predominantly related to the inability to cross the lesion. However, technical advances in the design of angioplasty equipment, particularly of specialized wires, have improved recanalization rates. The choice of therapy for patients with a CTO (PCI versus CABG versus medical therapy) is dependant on local policies, and outcomes of revascularization are dependent on operator experience. In the current study, we analysed the trends in revascularization and the treatment of CTOs at the Thoraxcenter, Rotterdam between 1992 and 2002.

In addition, the long-term outcomes of patients with PCI for a CTO were analysed. Previously, a large single centre series of more than 2000 patients importantly demonstrated that successful percutaneous revascularization of a CTO confers a significant 10-year survival rate compared with failed revascularization. [2] This study, analysed patients treated between 1980 and December 1999 in the Mid-America Heart Institute, and included all patients treated for an occluded vessel provided they had not had a myocardial infarction within the preceding 7 days. Therefore, those with relatively recent thrombotic occlusions and unstable angina were included. Indeed, one of the multivariable predictors for long-term mortality was percutaneous intervention undertaken in patients with unstable angina. In addition, only 7% patients with successful revascularization were treated with stent implantation. Long-term outcomes of CTOs have been improved since the widespread introduction of stent utilization, which is associated with reduced rates of restenosis and re-occlusion compared with balloon-only angioplasty. [3-6] In the current study, we analysed whether the benefits demonstrated in the MAHI study are applicable to PCI carried out in chronic occlusions in another tertiary centre. In our study, chronic total occlusion was more strictly defined, those with occlusion related to unstable angina and recent (<1 month) occlusion were excluded, and in addition, stent implantation was used in the majority.

Methods

Demographic and procedural data regarding all patients undergoing PCI at our centre are prospectively entered into a dedicated database. All procedures undertaken for an occluded vessel between 1st January 1992 and 31st December 2002 were retrospectively identified (n=2131). Those treated in the setting of acute myocardial infarction (AMI), and recent (<1 month) occlusion were excluded, leaving a total of 874 consecutive patients treated for CTO.

Chronic total occlusion was defined as a lesion exhibiting Thrombolysis In Myocardial Infarction flow grade 0-1. All patients included had at least one occlusion within a native vessel; occlusions within saphenous vein grafts were excluded. Duration of occlusion was estimated to be at least 1 month, on the basis of either a history of sudden chest pain, a previous AMI in the same target vessel territory, or the time between the diagnosis made on coronary angiography and PCI. Procedures were undertaken using standard techniques of the time. All patients were treated with heparin to maintain an ACT>250 seconds, and all were on long-term aspirin therapy. For those treated with stent implantation prior to 1996, additional anticoagulation was provided with the use of warfarin given for 1 month. Subsequent to that time, a thienopyridine was used (ticlopidine or clopidogrel). Procedural success was defined as successful recanalization and dilatation of the vessel with or without stent implantation, with a final residual diameter stenosis <50%.

Median follow-up time was 4.48 years (quartiles 2.72, 6.64 years). All patients were assessed for the occurrence of major adverse cardiac events (MACE) comprising death, non-fatal AMI, and repeat revascularization (PCI and / or CABG). Long-term survival status was assessed by written inquires to the Municipal Civil Registries. Follow-up clinical data were determined from electronic hospital archives and by questionnaires sent to all living patients. The referring physician and institutions as well as the general practitioners were directly approached whenever necessary. Complete 30-day clinical follow-up was obtained in all patients, with complete long-term follow-up data obtained in 99% patients up until 1st April 2004. The diagnosis of AMI required an elevation of creatine kinase to twice the upper limit of normal, together with a rise

in creatine kinase-MB fraction. If made following patient admission to another hospital, the diagnosis of AMI was confirmed through direct contact with the referring physician, using the same criteria.

Statistics: Discrete variables are presented as percentages and compared with Fisher exact test. Continuous variables are expressed as mean ± standard deviation and compared with Student's t test. Cumulative survival-free of major adverse events were calculated according to the Kaplan-Meier method. The log-rank test was used to compare event-free survival between the groups. Multivariable analyses were performed using backward and forward stepwise Cox regression. Baseline characteristics were included if they were (i) associated with high incidence of cardiac events ($p<0.1$), or (ii) known risk factors from literature. Pre-selected variables were: age, gender, diabetes mellitus, hypertension, hypercholesterolaemia, presence of multivessel disease, impaired left ventricular function, prior AMI, prior PCI, prior CABG, use of a glycoprotein IIb/IIIa inhibitor, target vessel, successful procedure, and use of a stent. The proportional hazard assumptions were investigated by testing the constancy over time of the log hazard ratio for each model. In addition, the proportional hazard assumption for all covariates was tested using Schoefeld residuals. According to these tests, the proportional hazard assumption was not validated. Linearity was checked graphically and by inclusion continuous variables both as such according to quintiles. Absence effect of the grouped variable indicates that the effect is linear. Also assumptions of linearity were assessed and satisfied using a general linear model (GLM) univariate method. No deviation from linearity was found in any continuous variable. To investigate interaction, an interaction model was performed using a likelihood ratio test in the multivariable Cox. Interaction was performed on all selected variables. However, no interaction was found. Odds ratio with corresponding 95% confidence intervals are reported. All tests were two-tailed; due to the large number of statistical tests, p-values should be interpreted with caution. While no specific level of significance is defined, a p-value of 0.01 should be considered for strong evidence in support of a true effect.

Table 1: Baseline patient demographics and target vessel site with respect to a successful versus an unsuccessful chronic total occlusion revascularization procedure

	CTO success n=567	**CTO failure n=304**	**p value**
Age (years)	59.6 ± 10.8	60.5 ± 10.4	0.2
Male sex (%)	73.6	72.2	1.0
Diabetes mellitus (%)	12.0	9.1	0.2
Hypertension (%)	20.3	21.0	0.7
Hypercholesterolaemia (%)	48.6	43.3	0.2
Family history of coronary disease (%)	21.9	18.8	0.3
Impaired LV function (%)	32.5	38.1	0.5
Previous myocardial infarction (%)	55.7	49.2	0.2
Previous PCI (%)	24.3	23.0	0.9
Previous CABG (%)	8.7	10.4	0.4
Vessel disease			0.03
Single-vessel (%)	46.0	32.6	
2 vessel (%)	36.2	40.5	
3 vessel (%)	17.8	27.0	
Number of lesions	573	306	
Target vessel of the lesion			0.8
RCA (%)	42.2	52.6	
LAD (%)	33.2	26.5	
LCX (%)	24.4	20.6	
LMS (%)	0.2	0.3	

Results

Between 1st January 1992 and 31st December 2002, a total of 874 patients underwent PCI for at least one CTO. Of these, 11 had attempted revascularization of 2 CTO's, making a total of 885 attempted lesions. Overall, successful revascularization was achieved in 576 lesions (65.1%), with failure in the remaining 309 (34.9%). Of the 11 patients with attempted therapy of 2 CTOs, PCI outcome was the same in both lesions in 8 patients. The remaining 3 patients with both one success and one unsuccessful PCI have been excluded from further analysis. The baseline demographics for the remaining patients are presented in table 1.

There were no significant differences in characteristics, though a trend towards an increase in 2- and 3-vessel disease in those in whom PCI for occlusion was unsuccessful. Over time, the proportion of patients with coronary disease who underwent revascularization with PCI as opposed to CABG surgery, increased with time (figure 1). Similarly, there was a trend to an increased proportion of PCI for CTO (figure 2). Percutaneous CTO therapy was undertaken utilizing the contemporary techniques of the time including specialized hydrophilic, tapered tip, and stiff wires when available, with the laser wire used in 72 (8.1%). However, despite the introduction of more specialised technologies, the success rate of recanalization did not improve (figure 2). Following successful recanalization, the overall use of stent implantation was 81.0%, with stent utilization increasing with time (figure 3).

Figure 1: Trends in the number of revascularization procedures with percutaneous coronary intervention (PCI) versus coronary artery bypass surgery (CABG) at the Thoraxcenter.

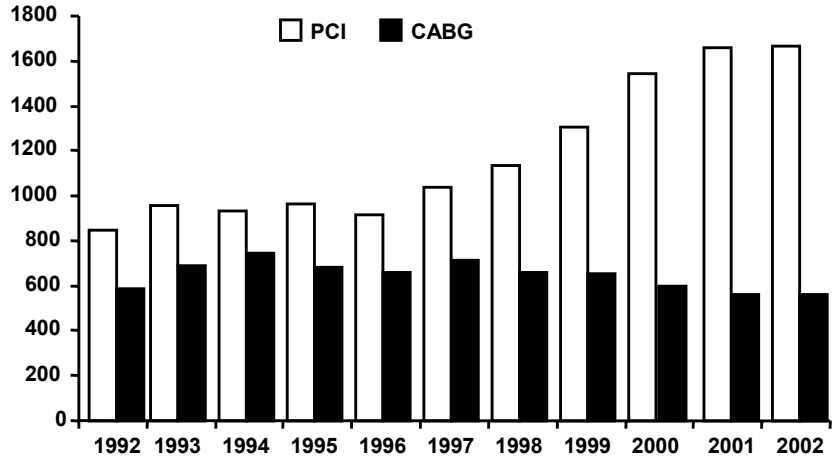


Figure 2: Trends in the increase in the proportion of percutaneous intervention (PCI) for a chronic total occlusion (CTO), and success rates for PCI for CTO with respect to year of intervention.

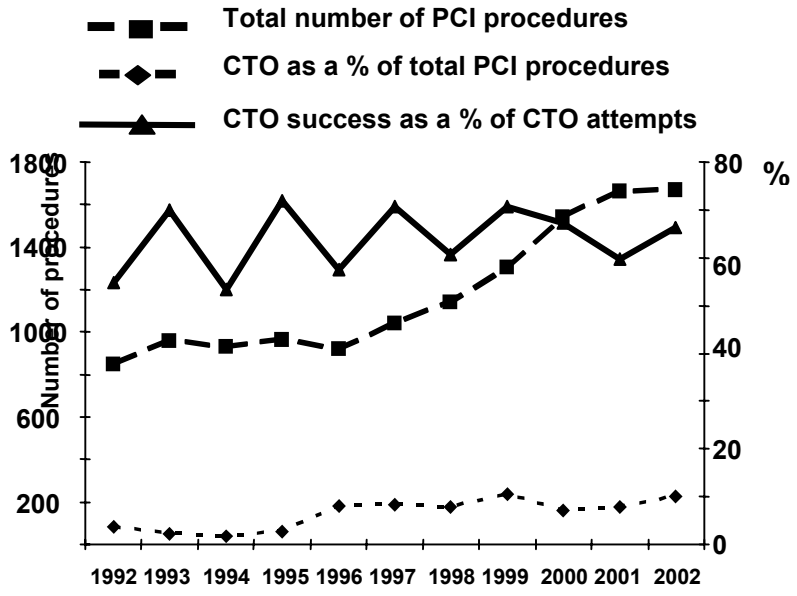
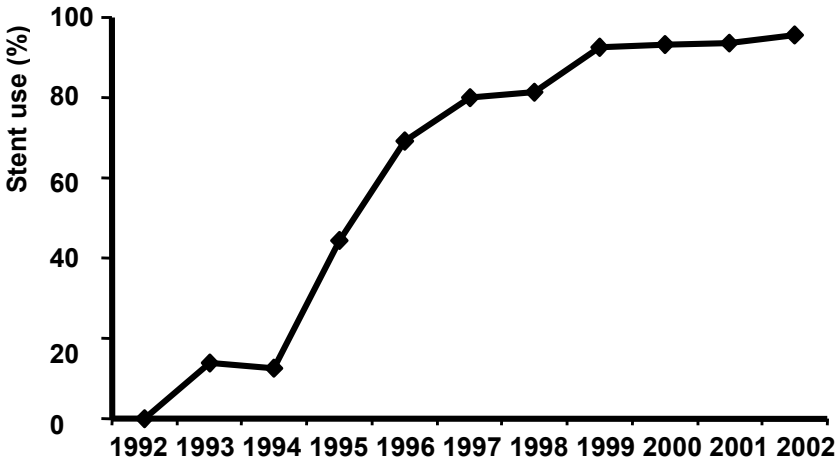


Figure 3: Utilization of stent implantation following successful recanalization of a chronic total occlusion with respect to the year of intervention.



The 30-day MACE rates are presented in table 2. In addition, this table demonstrates the events directly related to the procedure and occurring within the first 48 hours. A failed recanalization procedure was associated with a significantly higher rate of MACE in the immediate period following the procedure.

Table 2: Incidence of major adverse cardiac events at 2 and 30 days

		CTO success n=567	CTO failure n=304	p value
Death, n (%)	2 days	2 (0.4)	3 (1.0)	0.2
	30 days	4 (0.7)	6 (2.0)	0.09
Death or acute myocardial infarction, n (%)	2 days	3 (0.5)	5 (1.6)	0.1
	30 days	7 (1.2)	7 (2.3)	0.2
Death or CABG, n (%)	2 days	7 (1.2)	13 (4.3)	0.004
	30 days	10 (1.8)	30 (9.9)	<0.00001
MACE, n (%)	2 days	14 (2.5)	17 (5.6)	0.02
	30 days	31 (5.5)	45 (14.8)	<0.00001

In the long-term, all outcomes were significantly worse following a failed attempt at revascularization. The 5-year survival was significantly lower than when revascularization was successful (figure 4), and the survival-free of AMI, CABG, and MACE were also significantly lower (figures 5-7). By multivariable analysis, the independent predictors for survival and MACE following PCI for CTO are presented in table 3. The presence of multivessel disease was an independent predictor for both survival and MACE. The cumulative survival-free of MACE with respect to the presence of single versus multivessel coronary disease is shown in table 4.

Table 3: Independent predictors of death and major adverse cardiac events (MACE) after attempted percutaneous coronary intervention of a chronic total occlusion

	Hazard ratio	95% confidence intervals	p value
Death			
Successful revascularization	0.58	0.34 – 0.98	0.04
Age	1.04	1.02 – 1.07	0.002
Diabetes mellitus	2.49	1.33 – 4.66	0.005
Multivessel disease	4.29	1.93 – 9.55	<0.001
Major adverse cardiac events			
Successful revascularization	0.55	0.44 – 0.70	<0.001
Multivessel disease	1.43	1.14 – 1.79	0.002
Use of a stent	0.69	0.54 – 0.88	0.002

Figure 4: Cumulative survival at 5 years with respect to the outcome of attempted recanalization of a chronic total occlusion.

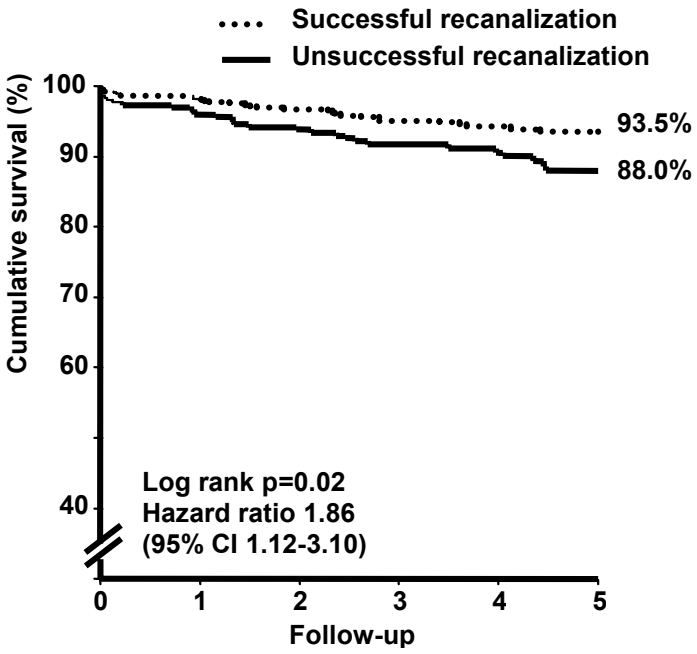


Figure 5: Cumulative survival-free of acute myocardial infarction (AMI) at 5 years with respect to the outcome of attempted recanalization of a chronic total occlusion.

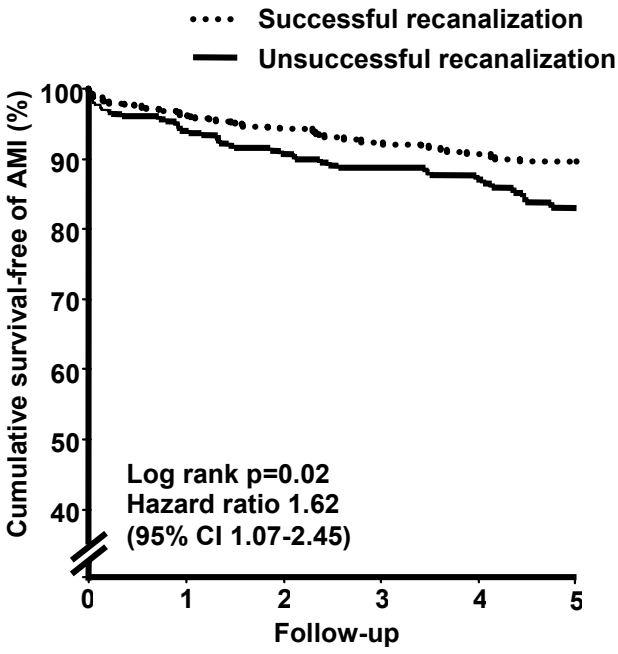


Figure 6: Cumulative survival-free of coronary artery bypass surgery (CABG) at 5 years with respect to the outcome of attempted recanalization of a chronic total occlusion.

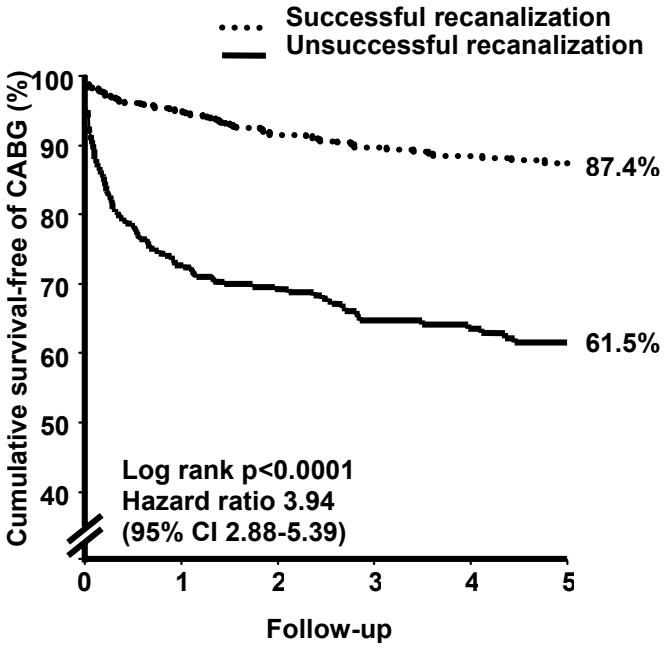


Figure 7: Cumulative survival-free of major adverse cardiac events (death, acute myocardial infarction, or repeat reintervention (percutaneous or bypass surgery)) at 5 years with respect to the outcome of attempted recanalization of a chronic total occlusion.

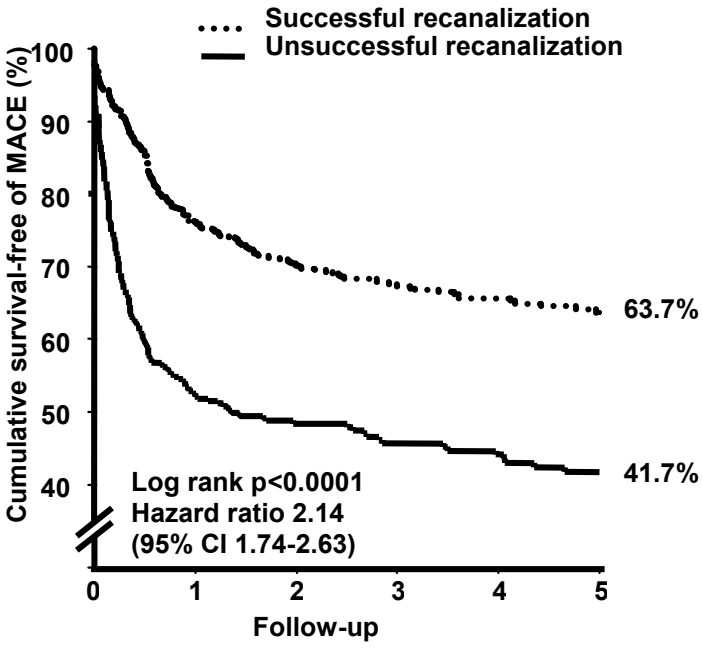


Table 4: Cumulative survival-free of major adverse cardiac events at 5 years with respect to the presence of single versus multivessel coronary disease

	Single vessel			Multivessel		
	CTO success n=261	CTO failure n=99	p value	CTO success n=306	CTO failure n=205	p value
Death (%)	97.3	99.0	0.3	92.5	86.3	0.02
Death / AMI (%)	94.6	96.0	0.6	88.6	82.0	0.03
Death / CABG (%)	91.6	70.7	<0.0001	86.9	61.5	<0.0001
MACE (%)	72.0	47.5	<0.0001	61.1	42.9	<0.0001

Figure 8: Cumulative survival at 5 years with respect to diabetic status

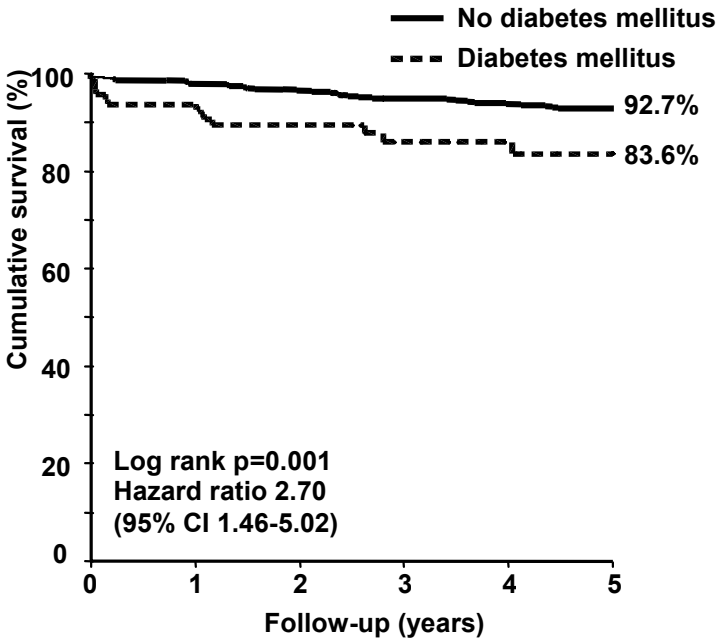
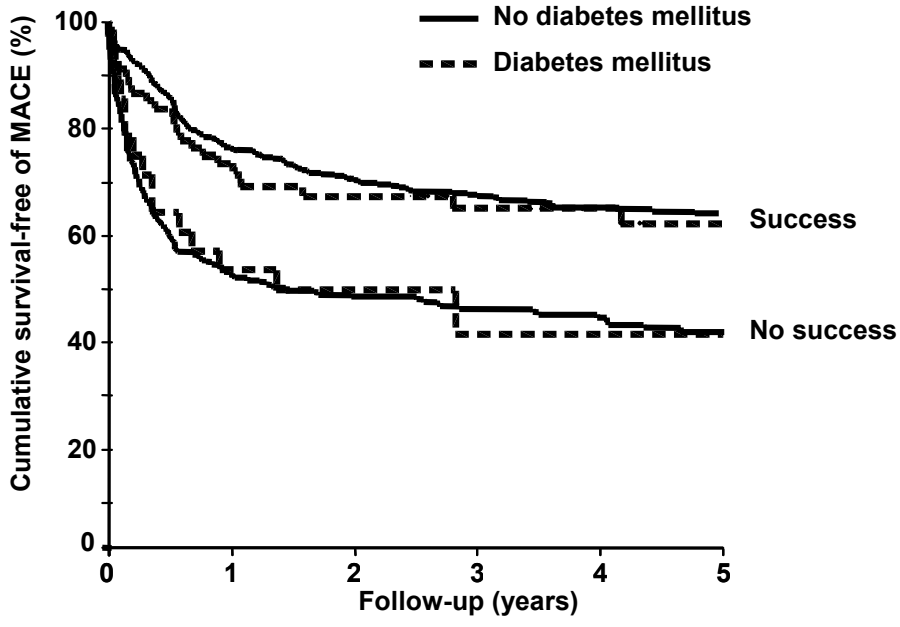


Figure 9: Cumulative survival-free of major adverse cardiac events (death, acute myocardial infarction, or repeat reintervention (percutaneous or bypass surgery)) at 5 years with respect to diabetic status, and the outcome of attempted recanalization of a chronic total occlusion



Overall survival was significantly lower in those patients with diabetes mellitus (figure 8). Within the diabetic population, 5-year survival was 84.9% in those with a successful recanalization versus 79.1% following unsuccessful recanalization (p=0.4), suggesting that most of the benefit in terms of survival following successful recanalization is in the non-diabetic group. However, the beneficial effect of successful recanalization of a CTO on survival-free of MACE remains clearly apparent (figure 9), irrespective of diabetic status. Successful recanalization led to a 5 year MACE-free survival of 63.7% and 62.3% in those with and without diabetes mellitus respectively. Following unsuccessful recanalization, the 5 year MACE-free survival was 42.0% and 41.5% for those with and without diabetes mellitus respectively, p<0.0001.

Discussion

The present study evaluated only consecutive patients with chronic total occlusions (CTO) of at least one months' duration, and for the first time confirms a 5-year survival benefit in successful recanalization of these lesions. In addition, there was a significant reduction in major adverse cardiac events, particularly the need for revascularization with CABG. Independent predictors of survival were a successful recanalization, lower age, and the absence of diabetes mellitus and multivessel disease. Independent predictors of major adverse events were an unsuccessful recanalization, multivessel disease, and non-usage of stent implantation.

Although one large series of the long-term outcomes of patients following PCI for CTO has been published, the authors acknowledged that their study was limited as they did not always know the duration of occlusion. [2] Indeed, analysis of 100 consecutive patients who had been included in the study demonstrated that 42% were <1 months' duration. These patients are likely to have thrombotic occlusions, rather than the fibrotic / calcific lesion of a CTO. This difference in lesion pathophysiology may affect the long-term outcome, indeed one of the independent predictors for survival in the MAHI study, was therapy for unstable angina. In the present study, we have confirmed that a successful outcome following PCI for a truly chronic occlusion does confer a significant benefit on survival, and reduces the rate of MACE with a marked reduction in the need for CABG.

The difference in the rate of MACE between those with a successful versus unsuccessful recanalization was apparent immediately (at 48 hours), predominantly related to the need for emergency CABG in the failed recanalization group. An acute complication of CTO recanalization therefore confers serious adverse consequences in the short-term, which would have been potentially avoided if an alternative treatment option had been undertaken. It is particularly important to note that the mortality rate of those with a failed procedure was not insignificant at 1.9% at 30 days.

The present study demonstrated a 5-year survival benefit following successful CTO recanalization. The possible reasons for the improved survival are beyond the scope of the present study. There were differences in the medical therapy received by the 2 groups which could potentially be a confounding factor. Unlike those with a failed recanalization, the group with a successful recanalization together with stent implantation were treated with additional medical therapy with warfarin, ticlopidine, or clopidogrel. However, this was given for only 1 month, and it is unlikely that such a short duration of therapy is the reason for the improved long-term outcomes. More likely, improved survival may relate to the greater proportion of viable but inadequately perfused myocardium. The improvement in prognosis following successful revascularisation might relate to the associated improvement in left ventricular function, [7] or a reduction in the risk of ischaemic-driven malignant arrhythmia. In addition, a successful procedure could potentially avoid the need for CABG with its' associated mortality risk.

In the present study, the survival benefit of successful CTO recanalization was most apparent in those with multivessel rather than single vessel disease. Indeed, the patients with single vessel disease and failed recanalization had a very high rate of survival at 5-years of 98.9%. Approximately half of these patients underwent CABG or repeat re-intervention with PCI, with a survival-free of MACE at 5 years of 45.8%. The remaining patients were treated with medical therapy alone, and although this constitutes only a relatively small number of patients, the excellent survival rate suggests that from a prognostic point of view medical therapy may not be unreasonable. Little data is currently available on the outcomes of patients with a CTO who are managed with optimal medical therapy (aspirin, beta-blocker, statin, ACE-inhibitor etc). In particular, those with an excellent collateral circulation may have a very good prognosis. Our manuscript does not therefore provide

scientific proof to support a broad generalized recommendation to try to open all CTOs; a randomised study comparing “best” medical therapy with a more aggressive strategy of attempted recanalization would be required to assess this. Importantly, studies are needed with more detailed assessment of left ventricular function, degree of viability, and ischaemic burden both pre-procedure and at follow-up, to determine the relationship these have with long-term survival.

The Thoraxcenter in Rotterdam is a tertiary referral centre for PCI, taking referrals from 13 surrounding hospitals covering a large region. The majority of patients requiring repeat re-intervention, whether it be percutaneous or surgical, come back to be re-treated in our centre. As in other centres, the number of percutaneous revascularizations increased over time, whilst that of CABG gradually decreased. In addition, the relative number of PCI procedures carried out for a chronic occlusion also increased with time. However, the overall success rate of recanalization remained stable despite advances in the technology of specialised wires and other equipment. The chances of successful recanalization are known to be dependent on lesion morphology and it is possible that with time and the increase in PCI for CTO, relatively more complex lesions were attempted.

It is well recognised from large scale studies that mortality is higher following percutaneous coronary intervention procedures in those with diabetes compared to those without diabetes mellitus. [8,9] Our study concurs with these results, with a significantly lower 5 year survival in diabetics (83.6% versus 92.7%, p=0.001). However, the beneficial effect of successful recanalization of a CTO on overall survival-free of major adverse events was clearly apparent to be irrespective of diabetic status (figure 9).

Of those patients with a successful revascularization, the majority of subsequent adverse events relate to a need for repeat reintervention. Long-term results have been shown to improve with the advent of stent implantation, with reduced rates of restenosis and re-occlusion when compared with results of balloon-only angioplasty. However, the recent introduction of drug-eluting stents will further improve on these results. Data from our own centre have shown a significant higher cumulative survival-free of major adverse cardiac events at 1 year with the sirolimus-eluting stent compared with bare metal stent implantation (96.4% versus 82.8%, $p<0.05$). [10] These results encourage the development of further technologies to facilitate safe and successful CTO recanalization.

Limitations:

The present study is limited by being a retrospective observational analysis of outcomes. However, it is comprised of a large cohort of patients with complete clinical follow-up obtained in virtually all. The study is further limited by the lack of randomised comparison with a group of patients treated with medical therapy alone, or those treated directly with CABG. In addition, the possible reasons for improved survival in the successful recanalization group have not been fully explored and require further study.

Conclusions:

Successful percutaneous revascularization of a CTO leads to a significantly improved survival rate, and a reduction in major adverse events at 5 years. Most events relate to the need for repeat re-intervention, and the introduction of drug-eluting stents, with reduced restenosis rates, encourages the development of further technologies to improve recanalization success rates. However, failed recanalization may be associated acutely with a major adverse event, and new technologies must focus on a safe approach to successful recanalization. Additional studies are needed to evaluate the comparative prognostic value of CTO recanalization compared with optimal medical therapy, particularly in patients with single vessel disease.

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Chapter 4

Predictors, Incidence and Prognosis of Coronary Occlusion following Intracoronary Beta-radiation Therapy

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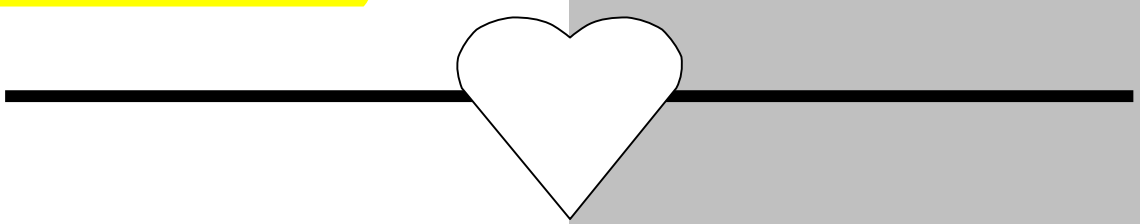


Abstract

Background: Intracoronary brachytherapy (IRT) has been associated with the development of late vessel occlusion.

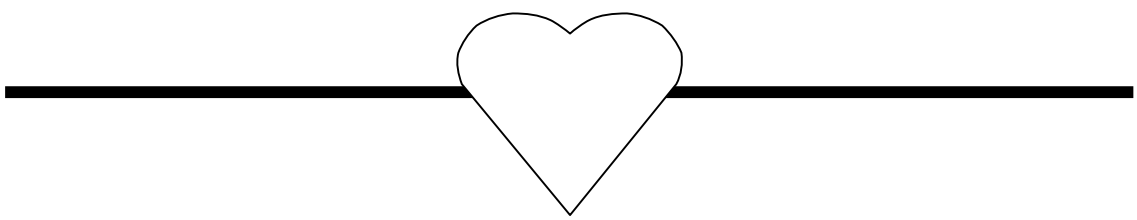
Objectives: To assess the incidence, predictors and prognosis of coronary occlusion in a consecutive series of patients following beta-radiation therapy

Methods: Between April 1997 and December 2001, 301 consecutive patients were successfully treated with IRT, and 37 patients (12.3%) were subsequently found to have an occlusion of the treated vessel and form the present study population. Patient and procedural data were retrospectively analysed from a dedicated database.

Results: One patient had subacute thrombosis on day 21, and over a mean follow-up of 40.3 months, target lesion occlusion was found in a further 36 patients at a mean time after IRT of 16.0 months (range 3.4-66.8 months). In 12 patients (32.4%), vessel closure caused an acute myocardial infarction, and was associated with 3 (8.1%) cardiac-related deaths. At 4 years, the cumulative survival-free of target lesion closure was 85.4%.

By multivariate analysis, the factor predictive for development of occlusion was treatment of a de novo lesion rather than in-stent restenosis (15.4% versus 7.9%, p=0.03 (HR=2, 95% CI: (1.1-5)). Occlusion was not related to the dosage administered, the source length, the duration of dual anti-platelet agents, or the “learning curve” of therapy.

Conclusions: A high incidence of late vessel occlusion is observed after IRT. Prolongation of dual anti-platelet therapy to 6 months duration is insufficient to protect against the development of occlusion, which is associated with significant morbidity.



Chapter 5

Value of Pre-Procedure Multislice Computed Tomographic Coronary Angiography to Predict Percutaneous Recanalization of Chronic Total Occlusions

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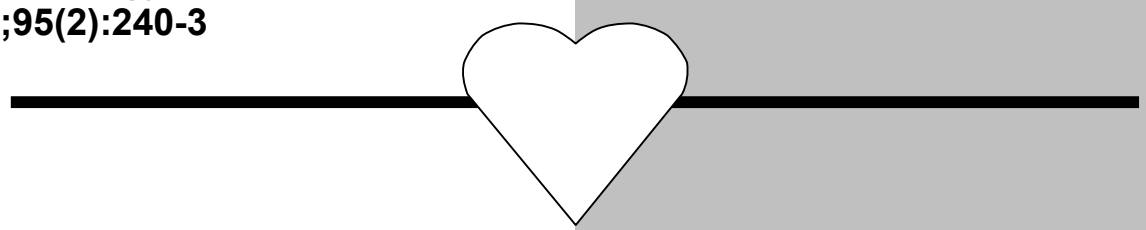
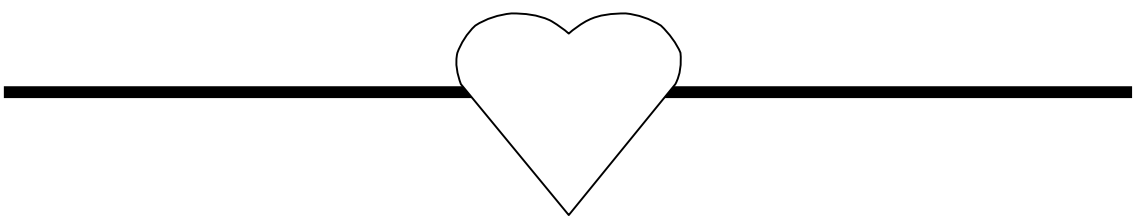
Americal Journal
Of Cardiology
2005;95(2):240-3



Abstract

We performed multislice computed tomographic coronary angiography in 45 patients who had chronic total occlusions and were scheduled for percutaneous recanalization. Multivariate analysis identified a blunt stump (by conventional angiography), occlusion length >15 mm, and severe calcification (by multislice computed tomographic coronary angiography) as independent predictors of procedural failure.



Sixteen-row multislice spiral computed tomographic (MSCT) coronary angiography has recently been shown to allow reliable noninvasive evaluation of coronary morphology.[1-3] In the present study, we analyzed the potential of preprocedural MSCT coronary angiography to provide additional information and thus predict the procedural outcome in patients who had chronic total occlusion (CTO) and were referred for percutaneous coronary recanalization.

Forty-five patients referred for percutaneous recanalization of ≥1 CTO lesion underwent MSCT coronary angiography before the coronary procedure (median interval 29 days, interquartile range 9 to 53). The diagnosis of CTO was made on diagnostic angiograms that demonstrated complete occlusion of a major epicardial coronary artery, which was deemed to be of ≥3 months' duration from the date from the previous angiogram, a clinical history of myocardial infarction, or onset of or a severe episode of prolonged anginal chest pain. In addition, inclusion into the study required a serum creatinine level <120 mmol/L, presence of sinus rhythm, and the ability to hold a breath for 20 seconds. The protocol was approved by the institutional review board, and all patients gave written informed consent.

Conventional angiographic assessment was performed by observers who were unaware of the results of MSCT scans. Parameters previously reported to have prognostic importance for procedural failure were assessed: absence of anterograde flow through bridging collaterals, absence of a tapered stump, presence of severe calcification at the occluded segment, side branch at the occlusion site, and tortuosity of the vessel proximal to the occlusion (defined as an angle >45° in any projection). Where possible, occlusion length was measured from the view with the longest lesion on quantitative coronary angiography as the distance between a stump and a distal vessel as visualized by anterograde filling through bridging collaterals. In addition, in some other patients, length was determined from the baseline angioplastic procedure film using a bilateral coronary injection.

Twenty-two patients who had a heart rate >65 beats/min before multislice spiral computed tomography received an oral dose of 100 mg of metoprolol 1 hour before scanning. All examinations were performed with a 16-row MSCT scanner (Sensation 16, Siemens, Forehheim, Germany; collimation 16 × 0.75 mm, rotation time 420 ms, table feed 3.0 mm/rotation, tube voltage 120 kV, tube current 400 to 450 mA). After intravenous administration of 120 ml of nonionic contrast material (Visipaque 320, Amersham Health, Little Chalfont, United Kingdom), an automatic bolus-tracking technique triggered the start of MSCT scanning. Images were reconstructed with retrospective electrocardiographic gating during the mid- to end-diastolic phase to provide nearly motion-free image quality; additional reconstruction windows (e.g., early diastolic phase) were explored when necessary.

All MSCT scans were analyzed off-line by operators who were blinded to angiographic and procedural data. Parameters similar to those of conventional angiography were evaluated: a blunt rather than tapered stump, severe calcification, side branch at the occlusion site, proximal tortuosity, and occlusion length. Severe calcification was defined as the presence of high-density plaques (≥130 HU) involving >50% of the coronary wall on a cross-sectional image and localized within the occlusion stump or occluded segment.

All procedures were performed by operators who were highly experienced in the treatment of CTOs, with the interventional strategy left to the discretion of the operator. Wires were used in a stepwise progression, starting with a wire that had a relatively less traumatic tip (Graphix Intermediate, Boston Scientific Corporation, Miami, Florida) or a hydrophilic wire (Choice PT Plus, Boston Scientific Corporation, or Crosswire NT Terumo Corporation, Tokyo, Japan) and progressing to stiffer wires (Miracle, Asahi Intec, Nagoya, Japan) and specialized technologies (Safe-Cross, Intraluminal Therapeutics, Carlsbad, New Mexico).[4,5] Procedural failure was defined as an inability to cross the occlusion with a guidewire.

Multivariate logistic regression analyses were performed to identify angiographic and MSCT parameters associated with procedural failure (all univariate predictors with a p value ≤0.1 were tested for their multivariate predictive value, and final models were built by backward stepwise selection). Angiographic parameters assessed were those identified in previous studies: [6] the occluded artery, duration of occlusion, multivessel

disease, anterograde and retrograde collateral filling, type of stump, side branch at the site of occlusion, calcific deposits, vessel tortuosity, and occlusion length >15 mm. The predictive strengths of the models were evaluated by means of the −2 log-likelihood statistic, and models' lack of fit with the Hosmer-Lemeshow test, and their global predictive accuracy were assessed by the C index (area under the receiver-operating characteristic curve).

Patients' mean age ± SD was 57.0 ± 10.1 years, 40 (89%) were men, 10 (22%) were diabetic, and 14 (31%) had multivessel disease. Forty-seven CTO lesions were treated. Angiographic measurement of CTO length was possible in 39 lesions (83%), 31 (66%) from the diagnostic film and an additional 8 (17%) from bilateral injection and assessment of retrograde collateral filling. The mean length of occlusion was longer by MSCT coronary angiography than by angiography (21.8 ± 18.6 vs 14.6 ± 10.9 mm, respectively). Procedural data, including type and number of guidewires used, are presented in Table 1. The only difference between success and failure was in the increased use of the Miracle wire in the failure group. Overall mean procedural time was 148 ± 53 minutes, with a mean fluoroscopic time of 47 ± 24 minutes. Overall, 45% of interventional procedures failed (Table 2). Success versus failure was not dependent on the operator or choice of interventional strategy. At univariate analysis, the following were associated with procedural failure: clinical assessment (occlusion duration ≥9 months), angiographic assessment (lack of anterograde collateral filling, a blunt rather than a tapered stump, and side branch at the occlusion site), and MSCT coronary angiographic assessment (a blunt rather than a tapered stump, severe calcification, and occlusion length >15 mm; Table 2).

Table 1: Procedural Duration and Use of Contrast Material and Guidewires for Percutaneous Intervention of a CTO With Respect to Successful Versus Unsuccessful Recanalization

	Success (n = 26 lesions)	**Failure (n = 21 lesions)**	**p value**
Mean total procedural time (min)	148 ± 61	148 ± 44	1.0
Mean volume of contrast used (ml)	451 ± 258	453 ± 265	1.0
Mean no. of wires	2.0 ± 1.2	2.1 ± 0.8	0.9
Wire type*			
Graphix Intermediate	20 (76.9%)	12 (57.1%)	0.2
Choice PT Plus	5 (19.2%)	3 (14.3%)	0.8
Crosswire NT	8 (30.8%)	10 (47.6%)	0.3
Miracle	5 (19.2%)	12 (57.1%)	<0.01
Intraluminal	3 (11.5%)	4 (19.0%)	0.5
Over-the-wire balloon support	15 (57.7%)	17 (81.0%)	0.1

* Wire type not mutually exclusive.

When analyzed separately, the following “traditional” clinical and angiographic characteristics were identified as multivariate predictors of procedural failure: occlusion duration >9 months and stump morphology (Table 3). Separate multivariate analysis that assessed only MSCT coronary angiographic parameters identified the following predictors: occlusion length >15 mm, severe calcification, and stump morphology. Final best model testing for pooled clinical, angiographic, and MSCT parameters identified a blunt rather than a tapered stump (by angiography), occlusion length >15 mm (by MSCT coronary angiography), and severe calcification (by MSCT coronary angiography) as multivariate independent predictors of procedural failure (Figure 1).

The current selection process of technically appropriate candidates for percutaneous recanalization of CTO is based on the evaluation of a relatively restricted number of clinical and angiographic characteristics. In this study, we show that noninvasive evaluation of patients who have CTO by preprocedural MSCT coronary angiography improves the ability to predict the outcome of a percutaneous recanalization attempt. Our findings indicate that MSCT coronary angiography may aid in the therapeutic decision making for patients who have CTO. In addition, accurate preprocedural characterization of CTO features may assist in outlining the therapeutic interventional strategy.

Table 2: Clinical, angiographic and MSCT coronary angiography lesion characteristics (n=47)

	Angiography				MSCT coronary angiography			
	Frequency (%)	Failure rate (%)	OR (95% CI)	p value	Frequency (%)	Failure rate (%)	OR (95% CI)	p value
Right coronary artery	43	50	1.45 (0.45-4.66)	0.5	-	-	-	-
Left anterior descending artery	43	40	0.72 (0.22-2.32)	0.6	-	-	-	-
Left circumflex artery	15	43	0.92 (0.18-4.64)	0.9	-	-	-	-
Occlusion duration ≥9 mo	51	63	4.72 (1.36-16.39)	0.02	-	-	-	-
Multivessel disease	34	38	0.64 (0.19-2.20)	0.5	-	-	-	-
Anterograde filling	60	32	0.27 (0.08–0.94)	0.04	-	-	-	-
Retrograde collateral filling	72	44	0.92 (0.26–3.32)	0.9	-	-	-	-
Bridging collaterals	38	39	0.68 (0.21–2.25)	0.5	-	-	-	-
Tapered stump	60	25	0.12 (0.03–0.45)	<0.01	60	32	0.16 (0.03–0.73)	0.02
Stump morphology not determinable	0	-	-	-	15	43	0.25 (0.34-1.82)	0.2
Side branch at occlusion site	57	59	4.37 (1.23–15.54)	0.02	45	52	1.76 (0.55-5.64)	0.3
Severe calcification	34	50	1.39 (0.41–4.65)		38	67	4.44 (1.27-15.61)	0.02
Vessel tortuosity	23	64	2.75 (0.68–11.14)	0.2	21	50	1.31 (0.32-5.32)	0.7
Occlusion length >15 mm	26	67	3.39 (0.85–13.48)	0.08	51	63	4.72 (1.36-16.39)	0.02
Occlusion length not determinable	17	50	1.29 (0.28–5.94)	0.7	0	-	-	-
Overall	100	45	-	-	-	-	-	-

CI = confidence interval; MSCT = multislice computed tomographic; OR = odds ratio

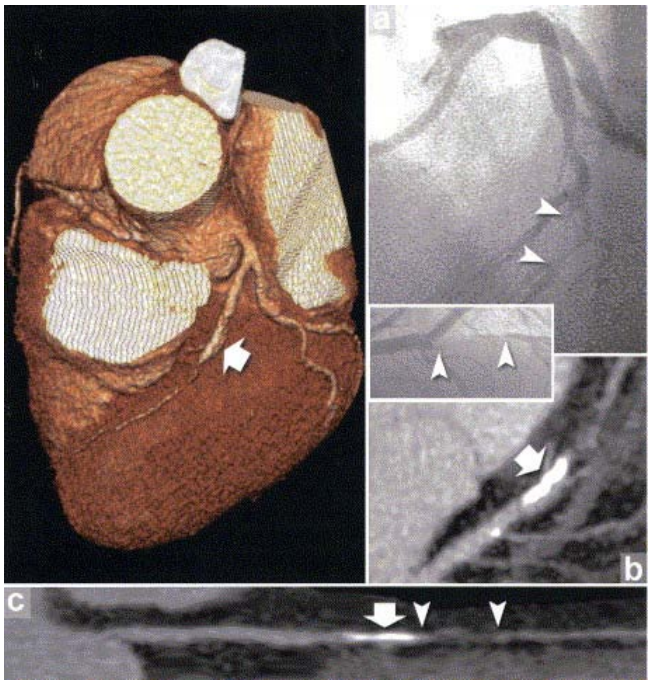
DF = degrees of freedom; other abbreviations as in Table 2. * A −2 log-likelihood change in the global model if 1 variable is removed: tapered stump −10.7 (p <0.01 for change), occlusion length −8.2 (p <0.01), and calcification −6.6 (p = 0.01 for change).

	Coefficient	Wald's Chi-square	DF	p value	OR (95% CI)	-2 Log Likelihood	Hosmer-Lemeshow test		C Index
							DF	p value	
Clinical / angiographic predictors						50.0	2	0.66	0.80
Occlusion duration >9 mo	1.27	3.30	1	0.07	3.56 (0.90-14.02)				
Tapered stump	-1.93	7.46	1	<0.01	0.15 (0.04-0.58)				
Constant	0.24	0.13	1	0.7	-				
MSCT coronary angiography predictors						44.2	6	0.99	0.84
Occlusion length >15 mm	1.86	5.21	1	0.02	6.39 (1.30-31.41)				
Severe calcification	2.49	6.51	1	0.01	12.01 (1.78-81.1)				
Stump morphology	-	5.63	2	0.06	-				
Blunt	1 (reference)	-	-	-	-				
Tapered	-2.19	5.23	1	0.02	0.11 (0.02-0.73)				
Not determinable	-2.65	3.46	1	0.06	0.07 (0.00-1.15)				
Constant	-0.45	0.26	1	0.6	-				
Clinical/angiographic + MSCT coronary angiographic predictors						41.0	5	0.60	0.85
Tapered stump*	-2.43	7.98	1	<0.01	0.09 (0.02-0.48)				
Occlusion length >15 mm	2.17	6.16	1	0.01	8.77 (1.58-48.76)				
Severe calcification	2.03	5.18	1	0.02	7.62 (1.33-43.74)				
Constant	-0.67	0.74	1	0.4					

MSCT coronary angiography of CTOs adds important information compared with “conventional” coronary angiography. The length of the occluded segment has long been identified as an important predictor of failed recanalization. However, accurate measurement of lesion length using conventional angiography may be difficult, mainly due to foreshortening, calibration limitations, and lack of visualization of the distal vessel in the absence of collateral filling. In the present study, lesion length could be measured in only 66% of diagnostic films. Conversely, MSCT coronary angiography allowed reliable 3-dimensional length measurement of coronary segments.[7] In the present series, when angiographic and MSCT coronary angiographic occlusion lengths were measured, results of the MSCT coronary angiography were “longer,” perhaps reflecting the inaccuracy of quantitative coronary angiography as previously described. Moreover, MSCT coronary angiography allows evaluation of the morphology of the occlusion trajectory, including detailed delineation of coronary calcification. Long occlusions and severe calcifications on MSCT coronary angiograms were found to be important predictors of procedural failure, whereas neither feature was identified as an independent predictor on conventional angiograms.

The need to use contrast material may pose a limitation to preprocedural MSCT coronary angiography for interventions scheduled to be performed shortly after scanning. However, the elective nature of CTO recanalization angioplasty allows a safe time lag between these procedures. In our study, multislice computed tomography was performed ~1 month before coronary intervention. The relatively high radiation exposure during MSCT coronary angiography, reportedly between 6.7 and 13.0 mSv,[8-10] remains a matter of concern. However, MSCT coronary angiography may optimize therapeutic strategy (e.g., calcifications may require intraluminal techniques), resulting in shorter procedures. MSCT coronary angiography is currently feasible for selected patients, and further studies are needed to evaluate its value in a more general patient population.

Figure 1: *(A, inset)* CTO of the left anterior descending coronary artery with favorable invasive angiographic CTO characteristics, tapered stump, absence of calcifications, and occlusion length <15 mm *(arrowheads)* in a patient who had been referred for percutaneous recanalization. Volume-rendered MSCT image that provides a 3-dimensional overview of the coronary arteries, and *(B)* maximum intensity projection of the same MSCT image show a severely calcified occlusion stump *(arrows)*. *(C)* Curved multiplanar reconstructed MSCT image of the left anterior descending coronary artery shows a severely calcified stump *(arrow)* and an occluded segment *(arrowheads)*. Collateral filling is clearly visible distal to the occlusion. This percutaneous attempt at recanalization of the CTO was unsuccessful.



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Chapter 6

Improved Recanalization of Chronic Total Coronary Occlusions Using an Optical Coherence Reflectometry-Guided Guidewire

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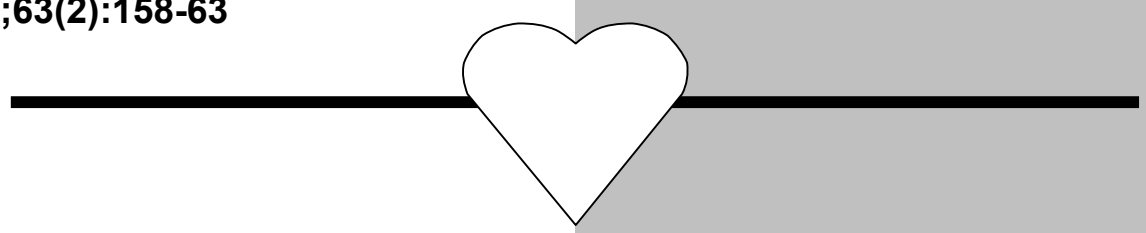
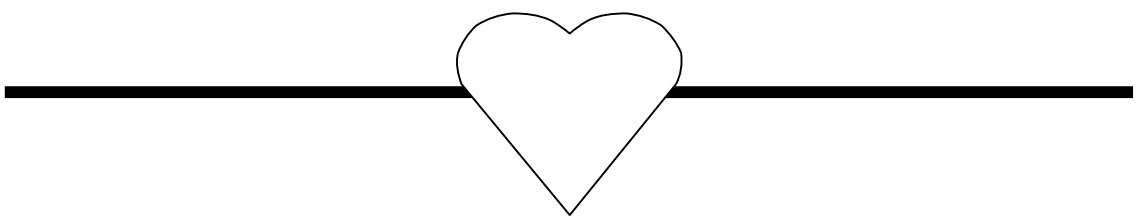
Catheterization and Cardiovascular Interventions 2004;63(2):158-63



Abstract:

Successful percutaneous therapy of chronic total occlusions is limited predominantly by the inability to cross the lesion. We report our experience of 29 chronic total occlusions (CTO) that could not be crossed with conventional wires and subsequently underwent attempted recanalization facilitated using a wire navigated with optical coherence reflectometry. Mean length of occlusion was 22.1mm (range 4.5-88.7mm). Successful recanalization was achieved in a further 15 (51.7%), with no complications of tamponade, myocardial infarction or death. These results demonstrate that this wire can be a useful tool in addition to conventional wires in the treatment of chronic total occlusions.



Introduction:

Chronic total occlusions (CTO) are common and continue to present a challenge to the Interventional Cardiologist. In patients undergoing angiography who are found to have significant coronary disease, at least one CTO will be found in approximately one third.[1] Yet most of these patients are currently treated with either medical therapy or are referred for bypass surgery with percutaneous intervention of a CTO accounting for approximately only 10% of all angioplasties. The major limitation of percutaneous intervention is the inability to cross the occlusion with a wire. Success rates in CTO`s vary, and are dependant on both patient selection and operator experience; even in those patients selected to be suitable for percutaneous therapy, success rates are between 40 and 80%.[2,3]

The Safe-Cross system (Intraluminal Therapeutics, Carlsbad, CA):

This is comprised of the Intraluminal™ guidewire which is plugged directly into a console. [4] The wire itself is 0.014" in diameter and notably has a blunt tip (figure 1A); the distal 10mm is seen as opaque on fluoroscopy. The system uses optical coherence reflectometry to enable accurate guidance of the wire and a reduced risk of wire perforation. Near-infrared light is emitted from the tip of the 0.014" Intraluminal™ guidewire (figure 1B) and the system then measures the reflectivity of the beam. Near-infrared light is used because it has a much shorter wavelength (1.3microns) compared to the sound waves used in conventional ultrasonography (100microns). This confers several advantages: firstly, light is less strongly reflected by calcified tissues so that information can still be gathered even from behind calcified plaque. In addition, it enables the system to be `forward looking` with a very high resolution of up to 15 microns. Different tissue types such as plaque and intima can be accurately differentiated on the basis of variable absorption rates and scattering coefficients. [4,5]

In addition to this, the current Intraluminal™ Guidewire has the capability of radiofrequency ablation with short duration bursts (100 millisecond pulses) of low frequency energy (250-500 kHz) delivered at the tip to enhance forward wire passage.[5] Histological examination has shown that the associated collateral damage around the ablated hole is contained, and lies within a 75-100 micron zone. When the tip detects lumen or plaque, the systems` monitor demonstrates a green bar (figure 2) and radiofrequency ablation is enabled. However, when the tip is too close to the vessel wall, a red bar is demonstrated on the system monitor, ablation is disabled, and the operator is alerted with an audible sound. The operator then gently rotates the wire until the green bar returns to confirm the tip is heading in a proper direction, and the wire may then be advanced.

Previous reports have shown the efficacy of this wire in the therapy of long occlusive in-stent restenosis. [6] We present our results utilising this wire in a consecutive series of patients with at least one chronic total occlusion who had had failed recanalization using conventional wire techniques.

Figure 1: A close-up view of the 0.014" Intraluminal™ Guidewire. The tip is relatively blunt (**A**), and emits a beam of near-infrared light which can be seen (arrow **B**).

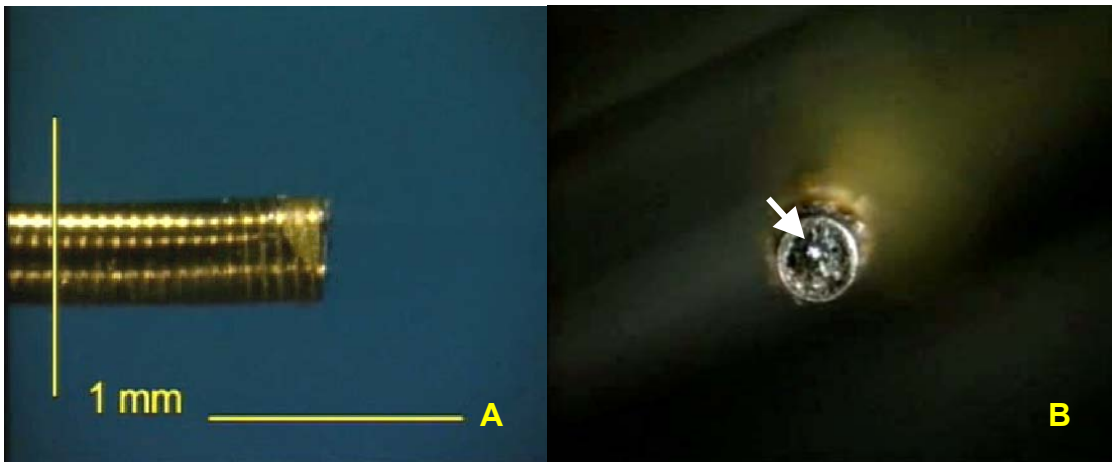
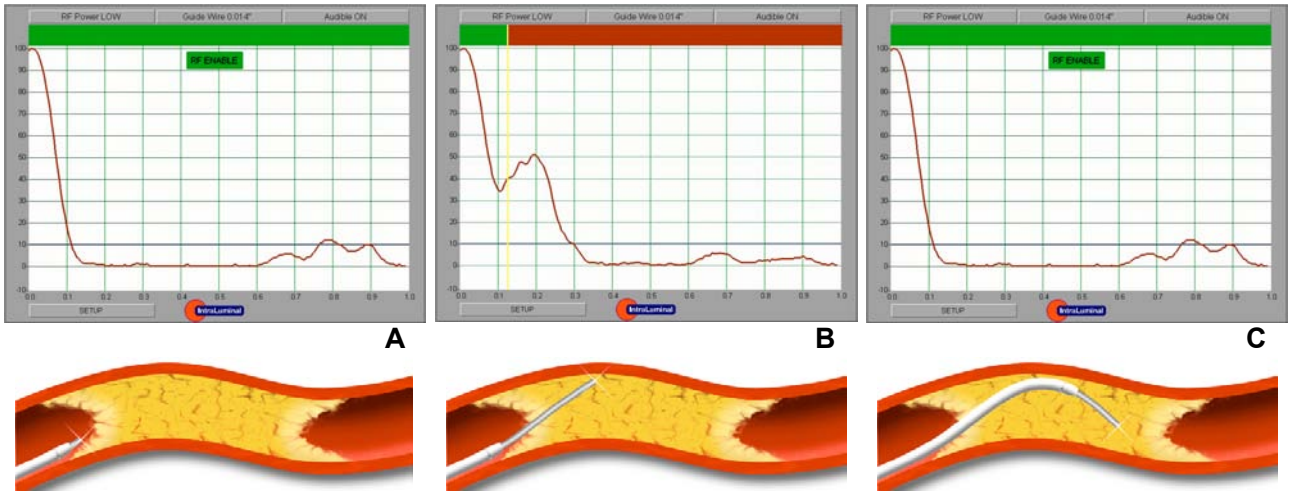


Figure 2: The display seen on the monitor derived from the optical coherence reflectometry waveform from the wire tip.



A: When the wire tip is within the vessel lumen, the display features a green bar, and the radiofrequency ablation capability is enabled. **B:** The wire tip is now at the vessel wall and taking an incorrect path, the monitor displays a red bar, and ablation is disabled. **C:** The wire tip is gently rotated until it once again takes an intraluminal course, the bar changes to green, and once again ablation is enabled.

Materials and Methods:

Following failed recanalization of a chronic total occlusion with conventional techniques, the Intraluminal^{TM} wire was used in a series of 27 patients. Total number of lesions was 29; mean length of occlusion could be estimated in 25 lesions (86.2%) either due to antegrade flow from bridging collaterals, or retrograde filling evaluated using simultaneous double injection technique into both coronaries. All occlusions were estimated to be at least 3-months old on the basis of either the time between the diagnostic angiogram and intervention (in 59%), or the time from the onset of angina or a prolonged period of pain (in 41%).

All patients were initially treated with conventional wires. In the majority, the policy was to first use a Graphix Intermediate tip wire (Boston Scientific, Miami, Florida, USA), followed by a Miracle 3 wire (Asahi Intecc Co. Ltd, Aichi, Japan). Wires were used with additional support provided by an over the wire Maverick balloon (Boston Scientific, Miami, Florida, USA). If successful recanalization was not achieved despite aggressive use of these wires, the Intraluminal^{TM} wire was then utilised to facilitate further progress, though with the option of switching back to a conventional wire if wanted. All the Intraluminal^{TM} wire procedures were carried out by operators who are highly experienced in the treatment of CTO`s, with the majority done by a single operator. All patients provided written informed consent.

Multivessel disease was defined as >50% diameter stenosis of more than one major epicardial artery. Procedural success was defined as wire passage through to the lumen of the distal vessel with subsequent angioplasty leading to a residual diameter stenosis of <30% together with TIMI 3 flow.

Results:

Baseline patient demographics and lesion characteristics are presented in tables 1 and 2 respectively. Multivessel disease was present in 13 patients (48.1%). Of these, during the CTO procedure, stenting was carried out in at least one other major epicardial artery 7 (25.9%). Two patients had two separate procedures with recanalization attempted on 2 CTO`s for each patient, therefore in total, 29 lesions were treated in 27 patients. All occlusions were more than 3 months old, with a mean age estimated to be 1.9 years (range 3 months to 19 years). Mean length of occlusion was 22.1 $\pm$ 17.2mm (range 4.5mm to 88.7mm). A previous failed attempt to recanalize the target lesion had been carried out on a separate occasion in 6 lesions (20.7%). Only one lesion (3.4%) was a chronic in-stent occlusion. This patient was previously treated with brachytherapy for

in-stent restenosis, but presented 2 years later with stable angina, and had complete stent occlusion. After an initial attempt to recanalize the artery failed, he returned for a second (successful) procedure utilising the Intraluminal™.

Table 1: Baseline patient characteristics

	Patient population n=27
Male sex	20 (74.1%)
Diabetes mellitus	3 (11.1%)
Hypercholesterolemia	24 (88.9%)
Hypertension	13 (48.1%)
Current smoking (%)	5 (18.5%)
Presence of multi-vessel disease (%)	13 (48.1%)
Previous myocardial infarction (%)	17 (63.0%)
Previous PCI (%)	12 (44.4%)
Previous CABG (%)	2 (7.4%)

PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft surgery

Table 2: Baseline lesion characteristics

		Lesion n=29
Target vessel (%)	LAD	9 (31.0)
	LCX	3 (10.3)
	RCA	17 (58.6)
Ostial location of occlusion * (%)		5 (17.2)
Length of occlusion >15mm (%)		15 (51.7)
Stump morphology (%)	Central	7 (24.1)
	Eccentric	2 (6.9)
	Blunt	20 (69.0)
Side branch at the site of occlusion (%)		18 (62.1)
Bridging collaterals (%)		14 (48.3)
Retrograde collateral filling (%)		26 (89.7)
Angiographic evidence of calcification (%)		8 (27.6)
Proximal tortuosity (>45° angle) (%)		3 (10.3)

LAD: left anterior descending; LCX: left circumflex artery; RCA: right coronary artery
*The occlusion was defined as ostial if it occurred <5mm from the origin of the vessel

Visualisation of the distal vessel was enhanced by using 'double injection technique' (simultaneous injection into both the left and right coronary arteries) in 21 of 29 lesions (72.4%). The mean total procedure time was 165 ± 45 minutes with a mean fluoroscopy time of 82 ± 35 minutes. The mean total amount of contrast used was 465 ml. The mean procedural time between starting the attempt with conventional wires, and the decision to switch to the Intraluminal™ wire was approximately 30 minutes. Successful recanalization was achieved in 15 of the 29 lesions (51.7%). All were subsequently stented with either bare stents (n=5) or drug-eluting stents (n=10), and, at the end of the procedure had a successful angiographic result with a residual diameter stenosis of <30%. For the CTO lesion, mean number of stents implanted was 2.8 with a mean diameter of 2.8 ± 0.33mm, and a mean length of stented segment of 63.9 ± 27.5mm (range 26-112mm).

There were no patient or lesion characteristics predictive for success versus failure. There were no procedural / in-hospital complications of tamponade, acute myocardial infarction or death. The procedure was unsuccessful in 14 patients. The decision to halt the procedure was at the operator`s discretion and related to

failure to cross the lesion in 8 (57.1%), and the occurence of dissection in the remaining 6 (42.9%). All episodes of dissection occurred whilst a conventional wire (rather than the Intraluminal™ wire) was in use, and all were without clinical sequelae. Of these 14 patients with unsuccessful recanalization, 3 (21.4%) were referred for coronary artery bypass graft surgery, and the remaining 11 (78.6%) were managed with medical therapy.

Discussion:

Previous studies have demonstrated the importance of the revascularization of chronic total occlusions with significant benefits on quality of life with improvement in both anginal symptoms and exercise capacity. [7] In addition, successful recanalization of a chronically occluded artery reduces the need for subsequent bypass surgery and the rate of myocardial infarction. [8] There is also evidence that, provided the artery remains patent, there is an improvement in left ventricular function. [9] Importantly, long-term evaluation has shown a 10-year survival advantage following successful PCI compared to those in whom PCI is unsuccessful (survival 73.5% versus 65.1%, p=0.001). [10]

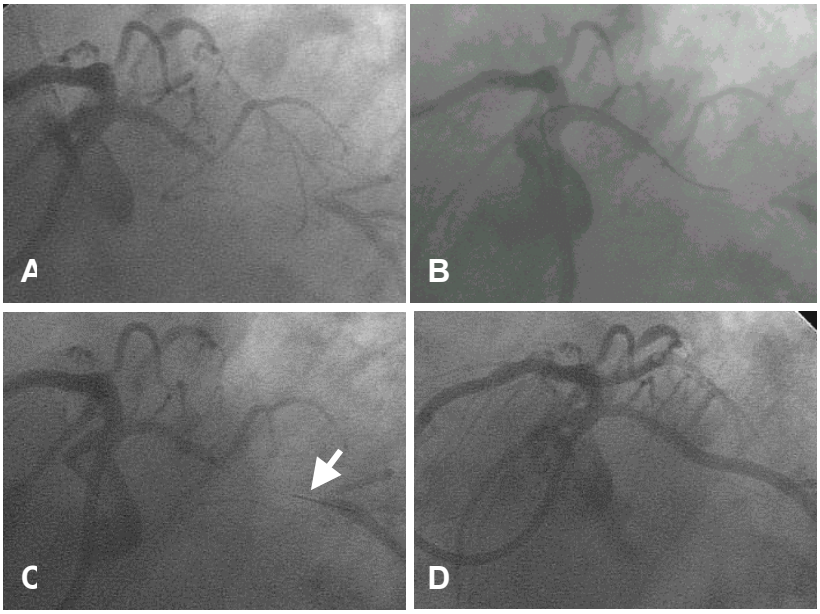
The inability to cross the lesion is the primary reason why a percutaneous strategy for revascularization is unsuccessful. Results of other guidewire technologies specifically designed for treating CTO`s, including the hydrophilic coated wire, the ball-tipped wire, and laser wire, have been disappointing with success rates of 45-60%.[3,11,12] Failure generally relates to either perforation with an extraluminal passage of the wire, or failure of the wire to advance forwards due to dense fibrous tissue or heavy calcification within the occlusion. With regards to the laser wire, the TOTAL surveillance study [13] suggested that because of its ablation capacity, there was an advantage conferred by the wire in improving successful recanalization rates. Following a failed attempt utilising a mechanical guidewire, 182 patients were treated with the laser wire, with success achieved in 105 patients (58%). However, perforation occurred in 21%, with tamponade in 1% cases. The subsequent TOTAL trial [3] randomized patients to either the laser wire or “conventional” mechanical wires, with the possibility of crossover to the other modality for a second attempt, should the first fail. In all, 303 patients were treated, with no significant difference in overall success rates between the 2 groups. Failure with the laser wire was primarily related to it taking a false route, whereas failure with mechanical wires was felt to be mainly due to absence of wire progression. The Safe-Cross system provides the operator with the potential to overcome both of these limitations. The technology of optical coherence reflectometry provides the means to precisely navigate the guidewire forward thereby minimising the risk of perforation, and the capability of radiofrequency ablation increases the crossing potential of the wire. In-vitro studies have confirmed that the system is able to accurately differentiate plaque from the media / adventitia boundary, [14] and in vivo evaluation has shown efficacy of the ablation capacity even when used in heavily calcified vessels. [5] In the current study, failure of successful recanalization occurred in 48.3% lesions, related to dissection in six (42.9%). However, all these episodes occurred whilst a conventional wire was in use and not the Intraluminal™ wire.

One of the most important drawbacks of percutaneous revascularization of a CTO is that the prolonged procedural time is associated with increased radiation exposure to both the patient and operator. Excessive radiation dosage can cause skin injury ranging from a temporary erythema, to deep ulceration and permanent scarring. [15] One further advantage of the Safe-Cross system is that the wire has the potential to be manipulated with guidance from the monitor display, without the need for continuous fluoroscopy. The fluoroscopy times in the current study (82 minutes) are slightly lower than those seen during the pilot study of the laser guidewire (99 minutes). [16] Importantly, there were no complications utilizing this system, in particular no episodes of tamponade, and this now provides reassurance of the ability to use the system with less fluoroscopy in the future. In addition to this, although the mean amount of contrast used in the present study (465ml) is comparable to that of the laser wire pilot study [16] (515ml), less fluoroscopy should correlate with a lower amount of contrast utilization.

Our population was a difficult one with all occlusions being older than 3 months duration (a typical case example is presented in figure 3). Other than age, other factors suggested to be predictive for unsuccessful percutaneous therapy include multivessel disease, a blunt stump, the presence of a side branch at the site of occlusion, calcification, bridging collaterals, and lesion length >15mm. [2,8,17] The overall mean length of occlusion in our patients was long at 22.1mm, and following successful recanalization, a relatively long total

length of stents (mean 63.9mm) was required to ensure coverage of the entire lesion. All the lesions treated had at least one of these additional characteristics, with the majority (69.0%) having at least 3 additional adverse characteristics. With such a high prevalence of these characteristics in our group of patients, there were no patient or lesion characteristics that appeared to be predictive for successful recanalization.

Figure 3: Case example



A 74-year old man with two previous coronary bypass surgery operations in 1983 and 1997. **A)** Left circumflex artery occlusion estimated to be at least 5 years old, 12mm in length, and with a blunt stump. **B)** Progress made with a Miracle wire (Asahi Intecc Co. Ltd, Aichi, Japan) but unable to fully cross the lesion. **C)** Successful recanalization utilising the Intraluminal™ wire, the final 10mm of the wire is opaque and can be seen within the lumen of the distal vessel (arrow). **D)** Final results following pre-dilatation and stenting with a 2.5x33mm Cypher stent (Cordis, Johnson and Johnson).

The Safe-Cross system is easy to use, with a fairly short learning curve. The main difference compared to conventional wires is that wire manipulation / torquing needs to be done relatively slowly in order to give the system time to interpret the optical coherence reflectometry signal. In addition, as the wire has a blunt tip (and therefore some potential for perforation), following successful recanalization, care must be taken to ensure safe positioning in the distal vessel. Once a lesion is crossed, the wire can be disconnected from the console and an outer sheath removed to maintain sterility; the wire can then be used like any other 0.014” wire.

In our patients in whom attempted recanalization with conventional wires had failed, the Safe-Cross system improved the rate of successful CTO recanalization with a further 51.7% vessels successfully opened. The major limitation at present is some difficulty in steering the wire, but it is hoped that this will improve with the next generation of Intraluminal™ Guidewires, which have a tip that can be pre-shaped. Although this study is limited by the fact that it is non-randomized and carried out in a single center on a small number of selected patients, our preliminary data suggests that this system is a useful adjunctive device in the therapy of chronic total occlusions. Further evaluation in the context of a large randomized study is warranted to assess the impact of this new device in the treatment of this technically challenging patient population.

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Chapter 7

Successful Use of a New Guidewire with Radiofrequency Ablation Capability for the Treatment of Chronic Total Occlusion at the Ostium of the Left Anterior Descending Artery

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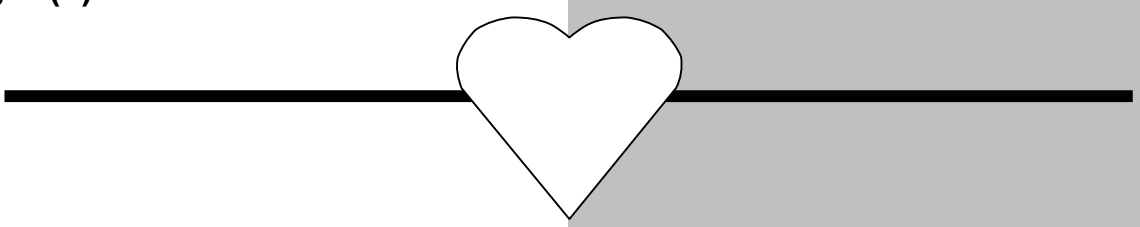
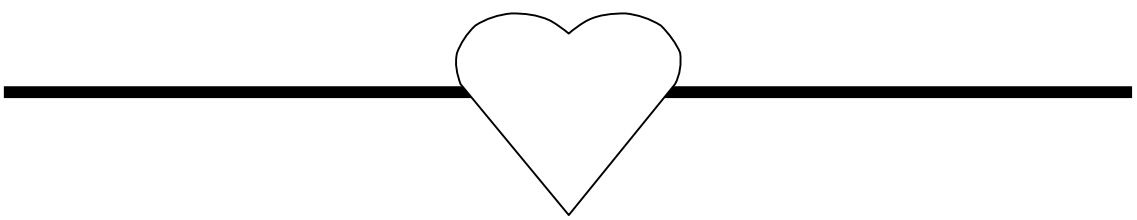
Journal of Invasive Cardiology
2005;17(5):277-9



Summary

The major limitation of percutaneous therapy (PCI) for the treatment of chronic total occlusions (CTOs) is the inability to cross with a wire. We report successful recanalization of a CTO situated at the ostium of the left anterior descending artery. The lesion demonstrated several anatomical features known to be associated with an unsuccessful outcome, and attempts with conventional wires failed. However, recanalization was facilitated with the Intraluminal wire™, (Intraluminal Therapeutics Inc, Carlsbad, California) a novel technology that combines guidance of the wire tip with the capability of radiofrequency ablation.

The majority of patients with CTOs are currently managed medically or referred for coronary bypass surgery. However, drug-eluting stent (DES) implantation for the treatment of CTOs have been shown to reduce the subsequent rate of restenosis compared with bare metal stents. If rates of successful recanalization can be increased with new technologies such as demonstrated here, then the advent of DESs will lead to more widespread applicability of PCI for this complex group.



Case Report: A 58-year old woman was referred with a 2-year history of chest pain. Risk factors for coronary disease were smoking, hypertension, and a positive family history. Though the resting ECG was normal, an exercise test demonstrated ST-depression across the anterior leads during stage 2 of a Bruce protocol. Subsequent coronary angiography showed single vessel disease of the left anterior descending artery (LAD) which was completely occluded at the ostium, with a blunt stump (figure 1). Notably, there was clearly identified heavy calcification, and a ring of calcium can be seen in figure 1B (arrow). There was some antegrade filling via small bridging collaterals originating from the proximal part of the left circumflex artery (figure 1A). The distal vessel was also filled via retrograde collaterals from the right coronary artery (figure 1B). Left ventricular function was normal with no anterior wall movement abnormality.

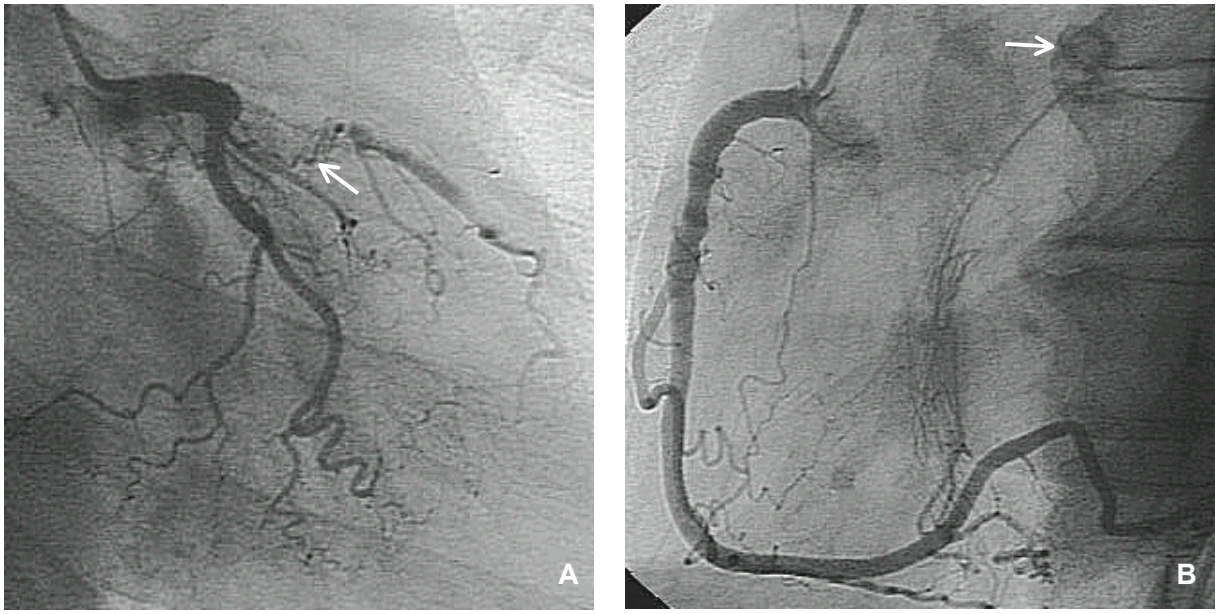
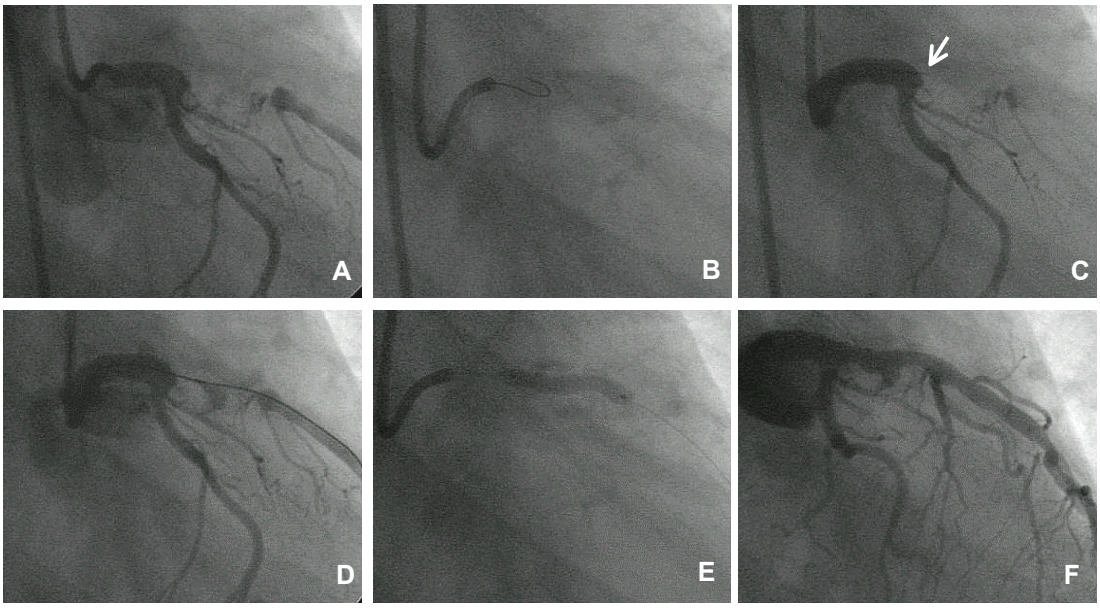


Figure 1A: Diagnostic angiography of the left coronary artery demonstrating complete occlusion at the ostium of the left anterior descending artery (LAD). The distal vessel is filled via small bridging collaterals originating from the proximal left circumflex artery (arrow). **B:** Diagnostic angiography of the right coronary artery which supplies retrograde collateral filling of the LAD. A ring of heavy calcification at the occlusion site is readily apparent (arrow).

The patient was taking long-term aspirin, and before the procedure was pre-loaded with 300mg clopidogrel. Heparin was administered to maintain the activated clotting time >250 seconds. A 7F left Amplatz 2 guiding catheter was used to catheterize the left main coronary artery, and the procedure was carried out utilising biplane X-ray screening. By quantitative coronary angiography, the estimated length of the occlusion was 13.6 mm. Initial attempts to open the LAD were made using an Intermediate tip 0.014" guidewire (Boston Scientific), and then a 0.014" Miracle 3g wire (Asahi Intecc Co. Ltd, Aichi, Japan) with over-the-wire balloon support. However, both these wires prolapsed into the circumflex artery with no antegrade progress into the LAD (figure 2B). The Intraluminal wire™ was then advanced to the stump and radiofrequency ablation applied which was able to penetrate the proximal cap of the occlusion (figure 2C). The Intraluminal wire™ was substituted for the Miracle wire, with successful wire passage into the distal vessel lumen (figure 2D). Following pre-dilatation, a 3.0x18mm sirolimus-eluting stent (Cypher stent, Cordis Corporation, Miami, Florida) was implanted (figure 2E) and subsequently post-dilated with a 3.5mm balloon; the final result was excellent (Figure 2F). At 6-months follow-up the patient was symptom-free and underwent a repeat exercise test. On this occasion she managed 10 minutes of a Bruce protocol (maximum predicted heart rate attained) without chest discomfort or ECG changes.

Figure 2A: Baseline angiography of the occlusion at the time of angioplasty. **B:** Conventional wires with over-the-wire balloon support failed to penetrate the proximal cap of the occlusion and simply prolapsed into the left circumflex artery. **C:** The tip of the Intraluminal wire™ can be seen penetrating through the cap (arrow). **D:** Successful crossing of the occlusion into the lumen of the distal vessel with a Miracle 3g wire. **E:** Stent implantation with a 3.0x18mm sirolimus-eluting stent. **F:** Final result.



Discussion:

Previous studies have demonstrated the importance of CTO revascularization, with improvement in anginal symptoms, exercise capacity, and left ventricular function. [1-3] In addition, successful recanalization reduces the need for subsequent coronary artery bypass surgery, [4] and long-term evaluation has shown a 10-year survival advantage of 73.5% compared to 65.1% in those in whom PCI is unsuccessful. [5]

The Safecross system with the Intraluminal guidewire™ (Intraluminal Therapeutics, Carlsbad, California) uses optical coherence reflectometry to determine the position of the wire tip. The system has been previously described, [6-9] briefly, a beam of near-infra red light is emitted and the reflected beam analysed to differentiate the vessel lumen from the outside vessel wall. The technology therefore provides information for guidance of the wire, to reduce the risk of taking an extra-luminal passage potentially leading to perforation and pericardial tamponade. In addition, the wire has the capability of radiofrequency ablation at the tip, emitting short bursts (100ms) of low frequency 250-500 kHz energy. This facilitates forward passage of the wire with efficacy demonstrable even in calcified vessels. [7] The system combines these 2 capabilities such that ablation is only enabled when the wire tip is heading correctly. In the present case, the Intraluminal was of great value in penetration of the proximal cap of the occlusion which, particularly when the stump appears blunt, can be composed of very dense fibrotic material. The cap was unable to be breached by conventional wires, yet once a few millimetres of antegrade passage had been made with the Intraluminal wire™, the remainder of the occlusion could be traversed.

Importantly, the distal LAD was filled via collaterals thereby facilitating wire guidance, and enabling reassurance of successful recanalization with visualization of the wire within the distal lumen. However, the Intraluminal system uses optical coherence reflectometry to determine the position of the distal tip of the wire in relation to the vessel wall. This does not therefore rely on angiographic visualization, and with more experience in the future, it may be possible to use the system even when the distal vessel is not well seen.

When treating CTO's, whatever the technology used, the principles of good backup support remain important, and in this case a left Amplatz guide catheter proved effective. In addition, to facilitate the exchange of wires and to provide additional backup, we routinely utilize a 1.5mm over-the-wire balloon, which can then be used for pre-dilatation once the occlusion has been successfully crossed with a wire.

Certain lesion characteristics have been shown to affect the success rate of recanalization. Some of the most important adverse features include increased age and length of the occlusion, the presence of bridging collaterals, a side branch at the site of occlusion, calcification, and an abrupt rather than tapered stump. [10] Our patients' clinical history suggested that the occlusion was 2-years old, it was ostial in location with the large circumflex artery originating at the occlusion, was heavily calcified and the stump abrupt (figures 1 and 2). All these features suggested that the chances of successful recanalization would be low, and might have lead many cardiologists to refer similar patients directly for bypass surgery. Indeed, in the BARI study, clinicians provided their views on the suitability of lesions for a revascularization strategy of PCI versus CABG, and both ostial lesion location and a CTO were deemed to be strong non-favourable characteristics for PCI. [11]

Percutaneous treatment of ostial LAD lesions could potentially jeopardize the circumflex artery, however in the present case, the use of biplane imaging facilitated precise stent positioning, which, together with a relatively large angle of the left main stem carina meant that the final result was excellent. Long-term results of PCI with bare metal stents have been hindered by the development of restenosis, with rates of non-occlusive ostial LAD lesions as high as 26%. [12] Furthermore, CTOs are well-known to be at increased risk of restenosis, with rates of 32-55%. [13-16] However, recent data have confirmed the efficacy of sirolimus-eluting stents for CTOs, with a 1 year survival-free of major adverse events of 96%, and binary restenosis rate of 9%. [17]

Conclusions:

This case demonstrates the potential of this novel technology, in particular at successfully penetrating the proximal cap of a CTO following failed attempts using conventional guidewires. Future improvements in such specialized technologies will improve the ability to achieve successful recanalization of CTOs. This, together with the use of drug-eluting stents, means that the use of PCI, rather than CABG, will be more widely applicable for the revascularization of patients with complex CTOs.

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Chapter 8

Multimodality Plaque Ablation to Allow Successful Stent Implantation Following Failure of Conventional Wires and Balloons to Cross a Chronic Total Occlusion

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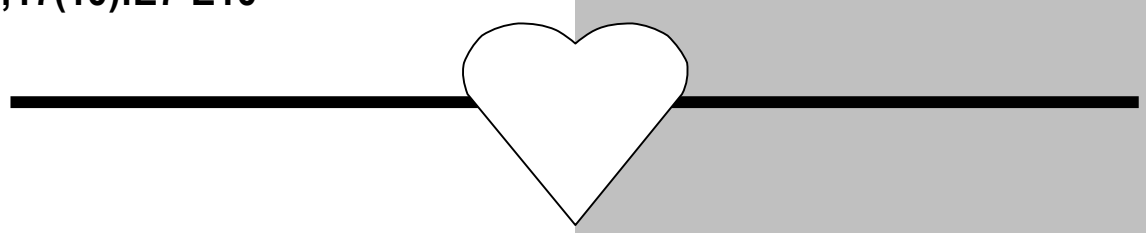
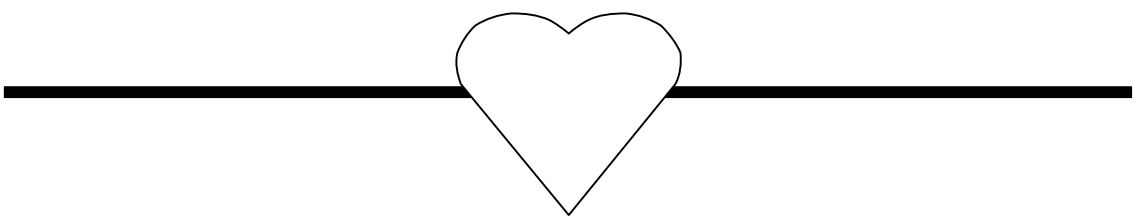
Journal of Invasive Cardiology
2005;17(10):E7-E10



Abstract:

The present report illustrates several potential difficulties that may arise when treating a chronic total occlusion, one of the most challenging coronary lesions to be faced in the catheterization laboratory. We describe how we overcame each of these problems, including the utilization of specialized technologies with the Intraluminal wire™ and rotablator.



Introduction

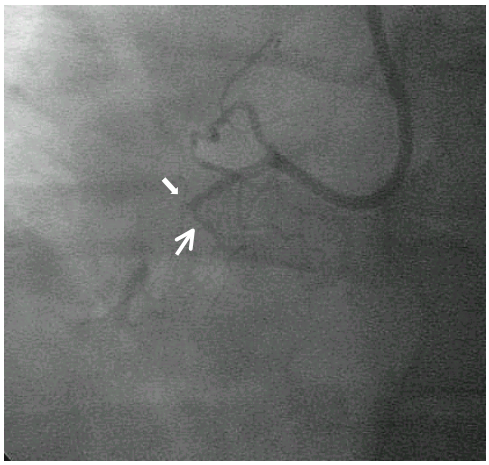
Percutaneous coronary intervention (PCI) for chronic total occlusion (CTO) has procedural and ultimate long term success rates that are significantly less than those currently reported for non-occlusive lesions. A CTO is generally defined as an occlusion with Thrombolysis In Myocardial Infarction (TIMI) grade 0 or 1 antegrade flow, that is more than 3 months old. On angiography, CTO lesions occur in approximately one third of patients with significant coronary lesions, but PCI for CTO only accounts for around 10% of patients undergoing PCI. [1] Successful recanalization of CTO with PCI reduces the need to resort to bypass surgery; furthermore, observational studies have shown lower cumulative rates of cardiac death or myocardial infarction and an improvement in symptomatic status after successful PCI for CTO. [2-5]

The lower procedural success and higher restenosis rates in the era of balloon angioplasty have improved in recent years. However, inability to cross the lesion remains the major cause of procedural failure. [6-8] Improvements in guidewire technology and novel approaches such as the optical coherence reflectometry-guided radiofrequency ablation (Intraluminal^{TM} guidewire, Intraluminal Therapeutics, Carlsbad, California), the Frontrunner catheter (LuMend, Redwood City, California), and other technological advances have improved the ability to cross the lesion. [9-13] The second major cause of procedural failure is the inability to cross or to dilate the lesion with a balloon. In this situation, rotational atherectomy or an excimer laser may lead to a successful outcome. [14,15] Finally, the long term success rate of PCI in general has been improved by the use of stent implantation. [16,17] Though experience with CTO lesions is currently limited, the introduction of drug-eluting stents, in particular, has reduced the subsequent rate of restenosis. [18-21] This case report illustrates many of the technical problems encountered in treating CTOs and shows how they were successfully overcome with both classic and novel technology.

Case Report

A 51-year-old man with a six-month history of Canadian Class 3 stable angina was referred for percutaneous revascularization. Risk factors for atherosclerosis were non-insulin-dependent diabetes mellitus, hypercholesterolemia, previous smoking, and a positive family history of premature coronary artery disease. Coronary angiography performed at the referring center, showed a chronic total occlusion of the mid-right coronary artery. The left coronary artery had no significant stenosis and the left ventricular function was normal. Based on the history, the duration of the occlusion was estimated to be around 6 months. Medical therapy consisted of aspirin, statin, beta-blocker, and clopidogrel, with tight glycemic control maintained through oral hypoglycemic agents.

Figure 1: Baseline angiography of the right coronary artery, right anterior oblique view, with a CTO in segment 2. The stump is blunt in morphology (block arrow), there is a side branch at the level of the occlusion (open arrow), and bridging collaterals are filling the distal vessel.

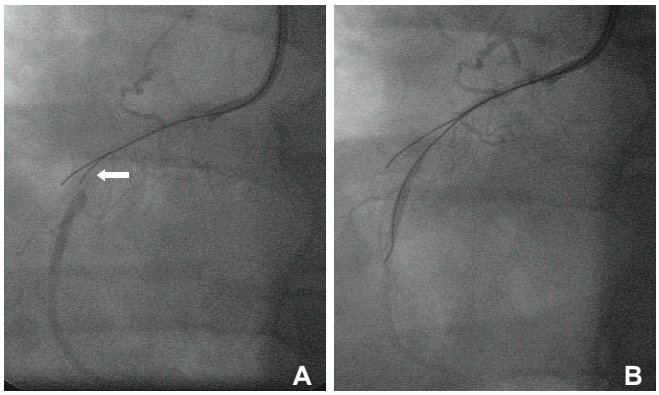


Coronary angiography showed a total occlusion of segment 2 of the right coronary artery (RCA) with antegrade TIMI 0 flow. Bridging collaterals filled the distal RCA. The occlusion site had a blunt stump and there was a side branch at the level of the occlusion (figure 1). The estimated length of the occlusion at quantitative coronary angiography (CAAS II; Pie Medical Imaging, The Netherlands) was 8 mm. Heparin (10,000 IU) was given at the start of the procedure and additional heparin boluses were administered to maintain activated clotting time >250 seconds. A biplane X ray system was used.

The first difficulty encountered was the appropriate choice of guiding catheter to provide coaxial intubation and adequate support. The RCA had an anteriorly located ostium with an intermediate lesion. Multiple guiding catheters were tried; a 6 French Mach1 ART 3.5 gave optimal coaxial intubation. However, due to the intermediate ostial lesion, there was suboptimal support and the guiding catheter repeatedly became disengaged when the wire was advanced to cross the lesion. A Taxus stent 2.5x12 mm (Boston Scientific, Maple Grove, Minnesota) was deployed at the ostium, thus allowing a deeper intubation and improved back-up.

Despite the use of multiple guidewires including a 0.014" PT Graphix Intermediate (Boston Scientific), and a 0.014" Miracle 3g (Asahi Intecc Co. Ltd, Aichi, Japan), through a Maverick (1.5/15 mm) over-the-wire balloon (Boston Scientific), it proved impossible to cross the lesion. When the Miracle wire appeared to have taken a sub-intimal course, a second wire, the Safe-Cross straight (Intraluminal Therapeutics) was advanced parallel to the first (figure 2A). At this point, the Safe-Cross Straight wire was advanced through the over-the-wire balloon to the level of the occlusion, with eventual success. The system was activated and the wire was used to burn a channel through the first few millimeters of the occlusion. Subsequently, this wire was removed and replaced by a second Miracle 3g wire that then easily crossed into the distal vessel (figure 2B).

Figure 2A: Double-wire technique: a Miracle wire has taken an incorrect sub-intimal path. In order to "block" entry into the abnormal path, this wires' position is maintained, and a second wire (Intraluminal wire™) is advanced and directed into the correct lumen (block arrow). **B:** The Intraluminal wire has been replaced by a second Miracle 3g wire, with successful passage into the distal vessel.

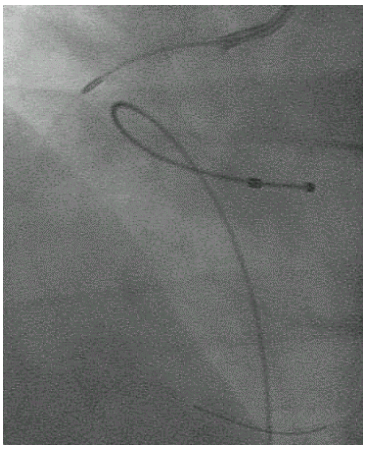


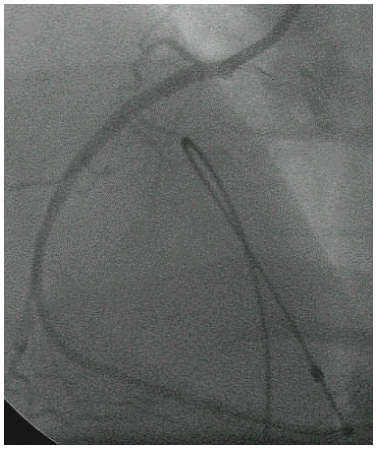
Despite several attempts, the occlusion could not be crossed with any available balloon: Maverick (1.5/15) over-the-wire balloon, Worldpass rapid-exchange balloon 1.5x30mm (Cordis Corporation), or Hayate balloon Pro 1.5x20mm (Terumo, Tokyo, Japan). Furthermore, the guiding catheter position was lost. This required a difficult reintubation of the guiding catheter in the presence of a stent protruding into the aorta; and the wire was readvanced across the occlusion. However, the balloon could not then be advanced into the ostium. It became apparent that the wire had passed through the struts of the stent that were protruding in the aorta. Thus, a second wire was advanced into the artery and the balloon was advanced without difficulty over this wire to the lesion. However, crossing still proved impossible. As a last resort, we decided to advance a Rotablator wire (Boston Scientific) parallel to the first wire; this did not cross the lesion until the first wire was removed. Then, the Rotawire floppy 0.009 inch wire was successfully manipulated into the distal vessel. A 1.5 mm burr was advanced and easily crossed the lesion (figure 3). Successive inflations with a Hayate Pro 1.5x20mm and a Maverick 2.5x20mm were followed by placement of a Taxus stent (2.5x24mm) in segment 2. The residual diameter stenosis was 10%, the minimal lumen diameter 1.93mm, and the reference vessel

diameter 2.14mm, with TIMI 3 flow and a normal blush (figure 4). The patient was discharged 24 hours later, and has since been symptom-free.

Figure 3: Rotablator wire 0.009 inch in the lumen of the RCA and a 1.5 mm burr crossing the lesion. A provisional pacemaker wire has been placed in right ventricle apex.

Figure 4: Angiography of the RCA showing the final result, with TIMI 3 flow, a normal blush and a residual diameter stenosis of 10%.





Discussion

This case illustrates many of the problems that can be encountered during attempted PCI of a CTO. Although there were somewhat unfavorable angiographic characteristics (blunt stump morphology, side branch at the level of the CTO, and bridging collaterals), the RCA location in conjunction with the absence of other significant lesions, the short length of the occlusion, and it's relatively short presumed duration, led us, after consultation with our surgical colleagues, to attempt PCI.

The initial problem was related to the ability to obtain coaxial intubation and adequate guiding catheter support that required the use of multiple catheters in conjunction with implantation of a stent at the ostium. The second problem was the inability to cross the lesion with a wire. Many different types of wire are available and the initial choice is generally a matter of operator preference. Usually, softer tip wires are used first, followed by progressively stiffer wires in order to minimize the risk of perforation. [9] When a wire appears to have taken a subintimal course, as occurred in this case, it is sometimes useful to leave it in place thereby blocking the entrance into this channel, and to advance a second wire in parallel to the first, to find an alternative route.

The Intraluminal^{TM} guidewire is a recently developed technology that delivers radiofrequency energy pulses capable of ablating tissue. In addition, the system monitors, in real-time, the position of the 0.014 inch wire using optical coherence reflectometry. Near-infrared light is emitted and by analyzing the signal that is reflected from tissue interfaces, the system is able to determine whether the position of the distal tip of the wire is correct, or too close to the outer vessel wall. Ablation pulses are only allowed when the wire is in the true lumen. Initial studies have demonstrated the utility of this technique to cross CTO's. [11,12]

The next problem we encountered was the inability to cross the lesion with several different balloons. Attempted balloon crossing resulted in loss of guiding catheter position which was resolved with difficulty due to the fact that the stent in the ostium protruded in the aorta. The use of rotational atherectomy finally allowed a balloon to cross and to dilate the lesion, and the procedure was completed with placement of a paclitaxel-eluting stent, our default strategy.

Although the use of such complex technologies undoubtedly increased the procedural costs, such a successful outcome reduces the likelihood that the patients will undergo bypass surgery and improves his long-term survival. [2,5] Stenting CTO lesions has been shown to improve long term outcome; the use of a drug eluting stent in this diabetic patient with a small diameter vessel reflects current best medical practice. [16-22] Preliminary studies suggest that drug-eluting stents remain patent in more than 95% of cases. [21]

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Chapter 9

Significant Reduction in Restenosis Following the Use of Sirolimus-Eluting Stents in the Treatment of Chronic Total Occlusions

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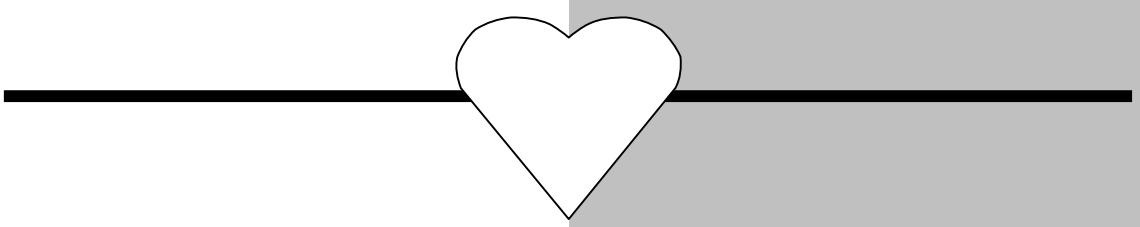
Journal of the American College Of Cardiology 2004;43:1954-8



Abstract

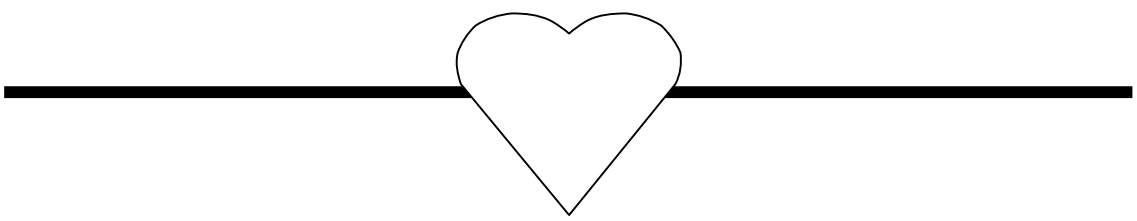
Objectives: The aim of this study was to assess sirolimus-eluting stent (SES) implantation for the treatment of chronic total coronary occlusions (CTO).

Background: Long-term results after percutaneous coronary intervention (PCI) in the treatment of CTOs is hindered by a significant rate of restenosis and reocclusion. In the treatment of relatively simple nonocclusive lesions, SESs have shown dramatically reduced restenosis rates compared with bare metal stents (BMS), but whether these results are more widely applicable is unknown.

Methods: From April 2002, all patients at our institution were treated with SES as the device of choice during PCI. During the first six months, 563 patients were treated solely with SES, with treatment of a de novo CTO in 56 (9.9%). This CTO cohort was compared with a similar group of patients (n = 28) treated in the preceding six-month period with BMS.

Results: At one year, the cumulative survival-free of major adverse cardiac events was 96.4% in the SES group versus 82.8% in the BMS group, $p < 0.05$. At six-month follow-up, 33 (59%) patients in the SES group underwent angiography with a binary restenosis rate (>50% diameter stenosis) of 9.1% and in-stent late loss of 0.13 ± 0.46 mm. One patient (3.0%) at follow-up was found to have reoccluded the target vessel.

Conclusions: The use of SESs in the treatment of chronic total coronary occlusions is associated with a reduction in the rate of major adverse cardiac events and restenosis compared with BMS.



Introduction

Chronic total occlusions (CTO) are common, and found in approximately one-third of patients with significant coronary disease who undergo angiography. [1,2] Percutaneous intervention (PCI) of CTOs accounts for 10% to 15% of all angioplasties; however, after successful recanalization, there is an increased rate of subsequent restenosis and reocclusion compared with nonocclusive stenoses. [3,4] Although several randomized trials demonstrated the efficacy of stent implantation over balloon-only angioplasty, even with stents there remains a significant rate of both restenosis (32% to 55%) and reocclusion (8% to 12%). [5-9]

In the treatment of relatively simple lesions, sirolimus-eluting stents (SES) markedly reduce the restenosis rate, with continued benefit documented up to two years follow-up. [10,11] Whether these results can be extrapolated to more complex lesions such as CTOs has yet to be determined. We sought to evaluate the effectiveness of the SES in a consecutive series of patients with at least one de novo CTO compared with a similar series treated with bare metal stents (BMS).

Methods

Patient population

Commencing in April 2002, all PCI at our institution was done solely with SESs, irrespective of clinical presentation or lesion morphology; these patients comprise the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital registry (RESEARCH) registry (further details of the methodology are described elsewhere). [12,13] Those deemed at an increased risk of restenosis (including the CTO population) were considered for six-month angiographic follow-up. Sirolimus-eluting stents were available in lengths between 8 mm and 33 mm, and diameters 2.25 mm to 3.0 mm. In the first six months, 563 patients were treated, including 56 (9.9%) with successful revascularization of at least one CTO. These patients make up the present study cohort; all received six months dual antiplatelet therapy with clopidogrel in addition to aspirin. As predetermined by the RESEARCH protocol, this study cohort of patients were compared with all those treated for a CTO in the preceding six months with BMS, identified from the departments' dedicated database. Both groups were treated by the same operators utilizing standard techniques, the only difference being the type of stent. 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

CTO definition

Chronic occlusion was defined as an occlusion on angiography with no antegrade filling of the distal vessel other than via collaterals. All patients included had a native vessel occlusion estimated to be at least one month's duration [9] 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.

Length of occlusion

The length of occlusion was measured by quantitative coronary angiography either utilizing antegrade filling via collaterals, or assessment of the retrograde collateral filling. This was achieved by catheterizing both the left and right coronary arteries, and making a simultaneous injection to delineate the distance between the site of occlusion and the most proximal part of the vessel filled retrogradely.

Follow-up

Patients were followed up prospectively and evaluated for survival-free of major adverse cardiac events (MACE) using questionnaires and telephone enquiries; MACE was predefined as: 1) death; 2) nonfatal myocardial infarction; or 3) repeat target vessel revascularization (TVR). The diagnosis of acute myocardial infarction required an elevation of creatine kinase to twice the upper limit of normal, together with a rise in creatine kinase-MB fraction. Target vessel revascularization was defined as either surgical or percutaneous reintervention driven by significant (>50%) luminal narrowing within the treated vessel, and was undertaken in the presence of either anginal symptoms or objective evidence of ischemia.

Angiographic analysis

Quantitative analysis in those SES patients with follow-up angiography was undertaken in three coronary segments: in-stent (encompassing the entire length of stented segment), and the 5-mm proximal and distal edge segments either side of the in-stent segment. The target lesion comprised the in-stent plus the proximal and distal edge segments. Binary restenosis was defined as >50% diameter stenosis within the target lesion. Late lumen loss was calculated from the difference in minimal lumen diameter between postprocedure and follow-up.

Statistical analysis

Discrete variables are presented as percentages and compared with Fisher exact test. Continuous variables are expressed as mean ± SD and compared with Student *t* test. Survival-free of adverse events was calculated according to the Kaplan-Meier method. The log-rank test was used to compare MACE-free survival between the two groups. All tests were two-tailed, and a p value of <0.05 was considered statistically significant.

Results

The baseline patient and lesion characteristics of the two groups are presented in Table 1 and Table 2. One patient in the BMS group underwent successful recanalization and stent implantation in two CTOs, thereby making a total of 29 lesions in this group. Mean length of occlusion could be determined in 45 (80.4%) of the SES group and 17 (58.6%) of the BMS group. There was no significant difference between the groups with respect to the postprocedural quantitative angiography; however, the mean diameter of stent utilized was greater in the BMS cohort.

Table 1: Baseline patient demographics

	Bare stents n=28	**SESs n=56**	**p value**
Mean age (years)	59.8 ± 11.1	60.2 ± 10.0	0.89
Male sex (%)	85.7	71.4	0.2
Current smoker (%)	35.7	26.8	0.5
Diabetes mellitus (%)	7.1	14.3	0.5
Hypertension (%)	39.3	39.3	1.0
Hypercholesterolemia (%)	57.1	55.4	1.0
Previous myocardial infarction (%)	46.4	55.4	0.64
Previous PCI (%)	21.4	12.5	0.34
Previous CABG (%)	0	0	-
Glycoprotein IIb/IIIa inhibitor usage (%)	25.0	21.4	1.0
Presence of multivessel disease (%)	60.7	46.3	0.25
PCI in at least one additional (non-occluded) major epicardial vessel during the index procedure (%)	28.6	42.6	0.24

SES: sirolimus-eluting stents, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention

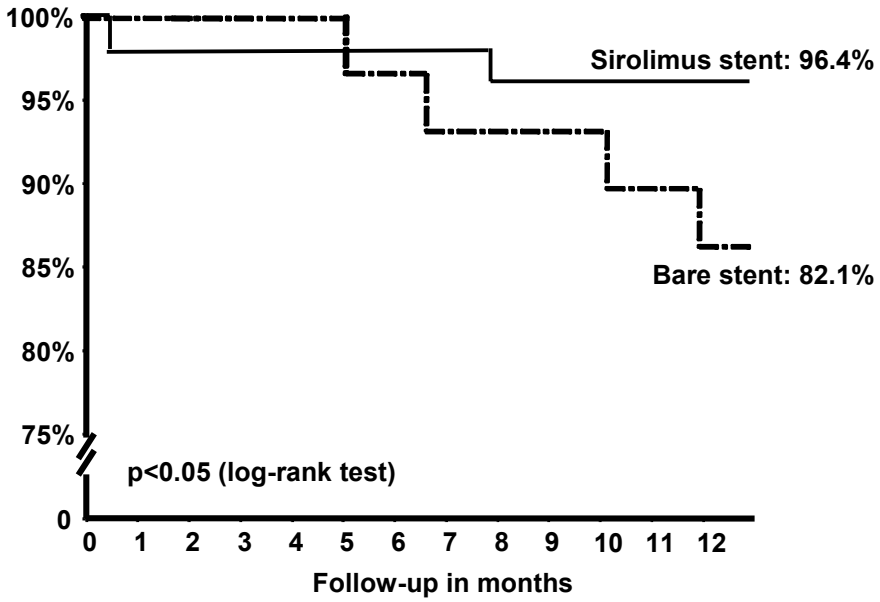
There were no in-hospital MACE. Clinical follow-up data was obtained in 100% of both groups. There were no deaths in either group; one non–Q-wave acute myocardial infarction occurred related to subacute stent thrombosis 11 days after SES implantation. This was successfully recanalized percutaneously; intravascular ultrasound suggested underexpansion of the SES (2.5 × 33 mm), and the patient was treated with abciximab and balloon dilation of the previously implanted stent. At one year, the cumulative survival-free of MACE was 96.4% in the SES group compared with 82.8% in the BMS group, p < 0.05 (Fig. 1). One patient in each group had a reocclusion (1.8% SES group vs. 3.6% BMS group, P = NS).

Table 2: Baseline procedural characteristics

		Bare stents n=29	SESs n=56	p value
Target vessel				0.06
LAD (%)		27.6	51.8	
LCX (%)		27.6	25.0	
RCA (%)		44.8	23.2	
Mean length of occlusion (mm), (range)		12.7 (2.4 - 31.8)	11.3 (4.0 - 32.1)	0.5
Bifurcation stenting (%)		17.9	14.3	1.0
Mean number of stents in the target vessel		1.8	2.0	1.0
Mean nominal diameter of stent in the main vessel (mm)		3.03 ± 0.56	2.75 ± 0.26	<0.001
Mean length of stent in the main vessel (mm)		23.31 ± 9.34	23.89 ± 9.21	0.7
Mean total length of overlapping stents in the main vessel (mm), (range)		41.8 (18 - 112)	45.2 (8 – 117)	0.7
Post-procedure	Reference diameter (mm)	2.37 ± 0.50	2.35 ± 0.46	0.9
QCA data	Minimal lumen diameter (mm)	2.18 ± 0.49	2.06 ± 0.48	0.3
	Diameter stenosis (%)	10.4	11.6	0.6

LAD: left anterior descending artery, LCX: circumflex artery, RCA: right coronary artery, QCA: quantitative coronary angiography

Figure 1: Kaplan-Meier curves for survival-free of death, acute myocardial infarction, or target vessel revascularization.



At six months, 33 (58.9%) patients in the SES group underwent follow-up angiography (none in the BMS group) (Table 3). The binary restenosis rate was 9.1%: one occlusion, one stenosis at the ostium of a side branch after T-stenting, and the third at the distal outflow of the SES (this is the same patient with the subacute thrombosis, and restenosis occurred at the site of balloon dilation during the second procedure). The patient with occlusion had undergone bifurcation T-stenting after successful recanalization of a heavily calcified left anterior descending artery. At follow-up, the artery had reoccluded, and there was new akinesis of the left ventricular anterior wall. This patient with occlusion was managed with medical therapy; the other two patients with restenosis underwent percutaneous revascularization.

Table 3: Post-procedural and 6 month follow-up quantitive angiographic data for the sirolimus-eluting stent (patient number n=33)

Post-procedure	Proximal 5mm	In-stent	Distal 5mm
Mean diameter (mm)	2.82 ± 0.66	2.58 ± 0.55	2.10 ± 0.64
Minimal lumen diameter (mm)	2.43 ± 0.51	2.04 ± 0.45	1.75 ± 0.53
% diameter stenosis	14.1	12.9	21.8
6 month follow-up			
Vessel reference diameter (mm)	3.02 ± 0.53	2.46 ± 0.81	2.12 ± 0.83
Minimal lumen diameter (mm)	2.33 ± 0.90	1.91 ± 0.68	1.81 ± 0.75
% diameter stenosis	20.1	21.9	18.2
Late lumen loss (mm)	0.10 ± 0.80	0.13 ± 0.46	-0.06 ± 0.54

Discussion

Previous studies have demonstrated the importance of revascularization of CTOs, with improvement in anginal symptoms, exercise capacity, and left ventricular function. [14-16] In addition, successful recanalization reduces the subsequent need for bypass surgery and, importantly, long-term evaluation has shown a 10-year survival advantage of 73.5% after successful PCI compared with 65.1% in those with unsuccessful PCI. [4,17]

To our knowledge, this is the first report regarding the efficacy of SES in CTOs, a subset of patients previously excluded from other protocols and, importantly, at increased risk of developing restenosis after conventional stent implantation. [3] Of the patients who underwent follow-up angiography, both the in-stent and proximal 5-mm segments analyzed showed an encouraging late loss of 0.13 ± 0.46 mm and 0.10 ± 0.80 mm, respectively. The distal 5 mm actually showed an overall benefit, with enlargement of the vessel (late loss, −0.06 ± 0.54 mm).

In addition to the angiographic data, the clinical follow-up is very encouraging. Importantly, there were no significant differences in baseline demographics between the SES and BMS groups, and all procedures were carried out in the same center by the same operators. There was an episode of subacute thrombosis in the SES group, but there appears to be an underlying mechanical cause with underexpansion of the stent documented on intravascular ultrasound. The restenosis rate for BMS is known to be inversely related to the postprocedural minimal lumen diameter and the number of stents utilized. [18] In the current study, although the mean diameter of stent used was significantly greater in the BMS cohort (related to a maximum available SES diameter of 3.0 mm) with free utilization of postdilation, the postprocedural minimal lumen diameter was not significantly different between the two groups. The majority of events related to TVR, with, at one year, a significantly higher rate of survival free of MACE of 96.4% in the SES group versus 82.8% in the BMS group.

Four major randomized trials have demonstrated the efficacy of stent implantation over balloon-only angioplasty in the treatment of CTOs, reducing the six-month restenosis rate from 68% to 74%, to 32% to 55%. [5-8] Compared with this historical data, our study suggests that the SES confers a marked further advantage with a significantly lower binary restenosis rate of 9.1% ($p < 0.05$) (Fig. 2). In addition, we had only one patient (3.0%) with vessel reocclusion, compared with rates of between 8% to 12% in the same published trials utilizing BMS. A recent study of the clinical results of 376 patients discharged from hospital without an adverse event after successful intervention of a CTO showed, at one-year follow-up, a MACE rate of 12.2%; [19] our results are, therefore, quite remarkable, with a MACE-free survival rate of 96.4%.

Study limitations

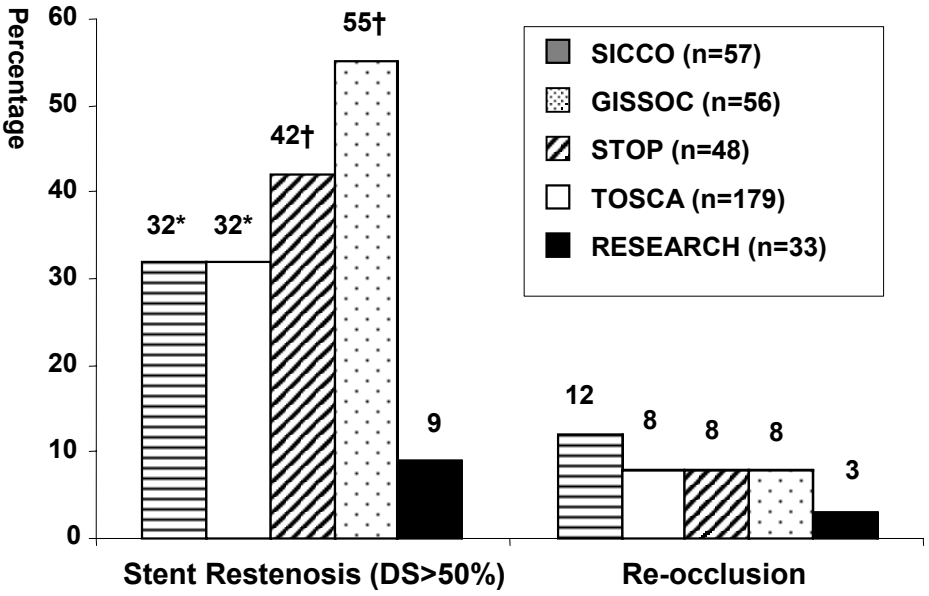
This study evaluated only a small cohort of patients, and angiographic follow-up was not obtained in all, so additional patients with silent reocclusion cannot be excluded. However, those who did not undergo repeat angiography were all symptomatically well at follow-up. In addition, despite the discrepancy in follow-up angiography rates between the two groups, which might have biased the results towards more revascularization in the SES group, the MACE rate remained statistically significant with a beneficial effect in

favor of the SES. The study was not randomized, and used a retrospective comparitive population; however, the same operators and interventional techniques were utilized.

Conclusions

The use of SESs in the treatment of complex patients with CTOs is associated with a reduction in the rate of MACE and restenosis compared with BMS.

Figure 2: The percentage binary restenosis rate (>50% diameter stenosis) and reocclusion rate of Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital registry (RESEARCH) compared with published data from the patients treated with stent implantation in the randomized trials Stenting in Chronic Coronary Occlusion (SICCO), [5] Gruppo Italiano di Studio sullo Stent nelle Occlusioni Coronariche (GISSOC), [6] Stents in Total Occlusion for Restenosis Prevention (STOP), [7] and the Total Occlusion Study of Canada (TOSCA). [8]



* p<0.05 compared with the results of RESEARCH

† p<0.01 compared with the results of RESEARCH

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Chapter 10

Drug-Eluting Stent Implantation for Chronic Total Occlusions: Comparison between the Sirolimus- and Paclitaxel-Eluting Stent

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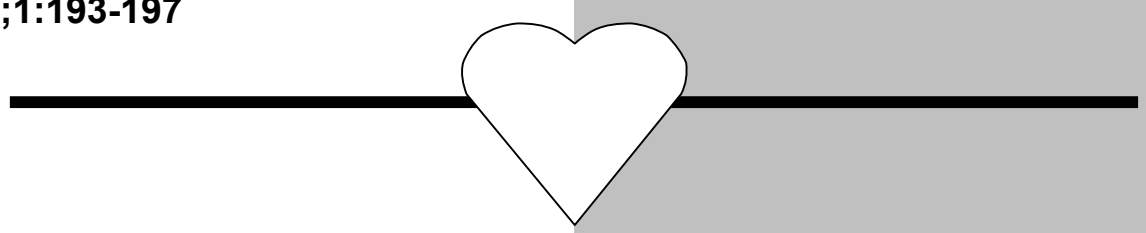
2005;1:193-197



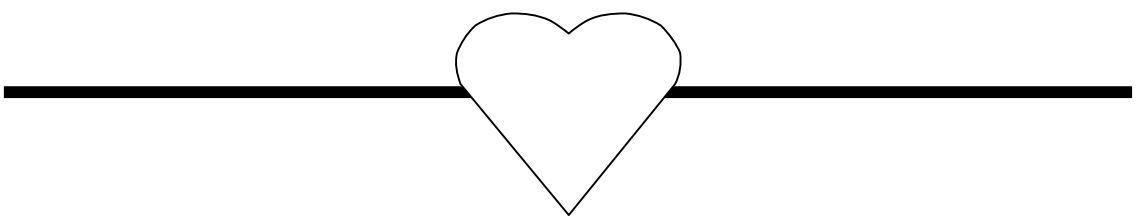
Abstract:

Objectives: Long-term results following percutaneous coronary intervention (PCI) with bare metal stents in the treatment of chronic total occlusions (CTOs) is hindered by a significant rate of restenosis and re-occlusion. Drug-eluting stents have shown dramatically reduced restenosis rates for the treatment of relatively simple non-occlusive lesions, though there is only limited data as to the efficacy in CTO's. We evaluated the long-term results of the sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES) for the treatment of CTOs.

Methods and results: From April 2002, all patients at our institution were treated with SES as the device of choice during PCI. During the first quarter of 2003 the default strategy changed to the use of PES. Drug-eluting stent implantation was carried out in CTOs (defined as >3 months' duration) in 9% of *de novo* PCI procedures. A total of 76 consecutive patients were treated with SES implantation, followed by a consecutive series of 57 patients treated with PES implantation. These patients were compared with a similar group of patients (n=26) treated with BMS in the 6-month period preceding April 2002.

At 400 days, the cumulative survival-free of target vessel revascularization was 80.8% in the BMS group versus 97.4% and 96.4% in the SES and PES groups respectively (p=0.01).

Conclusions: The use of both the SES and PES in the treatment of chronic total coronary occlusions reduces the need for target vessel revascularization compared to bare metal stents.



Introduction

Successful percutaneous therapy of chronic total occlusions (CTOs) has been shown to improve symptoms of angina and left ventricular function, and reduce the subsequent need for coronary artery bypass surgery. [1-5] In addition, in the long-term, recanalization of a CTO can reduce mortality compared with those with an unsuccessful attempt at recanalization. [6] However, the long-term outcome of percutaneous coronary intervention (PCI) for chronic total coronary occlusions is subject to an increased risk of restenosis and re-occlusion compared with non-occlusive lesions. [1,7] The advent of drug-eluting stents is revolutionising the practice of interventional cardiology. Several randomized trials have demonstrated a dramatic reduction in restenosis rates compared with bare metal stents when used for the treatment of relatively simple lesions. [8-11] In addition, preliminary data has confirmed the efficacy utilizing the sirolimus-eluting stent (SES) for the treatment of chronic total occlusions. [12] In the present report, we evaluate the use of drug-eluting stent implantation for chronic total occlusions in a consecutive series of patients, with comparison between the sirolimus- and paclitaxel-eluting stents.

Methods

The sirolimus-eluting stent (Cypher™, Johnson & Johnson - Cordis unit) received CE mark approval in April 2002. Since that time, all patients undergoing percutaneous therapy in our institution have been treated with drug-eluting stent implantation as the default strategy. During the first quarter of 2003, our strategy switched from the sirolimus- to the paclitaxel-eluting stent (Boston Scientific) enabling a comparison of the two stent types. All consecutive patients with successful chronic occlusion recanalization were enrolled. Those patients treated with drug-eluting stent implantation were compared to all those treated for a CTO in the preceding 6-months with bare metal stents (BMS), identified from the departments` dedicated database. All groups were treated by the same operators utilizing standard techniques; the only difference being the type of stent.

During the procedure, heparin was given to maintain an activated clotting time ≥ 250 seconds. All patients received lifelong aspirin, and before the procedure were pre-treated with a loading dose of 300mg clopidogrel. Addition anti-platelet therapy was given with clopidogrel for 1 month in the BMS group, and for 6-months in the drug-eluting stent groups. The use of Glycoprotein IIb/IIIa inhibitor therapy was at the discretion of the operator and was only given once wire passage was confirmed as successful. 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

Chronic total occlusion definition: Complete occlusion of a coronary artery on angiography, with no antegrade filling of the distal vessel other than via collaterals. All patients included, had a native vessel occlusion estimated to be of at least 3-months` 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.

Length of occlusion: This was measured by quantitative coronary angiography (CAAS II; Pie Medical Imaging, The Netherlands) either utilizing antegrade filling via collaterals, or assessment of the retrograde collateral filling achieved through making a simultaneous injection into both the left and right coronary arteries to delineate the distance between the site of occlusion and the most proximal part of the vessel filled retrogradely. This length evaluated only the occluded vessel, and did not therefore include stenosis of the vessel pre- and post- the occlusion.

Follow-up: Patients were prospectively followed-up for clinical events, and evaluated for survival-free of major adverse cardiac events (MACE) using questionnaires and telephone enquiries. MACE was pre-defined as: 1) death, 2) non-fatal myocardial infarction (AMI), or 3) repeat target vessel revascularization (TVR). The diagnosis of AMI required an elevation of creatine kinase to twice the upper limit of normal, together with a rise in creatine kinase-MB fraction. TVR was defined as either surgical or percutaneous reintervention driven by

significant (>50%) luminal narrowing within the treated vessel, and was undertaken in the presence of either anginal symptoms or objective evidence of ischemia. Follow-up angiography was undertaken in all patients in the presence of anginal symptoms at clinical evaluation; in addition those patients treated during the first 6-months of DES implantation were invited.

Statistical analysis: Discrete variables are presented as percentages and compared with Pearson's chi-square test. Continuous variables are expressed as mean ± standard deviation and compared with one-way ANOVA. Cumulative survival and MACE-free survival were calculated according to the Kaplan-Meier method. The log-rank test was used to compare MACE-free survival between the groups. A p value of <0.05 was considered as significant.

Results

There were no significant differences between the groups with respect to baseline patient characteristics (table 1). Procedural characteristics are presented in table 2. One patient in both the BMS and PES groups had stent implantation in 2 chronic occlusions. Occlusion length was able to be measured in 74.1%, 84.2%, and 72.4%of the BMS, SES, and PES groups respectively (p=0.3). Both drug-eluting stent cohorts were treated with a higher number of stents resulting in a longer length of stented segment.

At one year, there was a single death occurring in hospital, 22 days after successful RCA recanalization and PES implantation. The patient had been admitted 1 week previously, with no evidence of a cardiac problem, and the cause of death was related to an inoperable glioblastoma. There were 4 patients who had an acute myocardial infarction, all treated with drug-eluting stent implantation. The first had SES implantation for a RCA CTO together with PCI of the LAD. There was a peri-procedural elevation of creatine kinase (maximum elevation of 854IU/l) related to loss of a sizeable septal branch related to the LAD stent (non-occluded vessel). The second related to subacute thrombosis occurring 11 days after SES implantation (a 2.5x33mm and a 3.0x33mm) in a LAD occlusion. IVUS suggested that 2.5mm stent was under-expanded and the patient was treated with a glycoprotein IIb/IIIa inhibitor and balloon dilatation. The third had PES implantation for a RCA CTO together with treatment of the left main stem. On day 14, he complained of chest pains and had a maximum CK elevation of 819. Angiography demonstrated an excellent result in the RCA, but haziness of the ostium of the left circumflex artery which was subsequently treated with further PCI (culprit lesion in other vessel). The fourth patient had SES implantation (a 2.5x33mm and a 3.0x33mm) for a LAD CTO. At 6-months, control angiography demonstrated no evidence of restenosis, but he was admitted 4 months later to another hospital with a myocardial infarction that was managed medically.

Table 1: Baseline patient demographics

	BMS n=26	**SES n=76**	**PES n=57**	**p value**
Mean age (years)	60.3 ± 11.0	61.1 ± 10.6	58.4 ± 10.4	0.3
Male sex (%)	92.3	65.8	80.7	0.3
Current smoker (%)	30.8	18.4	22.8	0.5
Diabetes mellitus (%)	7.7	14.5	19.3	0.4
Hypertension (%)	42.3	42.1	50.9	0.7
Hypercholesterolemia (%)	57.7	67.1	75.4	0.6
Previous myocardial infarction (%)	46.2	51.3	43.9	0.8
Previous CABG (%)	0	3.9	5.3	0.5
Glycoprotein IIb/IIIa inhibitor usage (%)	23.1	18.4	19.3	0.9
PCI in at least one additional (non-occluded) major epicardial vessel during the index procedure (%)	26.9	38.2	47.4	0.4

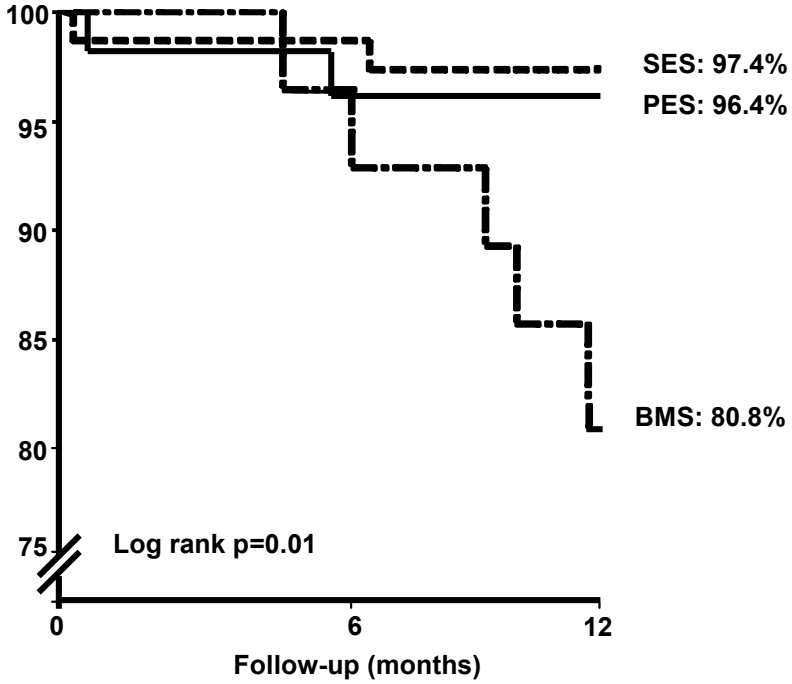
SES: sirolimus-eluting stents, PES: paclitaxel-eluting stents, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention

Table 2: Baseline procedural characteristics

Number of CTO lesions treated		BMS n=27	SES n=76	PES n=58	p value
Target vessel					0.5
	LAD (%)	29.6	46.1	22.4	
	LCX (%)	25.9	19.7	27.6	
	RCA (%)	44.4	34.2	50.0	
Bifurcation stenting (%)		7.4	13.2	13.8	0.7
Mean length of occlusion (mm)		13.0 ± 7.2	10.3 ± 5.9	11.2 ± 6.6	0.2
Mean number of stents in the target vessel		1.8 ± 0.8	2.2 ± 1.2	2.6 ± 1.3	0.03
Mean nominal diameter of stent in the main vessel (mm)		3.0 ± 0.6	2.8 ± 0.3	2.8 ± 0.4	<0.001
Mean total lengths of stent in the main vessel (mm)		41.5 ± 23.3	48.8 ± 27.4	58.0 ± 32.8	0.04
Post-procedure QCA data	Reference vessel diameter (mm)	2.34 ± 0.43	2.35 ± 0.51	2.60 ± 0.49	0.008
	Minimal lumen diameter (mm)	2.12 ± 0.51	2.04 ± 0.43	2.26 ± 0.42	0.02
	Diameter stenosis (%)	11.6	12.9	14.1	0.6

All events in the bare stent group related to the need for target vessel revascularization. At one year, the survival-free of target vessel revascularization was significantly higher in the SES and PES groups compared with the BMS group (97.4% and 96.4% versus 80.8% respectively, p=0.01). Figure 1.

Figure 1: Kaplan-Meier estimates of the cumulative survival-free of target vessel revascularization following stent implantation in a chronic total occlusion for patients treated with sirolimus-eluting (SES), paclitaxel-eluting (PES), or bare metal stent (BMS) implantation.



In the present report we have demonstrated the efficacy of drug-eluting stent implantation for the percutaneous treatment of chronic total occlusions when compared to bare metal stents. In addition, we have shown that both the sirolimus- and paclitaxel-eluting stent are associated with a low rate of target vessel revascularization at 6months.

There have been several randomized trials that have demonstrated the efficacy of stent implantation over balloon-only angioplasty for the percutaneous treatment of CTOs, reducing the 6-month restenosis rate from 68-74% to 32-55%. [13-17] Initial randomized studies of drug-eluting stent implantation, demonstrated efficacy in reducing restenosis compared to conventional stent implantation, but excluded patients with CTOs. [8-11] However, recent preliminary data from our own group have shown that the efficacy of the SES is applicable in the treatment of CTOs (defined as >1 months' duration), with a one year cumulative survival-free of major adverse cardiac events of 96.4%. [12] In the present study, we evaluate a larger series of consecutive patients treated for a truly chronic total occlusion (>3 months in duration) with drug-eluting stent implantation. We have shown that both the SES and PES significantly reduce the need for TVR, with a cumulative survival-free of TVR of 80.8% in the BMS group versus 97.4% and 96.4% in the SES and PES groups respectively (p=0.01). Figure 1.

Importantly, there were no significant differences in baseline demographics between the groups, and all procedures were carried out in the same centre by the same operators. Restenosis following BMS implantation is known to be inversely related to the post-procedural MLD and the number of stents utilized. [18] In the current study, the mean nominal diameter of stent used was significantly greater in the BMS cohort, related to a maximum available SES and PES diameter of 3.0mm and 3.5mm respectively. In addition, despite utilizing a greater number of stents, both the SES and PES demonstrated efficacy over the BMS. Furthermore, the beneficial effect of the SES occurred despite a smaller post-procedural MLD.

All major adverse cardiac events in the BMS group related to the need for TVR, including 1 patient who required coronary artery bypass surgery. Within the drug-eluting stent groups there were 5 additional non-TVR events. One patient had a subacute thrombosis, but this might have been avoidable with evidence from IVUS demonstrating a possible underlying mechanism of inadequate stent expansion. In addition, there is good evidence in a further 3 of these cases that the event was unrelated to treatment of the occluded vessel. One patient died of non-cardiac causes, and 2 of the myocardial infarctions were thought to be related to intervention carried out in another (non-occluded) vessel. The fifth patient presented with an AMI in the territory of the target vessel, 4 months after control angiography demonstrated patent stents. Clopidogrel medication had been stopped at the time of the follow-up angiogram, such that the patient was on aspirin therapy alone. The duration of dual anti-platelet therapy needed to reduce / abolish the risk of late stent thrombosis in patients treated with DES, particularly for complex disease, is still unclear. Recently, Ong et al reported on late (>30 days) stent thrombosis following DES implantation in a consecutive cohort of >2000 patients, they found a low incidence of 0.35% (95% confidence limits 0.17% to 0.72%). [19] Importantly, there were no episodes in patients continuing on dual anti-platelet therapy. However, whether there is a true benefit in continuing clopidogrel in addition to aspirin, over and above the possible disadvantages, requires further large scale evaluation.

In patients with significant coronary artery disease, although a CTO is found in at least one third, the majority are treated with either medical therapy or are referred for coronary artery bypass surgery, with percutaneous treatment of CTOs accounting for only 10-15% PCI procedures. [20] The major limitation of PCI for CTOs is the inability to cross the lesion with a wire, however great advancements have been made in the manufacture of specialized wires, and there are additionally promising novel technologies such as the Intraluminal wire™ and Frontrunner catheter. [21-23] The current report has demonstrated the efficacy of drug-eluting stent implantation in CTOs and, together with improvements in recanalization rates, a strategy of percutaneous therapy of CTOs will become more widely applicable.

Study Limitations

The study was not randomized, and angiographic follow-up data was not routinely obtained in all patients, so additional events such as silent re-occlusion cannot be excluded. However, clinical follow-up was obtained in >99% patients (all but one patient), and assessment of symptomatic status in those that did not require re-intervention, showed that all were symptomatically well at follow-up. The study was not randomized, and used a retrospective comparative population; however the same operators and interventional techniques were utilized.

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Chapter 11

Sirolimus-Eluting Stent Implantation for Chronic Total Occlusion of the Left Main Coronary Artery

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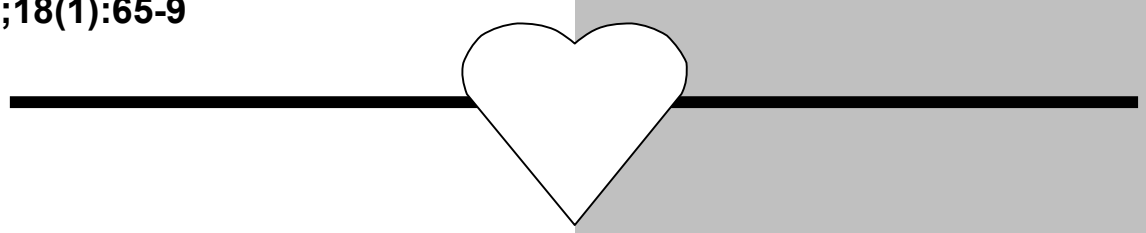
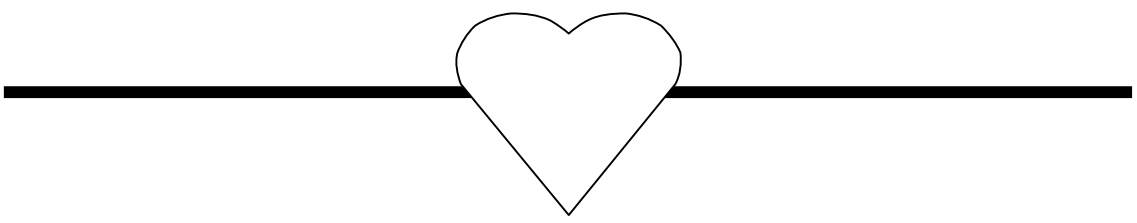
Journal of Interventional Cardiology
2005;18(1):65-9



Abstract

Chronic total occlusion of the left main coronary artery (LMCA) is rare. Recently, percutaneous coronary intervention has been increasingly applied to unprotected LMCA lesions. We describe a patient with chronic total occlusion of the left main coronary artery who was successfully treated with bifurcation stenting with sirolimus eluting stents.



Introduction

Chronic total occlusion of the left main coronary artery (LMCA) is a very unusual manifestation of coronary atherosclerotic disease in clinical practice. [1-4] The rarity of this lesion may be accounted for by the relatively high incidence of death in these patients. Coronary artery bypass graft surgery (CABG) has been the standard of care for LMCA disease, though recently, percutaneous coronary intervention (PCI) has been increasingly applied to unprotected LMCA lesions. [5-12] However, the development of restenosis remains a major limitation of late outcomes after PCI, with the occurrence of restenosis particularly associated with hazardous clinical manifestations. Sirolimus-eluting stents (SES) have been shown to dramatically reduce the restenosis rate in selected patients with relatively simple lesions. [13-15] We report a patient with chronic total occlusion of the left main coronary artery who was successfully treated percutaneously with SES implantation.

Case report

A 35-year-old male presented with an acute anterior myocardial infarction that was managed medically. He subsequently complained of on-going chest pain (CCS class II-III angina [16]) and underwent coronary angiography 9-month later. His resting 12-ECG revealed evidence of a previous Q-wave anteroseptal myocardial infarction and echocardiography demonstrated hypokinesis of the anteroseptal wall without left ventricle aneurysm. He was referred for coronary angiography which showed a total occlusion of the LMCA (Figure 1); the left anterior descending coronary artery (LAD) and left circumflex coronary artery (LCX) were retrogradely filled via Rentrop grade III collaterals [17] from the RCA, which was itself not significantly stenosed (Figure 2). The patient rejected coronary artery bypass grafting, but consented to undergo attempted revascularization with percutaneous coronary intervention.

A 6Fr introducer sheath was inserted in the right femoral artery. In addition, a 5Fr introducer sheath was inserted in the left femoral artery to enable simultaneous right and left coronary injections. In the absence of antegrade flow through the occlusion, such a dual injection technique allows visualization of the distal vessels (LAD and LCX) via the collateral filling from the RCA, thereby facilitating correct positioning of the wire. A 6Fr XB 3.5 guiding catheter (Cordis) was placed in the left main coronary segment, and successful recanalization was achieved with a 0.0014" Shinobi wire (Cordis), which was advanced into the distal LAD. A second 0.0014" Shinobi wire was taken, and passage in to the LCX was attempted. Unfortunately this was complicated by catheter / wire-induced dissection from the LMCA to the mid-LCX (Figure 3), and the wire was withdrawn. The LAD / distal LMCA was stabilized through stent implantation with a 3.0 x 23mm SES (Cypher, Cordis), which was then post-dilated with a 3.5mm balloon (U-pass, Cordis) giving a good result (Figure 4). After several attempts, a 0.0014" Sinobi wire was eventually successfully crossed, via the SES struts, into the true lumen of the LCX. After sequential predilatation using a 2.0mm balloon (Stomer, Medtronic), both the lesion and the mid-LCX dissection (Figure 5) were treated with implantation of a 2.5 x 33 mm SES deployed from LCX ostium. The final angiogram showed a good result with TIMI III flow in both the LAD and LCX [18] (Figure 6).

The patient made an unremarkable recovery and was allowed home. There were no major adverse cardiac events during the in-hospital period, and at 9-months clinical follow-up he remains well with no recurrence of angina.

Discussion

Chronic total occlusion (CTO) of the LMCA is rare. In patients who are investigated in the catheter laboratory its` prevalence varies from 0.04 percent to 0.4 percent. [1-4] CABG has been considered the treatment of choice in LMCA disease and in particular, is the most favored strategy for chronic total occlusion of the LMCA. There are a few published reports showing that the results of CABG for this group of CTO`s are beneficial compared to medical therapy, [1,2] however, there are no studies comparing PCI with CABG for such patients. The advent of improved PCI equipment including stents and atherectomy devices, have been shown to be a safe and effective in selected patients with unprotected elective LMCA stenosis, [5-12] and recently Trehan et al have reported a single case of successful percutaneous stenting of a CTO of an unprotected left main coronary artery. [19]

Figure 1: Left coronary artery angiogram, revealing total occlusion of the left main stem artery.

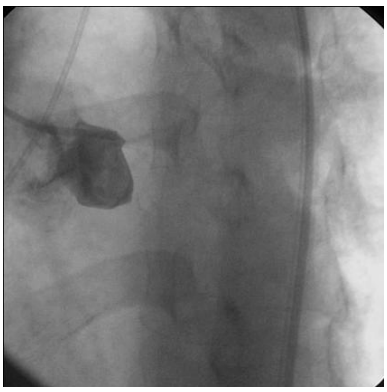


Figure 2: Right coronary angiogram demonstrating grade III retrograde collaterals arising from the right coronary artery to both the left anterior descending and left circumflex arteries.

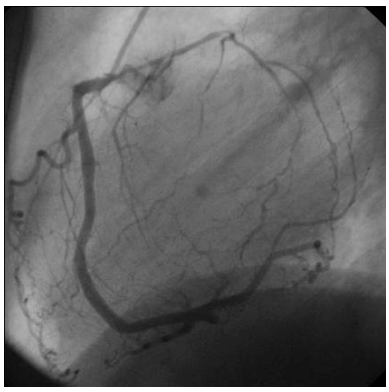


Figure 3: Left coronary angiogram showing the dissection of the left main stem artery to the mid-circumflex artery.

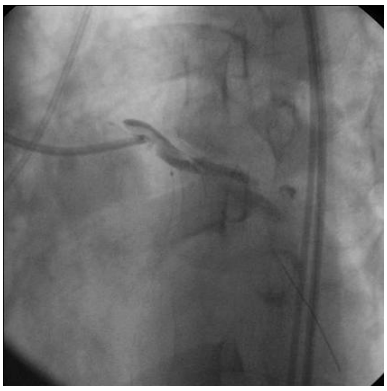


Figure 4: Left coronary angiogram following stent deployment with a 3.0 x 23mm sirolimus-eluting stent in the left main stem / left anterior descending artery.

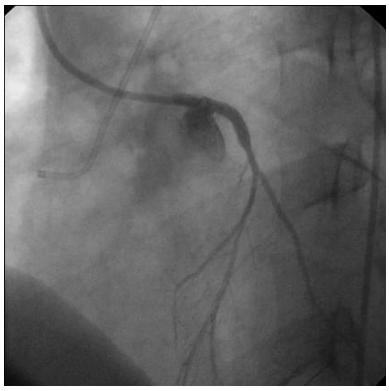


Figure 5: Left coronary angiogram showing that a wire has successfully crossed through the stent struts and into the true lumen of the distal left circumflex artery. The region of dissection can clearly be seen in the proximal and mid parts of the vessel (contrast staining).

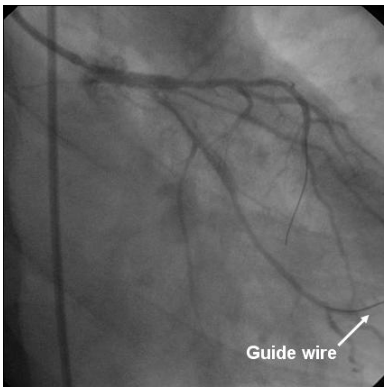
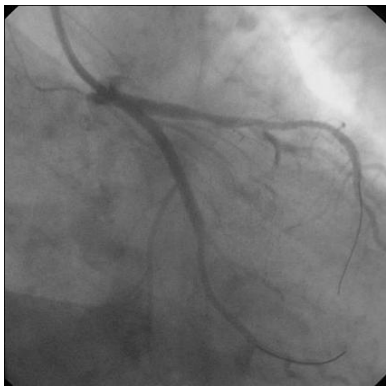


Figure 6: The final angiogram following additional stent implantation with a 2.5 x 33mm sirolimus-eluting stent up to the ostium of the circumflex artery, showing a good result in both the left anterior descending and left circumflex arteries.



There are 2 major problems associated with PCI for chronic total occlusion of the LMCA. The first relates to the initial procedural difficulty of crossing the occlusion with a wire; published procedural success rates for CTO`s are generally in the range of 40-81%. [20,21] The second relates to restenosis; both bifurcation lesions and CTO`s are subject to a higher rate of restenosis compared with simpler lesions, [22-25] and importantly, the occurrence of restenosis in the LMCA may be associated with a significant rate of mortality. In particular, PCI for bifurcation lesions of the distal LMCA whereby both the LAD and LCX arteries are stented, is both technically demanding and at high risk of restenosis. [26-28] Drug eluting stents have been shown to dramatically reduce the restenosis rate in elective patients with simple de novo lesions. [13-15] The development and more widespread application of drug eluting stents hold the promise of a significant reduction in restenosis and the need for repeat revascularization. Arampatzis et al have reported the effectiveness of SES for the treatment of LMCA. A total of 31 consecutive patients were treated solely with SESs either electively, for acute myocardial infarction, or due to procedural complication-related LMCA dissection. In this study, the rate of out-of-hospital clinical events was extremely low (mortality rate was 0% and target vessel revascularization rate was 4%). [29] In addition, low subsequent binary restenosis rates following SES implantation have been documented both in CTO`s (9.1% at 6 months) and bifurcation lesions (22.7% at 6 months). [30,31] The technique of bifurcation stenting (T, culotte, kissing, or crush stenting) with drug-eluting stents is still controversial. [30] Those techniques resulting in overlapping stent struts lead to an increase in the local concentration of drug, which may induce endothelial function impairment and thus be associated with an increased rate of stent thrombosis. In the current report, we present a patient who underwent successful recanalization of a LMCA CTO without the need for a cardiac support device, and underwent bifurcation stenting, with SESs. There were no major adverse cardiac events either in-hospital, or over the subsequent 9 months follow up period. Further data is needed to fully evaluate the use of this strategy in such an unusual patient population, however, SES supported angioplasty may be a reasonable alternative to CABG in the treatment of LMCA chronic total occlusion.

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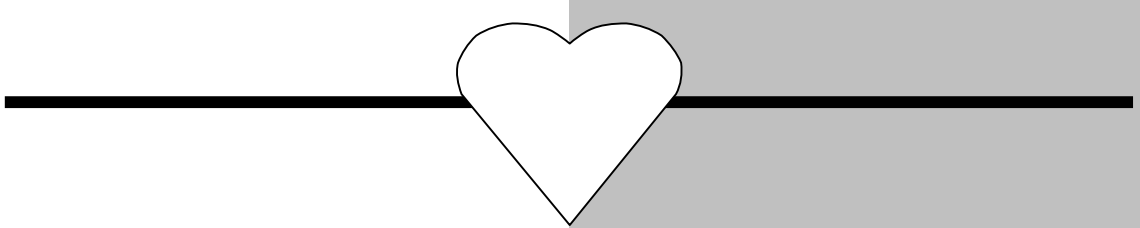
Part 2

BIFURCATIONS

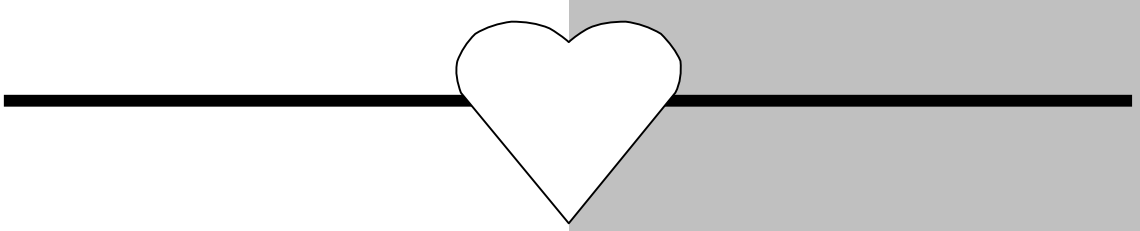


Chapter 12

Bifurcations

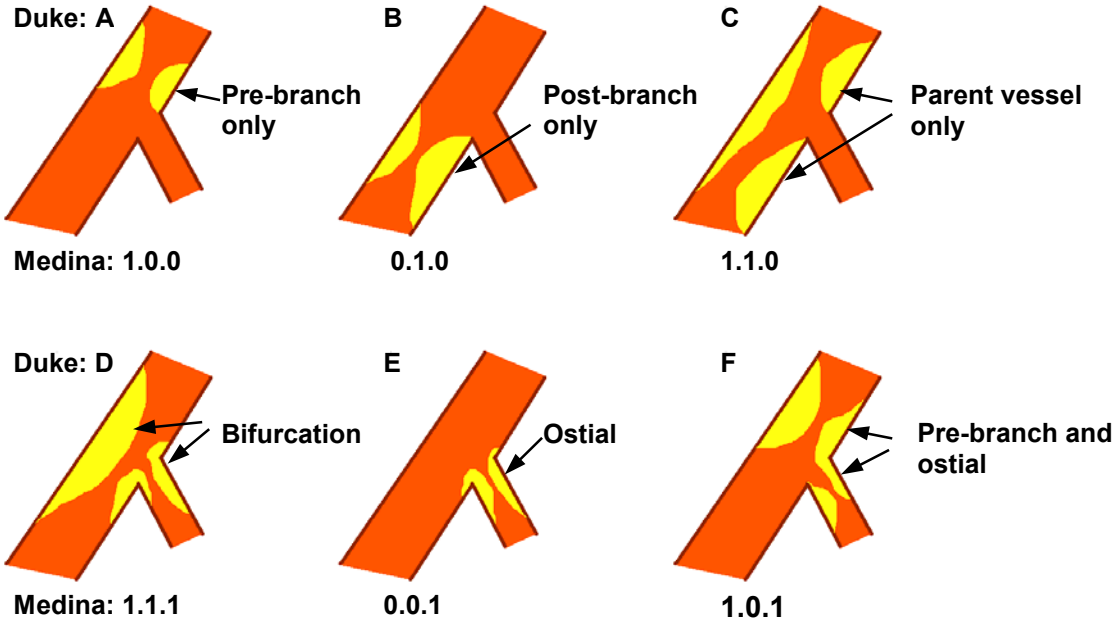
Angela Hoye

Chapter in A Colour Handbook of Adult Interventional Cardiology
Manson Publishing (in press)



Percutaneous coronary intervention (PCI) of bifurcation lesions is associated with a lower rate of procedural success,[1] and an increased subsequent rate of major adverse cardiac events (MACE) and restenosis compared with PCI of non-bifurcated lesions. The complexity of bifurcation lesions relates to the need to maintain patency of both the main vessel and (sizeable) side branch. However, the term "bifurcation lesion" covers a range of anatomical variations, and, at present, the most effective strategy of PCI for individual lesions is currently unknown. Indeed studies published thus far have evaluated the efficacy of different stenting strategies when applied to treat bifurcations in general, and have not been targeted to the individual lesion. There have been several proposed classifications of bifurcation lesions, one of these, the Duke classification, is depicted in figure 1. The recently introduced Medina classification is a simple binary system whereby the presence of significant plaque is represented by a 1 for the proximal main vessel, distal main vessel, and side branch. The corresponding Medina classification for each lesion subtype is also presented in figure 1. However, even when only one of the two branches is significantly stenosed at baseline, plaque shift or the "snow-plough effect" can pose a problem. In addition to plaque distribution, lesions also differ in respect of the degree of angulation between the main vessel and side branch, something which is of particular importance when utilizing techniques such as "T-stenting" and specialized bifurcation stents.

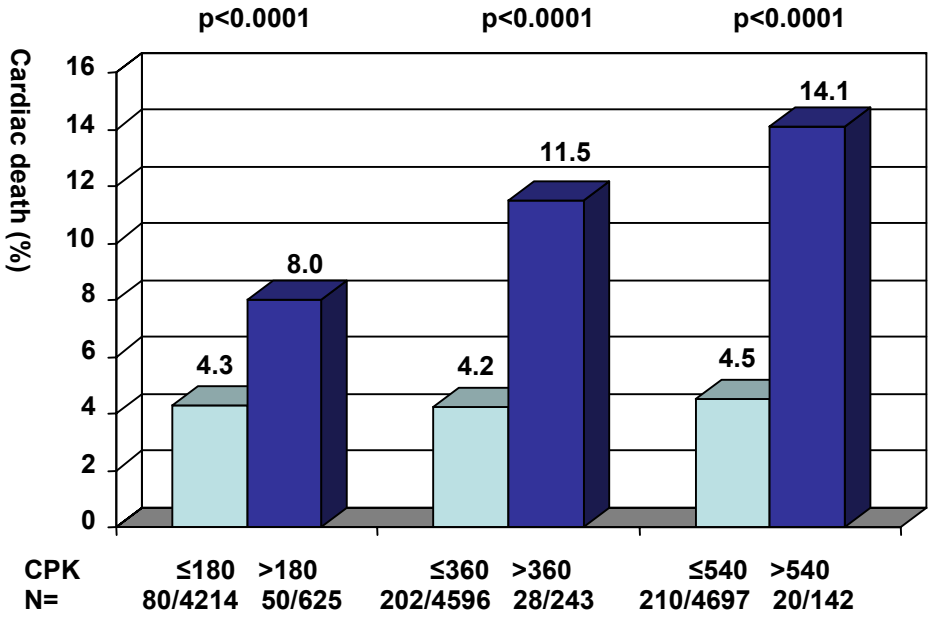
Figure 1: The Duke Classification of bifurcation lesions together with the corresponding Medina binary classification with respect to variations of plaque distribution.



Plaque shift

Following balloon dilatation or stent implantation, shift of atheromatous / thrombotic material may occur proximally, longitudinally, and/or circumferentially.[2,3] Importantly, plaque shift is unpredictable, but can lead to severe compromise of flow within the other vessel. Indeed, following dilatation of the main vessel, plaque shift can lead to side branch occlusion, particularly when the ostium of the side branch is itself diseased, the side branch is of relatively small diameter, or in the presence of soft thrombotic material in acute coronary syndromes. The clinical consequences of loss of the side branch depend on the vessel size, but may be associated with short-lived chest pain and a (modest) rise in cardiac enzymes. Fortunately at follow-up, angiography may demonstrate restoration of patency in up to 82%.[4] However even temporary vessel closure may result in a rise in cardiac enzymes, and even a relatively small cardiac enzyme release has been shown to have prognostic implications after PCI. The greater the enzyme rise, the higher the mortality rate at long-term follow-up (figure 2).[5,6]

Figure 2: Illustrates the rates of cardiac death with respect to the level of creatine kinase following a successful coronary angioplasty. A series of 4863 consecutive patients were followed up for a mean duration of 41 ± 23 months. If the procedure was associated with an increase in creatine kinase, there was a significant adverse effect on long-term outcome (p<0.001), even when the elevation was relatively small. From Abdelmeguid et al C*irculation*. 1995;91:2733-41. [6]



Strategy of PCI

Before the introduction of stents, most patients with a bifurcation lesion were referred for coronary artery bypass surgery. Balloon-only angioplasty was limited by plaque shift and compromise of the side branch. This was to some extent overcome with the introduction of kissing balloon dilatation, whereby simultaneous balloon dilatation is carried out in both the main vessel and side branch.[7,8] However, the technique remained limited by the occurrence of acute recoil / vessel closure, and subsequent restenosis. The CAVEAT I trial evaluated debulking with adjunctive atherectomy.[9] In theory, this might be potentially advantageous over balloon-alone angioplasty through removal of plaque and prevention of plaque shift. However, although there was less residual stenosis at the end of the procedure, this was at the expense of a higher rate of side branch occlusion and acute myocardial infarction. There was no difference in the incidence of death, myocardial infarction or restenosis at follow-up.

<u>Stent implantation: bare metal stents</u>

Stents provide a scaffold to reduce the risk of recoil and acute vessel closure. However, long-term results are hampered by the excessive development of neointimal hyperplasia. Stenting the main vessel alone may compromise side branch flow through a combination of plaque shift and “pinching” by the stent struts. In the NIRVANA study of the NIR stent implanted across a side branch, side branch compromise occurred in 27%, and occlusion in 5% of patients. Side branch occlusion was associated with Q-wave myocardial infarction in 7%, and non-Q-wave myocardial infarction in 20%.[10] It was hoped that a strategy of elective stenting of the side branch might be advantageous. Various techniques have been evaluated, with gratifying immediate angiographic results. However, studies with bare metal stents (albeit non-randomized), showed that a 2 stent strategy did not reduce the subsequent rate of MACE, and was associated with a trend towards a higher rate of restenosis compared to the utilization of a single stent strategy (table 1). Restenosis is known to be inversely related to stent diameter, and this is may be of particular importance in the therapy of bifurcation lesions where the side branch vessel diameter is often ≤2.5mm.

Table 1

Study Length of clinical follow-up	Strategy	No.	In-hospital MACE (%)	Restenosis (%)	TLR (%)	MACE (%)
Pan et al [11]	1 stent	47	4	-	17	25
18 months FU	2 stents	23	8	-	39	56
Yamashita et al [12]	1 stent	39	0	48	36	38
6 months FU	2 stents	53	13	62	38	51
Al Suwaidi et al [13]	1 stent	77	3	-	21	27
1 year FU	2 stents	54	6	-	19	48
Anzuini et al [14]	1 stent	45	4	28	16	20
1 year FU	2 stents	45	4	43	36	39
Sheiban et al [15]	2 stents	54	0	63	33	33
9 months FU						
Frontier stent [16]	Bifurcation	105	3	45	13	17
6 months FU	stent					
Colombo et al [17]	1 stent	22	9	19	5	14
6-months FU	2 stents	63	10	28	10	19
Pan et al [18]	1 stent	47	4	7	2	9
11-months FU	2 stents	44	2	20	5	7
Tanabe et al [19]	2 stents	58	2	23	9	10
6-months FU						

MACE: Major adverse cardiac events; TLR: target lesion revascularization

Stent implantation: drug-eluting stents

The advent of drug-eluting stents, with a marked reduction in the development of restenosis, has lead to the re-evaluation of bifurcation lesion stenting strategies. Preliminary data of the sirolimus-eluting stent (SES) has confirmed efficacy when compared with historical data, with overall rates of restenosis of 23-26%, and need for target lesion revascularization in 8-9%.[17,19] In an observational study of the SES in a consecutive group of patients, restenosis occurred particularly at the ostium of the side branch following the use of a T-stenting strategy (described below).[19] This might reflect incomplete coverage of the ostium thereby reducing the efficacy of the drug-elution, and suggested that it may be beneficial when using drug-eluting stents to adopt a strategy that ensures complete lesion coverage. There are currently several on-going randomised trials underway to evaluate this.

Preliminary data from Colombo et al of 85 patients randomized to either a single SES versus a 2-SES strategy, found no significance difference in restenosis rates between the two groups (19% for provisional side-branch stenting versus 28% for double-stenting).[17] However, these results are limited because of a notably high rate of crossover in the single-stent group to the 2-stent strategy because of a sub-optimal result (51%). In addition, the strategy of 2-stent implantation was not standardised. Pan et al also randomized patients with a bifurcation lesion to a single versus a 2-stent strategy, and showed no difference in terms of clinical outcomes.[18] At 6-months angiographic follow-up, restenosis occurred in the main vessel in 2% and 10%, and in the side branch in 5% and 15%, of patients treated with a single versus a 2-stent strategy respectively.

Techniques of stenting

General principles

Angiography must adequately evaluate the bifurcation, in particular whether the side branch ostium is involved or not. The use of 2 wires is a simple method to ensure that access to each branch is preserved throughout the intervention. In general the use of pre-dilatation is recommended, and has the advantage of assessing how the lesion behaves with evaluation of any plaque shift, and facilitation of subsequent stent implantation. Whatever the stenting strategy chosen, kissing balloon post-dilatation is strongly recommended particularly when both

branches are stented. Though not detectable on angiography, stent deformation may occur whatever the technique utilized, and is corrected with kissing balloons.[20]

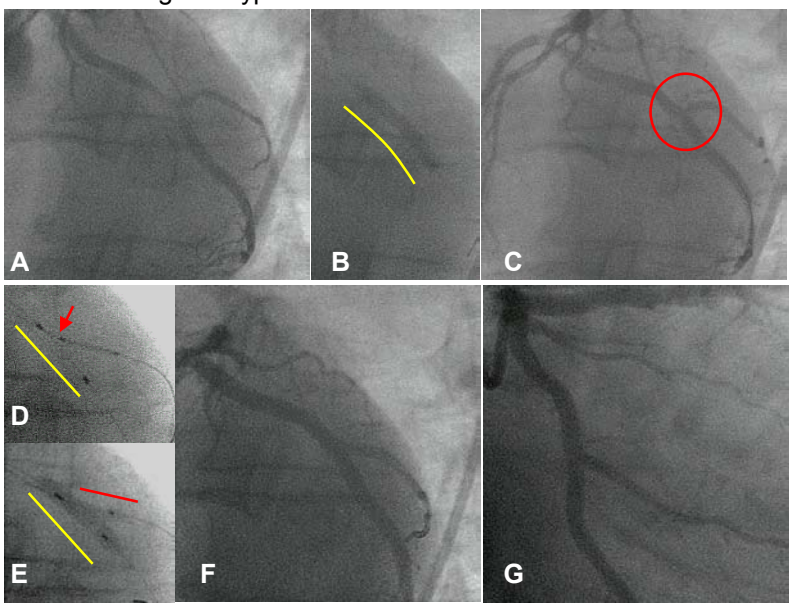
The most effective technique of stenting of bifurcation lesions remains undefined. Several techniques and variations of them have been described:

- Single stent with provisional side branch stenting
- T-stenting
- V-stenting
- Culotte technique
- Crush technique

Single stent with provisional side branch stenting (figure 3)

Bare metal stent data favour the use of a single stent within the main vessel. If, at baseline, the side branch ostium is significantly diseased, then stent implantation may be best preceded by balloon dilatation of the side branch. Following stent deployment, any compromise of side branch flow can be optimised by re-wiring the side branch through the stent struts, and carrying out kissing balloon post-dilatation. However, the side branch result may remain sub-optimal particularly if dissection has occurred. In this case, there remains the option of stenting the side branch, with the aim of placing the proximal part of the stent just at the side branch ostium without causing obstruction to the flow within the main vessel. An example is shown in figure 3. Following stent implantation in the main circumflex artery, the ostium of the obtuse marginal branch was pinched and this was associated with reduced (TIMI II) flow. After pre-dilatation, the side branch was stented with the proximal part of the stent located at the ostium. Following deployment, the bifurcation was treated with kissing balloon post-dilatation with an excellent final result.

Figure 3: Type B T-stenting of a type D bifurcation of the circumflex / obtuse marginal **(A).**



The main vessel is stented with a 3.0x16mm stent **(B).** This leads to compromise of the marginal branch with only TIMI II flow **(C).** A second wire was passed into the marginal branch and the stent struts opened with a 1.5mm balloon. This facilitated stent implantation and a 2.5x12mm stent was implanted in the marginal branch, positioning the proximal part just at the ostium **(D**, red arrow). The bifurcation stenting is then optimised with the use of kissing balloon post-dilatation: the side branch stent balloon is pulled back to lie more within the main vessel and alongside a 3.0x12mm balloon placed within the main vessel stent. The balloons are positioned such that dilatation only occurs within stented parts of the vessel, thereby avoiding inflicting trauma to other parts. The proximal markers of the balloons are next to each other, and both balloons are inflated simultaneously **(E).** The final result is excellent **(F, G).**

T-stenting (figure 4)

As shown in figure 4, this involves electively stenting first the side branch, positioning the proximal part at the ostium, followed by stent implantation within the main vessel. However, the efficacy of both provisional side branch stenting and T-stenting are limited due to the angle between the main vessel and side branch. Complete lesion coverage can be accomplished only when there is a large angle between the vessels (a T-shape). Figure 5. However, in >75% bifurcations, this angle is significantly <70˚ and more of a "Y" shape.[21] Even with precise stent positioning, this means that either the ostium of the side branch is incompletely covered (figure 5a), or the side branch stent protrudes into the main vessel (figure 5b).

Figure 4: Type A T-stenting of a type F bifurcation lesion of the LAD / diagonal **(A).** Both vessels were pre-dilated, and the diagonal branch was stented first with a 2.75x23mm stent placed at the ostium **(B),** and with a good result **(C).** The main vessel was then stented with a 3.0x23mm stent positioned to cover the lesion thereby covering the ostium of the diagonal **(D,E).** The final result in both vessels is good **(F).**

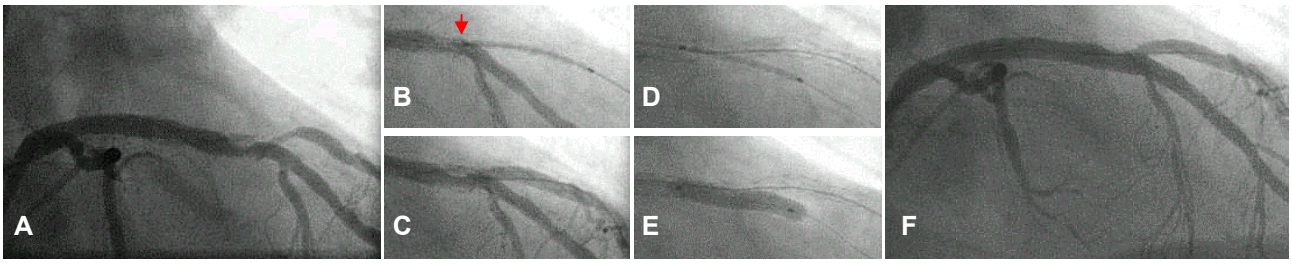
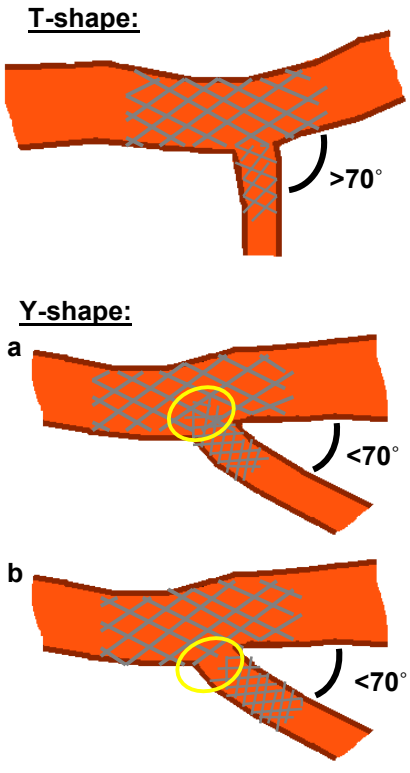


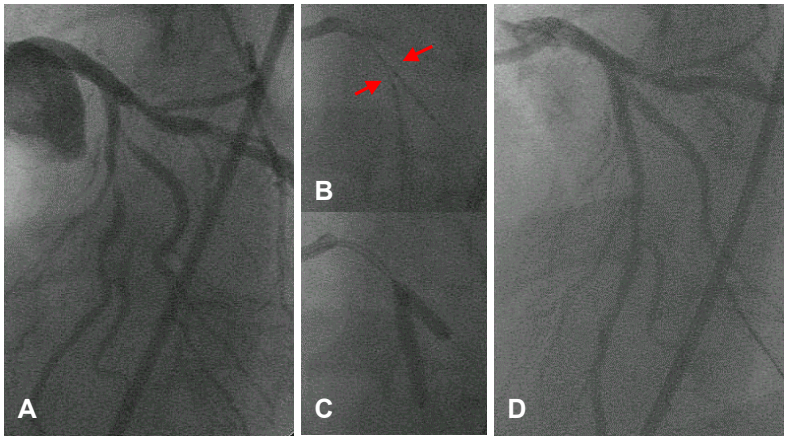
Figure 5: Only one quarter of bifurcations are of a "T" shape such that the angle between the 2 branches is >70˚. The majority of bifurcations are more of a "Y" shape. This means that when stenting both the main vessel and side branch, even with precise positioning, either part of the side branch stent lies within the main vessel thereby compromising flow **(a),** or part of the ostium of the side branch is incompletely covered by stent **(b).**



V-stenting and kissing stents (figure 6)

These techniques similarly involve implantation of both stents simultaneously and therefore require a guiding catheter of at least 7F. In general for these techniques both branches are of similar reference diameter. During kissing stent implantation, the proximal parts of each of the 2 stents are positioned at the same level and the stents lay side-by-side, similar to a "double-barrelled shotgun," and thereby bringing forward the carina. In V-stenting, the proximal parts of the stents only just touch and form a "V" shape. If necessary, a third stent can be implanted in the main vessel in a so-called "trouser stent" formation.

Figure 6: "V" stenting technique: there is significant plaque in the ostium of a large diagonal branch, and further plaque more distally within the LAD **(A).** To minimise problems associated with plaque shift from the diagonal into the main vessel, both are stented simultaneously. Each vessel is wired, and both stents positioned with the proximal markers lying alongside each other (arrows, **B).** The stents are deployed at the same time **(C),** with an excellent final result **(D).** This technique requires a guiding catheter of at least 7F. If there is additionally plaque within the proximal part of the main vessel, and in the situation whereby both branches are of similar diameter, the technique can be modified to a "kissing stents" strategy which is done in a similar manner but with the proximal parts of the stents lying parallel to ensure complete lesion coverage.



Culotte technique (figure 7)

Unlike T-stenting strategies, the Culotte technique ensures complete coverage of the lesion, but leads to a high concentration of metal with a double layer of stent struts at the carina and in the proximal part of the bifurcation. The technique fell out of favour, as studies with bare metal stents demonstrated high rates of restenosis. In one study of 50 patients, though the target vessel revascularization rate was 24%, of the 25 patients with follow-up angiography, restenosis was demonstrated in 14 (56%).[22] Furthermore, an observational study demonstrated a significantly higher rate of MACE at 1-year following Culotte versus T-stenting (86.3% versus 30.4%, p=0.004).[13] However, preliminary results with SES have been more encouraging, with one study demonstrating an 8-month rate of survival-free of TLR of 95%.[23]

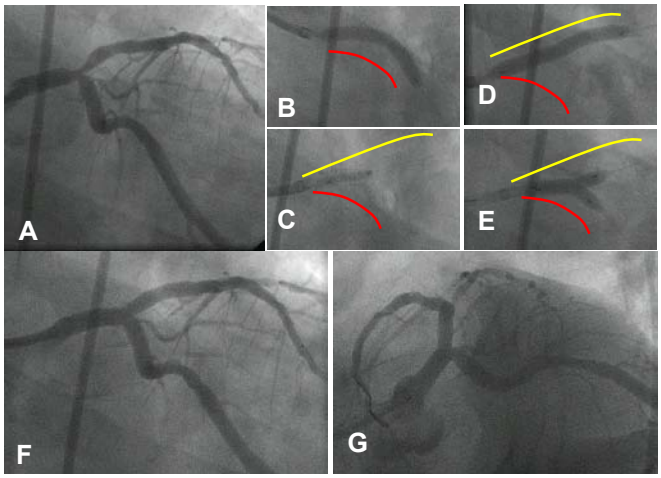
An example is depicted in figure 7. The technique is particularly useful when both branches are of a similar diameter, and gives excellent initial angiographic results. However, it can be time consuming, and crossing of the struts with a guidewire / balloon may, at times, be difficult.

Crush technique (figure 8)

The crush technique was first described by Colombo et al in 2003 and was designed as a technically straightforward method utilizing drug-eluting stents, which ensures complete coverage of the side branch ostium.[24] A case example is demonstrated in figure 8. Recent data has demonstrated that kissing balloon post-dilatation is important in reducing the risk of developing subsequent restenosis of the side branch.[25] This involves re-wiring of the side branch through potentially 3 layers of struts and can therefore be both difficult and time-consuming. To facilitate this, the stent within the main vessel should first be post-dilated with high pressure inflation with a balloon ≥nominal stent diameter size. Following successful wiring of the side branch,

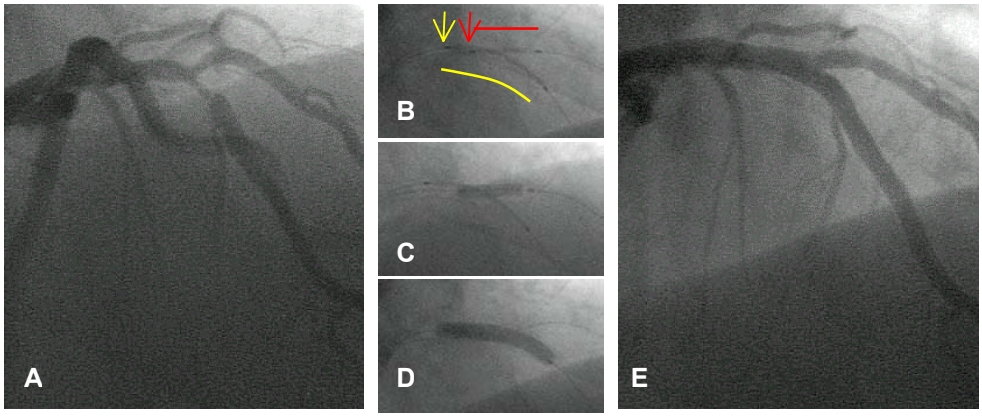
the struts are opened initially with a small balloon, and then with a balloon of ≥nominal stent diameter size taken to high pressure. The final result is optimised with kissing balloon post-dilatation.

Figure 7: Culotte stenting of a type D bifurcation lesion of the distal left main stem (A).



Both vessels are wired and pre-dilated to facilitate subsequent stent implantation. The circumflex vessel (LCx) is, in this case, the branch associated with the greatest degree of angulation from the main vessel and is therefore stented first **(B),** ensuring the proximal part lies well within the main vessel. This will "trap" the wire in the left anterior descending (LAD), and another wire is taken and passed through the LCx stent struts to lie within the lumen of the LAD. The first LAD wire is then withdrawn. After pre-dilatation to open the struts **(C),** the LAD is stented such that the proximal part lies in the main vessel within the LCx stent at the same level **(D).** This will "trap" the LCx wire, which will need to be withdrawn and the vessel re-wired through the LAD stent struts. A small balloon is used to open the struts of the LAD stent thereby facilitating passage of a larger balloon and enabling optimisation with kissing balloon post-dilatation **(E),** leading to an excellent final result **(F,G).**

Figure 8: Crush stenting of a type F bifurcation lesion of the LAD / diagonal **(A).**



Both vessels are wired, and pre-dilated to facilitated stent implantation and positioning. The stents are positioned as shown in **B.** Notably, the proximal part of the side branch stent (red arrow) lies well within the main vessel thereby avoiding incomplete stent coverage of the ostium. Importantly, the entire side branch stent is covered by the stent within the main vessel (yellow arrow, **B).** The side branch stent is implanted **(C)** and the balloon withdrawn carefully to avoid displacing the stent within the main vessel. The main vessel stent is then deployed, thereby crushing the proximal part of the side branch stent against the vessel wall **(D).** The final result is excellent **(E).**

Dedicated bifurcation stents (figures 9 & 10)

Several stents have been specifically designed for bifurcations with particular emphasis on maintaining ease of access to the side branch. The JoStent (figure 9A) is designed with an 8 cell mesh at either end, but only 4 larger cells in the middle potentially improving side branch access. Other specialized bifurcation stent designs incorporate a double balloon system (figure 9B,C) mounted on a single shaft. The Twin-Rail coronary bifurcation system (Invatec, Italy) consists of a single stent pre-mounted on two balloons in its proximal portion (both a main vessel and side branch vessel balloon), and only on the main-vessel balloon in its distal portion (figure 9B). During deployment, guidewire access to the side branch is maintained throughout, and the stent cell that faces the side branch is well dilated by the side branch balloon. Similarly the ML Frontier™ stent (Guidant Corporation) consists of a stainless steel stent mounted on a delivery system with two balloons and two guide wire lumens. The advantages of these designs are that guide wire crossing is avoided and side branch access is maintained throughout the whole procedure. The major disadvantage is that these stents are relatively bulky and can be difficult to track so are not as deliverable as standard stents. Evaluation of the Frontier™ stent in a multicenter study of 105 patients demonstrated successful implantation in 96 (91%). At 6-months, the rate of MACE was just 17%, with a main vessel in-stent binary restenosis rate of 25%, and side branch restenosis of 29%.[16]

The Petal™ Stent (AST / Boston Scientific Corp) is depicted in figure 9D. It incorporates a Petal feature in the middle of the stent (figure 9E), which is designed to expand into the side branch, permitting blood to flow into both branches of the bifurcation and providing mechanical support at the branch (9F). The combination of this technology with paclitaxel drug-elution is hoped to improve outcomes.

The Devax Axxess Stent (Devax, California) is a self-expanding, flared nitinol-based stent that can be implanted in the main vessel right to the carina (figure 10A). It allows for access to the distal branches so that additional stent(s) can be implanted in the branches as needed (figure 10B). A successful implant will span the ostia of both branches as indicated by the presence of distal markers, and will cover the entire carina (figure 10C). The uncoated Axxess stent received CE Mark approval in Europe in August 2003. However, an important recent advance is that the stent has been coated with a bio-erodable polymer together with the anti-proliferative drug biolimus A9 (Occam International BV, California) at a dose of 22 mcg/mm of stent length. This drug is an analogue of sirolimus, and has been shown in the animal model to suppress neointimal proliferation and reduce restenosis. The stent was evaluated in the non-randomized Axxess Plus Trial of 136 patients.[26] The Axxess stent was used together with the option of additional stent implantation distally. At follow-up, there was a low late loss within the stent (0.09 ± 0.56 mm); the majority (55%) of restenoses were found at the ostium of the side branch. These occurred mostly in lesions treated with only balloon angioplasty, rather than additional stent implantation.

Discussion

Bifurcation lesions present a challenge to the interventional cardiologist, with no clear data on the most effective strategy of PCI. The majority of published studies do not take into account the wide anatomical variability, and although there is a clear difference between a “true bifurcation” with disease involving both branches, and involvement of only one of the branches, the unpredictable nature of plaque shift makes it difficult to develop generally applicable strategy guidelines.

The inherent heterogeneity of lesions included in such studies, together with the lack of randomisation, means that any comparison between different strategies / stent types should be made with some caution. However, long-term results have improved since the introduction of drug-eluting stents with a reduction in the rate of restenosis. Future randomized studies are needed to evaluate the most effective strategy with respect to differing anatomical variations. In addition, there may be a role for dedicated bifurcation stents designed with the capability of drug-elution, such stents are able to provide adequate scaffolding with preservation of side branch access whilst avoiding double / triple layer of stent struts. Future stent designs may even allow for targeted anti-restenotic drug elution, with delivery of variable drug dosage dependent on the risk of restenosis in different localities.

Figure 9: Illustrations of some of the different stent types available that are specifically designed for side-branch access or bifurcation treatment. A: The middle section of the Jostent has fewer and larger cells to allow for easier side-branch access. B: The Twin-Rail coronary bifurcation system (Invatec, Italy). C: The ML Frontier™ stent (Guidant). D,E,F: The Petal™ Stent (AST / Boston Scientific Corp) incorporates a Petal feature in the middle of the stent to scaffold the ostium of the side branch.

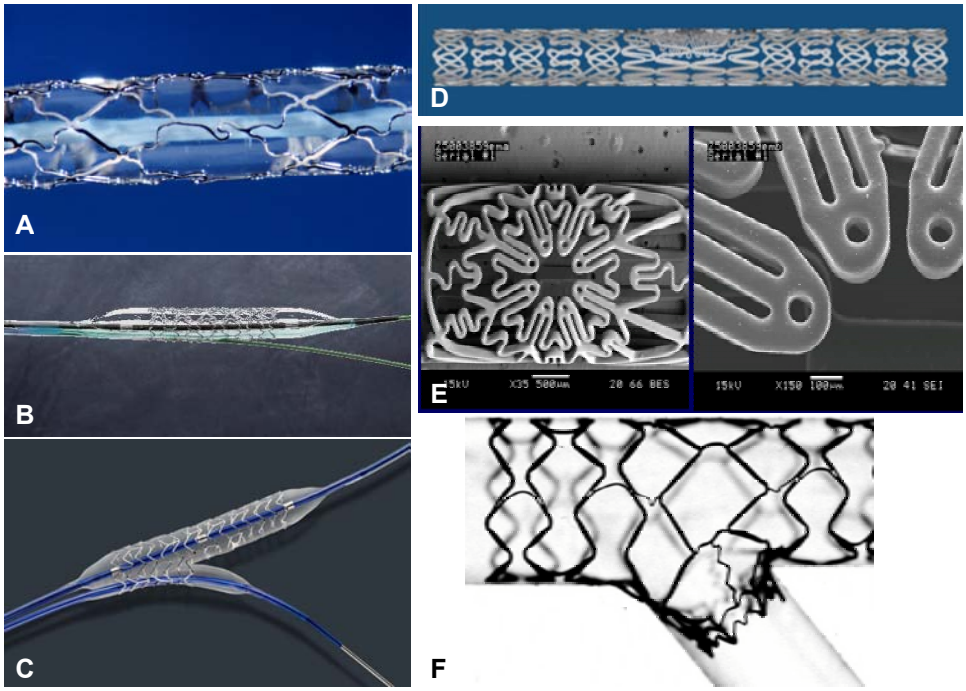
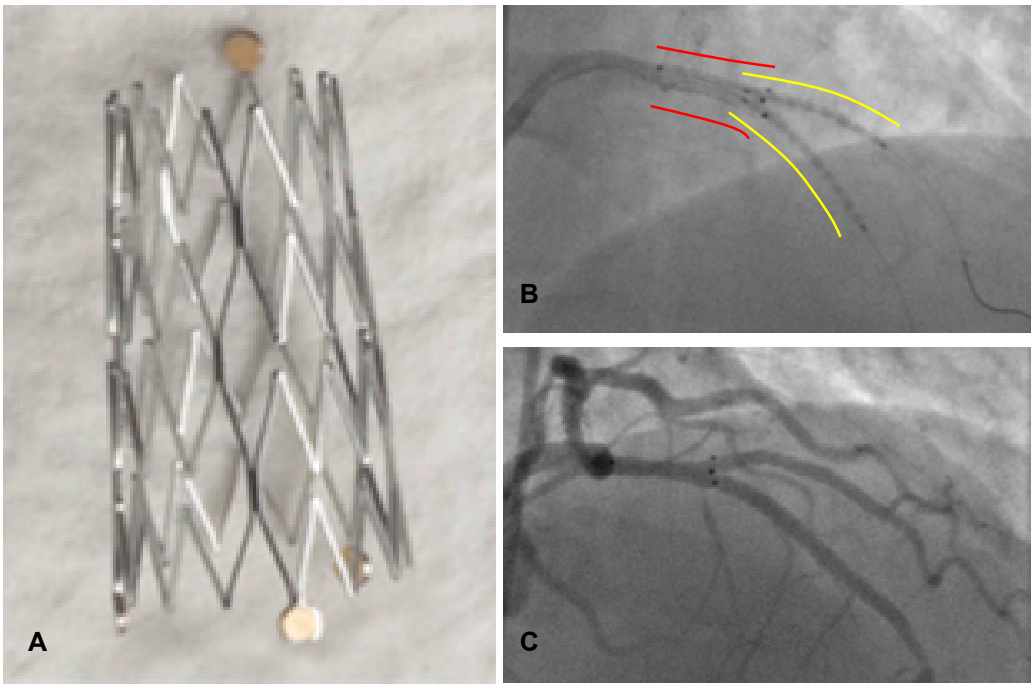


Figure 10: The Devax Axxess Stent (Devax, California) is a self-expanding, flared nitinol-based stent. It is implanted in the main vessel right to the carina (figure 10B, red line); it allows for access to both the distal branches so that additional stent(s) can be implanted in the branches as needed (yellow lines). The markers demonstrate that the stent has covered the carina and the ostia of both branches (figure 10C).



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Chapter 13

New approaches to ostial and bifurcation lesions

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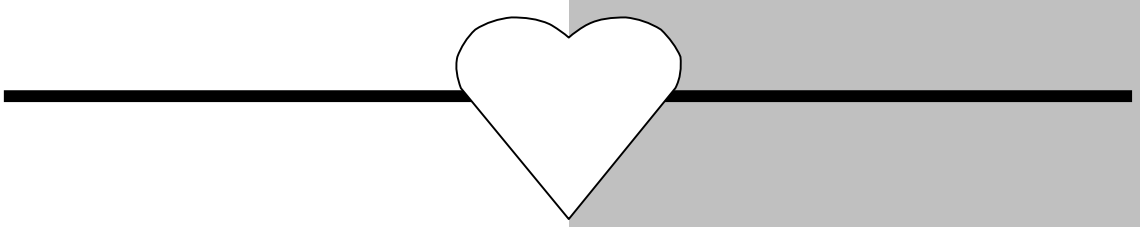
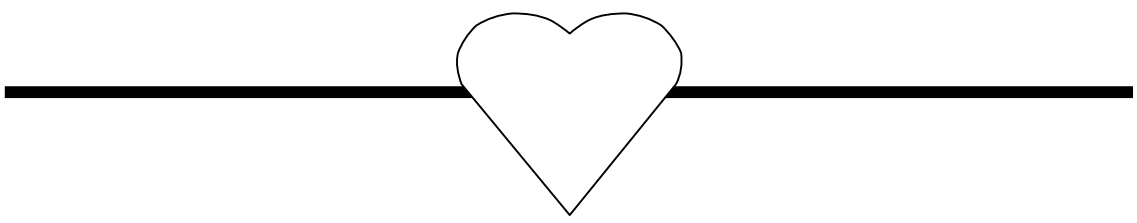
Journal of Interventional Cardiology
2004;17(6):397-403



Abstract

Percutaneous coronary intervention of bifurcation lesions is associated with lower procedural success rates, and an increased subsequent rate of major adverse cardiac events and restenosis. Currently, an array of stenting possibilities suggests a rational approach to treat various bifurcation lesions with appropriate techniques. This is however seldom the case. The main problems of treating bifurcation lesions remain plaque shift leading to (threatened) side branch occlusion, and either too much or insufficient side branch ostial stent coverage predisposing to impaired side branch access or restenosis respectively. This paper reviews the available technologies and their relative merits.

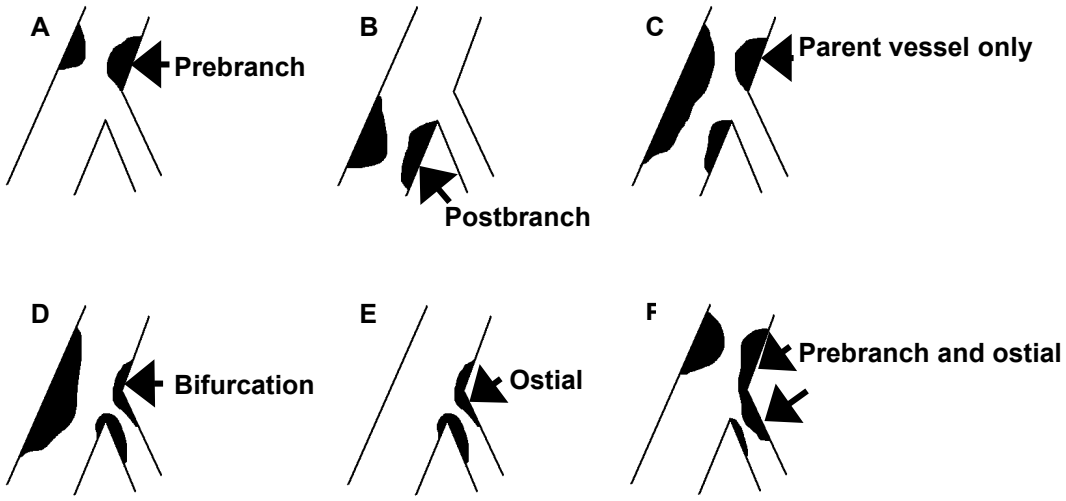


Introduction

Percutaneous coronary intervention of bifurcation lesions is associated with lower procedural success rates, [1] and an increased subsequent rate of major adverse cardiac events (MACE) and restenosis compared with non-bifurcated lesions. Various techniques and strategies have been applied in attempt to improve outcomes including double wire technique, kissing balloon pre- and post-dilatation, stent implantation in the main branch or both main and side branch by T-, Y-, culotte-, trousers-, skirt-, kissing stents-, crush-, or touching stents technique. [2-5] This array of stenting possibilities suggests a rational approach to treat various bifurcation lesions with appropriate techniques. This is however seldom the case. Usually new inventions are applied to most lesions in an attempt to treat bifurcations in general, and the most effective strategy for different anatomical variations is currently unknown. The present paper attempts to familiarize the reader with the successive technical advances available to the interventional community and discuss their successes and failures.

Coronary bifurcation anatomy

Lesions at a coronary bifurcation may involve either the main vessel alone, and / or the ostium of a side branch. A classical scheme to categorize coronary bifurcation lesions is the Duke classification (figure 1 below):



However, even when only one of the two branches is significantly stenosed at baseline, plaque shift or the "snow-plough effect" can pose a problem. Following balloon dilatation or stent implantation, shift of atheromatous material may occur proximally, longitudinally, and/or circumferentially. [6] When treating the main vessel, such shift of material can lead to side branch occlusion particularly when the ostium of the side branch is itself diseased, the side branch is of relatively small diameter, or in the presence of thrombus in acute coronary syndromes. The clinical consequences of loss of the side branch are dependant on the vessel size, and are not usually serious with short-lived chest pain and only a modest rise in cardiac enzymes. In addition, follow-up evaluation, frequently demonstrates restoration of patency. [7] However, following PCI, a more than three-fold rise in cardiac enzymes above the upper limit of normal has been shown to have prognostic implications. [8] In the NIRVANA study of the NIR stent implanted across a side branch, side branch occlusion occurred in 4.7% patients. Of these, occlusion was associated with acute myocardial infarction (creatine-kinase-MB ≥5x normal) in 40%, including Q-wave infarction in 7%. [9]

Balloon angioplasty

In the 1980's, the majority of patients with a bifurcation lesion were referred for coronary artery bypass surgery. However, in those who were treated with percutaneous intervention, following identification of the problems associated with plaque shift, kissing balloon dilatation became the technique of choice. [10,11] The major limitation of balloon only angioplasty was the occurrence of acute recoil and vessel closure, and subsequent restenosis. Technical advances in the 1990's, led to the evaluation of debulking techniques and scaffolding of the vessel(s) with stent implantation.

Adjunctive atherectomy

Debulking with the use of adjunctive atherectomy might potentially be advantageous over balloon-alone angioplasty through removal of plaque and prevention of plaque shift. However, results from the randomized CAVEAT I trial (atherectomy versus PTCA) were not encouraging. [12] Although there was an improved initial angiographic result with less residual stenosis, this was at the expense of a higher rate of side branch occlusion and acute myocardial infarction. In the long-term, there was no difference in the incidence of death, myocardial infarction or restenosis.

The use of atherectomy prior to stenting has been assessed in 3 studies with some suggestion that atherectomy might reduce the subsequent need for TLR though with an increased rate of procedural complications. However, none were randomized, and it's therefore difficult to make any firm conclusions. [13-15]

Stent implantation: bare metal stents

The use of stents provides a scaffold to reduce the risk of recoil and acute vessel closure. However, long-term results have been hampered by the excessive development of neointimal hyperplasia. Following bare stent implantation, restenosis is known to be inversely related to the stent diameter, and this can be of particular importance in the therapy of bifurcation lesions where the side branch vessel diameter is often ≤2.5mm. In addition, even though the side branch may not appear stenosed at baseline, simply stenting the main vessel may compromise side branch flow through a combination of pinching by the stent struts and plaque shift. It was thought therefore that stenting of the side branch might be advantageous. Immediate angiographic results following stent implantation of both the main vessel and side branch are gratifying. However, studies (albeit non-randomized), have shown that this strategy does not reduce the subsequent rate of MACE, [16] and is associated with a trend towards a higher rate of restenosis compared to the utilization of a single stent strategy. [17,18] Even with precise stent positioning, such a T-stenting strategy is frequently limited as the angle between the branches for the majority of bifurcations is significantly <90˚. (Figure 2). This means that either the ostium of the side branch is incompletely covered (figure 2A), or the side branch stent protrudes into the main vessel (figure 2B).

The culotte technique ensures complete coverage of the disease, but leads to a high concentration of metal with a double stent layer at the carina and in the proximal part of the bifurcation. In addition, crossing of the struts with a guidewire / balloon may, at times, be difficult. The technique can be time-consuming and fell out of favour, in one study of 50 patients, though the target vessel revascularization rate was 24%, of the 25 patients with follow-up angiography, restenosis was demonstrated in 14 (56%). [19] Furthermore, an observational study demonstrated a significantly higher rate of MACE at 1-year following Culotte versus T-stenting (86.3% versus 30.4%, p=0.004). [16]

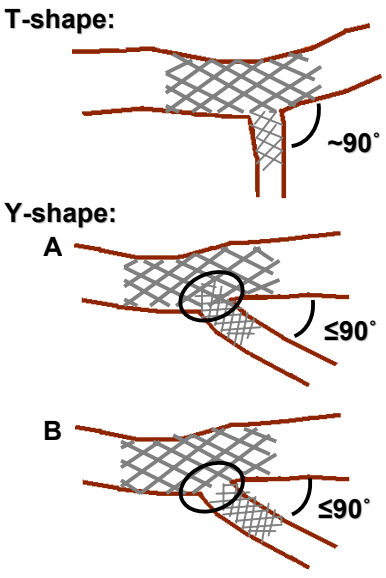


Figure 2: Complete lesion coverage can be obtained with precise stent positioning so long as the angle between the branches nears 90˚. The majority of bifurcations however are more of a "Y" formation. Attempts to use T-stenting will either leave an area at the side branch ostium uncovered by stent **(A)** or part of the side branch stent will protrude into the main vessel **(B).**

Dedicated stents

Several stents have been specifically designed for bifurcations with particular emphasis on maintaining ease of access to the side branch. The JoStent is designed with an eight-cell mesh at either end, and only 4 cells in the middle potentially improving side branch access (figure 3A). [20] The Devax Access Stent is a self-expanding, flared stent to allow for better access to bifurcation lesions. Additional stents are needed to treat the main branch and the side branch. Other specialized bifurcation stent designs incorporate a double balloon system (figure 3B, C). Most available data are in the form of case reports or registries.

The ML Frontier™ stent consists of a balloon expandable stainless steel stent mounted on a delivery system with two balloons and two guide wire lumens designed to maintain wire access to the side-branch vessel during stent deployment. The advantages of this design are that guide wire crossing is avoided and side branch access is maintained during the whole procedure. This two-balloon, two-wire system requires a 7F-guiding catheter. Evaluation of this device was carried out in 105 patients treated at 11 international sites (data presented by T. Lefèvre at TCT 2003). The ML Frontier ™ stent was successfully implanted in 96/105 patients, with the LAD/diagonal bifurcation as the target in 80% of cases. Acute device success by quantitative coronary angiography was 92%. Two patients had in-hospital myocardial infarction secondary to side branch occlusion (1 Q-wave and 1 non-Q-wave MI), and one patient underwent planned in-hospital CABG after PCI failure. No other MACE was observed during the 30-day clinical follow-up. At 180 days, the MACE rate was 17.1% (no death; Q-wave-MI: 1.9%; non-Q-wave-MI: 1.9%; TLR: 13.3%) and the main branch in-stent and in-segment binary restenosis rates were 25.3% and 29.9% respectively. These results are certainly comparable with best results obtained utilizing conventional bare metal stents (see table).

The DBS stent (Cordis) has been evaluated in a multicenter study of 34 patients. Procedural success was achieved in 94% with, at 6 months, a restenosis rate of 33% and TLR rate of 19%. [21] Other bifurcation stent devices have also been developed and some data exists in the form of case reports. The Bard-XT Carina stent is pre-mounted on 2 balloons which connect to a single shaft and are simultaneously deployed with a single indeflator (figure 4). [22] The AVE bifurcation stent is similarly delivered using the Bard delivery system. The AST SLK-View™ stent has an aperture in the middle segment of the stent to allow access to the side branch using a guiding tube. In an initial study of 8 patients, the stent was successfully delivered in all but one, with no adverse clinical events at 1 month. [23] The Invatec bifurcation stent has either a single or double balloon stent delivery system. The single balloon system is similar to the AST system mentioned above. The double balloon system is more like the ML Frontier™ stent except that the side branch balloon is a full dilatation balloon (but only 1.5 mm diameter) to be used for the kissing technique whereas the ML Frontier™ stent has a short tapered side branch balloon to allow for side branch access and the physicians choice in treating the side branch or not.

Especially the double balloon stent systems have a higher profile and are less flexible than the other designs. That means that, in particular, in calcified coronaries their optimal deployment may be less successful. [24]

Table: Comparative Data of Bifurcation Stenting Studies

Study		N	In-hosp MACE	6-Month RR	6-Month TLR (total)	6-Month MACE (total)
Lefevre [3]	Period 1	182	5.1	-	20.6	29.2
	Period 2	191	4.2	-	13.8	17.1
Yamashita [18]	2 stents	53	13	62	38	51
	1 Stent	39	0	48	36	38
Colombo [27]	2 stents	63	9.5	28	9.5	19
	1 Stent	22	9.1	18.7	4.5	13.6
Frontier (*Eur Heart J* 2004;25 (Abstract Suppl): 309)		105	2.7	44.8	13.3	17.1

Unless indicated, all parameters presented as percent of patients

RR=Restenosis Rate >50% binary restenosis rate

Figure 3: Illustration of different stent types designed for side-branch access or bifurcation treatment. **A:** The middle section of the Jostent has fewer and larger cells to allowfor easier side-branch access. **B:** The early BARD side-branch stent carrying a side-branch wire crimped under the proximal main branch stent half. **C:** The ML Frontier has a main branch balloon holding the distal stent and a side-branch balloon for ostial protection that contains the OTW side-branch guide wire. **D:** The AVE bifurcated stent that was built on the former BARD platform. This stent has been implanted in but a few patients.

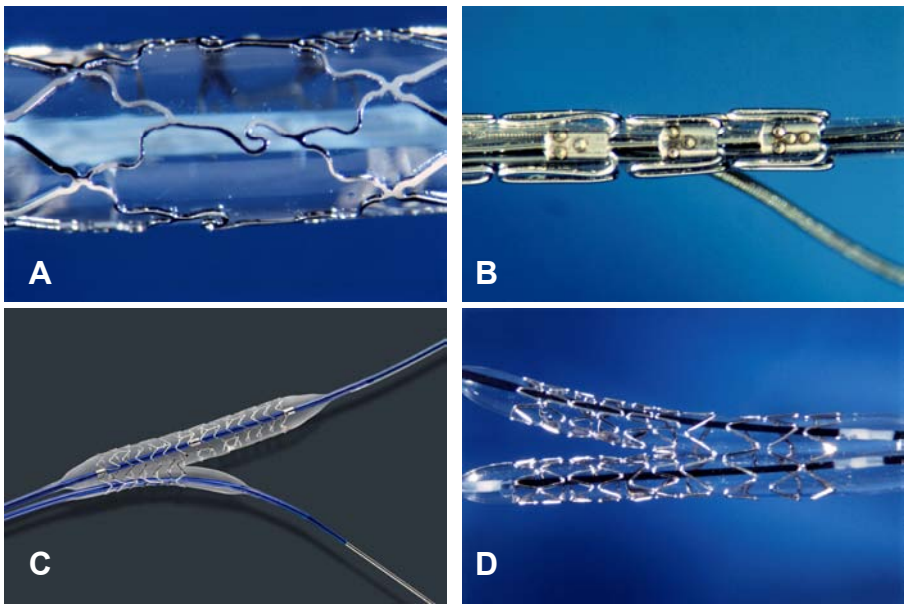
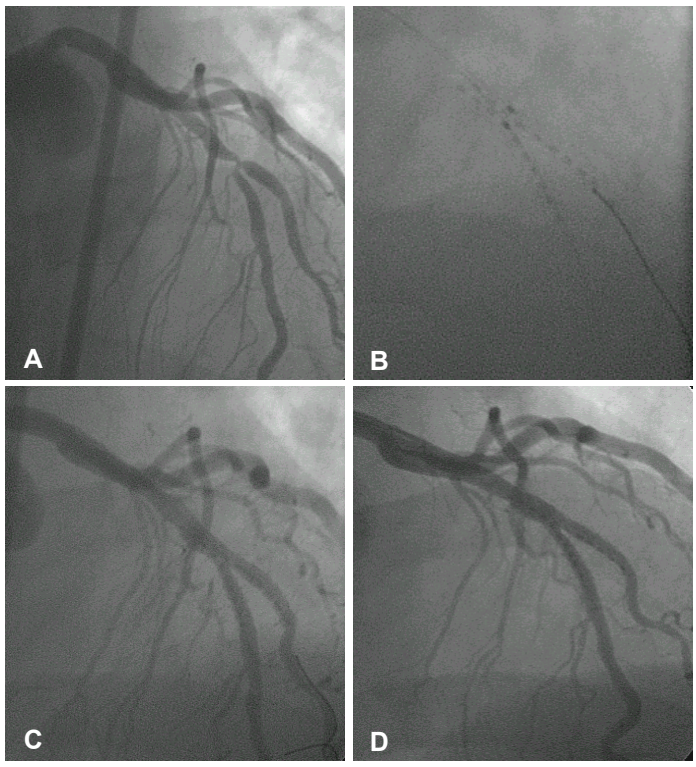


Figure 4: Clinical implantation of one of the very first bifurcated stents in a 47-year-old patient in 1997. [31] **A:** LAD/diagonal type-D bifurcation lesion at baseline. **B:** Positioning of the bifurcated stent at the carina after prior predilatation. **C:** Acute angiographic result. **D:** At 6-months follow-up the bifurcation still demonstrates nice patency. At 6-years clinical follow-up she was free of symptoms, and working full time.



Stent implantation: drug-eluting stents

Both the sirolimus- and paclitaxel-eluting stents have demonstrated significantly reduced rates of restenosis compared with bare metal stents, though bifurcation lesions were excluded from initial randomised studies. [25,26] Preliminary data of the sirolimus-eluting stent (SES) for bifurcation lesions has recently become available, and has confirmed efficacy when compared with historical data with overall rates of restenosis of 23-26%, and need for target lesion revascularization in 8-9%. [27,28] One of these studies randomized patients to either a strategy of using a single SES versus two stents and found that restenosis rates were similar between the two groups (19% for provisional side-branch stenting versus 28% for double-stenting). However, there was notably a high rate of crossover to the 2 stent strategy of 51%. [27] In an observational study of the sirolimus-eluting stent in a consecutive group of patients, restenosis occurred particularly at the ostium of the side branch following the use of T-stenting. [28] This might reflect incomplete coverage of the ostium thereby reducing the efficacy of the drug-elution, and suggesting that it may be beneficial when using these stents to adopt a strategy that ensures complete coverage. Colombo et al first reported the crush technique utilizing SES in 2003, as a technically straightforward method that ensures complete coverage of the side branch ostium. [29] Of 20 patients, an in-hospital adverse event occurred in 3 (2 myocardial infarctions, one re-PTCA related to dissection of the main vessel distal to the bifurcation), with no further events at 1 month. In particular there were no episodes of stent thrombosis. Further angiographic data on the subsequent rates of restenosis with this technique are pending.

General principles

Angiography must adequately evaluate the bifurcation, in particular whether the side branch ostium is involved or not. The use of two wires is a simple method to ensure that access to each branch is preserved throughout the intervention. In general the use of pre-dilatation is recommended, and has the advantage of assessing how the lesion behaves with evaluation of any plaque shift, and facilitation of subsequent stent implantation. The major drawback however, is the risk of dissection, or distal embolization particularly of thrombotic material in acute coronary syndromes. Whatever the stenting strategy chosen, post-dilatation with kissing balloon dilatation is strongly recommended particularly when both branches are stented. Though not detectable on angiography, stent deformation may occur whatever the technique utilized, and is corrected with kissing balloons. [30]

Ostial lesions represent a specific subset of bifurcations (Duke classification E). Although it may be attractive to simply stent the side branch, plaque shift into the main vessel may pose a problem, and the use of two wires is to be recommended to protect access to the other vessel. In addition, as with most bifurcations, the angle at the carina is not usually 90˚, so even with precise stent positioning either the disease is not entirely covered, or some stent struts protrude into the main vessel.

Discussion

Bifurcation lesions still present a challenge to the interventional cardiologist, with no clear data on the most effective strategy during PCI. Thus far, the majority of published studies do not take into account the wide anatomical variability, and although there is a clear difference between a “true bifurcation” with disease involving both branches, and involvement of only one of the branches, the unpredictable nature of plaque shift makes the development of hard and fast guidelines more difficult.

The inherent heterogeneity of lesions included in such studies, together with the lack of randomization, means that any comparison between different strategies / stent types should be made with some caution. However, through a reduction in restenosis, drug-eluting stents are certainly having a dramatic impact on the practice of interventional cardiology, and efficacy certainly appears to be applicable for the treatment of bifurcations (see table). However, restenosis at the side branch ostium can be a problem following T-stenting, and alternative strategies such as the crush or culotte technique automatically lead to a region of a double / triple layer of stent. This increased local dosage of drug could be potentially harmful with delayed re-endothelialization. In addition, both techniques involve the need to cross stent struts with a guidewire. Dedicated bifurcation stent systems can be bulky to implant and are, as yet, bare and subject to not

insignificant rates of restenosis. However, maintenance of side branch access is improved, and the need for several stent layers is avoided.

The introduction of drug-eluting stents means that new randomized studies are needed to define guidelines for PCI strategy in the modern era. These studies need also to better evaluate the best technique of stent implantation particularly with respect to anatomical variations. In addition, there may be a role for dedicated bifurcation stents designed with the capability of drug-elution. These may be able to provide adequate scaffolding with preservation of side branch access while avoiding double / triple layer of stent struts. In addition, future stent designs may even allow for targeted anti-restenotic drug elution, with delivery of variable drug dosage dependent on the risk of restenosis in different localities.

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Chapter 14

Restenosis Rates Following Bifurcation Stenting with Sirolimus-Eluting Stents for De Novo Narrowings

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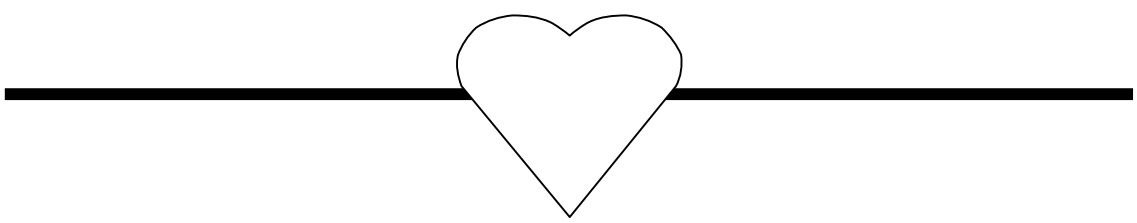
American Journal
Of Cardiology
2004;94(1):115-8

Abstract

The percutaneous treatment of coronary bifurcation stenoses is hampered by an increased rate of subsequent restenosis. The present study reports on the outcomes of a consecutive series of 58 patients with 65 de novo bifurcation stenoses treated with sirolimus-eluting stent implantation in both the main vessel and side branch. At 6 months, the incidence of major adverse cardiac events was 10.3% (1 death and 5 target lesion revascularizations) with no episodes of acute myocardial infarction or stent thrombosis.



Percutaneous coronary intervention of bifurcation lesions is associated with lower procedural success rates [1] and an increased subsequent rate of major adverse cardiac events (MACEs) and restenosis. Various techniques and strategies have been applied in an attempt to improve outcomes, including kissing balloon dilatation and the use of stent implantation in both branches. [2] The use of adjunctive atherectomy was found to be disadvantageous in the Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT-I) trial. [3] Although there was an improved initial angiographic result with less residual stenosis, this was at the expense of a higher rate of side branch occlusion and acute myocardial infarction. In the long-term, results of angioplasty in bifurcations have been hampered by problems of restenosis, particularly after stent implantation within the side branch. [4,5] Recently, sirolimus-eluting stents (SESs) have demonstrated dramatically reduced restenosis rates in patients with relatively simple lesions. [6,7] We sought to investigate the safety and efficacy of SESs in a consecutive series of unselected patients with de novo bifurcation lesions enrolled in the Rapamycin-Eluting Stent Evaluation At Rotterdam Cardiology Hospital (RESEARCH) registry. [8]

Since April 2002, SES implantation (Cypher, Johnson & Johnson–Cordis, Miami, Florida) has been used as the default strategy for all patients treated in our institution, as part of the RESEARCH registry. [8] Briefly, this single-center registry aims to evaluate the efficacy of SES implantation in the "real world" of interventional cardiology. All consecutive patients were enrolled, irrespective of clinical presentation and lesion characteristics, and the incidence of MACEs was prospectively evaluated during follow-up. At 6 months, a total of 563 consecutive patients were treated solely with SESs. Of these, 58 patients (10.3%) with de novo bifurcation lesions were treated with SES implantation in both the main and side branches; these patients comprise the present study population. The patients' informed written consent was obtained in accordance with the rules of the institutional ethics committee, which approved the study.

All procedures were performed with standard interventional techniques, except with the use of the SES as the device of choice. The strategy of bifurcation stenting employed and the use of kissing balloon dilatation after procedure was at the operators' discretion. One of 4 methods of stenting was used: T-stenting, culotte stenting, kissing stents, or the "crush" technique. T-stenting and culotte stenting have been previously described. [5,9] Kissing stents involved simultaneous implantation of the stents within both branches, with the proximal edges alongside each other, thereby bringing forward the point of divergence. The crush technique involves positioning both stents, with the proximal part of the side branch stent lying well within the main vessel, while ensuring that the edge of the stent in the main vessel is more proximal than the side branch stent. The side branch stent is deployed first, and the balloon and wire are carefully withdrawn. The main vessel stent is then deployed, thereby crushing the proximal part of the side branch stent. [10] SESs were available in diameters from 2.25 to 3.00 mm and lengths from 8 to 33 mm. During the procedure, intravenous heparin was given to maintain an activated clotting time of ≥250 seconds. All patients were prescribed lifelong aspirin and clopidogrel for 6 months. The use of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator.

Clinical and angiographic follow-up was performed at 6 months. MACEs were predefined as death, myocardial infarction, or target lesion revascularization. The diagnosis of myocardial infarction required an elevation of creatine kinase levels to twice the upper limit of normal, together with an increase in the creatine kinase-MB fraction. Target lesion revascularization was defined as either surgical or percutaneous reintervention driven by significant (>50%) luminal diameter narrowing either within the stent or the 5-mm borders proximal and distal to the stent, and was undertaken in the presence of either anginal symptoms or objective evidence of ischemia.

Coronary angiograms were obtained in multiple views after intracoronary injection of nitrates. For the main branches, 3 coronary segments were subjected to quantitative angiography: in-stent, proximal edge, and distal edge segment. The in-stent analysis encompassed the length of all stents used during the procedure. The proximal and distal edge segment included up to 5 mm from the proximal and distal edge of the total segment treated with the study stents, respectively. For the side branches, 2 segments were analyzed: in-stent and distal edge 5-mm segment. Quantitative coronary angiographic (QCA) analysis was performed using the Cardiovascular Angiography Analysis System II (CAAS II; Pie Medical, Maastricht, The Netherlands). The reference vessel diameter, minimal lumen diameter, and percent diameter stenosis were measured before and after the procedure and at follow-up. The late loss was calculated as the difference between the minimal lumen

diameter after the procedure and that at follow-up. Binary restenosis was defined as the presence of >50% diameter stenosis within the target lesion.

Fifty-eight patients with 65 bifurcation lesions were included in this study. Baseline patient characteristics are listed in Table 1. The lesion characteristics and stenting technique utilized are presented in Table 2. At 6 months, the survival-free of MACEs was 89.7%. One patient died after bifurcation stent implantation of the left main stem for an acute myocardial infarction. This patient was admitted in cardiogenic shock, and despite the use of abciximab and intra-aortic balloon pump support, died shortly after the procedure due to left ventricular failure. There were no episodes of acute or subacute stent thrombosis, and no patient had a myocardial infarction. Target lesion revascularization was undertaken in 5 patients (8.6%) as outlined in the following.

Table 1: Baseline Clinical Characteristics (n=58)

Age (yrs)		63 ± 10
Men		42 (72%)
Hypertension		26 (45%)
Hypercholesterolemia		35 (60%)
Diabetes Mellitus		16 (28%)
Current smoker		16 (28%)
Previous myocardial infarction		22 (38%)
Previous coronary angioplasty		5 (9%)
Previous coronary artery bypass surgery		3 (5%)
No. of coronary arteries significantly narrowed	1	15 (26%)
	2	28 (48%)
	3	15 (26%)
Presentation with an acute coronary syndrome		18 (31%)

Values are presented as the numbers (relative percentages) or mean value ± SD.

Table 2: Lesion and Procedural Characteristics (number of lesions = 65)

Coronary artery treated with bifurcation stenting	Left anterior descending / diagonal	39 60%)
	Left circumflex / obtuse marginal	16 (25%)
	Right coronary / posterior descending	4 (6%)
	Left main stem – left anterior descending / circumflex	6 (9%)
Stenting technique	T-stenting	41 (63%)
	Culotte stenting	5 (8%)
	Kissing stenting	2 (3%)
	Crush stenting	17 (26%)
Kissing balloon dilatation after stenting		20 (31%)
Glycoprotein IIb/IIIa inhibitor use		20 (31%)

Values are presented as the numbers (relative percentages).

Of 65 lesions, 6-month angiographic follow-up was performed in 44 lesions. The binary restenosis rate was 22.7% (10 of 44 lesions). QCA data are presented in Table 3. Angiographic restenosis occurred in 4 lesions within the main branch (1 in the proximal segment; 3 in the in-stent segment), yielding a restenosis rate of

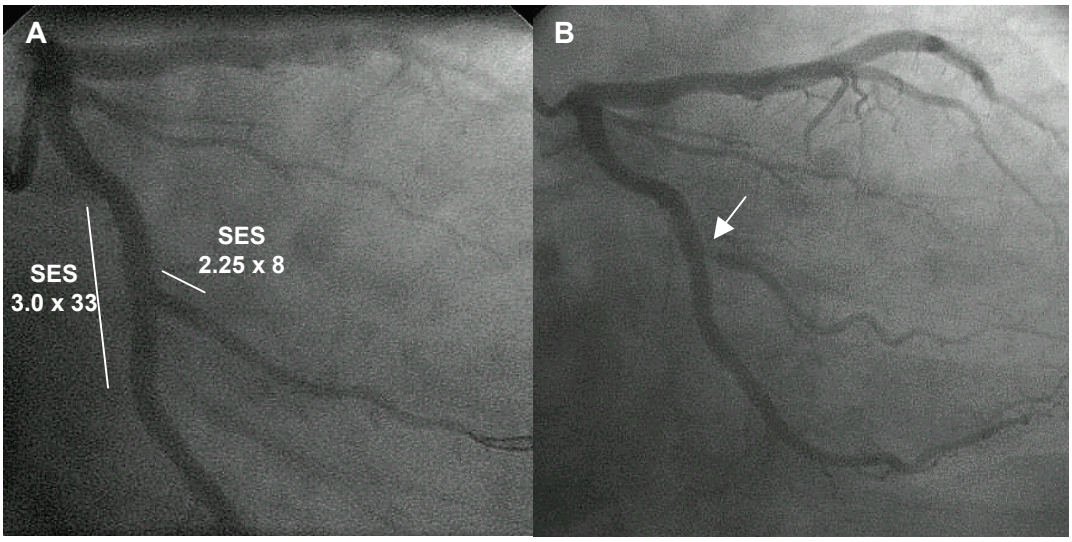
9.1%. Angiographic restenosis occurred in 6 of the side branches, all within the in-stent segment. Of these 6 restenoses, 5 occurred at the ostium of side branch after the use of T-stenting (Figure 1). All 4 patients with a restenosis within the main vessel and 1 patient with a restenosis at the ostium of a side branch underwent percutaneous target lesion revascularization with new drug-eluting stent implantation. Directional coronary atherectomy was additionally used in 1 patient. The remaining 5 patients, all with ostial side branch restenoses, were asymptomatic and treated with medical therapy alone.

Table 3: Quantitative Coronary Angiography

		Proximal Segment	In-stent Segment	Distal Segment
Main branch (n=44)				
Reference diameter (mm)		N/A	2.64	N/A
Minimal lumen diameter (mm)	Preprocedure	N/A	0.64	N/A
	Post-procedure	2.39	2.19	1.86
	6-mo follow-up	2.26	2.07	1.85
Diameter stenosis at 6 mo (%)		28.3	22.9	25.4
Late lumen loss (mm)		0.12	0.12	0.01
Restenosis rate (%)		2.3	6.8	0
Side branch (n=44)				
Reference diameter (mm)			1.99	N/A
Minimal lumen diameter (mm)	Preprocedure		0.61	N/A
	Post-procedure		1.80	1.57
	6-mo follow-up		1.49	1.47
Diameter stenosis at 6 mo (%)			31.0	21.9
Late lumen loss (mm)			0.31	0.09
Restenosis rate (%)			13.6	0

Values are presented as mean values or relative percentages.

Figure 1: A 3.0 × 33 mm SES was implanted in the circumflex artery, and a 2.25 × 8 mm SES was implanted in the side branch (obtuse marginal) with T-stenting technique **(A).** At 6-month angiographic follow-up, restenosis occurred at the ostium of the side branch *(arrowhead)* **(B).**



The major findings of this study of bifurcation stenting include the following. (1) SES implantation in both the main and side branches is feasible and associated with a low procedural complication rate and no episodes of stent thrombosis. (2) The target lesion revascularization rate of 8.6% is seemingly diminished compared with historical controls. (3) Angiographic restenosis rates of the main and side branches are 9.1% and 13.6%, respectively, with an overall restenosis rate of 22.7%. (4) Five of the 6 restenoses occurring in the side branch were located at the ostium after using the T-stenting technique.

Drug-eluting stent deployment in both vessels to treat bifurcation lesions may raise theoretical concerns that it could result in a propensity to stent thrombosis. When we treat bifurcation lesions with SESs using the culotte, kissing, or crush stenting techniques, there are some overlapping stent struts, where the higher concentration of sirolimus may induce endothelial function impairment and thus be associated with an increased rate of stent thrombosis. Although these stenting techniques were applied in 37% of the lesions treated, no stent thrombosis was reported during follow-up, implying that sirolimus has a wide safety margin.

Several strategies have been advocated to treat bifurcation lesions with percutaneous coronary intervention, such as deployment of stents in both vessels, stenting in 1 branch with balloon angioplasty in the other, and mechanical debulking. The published reports regarding the subsequent need for target lesion revascularization utilizing bare stents range from 17% to 53%; [5,11,12] thus, the rate of 8.6% in our study is very favorable. In addition, the rate observed in the present study may underestimate the true beneficial treatment effect of SES as explained in the following.

Five of the 6 restenoses in the side branch occurred at the ostium after T-stenting. When we apply T-stenting, stent positioning must be extremely accurate to ensure complete coverage of the side branch ostium. This is particularly difficult and/or impossible to achieve when the angle between the 2 branches is much <90°. Restenosis at this site may therefore be mainly a reflection of incomplete coverage. The restenosis rate in the side branch following T-stenting was 16.7% (5 of 30 lesions), whereas that following the other stent techniques was 7.1% (1 of 14 lesions). The present study is limited because the choice of strategy was nonrandomized, and there is no comparison with alternative strategies, such as the use of stent implantation in the main vessel alone, with balloon-only angioplasty of the side branch. In addition, the sample size was relatively small, and any difference between the different techniques was not statistically significant. However, our results suggest that it seems wise to ensure the complete coverage of the ostium with SESs using stenting techniques other than T-stenting. The crush technique is technically easier and quicker to do than a culotte, but further data with longer follow-up from a larger population are needed to fully determine the efficacy of these techniques.

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Chapter 15

Treatment of De Novo Bifurcation Lesions: Comparison of Sirolimus- and Paclitaxel-Eluting Stents

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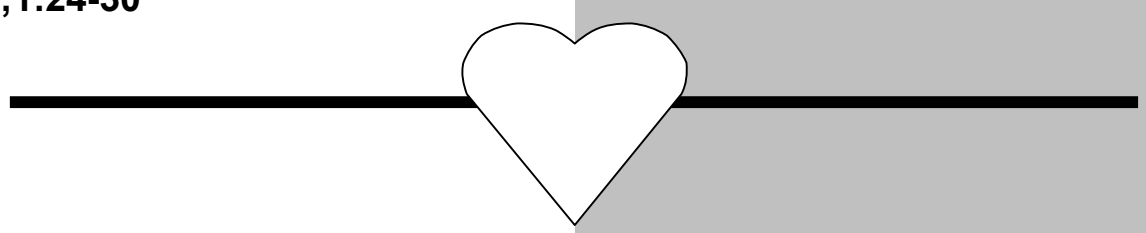
Eurointervention:
2005;1:24-30



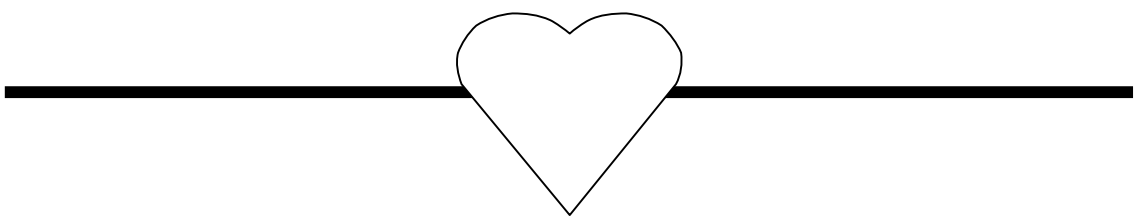
Abstract

Objective: Both the sirolimus-(SES) and paclitaxel-eluting (PES) stents have been shown to reduce restenosis rates when used in relatively simple lesions. This study aimed to evaluate the results of a consecutive series of patients treated with drug-eluting stent implantation for de novo bifurcation lesions, and compared outcomes with respect to stenting strategy and stent type.

Patients: From April 2002 to September 2003, all patients at our institution were treated with drug-eluting stent implantation. A consecutive series of 144 patients were treated for 167 de novo bifurcation lesions with SES, followed by 104 patients treated with PES for 113 lesions.

Results: Clinical follow-up at 9-months was obtained in 99% patients with survival-free of major adverse cardiac events (MACE) of 86.7% for SES versus 78.6% for PES, p=0.09. Independent predictors of MACE were diabetes mellitus, previous CABG, multivessel disease, and treatment for acute myocardial infarction. Survival-free of target lesion revascularization (TLR) was 90.9% for SES versus 81.6% for PES, p=0.03, with stent type being the only independent predictor. Technique of stenting was not a predictor of either MACE or TLR.

Conclusions: MACE rates for both the SES and PES are low compared with historical data of bare metal stents. The most effective techniques for bifurcation stenting remain undefined. Our data suggests a higher need for TLR for the PES compared with the SES, however further randomized studies are needed to fully evaluate both stenting strategy, and any difference between the stents.



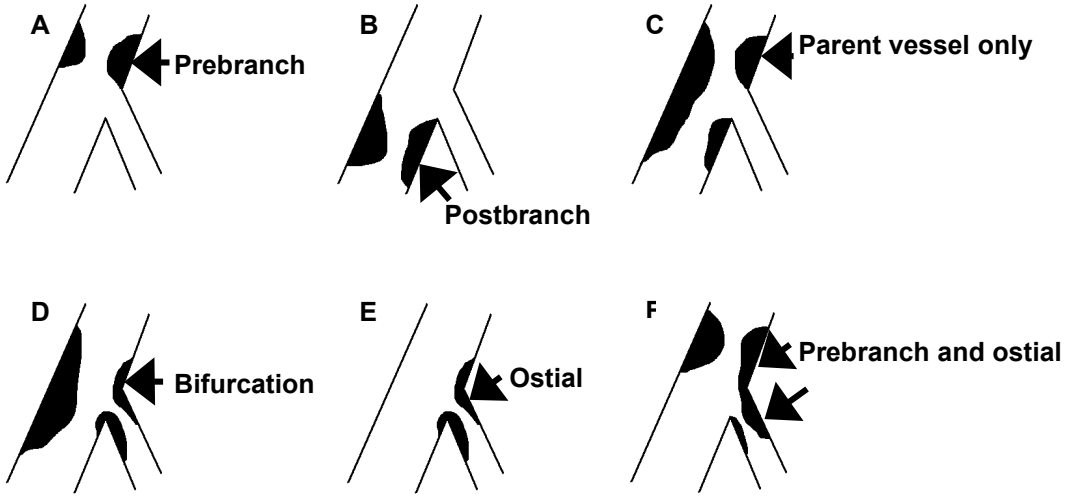
Introduction

The outcome of percutaneous therapy (PCI) of bifurcation lesions with bare metal stents is hindered by an increased rate of procedural complications, [1] and a high rate of restenosis particularly when both the main vessel and side branch are stented. [2-6] The advent of drug-eluting stents is revolutionising the practice of interventional cardiology by demonstrating a reduction in the subsequent rate of restenosis. There is evidence of efficacy in randomized trials for both the sirolimus- (SES) and paclitaxel-eluting (PES) stents for the treatment of relatively simple lesions. [7,8] In addition, the sirolimus-eluting stent for the treatment of bifurcation lesions has demonstrated a low rate of adverse cardiac events compared with historical data utilizing bare metal stents. [9,10] However, the most effective technique of stenting for bifurcation lesions with drug-eluting stents is currently unknown. In the present report we evaluate the rate of major adverse cardiac events following PCI for bifurcation lesions treated with either SESs or PESs in a consecutive series of patients. In addition, outcomes were assessed with respect to the baseline bifurcation anatomy and type of stenting strategy employed.

Methods

Bifurcation classification: All lesions were classified on baseline angiography according to the Duke classification (figure 1).

Figure 1: the Duke classification of bifurcation lesions



Procedure: The sirolimus-eluting stent (Cypher™, Johnson & Johnson - Cordis unit) received CE mark approval in April 2002. Since that time, all patients undergoing percutaneous therapy in our institution have been treated with drug-eluting stent implantation as the default strategy. During the first quarter of 2003, our strategy switched from the sirolimus- to the paclitaxel-eluting stent (Boston Scientific) enabling a comparison of the two stent types. All consecutive patients were enrolled irrespective of clinical presentation and lesion characteristics, and the incidence of major adverse cardiac events (MACE) was prospectively evaluated during the follow-up.

All procedures were performed with standard interventional techniques. The strategy of bifurcation stenting employed, and the use of kissing balloon dilatation post-procedure were at the operators' discretion. One of 6 methods of stenting was used: stenting of the main vessel with balloon-only angioplasty of the side branch; type A T-stenting (stenting first of the side branch, followed by stenting of the main vessel); type B T-stenting (stenting of the main vessel followed by stenting of the side branch because of a sub-optimal result); [2] the `crush` technique; [11] culotte stenting; [12] or kissing stents (simultaneous implantation in the main vessel and side branch with the proximal edges of the stents side by side). SESs were available in diameters from 2.25mm to 3.00mm and lengths from 8mm to 33mm. PESs were available in diameters from 2.25mm to 3.5mm and

lengths from 8mm to 32mm. During the procedure, intravenous heparin was given to maintain an activated clotting time ≥250 seconds. Patients were preloaded with 300mg clopidogrel, and received life-long aspirin together with 75mg clopidogrel per day for 6-months. The use of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. The protocol was approved by the Institutional 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

Follow-up: Clinical follow-up was obtained by investigators who were blinded to the PCI procedural details, using telephone calls and questionnaires. Follow-up evaluated the rate of major adverse cardiac events (MACE) which were pre-defined as death, acute myocardial infarction (AMI), or target vessel revascularization (TVR). The diagnosis of AMI required an elevation of creatine kinase levels to twice the upper limit of normal, together with a rise in creatine kinase-MB fraction. Target lesion revascularization was defined as either surgical or percutaneous reintervention driven by significant (>50%) luminal diameter narrowing either within the stent or the 5mm borders proximal and distal to the stent, and was undertaken in the presence of either anginal symptoms or objective evidence of ischemia. Target vessel revascularization was defined as revascularization within the target vessel including encompassing the target lesion. The definition of stent thrombosis was the presence of intra-stent thrombosis, with or without stent occlusion, documented on angiography, and was categorized as acute if occurring within 24 hours or subacute if within 30 days after stent implantation.

Statistical analysis: Discrete variables are presented as percentages and compared with Fisher exact test. Continuous variables are expressed as mean ± standard deviation and compared with Student's t test. Cumulative survival and MACE-free survival were calculated according to the Kaplan-Meier method. The log-rank test was used to compare MACE-free survival between the two groups. The variables shown in Tables 1 and 2 were tested in Cox regression modeling to identify the independent predictors of adverse events. Odds ratio with corresponding 95% confidence intervals are reported. All tests were two-tailed, and a p value of <0.05 was considered as significant.

Results

The baseline patient and procedural characteristics for the SES and PES cohorts are presented in tables 1 and 2 respectively. There were no significant differences between the 2 groups with respect to baseline patient characteristics, though there was a trend towards an increased usage of glycoprotein IIb/IIIa inhibitors in the PES group (38.5% versus 27.8% in the SES group, p=0.07). There was no significant difference in the number of stents used, however, the mean nominal diameter of stent used in the main vessel was greater with the PES (2.93 ± 0.34mm versus 2.85 ± 0.23 for the SES, p=0.007). For those patients treated with stent implantation in the side branch, though there was no significant difference in the number of stents used, the total length of stented segment in the side branch was longer for the PES-treated patients (18.8 ± 10.5mm versus 14.1 ± 7.6mm, p=0.0001). The choice of stenting strategy during the 2 treatment periods is presented in figure 2. The total number of lesions treated with each stenting technique was single stent utilization in 55 (19.6%), type A T-stenting in 47 (16.8%), type B T-stenting in 46 (16.4%), crush stenting in 88 (31.4%), culotte stenting in 24 (8.6%), and kissing stents in 20 (7.1%). There was no difference with respect to the use of kissing balloon post-dilatation between the SES and PES cohorts.

Clinical follow-up was obtained in 99.2% patients. Stent thrombosis occurred in 2 patients treated with SES (1.4%) and 3 patients treated with PES (2.9%), p=0.4. The demographics of these patients are in table 3. All episodes of stent thrombosis were subacute (within 30 days following stent implantation), and were treated percutaneously with kissing balloon dilatation and administration of a glycoprotein IIb/IIIa inhibitor. The only independent predictor for stent thrombosis was therapy for AMI (HR 9.4; 95% CI 1.57 to 56.21, p=0.01).

Table 1: Baseline patient demographics

	SES n=144	PES n=104	p value
Mean age (years)	62.4 ± 10.5	60.3 ± 11.8	0.1
Male sex (%)	74.3	73.1	1
Current smoker (%)	27.1	27.9	1
Diabetes mellitus (%)	18.8	17.3	1
Hypertension (%)	43.1	46.2	0.7
Hypercholesterolemia (%)	56.9	62.5	0.3
Previous myocardial infarction (%)	35.4	38.5	0.2
Previous CABG (%)	4.9	3.8	0.9
Clinical presentation			0.4
Stable angina (%)	65.3	67.3	
Unstable angina (%)	21.5	17.3	
Acute ST-elevation myocardial infarction (%)	13.2	16.3	
Glycoprotein IIb/IIIa inhibitor usage (%)	27.8	38.5	0.07
PCI in at least one additional major epicardial vessel during the index procedure (%)	40.3	39.4	1

Table 2: Baseline procedural characteristics

Total number of bifurcation lesions treated	**SES 167**	**PES 113**	**p value**
Target vessel			0.3
LAD / diagonal (%)	61.1	56.6	
LCX / obtuse marginal (%)	19.2	17.7	
RCA bifurcation (%)	9.6	8.0	
LMS (%)	10.2	17.7	
Bifurcation classification			0.4
A (%)	4.8	3.5	
B (%)	7.2	5.3	
C (%)	8.4	6.2	
D (%)	17.5	20.4	
E (%)	8.4	3.5	
F (%)	44.0	50.4	
Total occlusion (TIMI 0 flow) (%)	9.6	10.6	
Pre-dilatation of main vessel (%)	59.3	54.0	0.4
Pre-dilatation of the side branch (%)	42.5	31.9	0.07
Pre-dilatation with kissing balloons (%)	15.0	13.3	0.9
Mean number of stents in the main vessel	1.56 ± 0.84	1.48 ± 0.67	0.4
Mean nominal diameter of stent in the main vessel (mm)	2.85 ± 0.23	2.93 ± 0.34	0.007
Mean total lengths of stent in the main vessel (mm)	30.4 ± 17.7	30.3 ± 17.8	1.0
Mean number of stents in side branch	1.11 ± 0.36	1.13 ± 0.39	0.8
Mean nominal diameter of stent in the side branch (mm)	2.53 ± 0.29	2.60 ± 0.35	0.06
Mean total lengths of stent in the side branch (mm)	14.1 ± 7.6	18.8 ± 10.5	0.0001
Nominal diameter of balloon in side branch for POBA	2.28 ± 0.44	2.19 ± 0.49	0.5
Post-dilatation with kissing balloons (%)	47.3	45.1	0.9

SES: sirolimus-eluting stents, PES: paclitaxel-eluting stents, LAD: left anterior descending artery, LCX: circumflex artery, RCA: right coronary artery, LMS: left main stem, POBA: plain old balloon angioplasty, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention

Figure 2: the type of stenting strategy employed for the sirolimus-eluting (SES) and paclitaxel-eluting stent (PES)

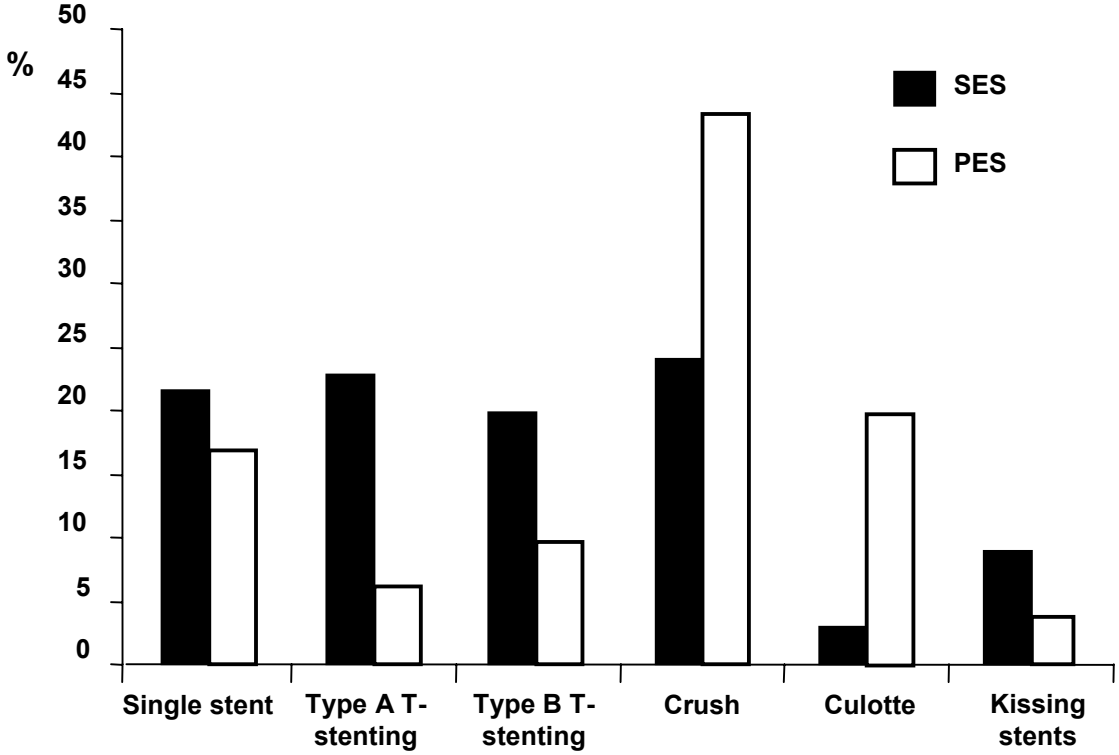


Figure 3: Kaplan-Meier curves for survival-free of major adverse cardiac events (MACE) for the sirolimus-eluting (SES) and paclitaxel-eluting stent (PES)

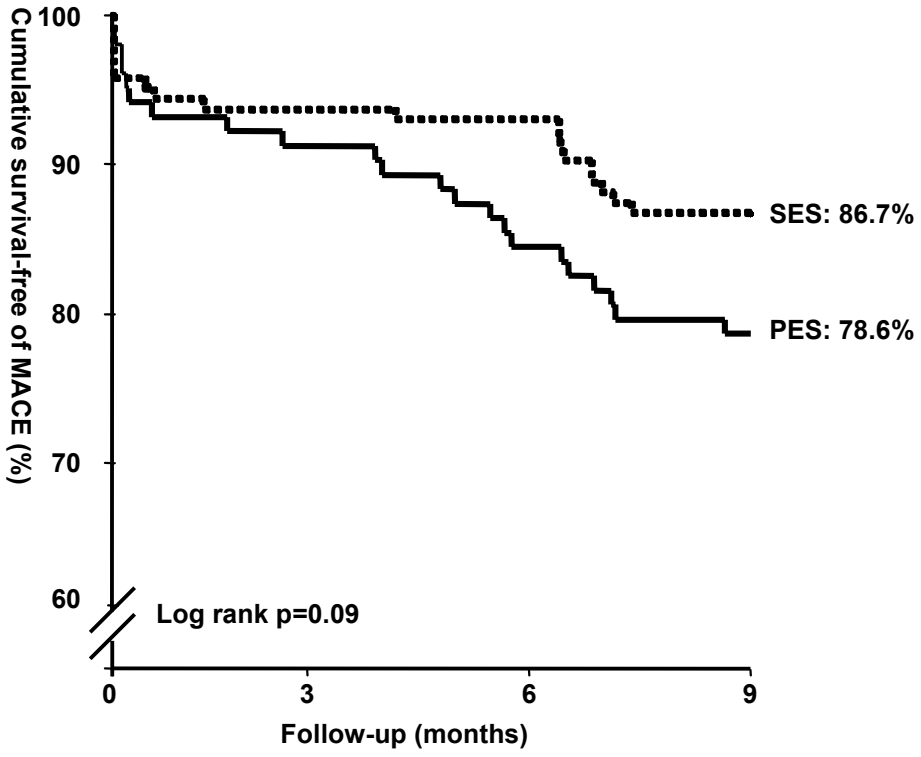


Table 3: Demographic data for the patients with subacute stent thrombosis

Pt. no	Age / sex	Stent type	Diabetes mellitus	Multivessel disease	Previous CABG	Target vessel	Index presentation	Index use of GP IIb/IIIa inhibitor	Stenting strategy	Kissing balloon dilatation	Time to thrombosis, days
1	74yr F	SES	N	Y	N	LAD	Stable angina	N	Crush	Y	1
2	57yr M	SES	Y	N	N	LAD	AMI	Y	Type A T-stenting	N	18
3	66yr M	PES	N	Y	N	LCx	Unstable angina	N	Crush	N	7
4	46yr F	PES	N	N	N	LAD	AMI	N	Type B T-stenting	N	6
5	51yr F	PES	N	Y	N	LCx	AMI	Y	Type A T-stenting	Y	4

The cumulative incidence of MACE at 9-months for the SES and PES groups are presented in table 4, and the survival-free of MACE at 9-months is illustrated in figure 3. The independent predictors for MACE and TLR are shown in table 5. The only factor found to be predictive for TLR was stent type. Neither the baseline bifurcation anatomy, nor the type of stenting strategy utilized, were predictive of events. At 9-months, survival-free of TLR was 90.9% for SES versus 81.6% for PES, p=0.03 (figure 4). TLR was for subacute thrombosis in 5 patients (see above), was for restenosis of the main vessel in 4 lesions treated with SES (2.4%) and 6 lesions treated with PES (5.3%), for restenosis of the side branch in 3 lesions treated with SES (1.8%) and 3 treated with PES (2.7%), and for restenosis of both branches in 2 lesions treated with SES (1.2%) and 2 treated with PES (1.8%).

Table 4: Cumulative incidence of major adverse cardiac events at 9-months for the sirolimus- and paclitaxel-eluting stents

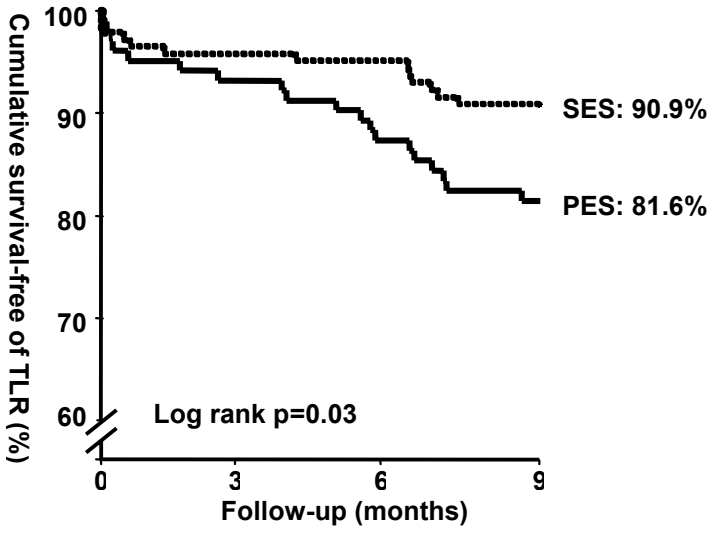
	SES n=144	PES n=104	p value (log rank)
Death (%)	2.8	4.8	0.4
Death or AMI (%)	6.2	11.4	0.2
Death, AMI, or TLR (%)	11.3	20.5	0.04
Death, AMI, or TVR (%)	13.3	21.4	0.09

SES: sirolimus-eluting stents, PES: paclitaxel-eluting stents, AMI: acute myocardial infarction, TLR: target lesion revascularization, TVR: target vessel revascularization

Table 5: Independent predictors of major adverse cardiac events and target lesion revascularization at 9-months

	Odds ratio	95% confidence intervals	p value
MACE			
Previous CABG	3.24	1.13 to 9.34	0.03
Multivessel disease	1.63	1.14 to 2.34	0.008
Diabetes mellitus	2.29	1.17 to 4.48	0.02
Presentation with acute myocardial infarction	2.85	1.31 to 6.24	0.009
TLR			
Therapy with sirolimus-eluting stent	0.35	0.14 to 0.84	0.02

Figure 4: Kaplan-Meier curves for survival-free of target lesion revascularization (TLR) for the sirolimus-eluting (SES) and paclitaxel-eluting stent (PES)



Discussion

In the present report we have demonstrated low rates of major adverse cardiac events at 6-months for both the sirolimus- and paclitaxel-eluting stents when used for the treatment of de novo bifurcation lesions. Independent predictors for MACE were previous CABG, diabetes mellitus, multivessel disease, and treatment for acute myocardial infarction. Target lesion revascularization at 9-months was higher in the PES group than the SES group, with a survival-free of TLR of 81.6% versus 90.9% respectively, p=0.03; stent type was the only independent predictor of TLR.

The most effective strategy for the treatment of bifurcation lesions with drug-eluting stents is currently unknown. In the present study, the choice of stenting strategy was at the operators' discretion. Previous data from our group following bifurcation stenting with the SES, demonstrated an overall restenosis rate of 23%. [9] The majority of restenoses of the side branch occurred at the ostium following T-stenting. Indeed, the restenosis rate in the side branch following T-stenting was 16.7% whilst that following other stenting techniques was 7.1%. We hypothesised that these restenoses might relate to inadequate / incomplete coverage of the ostium of the side branch thereby reducing the efficacy of the drug-eluting stent. This led to a shift away from a strategy of T-stenting, towards methods which ensure complete coverage – the crush and culotte techniques of stenting (figure 2). One potential disadvantage of these strategies however, is that they lead to an area of double or triple layer of stent struts raising theoretical concerns that the increased dosage of drug at this site might induce endothelial dysfunction and potentiate the risk of thrombosis. Despite the change in stenting technique in the present study, the choice of strategy was not an independent predictor for either MACE or the need for TLR, though interpretation is limited by the lack of randomization, and the relatively small number of patients in each treatment strategy group.

The SES has been evaluated in one randomized study of bifurcation stenting. [10] This randomized 85 patients to a single SES with balloon-angioplasty of the side branch, versus implantation of 2 SESs. The overall rate of restenosis at 6 months was 26% (19% in the single stent group versus 28% in the double stent group, p=NS). However, the study was limited by the high crossover rate with 51% of the patients in the single stent group crossing to the double stent group because of a suboptimal result in the side branch. In addition, the approach to stenting technique was not uniform. However, both this randomized study, and the registry data from our group [9] demonstrate an improvement in the restenosis rates compared with historical data of bare metal stenting. Despite a restenosis rate of 26%, the rate of TLR in the randomized study was just 8%, highlighting the fact that restenosis, particularly of the side branch, may not always cause symptoms. The current study is therefore limited by the lack of angiographic follow up, and cannot fully evaluate restenosis.

Restenosis following bare stent implantation is related to the length of stent, and inversely related to the diameter. [13] The majority of TLRs were for restenosis within the main vessel stent, yet the nominal stent diameter was actually bigger for the PES. This probably related to a larger available diameter of PES (3.5mm versus 3.0mm for the SES), and throughout the study, post-dilatation was carried out whenever necessary. The mean total length of stent used in the side branch of the PES group was significantly longer than the SES group. However, neither stent diameter nor length was an independent predictor for subsequent MACE or need for TLR.

Previous data of bare metal stent implantation in bifurcation lesions, demonstrate rates of target lesion revascularization of between 16% and 38%. [2-6] Compared with this historical data, in the current study, TLR was certainly lower for the SES (survival-free of TLR of 95.7% at 6 months). However, regression analysis demonstrated a significantly higher need for TLR following stenting with the PES compared with the SES, with the majority of TLRs in the main vessel. This might reflect a difference in the efficacy of the 2 drugs, at least at the current dosages, or relate to differences in stent design. [14] The SES is a closed-design stent whereby each cell is bound on all sides with the junction of each strut pair joined to another strut pair junction. The PES however, is an open-cell design meaning that some of the junction nodes are unattached within the stent structure. A previous of 54 patients undergoing elective stenting showed that platelet activation was lower in those receiving a closed versus open-cell designed stent. [15] The same authors examined stent implantation in the pig model and found that more tissue prolapse occurred following implantation of a stent with an open cell design. In the present study, though not significantly different between the 2 groups, subacute thrombosis did

occur in a higher percentage of the PES patients (2.9% versus 1.4%, p=0.4). A large randomized study would be needed to evaluate this. Importantly, the only independent predictor of stent thrombosis was bifurcation therapy for acute myocardial infarction. Further studies are needed to evaluate the most effective strategy of treating bifurcation lesions in the presence of such a high thrombotic environment, however, it would seem important in this situation to use an aggressive strategy of adjunctive medical therapy such as glycoprotein IIb/IIIa inhibition.

Both the SES and PES have been evaluated in large randomized studies and compared with their respective bare stents (Bx Velocity™ and Express™). [16,17] Though the inclusion criteria in these studies were not absolutely identical, both studies were very similar and included patients with stable or unstable angina and single de novo lesions; bifurcation lesions were excluded. Both the mean lesion length, and reference vessel diameter were similar. Evaluation of the angiographic follow-up of those treated with bare stents, showed a mean in-stent lumen loss of 1.00 ± 0.70mm in SIRIUS (Bx Velocity™), and 0.92 ± 0.58mm in TAXUS-IV (Express™). The higher late lumen loss in the Bx Velocity™ stent conflicts with the suggestion that the lower TLR rate with SES in the present study might relate to the difference in stent design. Both the SES and PES are covered by polymer coatings to facilitate drug-elution. Previous evaluation of other polymers has suggested that these can in themselves promote varying degrees of an inflammatory response and restenosis, [18] however, in the same randomized studies, evaluation of the drug-eluting stent cohorts showed excellent results suggesting safety of the polymers. The mean in-stent late loss was 0.17 ± 0.45mm in SIRIUS, and 0.39 ± 0.50mm in TAXUS-IV, this might perhaps suggest that the SES is more efficacious at inhibiting the development of neointimal hyperplasia than the PES, though the clinical importance of any difference is unclear.

Interpretation of the results of the present study with respect to stent type is limited by the lack of randomization. The REALITY study is a multicenter evaluation of more than 1000 patients with multivessel disease, randomized to either SES or PES implantation. Patients with bifurcation lesions were not excluded from this study. Recruitment is complete, and follow-up results are currently pending, but should provide further data as to whether there is a true difference in efficacy between the 2 stent types.

The most effective strategy for percutaneous therapy of bifurcation lesions with drug-eluting stents needs to be carefully evaluated in future studies. Interpretation of future randomized studies should take into account baseline anatomical differences of bifurcation lesions as the best strategy for a true bifurcation lesion (involving both the main vessel and side branch) may not necessarily be the same as that for lesions affecting only one of the branches. In addition, restenosis particularly at the side branch may not always lead to a recurrence in symptoms and follow-up angiography should be carried out to fully evaluate the results.

Study Limitations

The major limitations of this study are that it is a single centre registry and is non-randomized, with the choice of stenting strategy left entirely at the operators' discretion. In addition, routine angiographic follow-up data was not obtained, and additional restenoses giving rise to minimal / no symptoms, particularly at the ostium of the side branch, cannot be excluded. However, clinical follow-up data was available for >99% providing an accurate reflection of the rate of clinically important adverse events following therapy of bifurcation lesions in a consecutive series of patients without exclusion.

Conclusions

The use of both the sirolimus- and paclitaxel-eluting stents for the treatment of de novo bifurcation lesions appears feasible and safe, both demonstrating relatively low rates of major adverse cardiac events at 9-months. The increased rate of target lesion revascularization following PES implantation needs to be further evaluated in a randomized fashion, and at present, the most appropriate technique for bifurcation stenting remains unclear.

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Chapter 16

Long-term Outcomes Following Stenting of Bifurcation Lesions Utilizing the "Crush" Technique: Predictors of an Adverse Outcome

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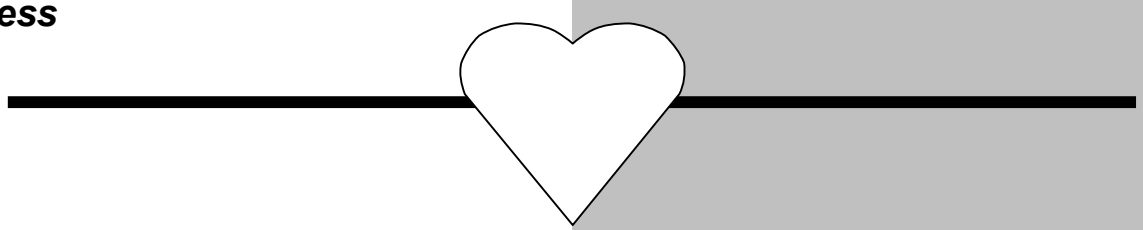


Abstract

Objectives: To evaluate predictors of an adverse outcome following “crush” bifurcation stenting.

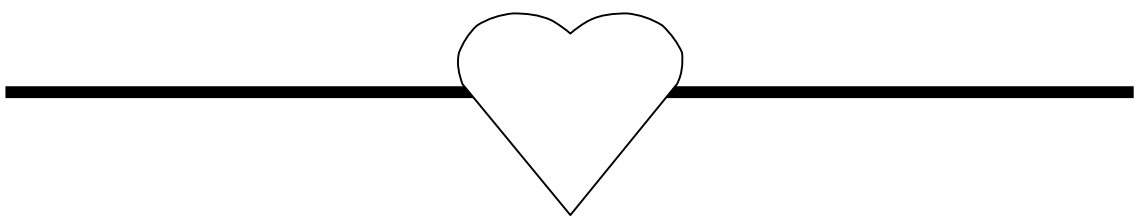
Background: The “crush” technique is a recently introduced strategy, with limited data regarding long-term outcomes.

Methods: We identified 231 consecutive patients who underwent “crush” stenting for 241 de novo bifurcation lesions. Stents used were sirolimus-eluting in 137(56.8%), and paclitaxel-eluting in 104(43.2%). Clinical follow-up was obtained in 99.6%.

Results: The in-hospital major adverse cardiac event (MACE) rate was 5.2%. At 9-months, 10 (4.3%) patients had an event consistent with post-procedural stent thrombosis. The survival-free of target lesion revascularisation (TLR) rate was 90.3%; the independent predictor of TLR was left main stem (LMS) therapy (OR 4.97; 95%CI 2.00 to 12.37, p=0.001). Survival-free of MACE was 83.5%, independent predictors of MACE were LMS therapy (OR 3.79; 95%CI 1.76 to 8.14, p=0.001), and treatment of patients with multivessel disease (OR 4.21; 95%CI: 0.95 to 18.56, p=0.058).

Angiographic follow-up (in 77% lesions) demonstrated a mean late loss of the main vessel and side branch of 0.30±0.64mm and 0.41±0.67mm respectively, with binary restenosis rates of 9.1% and 25.3%. Kissing balloon post-dilatation significantly reduced the side branch late lumen loss (0.24±0.50mm versus 0.58±0.77mm, p<0.001).

Conclusions: With drug-eluting stents, the crush technique is associated with favourable outcomes for most lesions; however, efficacy appears significantly reduced in LMS bifurcations, and further research is needed before the technique can be routinely recommended in this group. The incidence of possible stent thrombosis is of concern and requires further investigation. Kissing balloon post-dilatation is mandatory to reduce the rate of side branch restenosis.

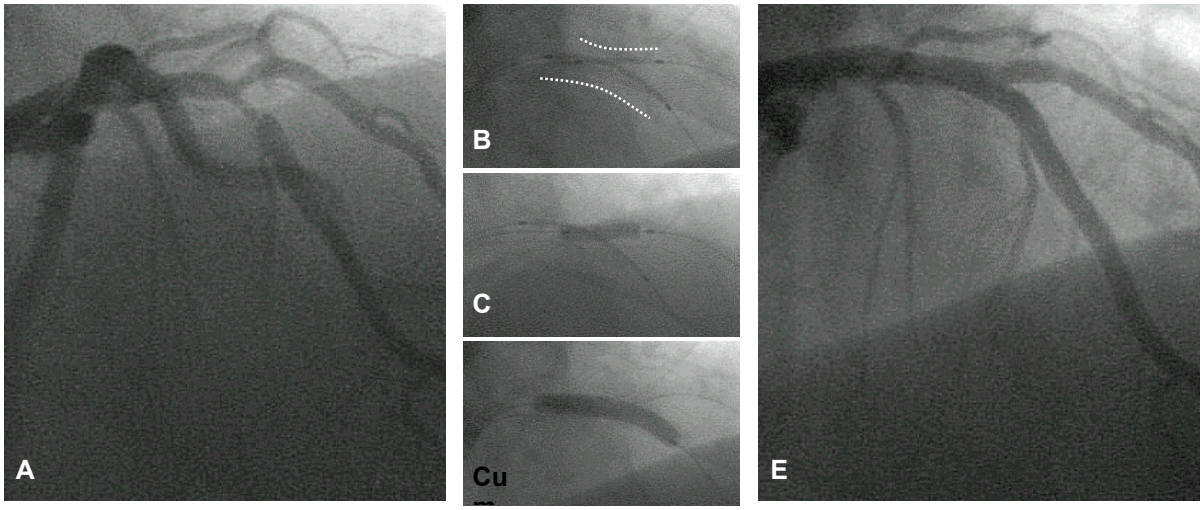


Introduction

The outcome of percutaneous coronary intervention of bifurcation lesions with bare metal stents (BMS) is hindered by increased rates of procedural complications and long-term major adverse cardiac events compared with non-bifurcated lesions. [1] Randomized studies have demonstrated that drug-eluting stents (DES) reduce restenosis when used in relatively simple lesions; [2-5] and recent data have demonstrated efficacy of the sirolimus-eluting stent (SES)(Cypher™, Cordis/Johnson & Johnson, Warren, NJ) for bifurcation lesions compared with historical data of BMS. [6-8] In one study of bifurcation lesions, [6] the overall restenosis rate was 23%, with the majority of side branch restenoses occurring at the ostium following use of a T-stenting technique. Indeed, side branch restenosis occurred in 16.7% following T-stenting, compared with 7.1% following other stenting techniques. We hypothesised that these restenoses might relate to incomplete coverage of the side branch ostium thereby reducing the efficacy of the DES.

The "crush" technique of bifurcation stenting with DESs was introduced by Colombo in 2002 as a relatively simple technique which ensures complete coverage of the side branch ostium (figure 1) thereby facilitating drug delivery at this site. [9] Initial data of 20 patients treated utilizing this technique with SES suggest it is a safe method, with an acceptable rate of procedural complications, and no further adverse events up to 30-days follow-up. Recently, angiographic data have shown the importance of simultaneous kissing balloon post-dilatation in reducing restenosis and need for target lesion revascularization. [10] We evaluated the clinical and angiographic outcomes of patients treated with either SES or paclitaxel-eluting stent (PES)(Taxus™, Boston Scientific, Natick, MA) implantation utilizing this strategy at our institutions, and evaluated the predictors of an adverse outcome.

Figure 1: The crush technique of bifurcation stenting.



A: baseline angiogram with significant stenosis of the left anterior descending / first diagonal bifurcation. **B:** both vessels are wired and both stents positioned. A 2.5x12mm Taxus stent is positioned in the side branch with its' proximal part well within the main vessel; at the same time, a 3.0x24mm Taxus stent is within the main vessel, ensuring it completely covers the proximal part of the side branch stent. **C:** the side branch stent is deployed and the balloon withdrawn. **D:** the stent in the main vessel is deployed. **E:** final result.

Methods

Study population

Demographic and procedural data regarding all patients undergoing angioplasty at EMO Centro Cuore Columbus, San Raffaele Hospital (Italy), and Thoraxcenter (The Netherlands), are prospectively entered into dedicated databases. We identified all consecutive patients who underwent bifurcation stenting with the crush technique utilizing DESs. Initially, therapy was undertaken with the SES beginning in April 2002 when the SES

received CE mark approval. In the first quarter of 2003, patients could also be treated with the PES. Patients with either stable or unstable angina were included if they were treated for a de novo bifurcation lesion. Those with acute ST-elevation myocardial infarction were excluded. SESs were available in diameters from 2.25mm to 3.00mm and lengths from 8mm to 33mm; PESs were available in diameters from 2.25mm to 3.5mm and lengths from 8mm to 32mm.

Procedures and intervention medications

The crush technique is depicted in figure 1, and has been previously described. [9] In short, the procedure requires a guide catheter of ≥7F. Both the main vessel and side branch are wired and prepared for stent implantation with pre-dilatation as necessary. The stents are both positioned such that the proximal part of the side branch lies well within the main vessel, but is completely covered by the stent within the main vessel (figure 1B). The side branch stent is deployed and the balloon carefully removed ensuring that the stent in the main vessel remains fixed. The wire within the side branch is commonly also removed, though providing the wire is not hydrophilic, it may be kept in position. The stent in the main vessel is deployed thereby crushing the proximal part of the side branch stent (and trapping the side branch wire if still in situ). If present, the wire in the side branch can then be withdrawn, and post-dilatation of the main vessel stent with high pressure balloon inflation facilitates use of the side branch wire to re-cross into the side branch to allow kissing balloon post-dilatation. Kissing balloon post-dilatation was undertaken at the operator's discretion. The protocol was approved by the Institutional ethics committees 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.

During the procedure, intravenous heparin was given to maintain an activated clotting time ≥250 seconds. Patients were preloaded with 300mg clopidogrel, and received life-long aspirin together with 75mg clopidogrel per day for at least 6-months. The use of glycoprotein IIb/IIIa inhibitors was at the operator's discretion.

Clinical Definitions and Follow-up

Clinical follow-up was obtained using either telephone calls or office visit, and evaluated the rate of major adverse cardiac events (MACE), pre-defined as death, acute myocardial infarction (AMI), or target vessel revascularization (TVR). The diagnosis of AMI both peri-procedural and at follow-up, required an elevation of creatine kinase levels to twice the upper limit of normal, together with a rise in creatine kinase-MB fraction. When in addition to enzyme elevation there were new pathological Q waves on the electrocardiogram, the event was defined as Q-wave MI. Target lesion revascularization (TLR) was defined as either surgical or percutaneous reintervention driven by significant (>50%) luminal diameter narrowing either within the stent or the 5mm borders proximal and distal to the stent, and was undertaken in the presence of either anginal symptoms or objective evidence of ischemia. TVR was defined as revascularization within the target vessel including encompassing the target lesion.

Stent thrombosis was defined as an acute coronary syndrome with angiographic documentation of either vessel occlusion or thrombus within or adjacent to a previously successfully stented vessel, or, in the absence of angiographic confirmation, either acute AMI in the distribution of the treated vessel, or death not clearly attributable to other causes. [11,12] Stent thrombosis was categorized according to the timing of the event into: intra-procedural (angiographic confirmed intra-luminal filling defect within the stent that occurred during the index procedure), [13] acute (occurred within the first 24 hours after the procedure), subacute (from 24 hours to 30 days) and late (>30 days after the index procedure).

Angiographic evaluation:

Procedural angiographic success was defined as a post-procedural final residual stenosis less than 50% with Thrombolysis In Myocardial infarction (TIMI) flow 3 in both the main vessel and side branch. Between 6 and 12 months after the index procedure, all living patients were invited back for angiographic follow-up. Coronary

angiograms were obtained in multiple views after intracoronary injection of nitrates. Quantitative coronary angiographic (QCA) analysis was performed using one of two validated edge detection systems (CMS, version 5.2, MEDIS, the Netherlands, and the Cardiovascular Angiography Analysis System II (CAAS II), Pie Medical, The Netherlands. The reference vessel diameter, minimal lumen diameter (MLD) and percent diameter stenosis were measured at pre-, post-procedure and follow-up. Reference vessel diameter for the side branch was taken as the diameter of the normal vessel distal to the bifurcation. The late lumen loss was calculated as the difference between the post procedure and follow-up MLD. [14] Binary restenosis was defined as the presence of >50% diameter stenosis within the target lesion.

Statistical analysis:

Discrete variables are presented as percentages and compared with Fisher exact test. Continuous variables are expressed as mean ± standard deviation and compared with Student's t test. Cumulative survival-free of adverse events were calculated according to the Kaplan-Meier method. Logistic regression models were established to investigate independent predictors of TLR and MACE. The following clinical variables were entered into the analysis model: age, gender, diabetes, stent type, unstable angina, premature antiplatelet therapy discontinuation, LMS (left main stem) bifurcation, glycoprotein IIb/IIIa inhibitor use, kissing balloon post-dilatation, nominal stent diameter, and stent length. Odds ratio with corresponding 95% confidence intervals are reported. All tests were two-tailed, and a p value of <0.05 was considered significant.

Results

The crush technique was utilized in 231 patients (241 lesions), with SES in 137 (56.8%), and PES in 104 (43.2%). The baseline patient and procedural characteristics are presented in tables 1 and 2. The use of glycoprotein IIb/IIIa inhibitor therapy was significantly higher in the SES group than the PES group (40.8% versus 19.8%, p=0.001). Attempted kissing balloon post-dilatation was undertaken in 128 lesions, and was successful in 122 (95%) cases; it was carried out more frequently in the PES group (61.5% versus 42.3% in SES, p=0.004).

Table 1: Baseline patient demographics

	All n=231	**SES n=130**	**PES n=101**	**p value***
Mean age (years)	62.8 ± 11.2	62.9 ± 11.2	62.6 ± 11.1	0.76
Male sex (%)	193 (83.5)	113 (86.9)	80 (79.2)	0.15
Current smoker (%)	44 (19.0)	24 (18.5)	20 (19.8)	0.87
Diabetes mellitus (%)	46 (19.9)	25 (19.2)	21 (20.8)	0.74
Hypertension (%)	125 (54.1)	76 (58.5)	49 (48.5)	0.14
Hypercholesterolemia (%)	162 (70.1)	91 (70.0)	71 (70.3)	1.0
Family history (%)	103 (44.6)	53 (40.8)	50 (49.5)	0.23
Previous myocardial infarction (%)	95 (41.1)	48 (36.9)	47 (46.5)	0.22
Previous CABG (%)	33 (14.3)	18 (13.8)	15 (14.9)	0.85
Multivessel disease (%)	174 (75.3)	98 (75.4)	76 (75.2)	1.0
Clinical presentation				1.0
Stable angina (%)	172 (74.5)	96 (73.8)	76 (75.2)	
Unstable angina (%)	59 (25.5)	34 (26.2)	25 (24.8)	
Glycoprotein IIb/IIIa inhibitor usage (%)	73 (31.6)	53 (40.8)	20 (19.8)	0.001

*p value for the SES group versus PES group

CABG: coronary artery bypass graft surgery; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent

Table 2: Baseline procedural characteristics

	All n=241	SES n=137	PES n=104	p value
Target vessel				0.15
LAD / diagonal (%)	130 (53.9)	82 (59.9)	48 (46.2)	
LCx / obtuse marginal (%)	52 (21.6)	28 (20.4)	24 (23.1)	
RCA bifurcation (%)	12 (5.0)	6 (4.4)	6 (5.8)	
LMS (%)	47 (19.5)	21 (15.3)	26 (25.0)	
Mean number of stents in the main vessel	1.2 ± 0.5	1.24 ± 0.51	1.22 ± 0.50	0.82
Mean nominal diameter of stent in the main vessel (mm)	3.01 ± 0.32	2.95 ± 0.29	3.09 ± 0.34	0.001
Mean total lengths of stent in the main vessel (mm)	29.3 ± 11.3	30.31 ± 10.96	28.05 ± 11.58	0.12
Mean number of stents in the side branch	1.1 ± 0.3	1.08 ± 0.32	1.03 ± 0.26	0.18
Mean nominal diameter of stent in the side branch (mm)	2.62 ± 0.32	2.58 ± 0.30	2.68 ± 0.34	0.02
Mean total lengths of stent in the side branch (mm)	21.3 ± 9.3	21.45 ± 10.11	21.01 ± 8.28	0.72
Post-dilatation with kissing balloons (%)	122 (50.6)	58 (42.3)	64 (61.5)	0.004

*p value for the SES group versus PES group
SES: sirolimus-eluting stent; PES: paclitaxel-eluting stent; LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery; LMS: left man stem

Table 3: Clinical outcomes

	All n=231	SES n=130	PES n=101	p value
In-hospital MACE, n (%)	11 (4.8)	5 (3.8)	6 (5.9)	0.5
Cardiac death, n (%)	0	0	0	1.0
Acute myocardial infarction, n (%)	11 (4.8)	5 (3.8)	6 (5.9)	0.5
Q-wave myocardial infarction	1 (0.4)	1 (0.8)	0	0.4
Non-Q wave myocardial infarction	10 (4.3)	4 (3.1)	6 (5.9)	0.3
Target lesion revascularization, n (%)	1 (0.4)	1 (0.8)	0	0.4
Target vessel revascularization, n (%)	1 (0.4)	1 (0.8)	0	0.4

Clinical Outcomes

The rate of in-hospital adverse events is shown in table 3. There were 3 (1.3%) intra-procedural stent thromboses (2 in the SES group, 1 in the PES group), 2 of these developed non-Q-wave AMI. The mean total stent length of these 3 cases was 69 mm and no glycoprotein IIb/IIIa inhibitor had been given electively. After thrombolytic therapy and further balloon inflation, thrombosis resolved. One additional patient in the SES group developed a Q-wave MI in hospital due to occlusion of septal branches during the index procedure. By logistic regression analysis, the only predictor for in-hospital MACE was those patients in whom a glycoprotein IIb/IIIa inhibitor was used (OR 3.25; 95%CI: 0.99 to 10.60, p=0.051).

Clinical follow-up data at 9-months was available in 99.6% patients. The cumulative rates of survival-free of MACE are shown in table 4. Post-procedural angiographically confirmed stent thrombosis occurred in 2 (0.9%) patients (1 acute, 1 subacute) who were both subsequently treated with glycoprotein IIb/IIIa inhibitor therapy and percutaneous TLR. In addition, 3 further patients died and 5 patients had an AMI within the territory of the treated vessel, giving a total rate of possible post-procedural stent thrombosis of 4.3%. The demographics of these 10 patients are presented in table 5. The incidence of post-procedural stent thrombosis was higher for the PES group than the SES group (6.9% versus 2.2%, p=0.08).

Table 4: Cumulative survival-free of major adverse cardiac events at 9-months

	All n=241	**SES n=137**	**PES n=104**	**p value***
Survival (%)	98.7	99.2	98.0	0.42
Survival-free of Q-wave acute myocardial infarction (%)	96.5	96.9	96.0	0.72
Survival-free of acute myocardial infarction (Q-wave or non-Q-wave) (%)	90.8	93.1	88.0	0.20
Survival-free of target lesion revascularization (%)	90.3	93.8	85.5	0.046
Survival-free of target vessel revascularization (%)	89.0	93.0	83.6	0.028
Survival-free of major adverse cardiac events (%)	83.5	87.7	78.0	0.053

*p value for the SES group versus PES group
PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent

The overall survival free of MACE and TLR were 83.5% and 90.3%, respectively (figure 2). Independent predictors for MACE were therapy of the LMS (OR 3.79; 95%CI 1.76 to 8.14, p=0.001), and therapy of patients with multivessel disease (OR 4.21; 95%CI 0.95 to 18.56, p=0.058). Significantly fewer of the SES treated patients required TLR compared with those treated with PES. However, logistic regression demonstrated that the only independent factor for TLR was therapy of the LMS (OR 4.97; 95% CI: 2.00 to 12.37, p=0.001). The rate of survival-free of TLR was 77.8% in those who underwent LMS stenting compared with 94.2% in the remainder (figure 3).

Quantitative Angiographic Analysis

Procedural angiographic success was achieved in 99.6% lesions. Follow-up coronary angiography was undertaken in 186 (77.2%) lesions, at a mean period of 8.3±3.7 months. Angiographic data with respect to the stent type and the use of kissing balloon post-dilatation are presented in tables 6 and 7. There was no significant difference in angiographic results with respect to the type of stent utilized. However, kissing balloon

post-dilatation significantly reduced the side branch late lumen loss and binary restenosis. Among the 47 restenotic lesions at the side branch, 34 (72.3%) were focal (<10mm) and located at the ostium.

Discussion

The main findings of this report are: (1) treatment of most bifurcation lesions with DES by the "crush" technique is associated with low rates of TLR and MACE at 9-months. However, therapy of the left main stem was an independent predictor of both TLR and MACE; (2) at 9-months, the incidence of possible post-procedural stent thrombosis was 4.3%; (3) the rate of side branch restenosis was significantly lower in lesions treated with kissing balloon post-dilatation compared to those without.

Figure 2: Cumulative survival-free of target lesion revascularization (TLR), and major adverse cardiac events (MACE) following bifurcation stenting utilizing the crush technique.

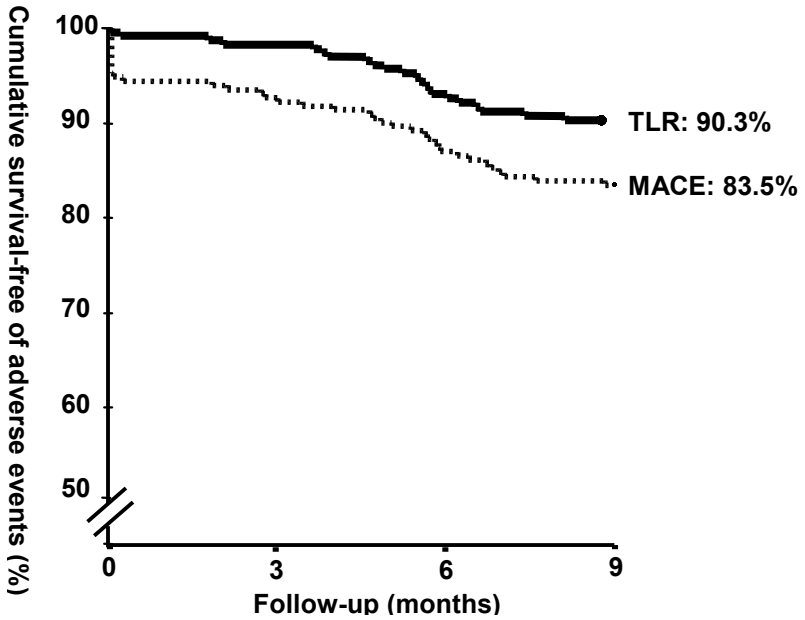


Figure 3: Cumulative survival-free of target lesion revascularization (TLR) for patients treated with the crush technique of bifurcation stenting for a left main stem (LMS) lesion compared with those treated for lesions outside the left main stem (non-LMS).

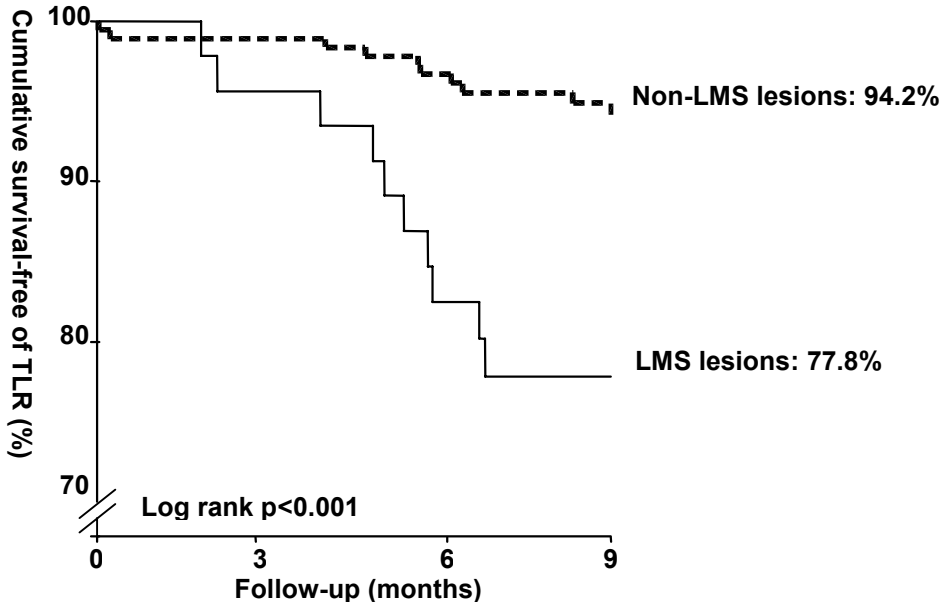


Table 5: Patients with a definite or probable post-procedural stent thrombosis

Pt no.	Age / sex	Stent type	DM	Multivessel disease	Previous CABG	Target vessel	Index presentation	Index use of GP IIb/IIIa	Kissing balloon post-dilatation	Time to definite or probable thrombosis,	Dual anti-platelet therapy at the time of the event	Presentation and therapy of thrombosis
1	74yr F	SES	N	Y	N	LAD	SA	N	Y	1	Y	AMI: underwent TLR with PCI; alive
2	66yr F	PES	N	Y	N	LCx	UA	N	N	7	Y	AMI: underwent TLR with PCI; alive
3	67yr M	PES	N	Y	Y	LMS	SA	N	Y	145	Y	AMI: managed medically; alive
4	73yr M	PES	Y	Y	Y	LMS	SA	N	N	204	N Stopped clopidogrel at 6-months	Sudden death
5	41yr M	PES	N	Y	N	LAD	UA	N	N	211	N Stopped clopidogrel at 6-months	AMI: managed medically; alive
6	82yr M	SES	Y	Y	N	LMS	UA	Y	Y	55	N Stopped clopidogrel because of pancreatitis	Death
7	61yr M	PES	N	Y	Y	LMS	SA	Y	Y	63	Y	AMI and death
8	71yr M	PES	N	Y	N	LMS	SA	N	Y	117	Y	AMI: managed medically; alive
9	65yr F	PES	Y	N	N	LAD	SA	Y	N	166	Y	AMI: managed medically; alive
10	80yr M	SES	Y	Y	N	LAD	SA	Y	N	26	N Stopped clopidogrel because of abdominal surgery	AMI: managed medically; alive

Stent coverage of the ostium of the side branch and clinical outcomes

Bifurcation lesions are subject to increased rates of restenosis and need for TLR compared with non-bifurcated lesions. Historical data of BMSs suggest a TLR rate of 16-38%, with a tendency to increased restenosis following stenting of both the main vessel and side branch compared with single vessel stenting. [15-19] In the same studies, the rate of MACE at 6-months ranged between 17-51%. In randomized studies of relatively simple lesions, DESs reduce restenosis compared with BMSs, though bifurcation lesions were excluded. [2-5] Preliminary data for the SES has recently suggested efficacy in bifurcation lesions. [6-8] However, the most effective stenting strategy is currently unknown. Previous data of the SES suggested a higher restenosis rate following T-stenting, with the hypothesis that this might relate to incomplete coverage of the side branch ostium. [6,7] In most bifurcations, the angle at the carina is significantly smaller than 90˚ meaning that even with precise positioning, the stents are unable to make a "T" and completely cover the bifurcation. [18] The crush technique is a relatively simple strategy that ensures complete lesion coverage, even for bifurcation lesions that have extensive disease within the side branch. Preliminary data have suggested acceptable short-term results suggesting it may therefore be an effective strategy for bifurcation lesions. [9]

In the present study, we have demonstrated encouraging long-term results, with a high rate of survival-free of TLR of 90.3%. Although TLR rates were higher in those treated with PES compared to SES, there were more patients in this group treated for LMS bifurcation (25.0% versus 15.3%). By logistic regression analysis, therapy of the LMS was the only independent predictor of TLR. Indeed, at 9-months, the survival-free of TLR was 77.8% in those who underwent LMS stenting, compared with 94.2% in the remainder. The rate of in-hospital MACE was 4.8%, the majority comprising non-Q wave AMI. The MACE rate was higher in those who received a glycoprotein IIb/IIIa inhibitor. However, this is likely to reflect the operators' decision to use such an agent only in the situation of a difficult or complicated procedure. There is evidence to suggest improved efficacy of glycoprotein IIb/IIIa inhibitors with early administration. Further work is needed to evaluate whether routine pre-procedural administration of such agents to all patients undergoing crush stenting might reduce the occurrence of in-hospital events.

At 9-months, the overall rate of survival-free of MACE was 83.5%. Independent predictors were the treatment of multivessel disease, and treatment of the LMS. Recent data has been published specifically evaluating the results of LMS stenting with DES implantation. [20-23] In all these studies, results suggested lower rates of restenosis compared with historical data of BMS. The incidence of TLR ranged from 2.0-14.1%. This appears to be much lower than the LMS cohort in our study where the rate of survival-free of TLR was just 77.8% (compared with 94.2% for non-LMS lesions). However, in the aforementioned studies, restenosis following LMS bifurcation stenting was higher compared with lesions localised to the ostium or body of the LMS. Chieffo et al [22] evaluated 85 patients including 69 (81.2%) with disease of the distal LMS. The majority of these patients were treated with stent implantation to both branches, most (59%) with crush stenting. All 12 patients who required TLR were initially treated with a 2 stent strategy. Park et al [21] demonstrated excellent results following LMS angioplasty, with a binary restenosis rate of 7.0%. In this study, 70.6% patients were treated for the LMS bifurcation, and all restenoses occurred in these patients.

Kissing balloon post-dilatation

Although the overall rate of TLR in the present study was relatively low, kissing balloon post-dilatation had a significant impact on the angiographic results, leading to a significantly larger post-procedural MLD within both the main vessel and side branch. This larger MLD was maintained in both vessels at follow-up, but was particularly evident within the side branch. As previously demonstrated by Ge et al, [10] in the present paper, kissing balloon post-dilatation in the present study significantly reduced both the side branch late lumen loss (0.24 ± 0.50mm versus 0.58 ± 0.77mm, $p<0.001$), and binary restenosis rate (9.6% versus 41.3%, $p<0.000001$).

The majority (72.3%) of these side branch restenoses were focal and occurred at the ostium. Bench study results have demonstrated the crush technique to effectively cover the bifurcation lesion, however, the absence of kissing balloon post-dilatation leads to under-expansion and mal-apposition of the side branch stent struts. [24] Kissing balloon post-dilatation opens the struts thereby facilitating access to the side branch, and corrects stent deformation to provide optimal scaffolding and delivery of drug. The crush technique is

Table 6: Quantitative coronary angiography

	All	SES	PES	p value
Follow-up angiography, n (%)	186 (77.2)	107 (78.1)	79 (76.0)	0.8
Main branch				
Reference diameter (mm)	2.71 ± 0.59	2.71 ± 0.58	2.71 ± 0.61	1.0
Length of lesion (mm)	15.38 ± 10.46	15.99 ± 9.09	14.57 ± 12.06	0.4
Minimal lumen diameter (mm)				
Pre-procedure	0.93 ± 0.52	0.90 ± 0.53	0.98 ± 0.52	0.3
Post-procedure	2.73 ± 0.56	2.70 ± 0.51	2.77 ± 0.62	0.4
6-month follow-up	2.43 ± 0.81	2.40 ± 0.76	2.47 ± 0.89	0.6
Diameter stenosis (%)				
Pre-procedure	65.9 ± 17.5	67.3 ± 17.1	63.9 ± 18.0	0.2
Post-procedure	13.0 ± 8.6	13.6 ± 8.3	12.1 ± 9.0	0.3
6-month follow-up	22.9 ± 19.9	24.1 ± 19.1	21.3 ± 21.1	0.3
Late lumen loss (mm)	0.30 ± 0.64	0.30 ± 0.60	0.30 ± 0.70	1.0
Binary restenosis rate (%)	17 (9.1)	10 (9.3)	7 (8.9)	1.0
Side branch				
Reference diameter (mm)	2.39 ± 0.51	2.36 ± 0.45	2.41 ± 0.60	0.6
Length of lesion (mm)	8.99 ± 6.03	9.46 ± 6.12	8.04 ± 5.80	0.09
Minimal lumen diameter (mm)				
Pre-procedure	0.89 ± 0.52	0.92 ± 0.51	0.86 ± 0.53	0.5
Post-procedure	2.26 ± 0.51	2.26 ± 0.49	2.26 ± 0.55	1.0
6-month follow-up	1.85 ± 0.86	1.89 ± 0.85	1.81 ± 0.87	0.5
Diameter stenosis (%)				
Pre-procedure	62.3 ± 20.5	60.9 ± 20.6	64.3 ± 20.3	0.3
Post-procedure	15.5 ± 9.5	15.0 ± 9.7	16.2 ± 9.3	0.4
6-month follow-up	30.7 ± 0.67	29.4 ± 27.7	32.5 ± 27.3	0.5
Late lumen loss (mm)	0.41 ± 0.67	0.37 ± 0.71	0.46 ± 0.60	0.4
ary restenosis rate (%)	47 (25.3)	29 (27.1)	18 (22.8)	0.6

* p value for the SES group versus the PES group
PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent

Table 7: Quantitative coronary angiography with respect to the use of kissing balloon post-dilatation

	Kissing balloon post-dilatation	No kissing balloon post-dilatation	p value
Follow-up angiography, n (%)	94 (77.0)	92 (77.3)	1.0
Main branch			
Reference diameter (mm)	2.78 ± 0.61	2.64 ± 0.57	0.1
Length of lesion (mm)	14.84 ± 10.40	15.97 ± 10.55	0.5
Minimal lumen diameter (mm)			
Pre-procedure	0.97 ± 0.53	0.89 ± 0.52	0.3
Post-procedure	2.89 ± 0.54	2.55 ± 0.53	<0.0001
6-month follow-up	2.64 ± 0.81	2.21 ± 0.75	<0.001
Diameter stenosis (%)			
Pre-procedure	65.5 ± 17.1	66.4 ± 18.0	0.7
Post-procedure	12.2 ± 8.7	13.8 ± 8.5	0.2
6-month follow-up	19.9 ± 20.2	26.1 ± 19.3	0.04
Late lumen loss (mm)	0.26 ± 0.65	0.35 ± 0.64	0.3
Binary restenosis rate (%)	6 (6.4)	11 (12.0)	0.2
Side branch			
Reference diameter (mm)	2.45 ± 0.53	2.32 ± 0.49	0.1
Length of lesion (mm)	9.01 ± 6.06	8.97 ± 6.03	1.0
Minimal lumen diameter (mm)			
Pre-procedure	0.90 ± 0.53	0.88 ± 0.52	0.8
Post-procedure	2.43 ± 0.53	2.10 ± 0.44	<0.00001
6-month follow-up	2.18 ± 0.71	1.52 ± 0.86	<0.0000001
Diameter stenosis (%)			
Pre-procedure	62.7 ± 20.7	61.9 ± 20.3	0.8
Post-procedure	12.8 ± 8.7	18.3 ± 9.5	<0.0001
6-month follow-up	20.5 ± 17.9	41.0 ± 31.5	<0.000001
Late lumen loss (mm)	0.24 ± 0.50	0.58 ± 0.77	<0.001
Binary restenosis rate (%)	9 (9.6)	38 (41.3)	<0.000001

technically relatively quick and simple; kissing balloon post-dilatation increases the procedural time and cost, however, our results suggest that it is a necessity.

Following stent implantation, it can be difficult and time-consuming to re-cross the side branch with a wire and/or balloon. We recommend routine post-dilatation of the main vessel stent with a balloon (≥nominal stent diameter) taken to high pressure. Following this, successful access of the side branch and subsequent post-dilatation, can be achieved in >95% procedures. Stent under-expansion remains one of the major reasons for restenosis, [25] even in the DES era. [26-28] To enable full stent strut expansion at the side branch ostium, we initially perform high pressure (>12atm) balloon inflation in the side branch with a balloon ≥nominal stent diameter. [29] Once both the main vessel and side branch stents have been individually post-dilated at high pressure, kissing balloon post-dilatation is then undertaken. Notably, the aforementioned bench study [24] emphasised that optimal kissing dilatation requires the size of the balloon in the main vessel ≥nominal stent diameter.

Bifurcation stenting is known to increase the risk of restenosis with BMS. Accordingly, compared with the results of randomized studies of non-bifurcation lesions, our results suggest that this also applies to DESs. Compared with the SIRIUS study, [4] the SES patients in our study demonstrated a higher rate of TLR (5.4% versus 4.1%) Similarly, compared with the results of TAXUS IV, [5] the PES patients in our study demonstrated a higher rate of TLR (11.9% versus 3.0%). In addition, compared with these published studies, both groups of patients in our study had a higher main vessel late lumen loss (0.30±0.60mm versus 0.24±0.47mm for the SES, and 0.30±0.70mm versus 0.23±0.44mm for the PES).

Stent thrombosis

The 1.3% incidence of intra-procedural stent thrombosis in the present report is slightly higher than the incidence previously reported in a large series of patients treated with SES (0.7%). [12] The 4.3% incidence of post-procedural stent thrombosis is of concern, and is higher than the findings of the trials that evaluated DES implantation in relatively simple lesions (0.4% for SES and 0.6% for PES). [4,5] This may reflect the complexity of the technique with an increased risk of thrombosis perhaps reflecting the triple layer of stent struts, polymer and drug at the site of the carina. Notably, in the present study, kissing balloon post-dilatation did not appear to reduce the risk of stent thrombosis.

The incidence of post-procedural stent thrombosis tended to be higher in the cohort treated with the PES compared with the SES (6.9% versus 2.2%). This is in accordance with the recently presented results of the REALITY study. [30] This multicenter study randomized 1353 patients (1911 lesions), to therapy with either SES or PES. There was a higher rate of stent thrombosis in the PES-treated group (1.8% versus 0.4%, p=0.02). In the present study, such a high incidence of thrombosis emphasises the importance of an aggressive strategy of anti-platelet therapy, with administration of dual anti-platelet therapy for a prolonged (though as yet undefined) period of time. Indeed, 4 of the 10 patients had stopped clopidogrel prior to the presumed thrombotic event. A recent study has shown that premature discontinuation of dual antiplatelet therapy is associated with an approximately 30 fold greater risk of stent thrombosis after SES implantation. [11] For patients treated with the crush technique, premature discontinuation of anti-platelet therapy has been shown to be a predictor of stent thrombosis, [10] and, in conjunction with our results, suggests that the technique should not be recommended in patients who cannot receive or tolerate dual anti-platelet therapy. Further work is needed to evaluate the potential benefit of routine pre-procedural administration of glycoprotein IIb/IIIa inhibitor therapy to all patients treated utilizing this technique.

Study limitations

The main limitation of the present report is its non-randomized design; therefore caution must be taken in evaluating any differences between the stent types. Furthermore, the study does not make comparison with alternative stenting strategies. The decision to use both glycoprotein IIb/IIIa inhibitor therapy, and the use of kissing balloon post-dilatation was at the operators' discretion and was therefore also not randomized.

Conclusions

The crush technique of bifurcation stenting with DESs is associated with favourable clinical outcomes when compared with historical data of BMS. However, the incidence of possible post-procedural stent thrombosis is of concern, and is higher than that following therapy of more simple lesions, suggesting that an aggressive strategy of anti-platelet therapy maybe of importance. Importantly, the efficacy of the technique appears to be reduced in LMS bifurcation lesions, and further research is needed before the technique can be routinely recommended in this group of patients. When utilizing this technique, kissing balloon post-dilatation is mandatory to reduce the rate of restenosis of the side branch. Randomized studies are warranted to directly compare the technique with other bifurcation stenting strategies.

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Chapter 17

Percutaneous Therapy of Bifurcation Lesions with Drug-Eluting Stent Implantation: the Culotte Technique Revisited

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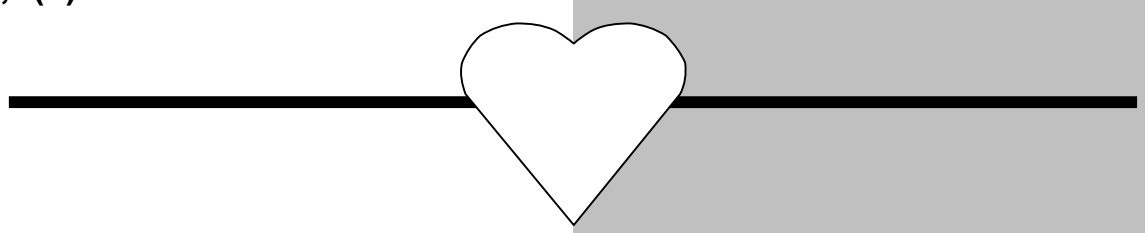
2005;7(1):36-40



Abstract

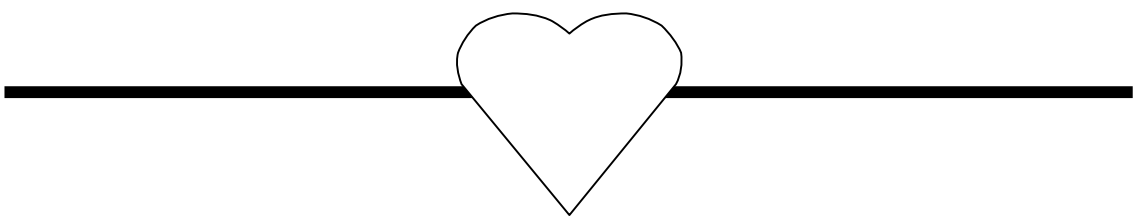
Introduction: The most effective strategy for bifurcation stenting is currently undefined. The Culotte technique was developed as a method that ensures complete bifurcation lesion coverage. However, it went out of favour due to a high rate of restenosis when utilizing bare metal stents. Drug-eluting stents reduce the rate of restenosis and need for repeat lesion revascularization compared with bare metal stents; we re-evaluated this technique with drug-eluting stent implantation.

Methods: Between April 2002 and October 2003, 207 patients were treated for at least one bifurcation lesion with drug-eluting stent implantation to both the main vessel and side branch. Of these, 23 were treated with the Culotte technique (11.1%) for 24 lesions. Sirolimus-eluting stents were used in 8.3%, and paclitaxel-eluting stents in the remaining 92.7%.

Results: Clinical follow-up was obtained in 100%. One patient had a myocardial infarction at 14 days (maximum rise in creatine kinase 872IU/L) related to thrombosis occurring in another lesion, and underwent repeat revascularization. There were no episodes of stent thrombosis in the Culotte lesions. At 8 months follow-up, there were no deaths and no further myocardial infarction. One patient required target lesion revascularization (TLR), and a second underwent target vessel revascularization. The cumulative rates of survival-free of TLR and major adverse cardiac events were 94.7% and 84.6% respectively.

Angiographic follow-up was obtained in 16 patients (69.6%) at a mean period of 8.3 ± 4.3months. The late lumen loss for the main vessel and side branch were 0.48 ± 0.56mm and 0.53 ± 0.33mm respectively, with binary restenosis rates of 18.8% and 12.5%.

Conclusions: In this small study of bifurcation stenting utilizing the Culotte technique with drug-eluting stent implantation, there was a low rate of major adverse events and need for target lesion revascularization at 8 months, when compared with historical data of bifurcation stenting with bare metal stents. Further re-evaluation of this technique utilizing drug-eluting stents, is warranted in the setting of larger randomized studies.



Introduction

The outcome of PCI of bifurcation lesions with is hindered by an increased rate of procedural complications, [1] and a high rate of restenosis compared with non-bifurcated lesions. The most effective strategy of bifurcation stenting is currently undefined, though the majority of historical data assessing bare metal stents evaluated a T-stenting strategy. [2-6] The angle between the main vessel and side branch in most bifurcation lesions is significantly smaller than 90˚ making it impossible to make an exact "T" shape even with precise stent positioning. [4] The Culotte technique ensures complete lesion coverage, however it fell out of favour as studies with bare metal stents demonstrated a high rate of restenosis at follow-up.

Randomized studies have demonstrated that percutaneous coronary intervention (PCI) with drug-eluting stent implantation reduces restenosis when used in relatively simple lesions; [7-10] and recent data have demonstrated efficacy of the sirolimus-eluting stent (SES) for bifurcation lesions compared with historical data of bare metal stents. [11,12] Data from our group demonstrated that the majority of restenoses of the side branch occurred at the ostium following T-stenting. [11] Indeed, the restenosis rate in the side branch following T-stenting was 16.7% whilst that following other stenting techniques was 7.1%. We hypothesised that these restenoses might relate to inadequate / incomplete coverage of the ostium of the side branch thereby reducing the efficacy of the drug-eluting stent. In the present study we evaluate the outcome of the Culotte technique utilizing drug-eluting stents.

Methods

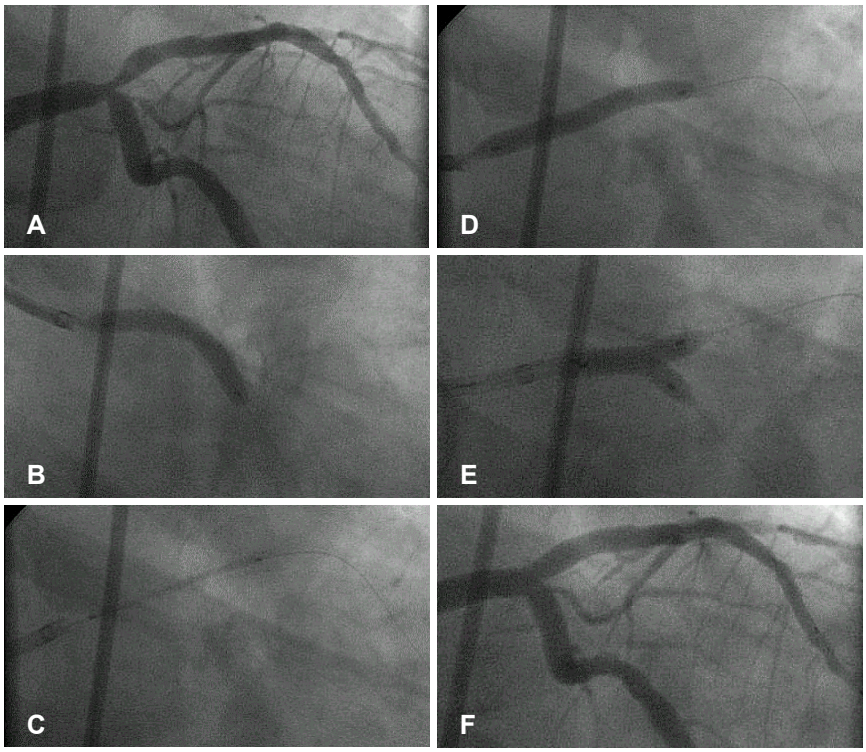
The sirolimus-eluting stent (Cypher™, Johnson & Johnson - Cordis unit) received CE mark approval in April 2002. Since that time, all patients in our institution undergoing PCI have been treated with drug-eluting stent implantation as the default strategy. During the first quarter of 2003, our strategy switched from the sirolimus-(SES) to the paclitaxel-eluting stent (PES) (Boston Scientific). All consecutive patients were enrolled irrespective of clinical presentation and lesion characteristics, and the incidence of major adverse cardiac events (MACE) was evaluated prospectively during the follow-up. SESs were available in diameters from 2.25mm to 3.00mm and lengths from 8mm to 33mm. PESs were available in diameters from 2.25mm to 3.5mm and lengths from 8mm to 32mm. Between April 2002 and October 2003, 207 patients with bifurcation lesions were treated with stenting of both the main vessel and side branch. The choice of stenting strategy was at the operators' discretion, and 23 patients (11.1%) were treated utilizing the Culotte technique.

The protocol was approved by the Institutional 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.

Outline of the Culotte technique: The Culotte technique has been well described previously, [13] and an example is depicted in figure 1. Both vessels are wired and pre-dilatation is generally recommended to facilitate subsequent stent passage. The vessel with the most acute angulation (usually the side branch) is stented first. This will "trap" the first wire placed within the main vessel behind the stent struts. The main vessel is therefore re-wired through the struts of the deployed stent, and the trapped wire is withdrawn. The struts are opened with balloon dilatation to enable passage of the main vessel stent through the struts such that it lies within the main vessel, but with its' proximal part lying within the proximal part of the side branch stent. The main vessel stent is deployed, thereby "trapping" the wire in the side branch. The side branch is therefore re-wired, and the "trapped" wire withdrawn. The side branch ostium is dilated to open up the struts of the main vessel, and the final result is optimised with the use of kissing balloon post-dilatation.

Intervention medications: Before the procedure, patients were preloaded with 300mg clopidogrel, and received life-long aspirin together with 75mg clopidogrel per day for 6-months. During the procedure, intravenous heparin was given to maintain an activated clotting time ≥250 seconds; the use of a glycoprotein IIb/IIIa inhibitor was at the discretion of the operator.

Figure 1: The Culotte technique of stenting a bifurcation lesion of the left main stem (LMS)(A). Both the left anterior descending (LAD) and circumflex (LCX) arteries are wired and pre-dilated to facilitate stent implantation. As the vessel with the most acute angle from the LMS, the LCX is stented first (B). The LAD is re-wired through the LCX stent struts, and the initial "trapped" LAD wire is withdrawn. Following balloon pre-dilatation, the LAD stent is positioned through the LCX stent, into the LMS and deployed (C,D). The LCX is re-wired through the LAD stent struts, and the "trapped" LCX wire withdrawn. Kissing balloon post-dilatation can then be carried out (E), with an excellent final result (F).



Clinical follow-up: Survival status was assessed by written inquires to the Municipal Civil Registries. Clinical follow-up was obtained using telephone calls and questionnaires to all living patients, with the referring physician and general practitioner directly approached whenever necessary. Clinical follow-up evaluated the rate of major adverse cardiac events (MACE), pre-defined as death, acute myocardial infarction (AMI), or target vessel revascularization (TVR). The diagnosis of AMI required an elevation of creatine kinase levels to twice the upper limit of normal, together with a rise in creatine kinase-MB fraction. Target lesion revascularization (TLR) was defined as either surgical or percutaneous reintervention driven by significant (>50%) luminal diameter narrowing either within the stent or the 5mm borders proximal and distal to the stent, and was undertaken in the presence of either anginal symptoms or objective evidence of ischemia. TVR was defined as revascularization within the target vessel including encompassing the target lesion. The definition of stent thrombosis was the presence of intra-stent thrombosis, with or without stent occlusion, documented on angiography.

Angiographic follow-up: Between 6 and 12 months after the index procedure, all patients were invited back for angiographic follow-up. Coronary angiograms were obtained in multiple views after administration of intracoronary nitrate. Quantitative coronary angiographic (QCA) analysis was performed using the Cardiovascular Angiography Analysis System II (CAAS II) (Pie Medical, Maastricht, The Netherlands). The reference vessel diameter, minimal lumen diameter and percent diameter stenosis were measured at pre-, post-procedure and follow-up. The late lumen loss was calculated as the difference in post procedure minimal lumen diameter and that at follow-up. Binary restenosis was defined as the presence of >50% diameter stenosis within the target lesion.

Statistical analysis:
Discrete variables are presented as percentages and continuous variables are expressed as mean ± standard deviation. Cumulative survival-free of adverse events were calculated according to the Kaplan-Meier method.

Results
The Culotte technique of stenting was utilized in 24 lesions in 23 patients. The baseline patient and procedural characteristics are presented in tables 1 and 2. Clinical follow-up data was obtained in 100% patients. One patient had a myocardial infarction at 14 days (maximum rise in creatine kinase 872IU/L) related to thrombosis occurring in another lesion, and underwent repeat percutaneous revascularization. There were no episodes of stent thrombosis in the Culotte lesions. At 8 months follow-up, there were no deaths and no further myocardial infarction. One patient required target lesion revascularization for restenosis within both the main vessel and side branch stents. A second patient underwent target vessel revascularization. The cumulative rates of survival-free of TLR and MACE were 94.7% and 84.6% respectively.

Table 1: Baseline patient demographics

	Patients treated with Culotte stenting n=23
Mean age (years)	63.0 ± 11.8
Male sex (%)	58.3
Current smoker (%)	13.0
Diabetes mellitus (%)	21.7
Hypertension (%)	56.5
Hypercholesterolemia (%)	73.9
Previous myocardial infarction (%)	43.5
Previous CABG (%)	4.3
Multivessel disease (%)	60.9
Clinical presentation	
Stable angina (%)	73.9
Unstable angina (%)	21.7
Acute ST-elevation myocardial infarction (%)	4.3
Glycoprotein IIb/IIIa inhibitor usage (%)	30.4
PCI in at least one additional lesion during the index procedure (%)	43.5

CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention

Angiographic follow-up was obtained in 16 patients (69.6%) at a mean period of 8.3 ± 4.3months, and results are presented in table 3.

Discussion
In the present study we have demonstrated efficacy of the Culotte technique of bifurcation stenting when using drug-eluting stent implantation, with, at 8-months, a high rate of survival-free of major adverse cardiac events (84.6%) and target lesion revascularization (94.7%), as compared with historical data of alternative stenting strategies that utilized bare metal stents. These results suggest that the utilization of this technique needs to be re-evaluated in current practice with drug-eluting stents.

Bifurcation lesions are subject to an increased rate of restenosis and need for repeat lesion revascularization as compared with non-bifurcated lesions. [1] The Culotte technique ensures complete lesion coverage, however, studies with bare metal stents demonstrated relatively high rates of TLR of 24-33%, [5,13] with an angiographic restenosis rate in one of these studies of 56%. [13] In addition, the rate of MACE at 1-year in the smaller study was extremely high at 86.3%. [5] Indeed, several studies of bare metal stents have

Table 2: Baseline procedural characteristics

	Lesions treated with the Culotte technique n=24
Target vessel	
LMS (%)	29.2
LAD / diagonal (%)	45.8
LCX / obtuse marginal (%)	12.5
RCA bifurcation (%)	12.5
Stent type utilized	
Sirolimus-eluting stent (%)	8.3
Paclitaxel-eluting stent (%)	91.7
Pre-dilatation of main vessel (%)	62.5
Pre-dilatation of the side branch (%)	37.5
Pre-dilatation with kissing balloons (%)	16.7
Mean number of stents in the main vessel	1.6 ± 0.6
Mean nominal diameter of stent in the main vessel (mm)	2.89 ± 0.41
Mean total lengths of stent in the main vessel (mm)	30.7 ± 14.5
Mean number of stents in side branch	1.1 ± 0.3
Mean nominal diameter of stent in the side branch (mm)	2.78 ± 0.41
Mean total lengths of stent in the side branch (mm)	22.8 ± 11.1

LAD: left anterior descending artery, LCX: circumflex artery, RCA: right coronary artery, LMS: left main stem

Table 3: Quantitative coronary angiography undertaken in 16 lesions.

	Main branch	Side branch
Reference diameter (mm)	2.44 ± 0.36	2.43 ± 0.66
Length of lesion (mm)	9.1 ± 3.4	8.4 ± 6.2
Minimal lumen diameter (mm)		
Pre-procedure	0.85 ± 0.65	0.84 ± 0.74
Post-procedure	2.20 ± 0.35	2.00 ± 0.44
6-month follow-up	1.60 ± 0.57	1.43 ± 0.52
Diameter stenosis (%)		
Pre-procedure	70 ± 19	66 ± 26
Post-procedure	15 ± 9	18 ± 11
6-month follow-up	34 ± 20	38 ± 15
Late lumen loss (mm)	0.48 ± 0.56	0.53 ± 0.33
Binary restenosis rate (%)	18.8	12.5

suggested that restenosis rates were generally higher when a more complex “2-stent” strategy is adopted (stent implantation in both the main vessel and side branch) compared with single stenting only. [2-5] In randomized studies, drug-eluting stents have been shown to reduce restenosis compared with bare metal stent implantation in relatively simple lesions, though bifurcation lesions were excluded. [7-10] Further preliminary data for the sirolimus-eluting stent (SES) has more recently suggested efficacy in bifurcation lesions, [11,12] though the most effective strategy of stenting is currently unknown. These studies suggested a higher restenosis rate following a strategy of T-stenting, with the hypothesis that this might relate to incomplete coverage of the side branch ostium thereby reducing the efficacy of drug-elution. [11,12] In the present study, there was a relatively high percentage of patients with diabetes mellitus (21.7%), and almost one third were treated for a bifurcation lesion of the left main stem. We have demonstrated impressive long-term results of the Culotte technique when drug-eluting stents are utilized, with only one TLR at 8-months. In addition, the survival-free of major adverse events was 84.6%, with one of the 3 events related to thrombosis of an entirely different lesion.

The SES has been evaluated in one randomised study of bifurcation comparing a single stent with a 2-stent strategy. [12] The results suggested that, even with drug-eluting stents, it may be preferable to only stent the main vessel, and carry out balloon-only angioplasty in the side branch. On follow-up angiography, there was a trend towards a lower rate of restenosis in those treated with 1 stent compared with a 2-stent strategy (18.7% versus 28.0%, p=0.5). However, there was a very high rate of crossover from the 1 stent group to the 2 stent group of 51%, related to a sub-optimal result in the side branch. Furthermore, the strategy used in the 2 stent group was at the operators' discretion and therefore heterogeneous. This study emphasises some of the difficulties faced when treating bifurcation lesions. At baseline, a true bifurcation will have significant narrowing of both the main vessel and side branch. However, whatever the baseline anatomy, implantation of a stent within the main vessel can lead to plaque shift into the side branch therefore compromising side branch flow. Importantly, occurrence of such shift is unpredictable, [14] and the operator is then faced with the question as to how to deal with the side branch most effectively. The Culotte technique ensures complete lesion coverage and, with drug-eluting stents, may offer a useful strategy for treating bifurcation lesions. In particular, it can be done using a 6F sheath (other techniques such as the crush technique [15] or kissing stents require a guide of at least 7F), and, by covering the entire lesion, will minimise the importance of any plaque shift. In addition, it can provide a "backup" strategy for stenting of the side branch if the result following single stent implantation in the main vessel is sub-optimal. The major drawback to the technique is that it tends to be quite time-consuming, predominantly related to the need to re-wiring the vessels. Though it has not occurred in our experience, failure to re-wire the vessels could lead to procedural failure. In addition, there will be a double layer of stent struts in the proximal vessel. This raises some concerns, as the increased dosage of drug at this site may predispose to stent thrombosis. The technique needs to be fully evaluated in large studies, and randomization is needed to compare the relative efficacy of different stenting strategies particularly related to baseline anatomy.

Study limitations

The present study comprises a consecutive series of patients treated with the Culotte technique. However, the study was small and non-randomized, with no direct comparison of drug-eluting stent implantation utilizing alternative stenting strategies.

Conclusions

In this small study of bifurcation stenting utilizing the Culotte technique with drug-eluting stent implantation, there was a low rate of major adverse events and need for target lesion revascularization at 8-months when compared with historical data of bifurcation stenting with bare metal stents. Further re-evaluation of this technique utilizing drug-eluting stents, is warranted in the setting of larger randomized studies.

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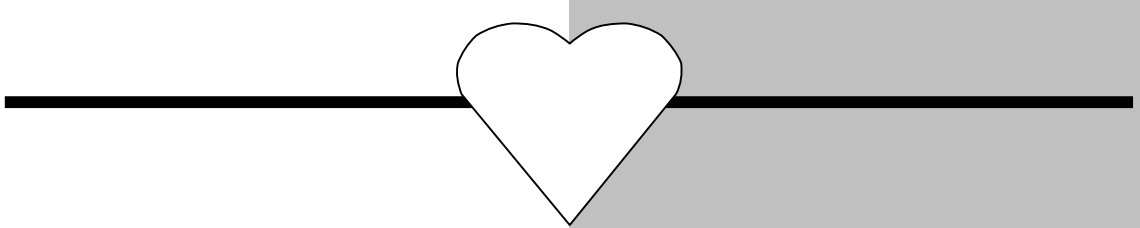
Part 3

THE UNRESTRICTED USE OF DRUG-ELUTING STENTS: PREDICTORS OF AN ADVERSE OUTCOME



Chapter 18

Thirty-day incidence and six-month clinical outcome of thrombotic stent occlusion after bare-metal, sirolimus, or paclitaxel stent implantation

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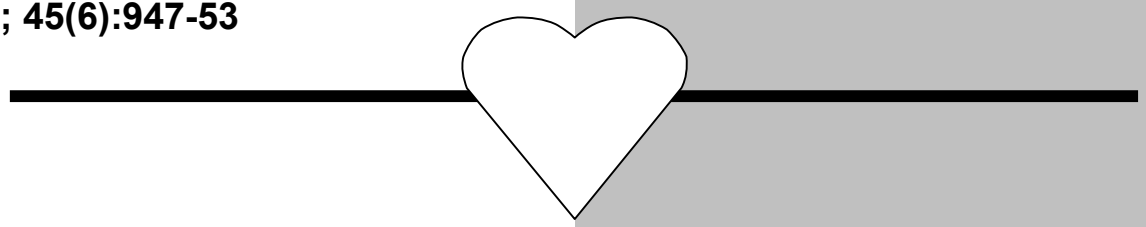
Journal of the American College of Cardiology
2005; 45(6):947-53



Abstract

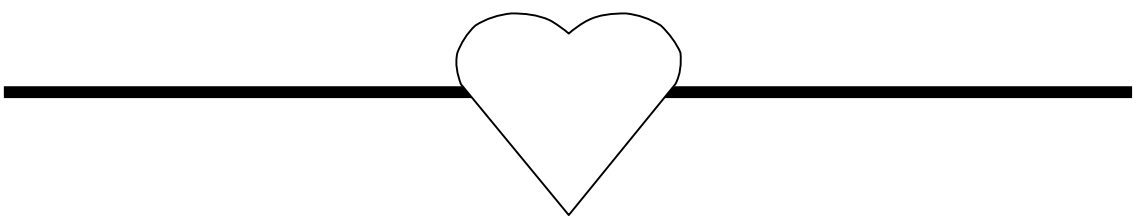
Objectives: We sought to determine the real-world incidence of angiographically confirmed and possible stent thrombosis (ST) in an unrestricted population during the first 30 days after bare-metal stent (BMS), sirolimus-eluting stent (SES), and paclitaxel-eluting stent (PES) implantation.

Background: Current data on ST in drug-eluting stents (DES) have come from randomized trials with strict entry criteria, which limits their generalizability to daily practice.

Methods: The study population comprised three sequential cohorts of 506 consecutive patients with BMS, 1,017 consecutive patients with SES, and 989 consecutive patients treated with PES.

Results: In the first 30 days after stent implantation, 6 BMS (1.2%, 95% confidence interval [CI] 0.5% to 2.6%; p = 0.9), 10 SES (1.0%, 95% CI 0.5% to 1.8%), and 10 PES (1.0%, 95% CI 0.6% to 1.9%) patients developed angiographically proven ST. Multiple potential risk factors were identified in most patients with ST. Bifurcation stenting in the setting of acute myocardial infarction was an independent risk factor for angiographic ST in the entire population (odds ratio [OR] 12.9, 95% CI 4.7 to 35.8, p < 0.001). In patients with DES who had angiographic ST, 30-day mortality was 15%, whereas another 60% suffered a nonfatal myocardial infarction; no further deaths occurred during six months of follow-up. Including possible cases, 7 BMS (1.4%, 95% CI 0.7% to 2.8%), 15 SES (1.5%, 95% CI 0.9% to 2.4%), and 16 PES (1.6%, 95% CI 1.0% to 2.6%) patients had ST.

Conclusions: The unrestricted use of SES or PES is associated with ST rates in the range expected for BMS. Stent thrombosis was associated with a high morbidity and mortality. Bifurcation stenting, when performed in patients with acute myocardial infarction, was associated with an increased risk of ST.



Introduction

Drug-eluting stents (DES) reduce clinical events related to restenosis. Concerns have been raised regarding the incidence of stent thrombosis (ST) with the unrestricted use of these stents. Data from the bare-metal stent (BMS) era report a high morbidity and mortality with ST. [1,2] Evidence for ST in DES has come from randomized controlled trials with strict entry criteria for the treatment of single lesions, limiting conclusions that are applicable to the real-world setting. [3-6] Other information has come from electronic registries with inherent biases that preclude generalization of the findings. A single-center registry recently reported its results with sirolimus-eluting stents (SES). [7] The aim of this present study is to describe the incidence of ST (both angiographically proven and including possible cases) in three consecutive populations while analyzing the unrestricted use of a control BMS group, SES, and paclitaxel-eluting stents (PES).

Methods

Study design and patient population

Since April 2002, SES (Cypher; Cordis Corp., Miami Lakes, Florida, a Johnson & Johnson Company) have been the stents of choice for all percutaneous coronary interventions irrespective of their clinical presentation or clinical outcome. [8] In the first quarter of 2003, PES (Taxus; Boston Scientific Corp., Natick, Massachusetts) replaced SES as the default stent. This present study comprises three sequential cohorts: a control group of the last 506 consecutive patients treated with BMS before April 2002; 1,017 consecutive patients with SES treated between April 2002 and February 2003; and 989 consecutive patients with PES treated between February 2003 and December 2003.

Procedure and antiplatelet management

All interventions were performed according to current standard guidelines, and the final interventional strategy including periprocedural glycoprotein IIb/IIIa and intravascular ultrasound use, was left to the discretion of the operator. Patients were pretreated with aspirin and a loading dose of 300 mg of clopidogrel. After their procedure, all patients were prescribed a lifelong aspirin regimen. Clopidogrel was prescribed for at least one month in the BMS group, for at least three months in the SES group, [8] and for at least six months in the PES group.

Follow-up

As part of the national health system, our institution as a tertiary referral center is the only interventional facility within our catchment area. The survival status of our patients at one and six months after discharge was obtained from the Municipal Civil Registries. Details of all repeat interventions (surgical and percutaneous) were collected prospectively during follow-up. Referring physicians and institutions were contacted whenever necessary for additional information. This protocol was approved by the Hospital Ethics Committee, and written, informed consent was obtained from every patient.

Definitions

Stent thrombosis was considered to have occurred when confirmed angiographically: either Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 or 1 or the presence of flow-limiting thrombus (TIMI flow grade 1 or 2) occurring in an acute (within 24 h of stent implantation) or subacute (between 1 and 30 days) time period after stent implantation. [9] In addition, a clinical definition of “possible stent thrombosis” was used for patients who within the first 30 days experienced sudden death, who suffered a fatal out-of-hospital cardiac arrest, or who suffered a myocardial infarction (MI) that was not clearly attributable to another coronary lesion and who did not undergo repeat angiography. All deaths and MIs were reviewed independently by two interventional cardiologists (A.O., E.Mc.F) for “possible stent thrombosis.”

Statistical analysis

Categorical variables were compared using the Fisher exact test and continuous variables with the Student *t* test or one-way analysis of variance where appropriate. Univariate and forward stepwise (entry criteria of 0.05

and exit criteria of 0.10) multivariate logistic regression analysis were performed to identify characteristics or variables independently associated with stent thrombosis. From the univariate analysis, the following baseline, clinical, angiographic and procedural variables were entered into the multivariate model: bifurcation stenting, diabetes, smallest stent diameter, multilesion stenting, and acute myocardial infarction (AMI) as the indication. All probability values are two-sided, and statistical significance was set at the 0.05 level. A cumulative event graph consisting of patients with angiographic stent thrombosis was generated plotting the proportion of patients with stent thrombosis (Y-axis) against time (X-axis) stratified by stent type. Incidences of stent thrombosis are reported as a percentage with associated 95% confidence intervals (CIs).

Results

Baseline and procedural characteristics

The patients in our cohort were at high risk, with unstable angina or AMI being the indication in more than one-half of the cases (Table 1). Multivessel disease was present in more than one-half of the population. One-third of the population had a previous AMI, whereas one-quarter had previous coronary interventions. Glycoprotein IIb/IIIa use was lower in the SES and PES groups compared with the BMS group.

Table 1: Baseline and Procedural Characteristics

	BMS (n = 506)	SES (n = 1,017)	PES (n = 989)	p value
Baseline characteristics				
Age, yrs, mean ± SD	61.0 ± 11.4	61.9 ± 11.3	61.7 ± 11.4	0.3
Male, %	73	70	74	0.1
Diabetes, %	16	18	17	0.6
Hypercholesterolemia, %	52	55	60	<0.01
Current smoker, %	35	28	28	<0.01
Hypertension, %	40	41	41	0.9
Previous MI, %	43	32	35	<0.01
Previous PCI, %	22	25	26	0.2
Previous CABG, %	11	9	8	0.2
Multivessel disease, %	54	57	56	0.4
Indication for index procedure				<0.01
Stable angina, %	42	43	41	
Unstable angina, %	35	36	30	
Acute MI, %	20	19	26	
Silent ischemia, %	3	2	3	
Number of vessels treated, mean ± SD	1.4 ± 0.6	1.4 ± 0.6	1.4 ± 0.6	0.8
LAD, n	281	594	540	
LCx, n	164	332	333	
RCA, n	194	398	384	
Others, n	29	75	90	
Total stent length, mm (mean ± SD)	31.9 ± 22.1	42.5 ± 29.6	44.2 ± 29.4	<0.01
Stents implanted, mm (mean ± SD)	1.9 ± 1.1	2.3 ± 1.5	2.2 ± 1.4	<0.01
At least one ≤2.5 mm stent implanted (%)	23	38	38	<0.01
Bifurcations stented, %	5	18	17	<0.01
Glycoprotein IIb/IIIa use (%)	37	21	28	<0.01

BMS = bare metal stent; CABG = coronary artery bypass grafting; LAD = left anterior descending; LCx = left circumflex; MI = myocardial infarction; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; RCA = right coronary artery; SES = sirolimus-eluting stent.

Clinical outcome

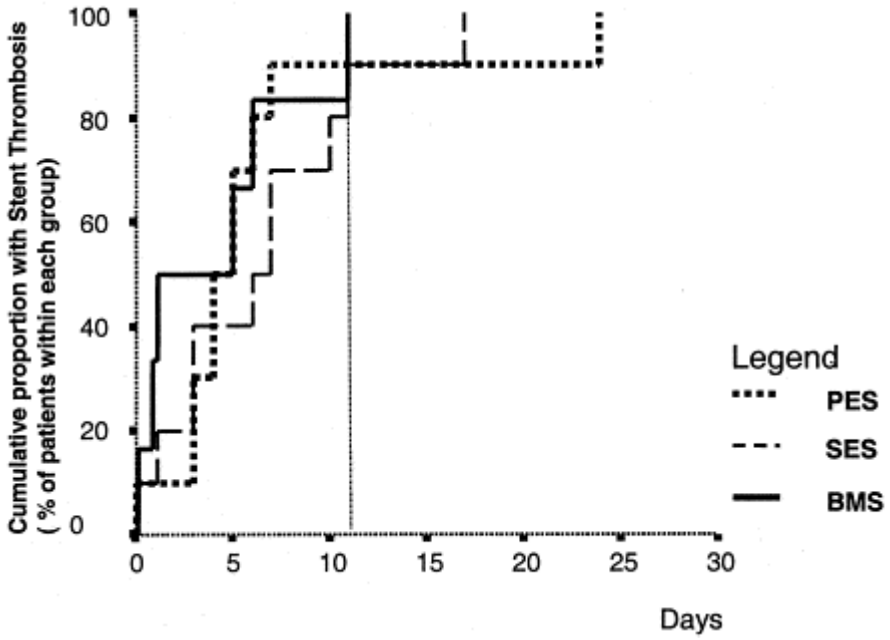
Angiographic ST was documented in 26 of 2,512 patients (Table 2). Six cases occurred in the BMS group (1.2%, 95% CI 0.5% to 2.6%), 10 cases occurred in the SES group (1.0%, 95% CI 0.5% to 1.8%), and 10 cases occurred in the PES group (1.0%, 95% CI 0.6% to 1.9%). The first two SES patients with ST have been reported previously. [10] Most stent thromboses occurred in the first 11 days, regardless of stent type, with a mean time to event of 5.8 ± 5.4 days (Fig. 1).

Table 2: Outcome Following Angiographic Stent Thrombosis

	BMS	SES	PES	p value
Angiographic stent thrombosis, n (%)	6 (1.2%)	10 (1.0%)	10 (1.0%)	0.9
Clinical presentation				
Acute MI, n	5	7	8	
Angina, n	1	3	2	
Maximum total CK, mean ± SD	4,983 ± 2,570	1,268 ± 476	3,361 ± 1,404	<0.01
Maximum CK-MB, mean ± SD	397 ± 186	171 ± 80	322 ± 166	<0.01
Outcome				
30-day mortality, n	0	0	3	
6-month mortality, n	0	0	3	

CK = creatine kinase; other abbreviations as in Table 1.

Figure 1: Cumulative incidence of angiographic stent thrombosis stratified by groups against time.



Vertical line = day 11 on horizontal axis. BMS = bare-metal stents; PES = paclitaxel-eluting stents; SES = sirolimus-eluting stents.

In the BMS population, there were two acute stent thromboses and four subacute stent thromboses. Among the six patients, ST presented as AMI in five patients. None died during the six months of follow-up (Table 2). In the combined group of SES and PES (2,006 patients), there were 2 cases of acute ST and 18 cases of subacute ST (Fig. 1). A detailed description of these patients is given in Table 3. Analysis via intravascular ultrasonography was performed in four patients. In most patients, at least one recognized risk factor for ST (i.e., long stented length, use of small stents, use of multiple stents, and residual dissection after stent implantation) was present. Importantly, 2 of the 20 patients had not taken clopidogrel.

Mortality and morbidity

Overall, 20 of 26 patients (77%) re-presented with an AMI, whereas the other 6 re-presented with angina pectoris (Table 2). Of these 26 patients, 3 (Patients #12, #18, and #20 from Table 3—all in the DES population) died at days 11, 5, and 3, respectively. Two patients died during reintervention from intractable ventricular fibrillation, whereas the third underwent emergency surgery after a suboptimal reintervention and could not be weaned from bypass. The incidence of death at 30 days was 12%, whereas another 65% suffered a nonfatal MI. Among the survivors of ST, there were no further deaths in the six months after reintervention.

Possible ST

Thirty-day survival data was complete for 98% of patients (Table 4). There were 12 patients who were judged with "possible stent thrombosis," of which 9 died and 3 had nonfatal MIs. Of the nine deaths, four were out-of-hospital sudden deaths, three occurred in hospital with ventricular tachycardia as the initiating preterminal rhythm, and two had ST-segment elevation and died before they could undergo reangiography. Among those with MIs, one patient developed a postprocedural enzyme leak, and another developed ventricular fibrillation requiring multiple cardioversions the day after the procedure. Repeat coronary angiography six months later demonstrated occluded stents in both of these patients; whereas a third underwent coronary angiography 14 days after stent implantation because of an increase in cardiac enzyme levels, which demonstrated an in-stent filling defect which was treated with abciximab, and subsequently underwent repeat percutaneous coronary intervention two weeks later. Including the suspected cases, the combined incidence of angiographic and possible ST was 1.4% (95% CI 0.7% to 2.8%) in the BMS control group, 1.5% (95% CI 0.9% to 2.4%) in the SES group, and 1.6% (95% CI 1.0% to 2.6%) in the PES group. In the combined total of 38 documented and possible ST, there were 12 deaths (32%) and 20 nonfatal MIs (53%) in the first 30 days.

Table 4: Incidence of Stent Thrombosis Classified by Definition

Stent Type	Number of Patients	Angiographically Proven Stent Thrombosis n (% [95% CI])	Possible Stent Thrombosis n (% [95% CI])	All Stent Thrombosis n (% [95% CI])
BMS	506	6 (1.2% [0.5%–2.6%])	1 (0.2% [0.0%–1.1%])	7 (1.4% [0.7%–2.8%])
SES	1,017	10 (1.0% [0.5%–1.8%])	5 (0.5% [0.2%–1.1%])	15 (1.5% [0.9%–2.4%])
PES	989	10 (1.0% [0.6%–1.9%])	6 (0.6% [0.3%–1.3%])	16 (1.6% [1.0%–2.6%])

CI = confidence interval; other abbreviations as in Table 1.

Multivariate analysis

By univariate analysis, bifurcation stenting was the only significant factor ($p = 0.01$). Multivariate analysis was performed with the following covariates based on their significance on univariate analysis as well as their potential clinical impact: diabetes ($p = 0.07$), smallest stent diameter ($p = 0.13$), multilesion stenting ($p = 0.17$), AMI as the indication ($p = 0.3$), and bifurcation stenting. By multivariate analysis, bifurcation stenting was the only independent predictor of ST (odds ratio [OR] 3.0, 95% CI 1.3 to 6.8, $p < 0.01$). When the interaction of bifurcation stenting by AMI was entered as a covariate, it was highly significant (OR 12.9, 95% CI 4.7 to 35.8, $p < 0.001$), and bifurcation stenting as a covariate was no longer significant.

Discussion

The main findings in this study can be summarized as follows: 1) the incidence of angiographic ST in an unselected, complex DES population was low (~1.0%), within the same range as the corresponding BMS population and concordant with previously published results from the BMS era; 2) the inclusion of possible ST increases the overall incidence of ST to ~1.5%; 3) angiographically proven ST was associated with a high mortality and morbidity; 4) patients who developed ST often had multiple high-risk features, regardless of stent type; and 5) the association of bifurcation stenting for AMI was a highly significant independent risk factor for ST.

Table 3: detailed description of drug-eluting stent patients with stent thrombosis

Patient	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Type of DES	**SES**	**SES**	**SES**	**SES**	**SES**	**SES**	**SES**	**SES**	**SES**	**SES**
Time to thrombosis (days)	**0.125**	**11**	**7**	**10**	**1.08**	**6**	**3**	**17**	**17**	**3**
Baseline characteristics										
Age (yrs)	72	61	86	57	75	55	53	58	58	74
Gender	F	F	F	M	F	F	M	M	M	M
Diabetes	+	+	-	+	-	-	+	-	+	-
Current smoker	-	-	-	+	-	-	-	-	-	-
Previous MI	-	+	-	+	-	-	+	-	+	+
Previous intervention	-	-	-	+	-	+	+	-	-	-
Index procedure										
Indication for procedure	UAP	AP	UAP	AMI, ST	AP	AP, ISR	UAP post-MI	AP	AMI	UAP post-MI
Glycoprotein IIb/IIIa inhibitor use	-	-	-	Y	-	-	-	Y	Y	-
Angiographic features of index procedure										
Culprit vessel	LAD	LAD	LAD	LAD	LAD/DIAG	LAD/DIAG	RCA	LAD	DIAG	LAD
Lesion type (AHA)	B1	C	C	C	B2	C	B2	B2	B2	B2
Bifurcation technique (where performed)	-	-	-	-	crush	t-stent	-	-	t-stent	-
Final kissing balloons (in bifurcations)	-	-	-	-	Y	N			N	
Minimum stent diameter (mm)	2.25	2.5	3	3	3	2.5	3	2.75	3	2.75
Total stent length (mm)	26	66	41	26	36	41	41	18	31	36
Total stents implanted	2	2	3	2	2	2	2	1	2	2
Re intervention										
Clinical presentation	AMI	AP	AMI	AP	AMI	AMI	AMI	AP	AMI	AMI
Additional stent implanted	Y	-	Y	Y	-	-	Y		-	-
IVUS findings (where performed)	RD	UD	-	RD	-	-	-		-	UD
Site of thrombosis in bifurcation lesions	-	-	-	-	MB+SB	SB	-	-	SB	-
Incomplete oral anti-platelet therapy	-	-	-	-	-	-	-	-	Y	-
Successful procedural outcome	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

AMI = acute myocardial infarction; AP = angina pectoris; DIAG = diagonal branch; IM = intermediate branch; LAD = left anterior descending artery; LCx = left circumflex artery; MB = mainbranch; N = no; OMCx = obtuse marginal branch; RCA = right coronary artery; RD = residual dissection; SB = sidebranch; ST = stent thrombosis; UAP = unstable angina pectoris; UD = underdeployment; Y = yes; other abbreviations as in Table 1.

Patient	11	12	13	14	15	16	17	18	19	20	Mean ± SD, %
Type of DES	**PES**	**PES**	**PES**	**PES**	**PES**	**PES**	**PES**	**PES**	**PES**	**PES**	
Time to thrombosis (days)	**0.04**	**4**	**7**	**6**	**3**	**4**	**24**	**5**	**5**	**3**	**6.3 ± 5.7**
Baseline characteristics											
Age (yrs)	59	50	67	47	61	52	60	54	65	31	59.7 ± 11.9
Gender	M	M	M	F	M	F	M	M	M	M	13M 7F
Diabetes	-	-	-	-	+	-	-	-	-	-	30%
Current smoker	-	-	-	+	+	+	-	+	-	+	30%
Previous MI	-	-	+	-	+	-	+	-	+	-	45%
Previous intervention	-	-	+	-	-	-	-	-	-	+	25%
Index procedure											
Indication for procedure	AMI	AMI	AP	AMI	AP	AMI	AP	AMI	AP	AP	
Glycoprotein IIb/IIIa inhibitor use	-	-	-	Y	-	-	-	Y	Y	-	30%
Angiographic features of index procedure											
Culprit vessel	RCA	LAD	OMCX	LAD/DIAG	LCx	LCX/OMCX	LCX	LAD/DIAG	LAD/IM/LCx	LAD	
Lesion type (AHA)	B2	B2	C	C	B2	C	C	C	C	B2	
Bifurcation technique (where performed)	-	-	Crush	Crush	-	t-stent	-	Crush	Culotte crush	-	40%
Final kissing balloon (in bifurcations)	-	-	N	N	-	N	-	N	Y	N	
Minimum stent diameter (mm)	3	3.5	2.5	2.5	2.5	2.25	2.25	2.75	2.25	3	2.7 ± 0.3
Total stent length (mm)	28	24	32	36	20	44	32	36	140	84	41.2 ± 27.8
Total stents implanted	1	1	2	2	1	2	2	2	8	4	2.2 ± 1.5
Re intervention											v
Clinical presentation	AMI	AMI	AMI	AMI	AMI	UAP	UAP	AMI	AMI	AMI	AMI = 75%
Additional stent implanted	-	-	Y	-	Y	-	Y	-	-	-	Yes = 35%
IVUS findings (where performed)	-	-	-	-	-	-	-	-	-	-	
Site of thrombosis in bifurcation lesions	-	-	SB	SB	-	SB	MB+SB	SB	MB+SB	-	
Incomplete oral anti-platelet therapy	-	-	-	-	-	-	-	-	-	-	10%
Successful procedural outcome	Y	Died	Y	Y	Y	Y	Y	Y	Died	Died	Death = 15%

AMI = acute myocardial infarction; AP = angina pectoris; DIAG = diagonal branch; IM = intermediate branch; LAD = left anterior descending artery; LCx = left circumflex artery; MB = mainbranch; N = no; OMCx = obtuse marginal branch; RCA = right coronary artery; RD = residual dissection; SB = sidebranch; ST = stent thrombosis; UAP = unstable angina pectoris; UD = underdeployment; Y = yes; other abbreviations as in Table 1.

The availability of DES as the default stent at our institution has allowed us to analyze this new technology in an unrestricted population, [8] a population that would have comprised any BMS population in the pre-DES era. Therefore, this availability allows us to analyze incidences in an "all-comers" population because patients were enrolled irrespective of clinical presentation or outcome. In this population sample, angiographic ST rates in the first 30 days for both DES, i.e., SES and PES, occurred within the range as that reported in the BMS era. [1,2,11,12]

The angiographic definition used is the most accurate for diagnosis but may underestimate the true incidence of ST because some patients who have a presumed ST may die before receiving medical attention. Conversely, the use of major adverse cardiac events (i.e., death and MI in addition to the angiographic findings) to define ST overestimates the true incidence because not all patients who die suddenly or suffer a MI do so because of ST. [13] This consideration is important in our heterogeneous unrestricted population with multivessel disease, previous MI, and previous revascularization. Furthermore, not all patients who die will undergo autopsy studies to determine the cause of death. To attenuate this overestimation and to provide an accurate figure, we have adjudicated all deaths and noncatheterized, nonfatal MIs within the first 30 days in the three groups and included them with the angiographically proven patients to provide an overall incidence for each group.

The incidences of ST for both groups of DES are within the range reported in the larger randomized clinical trials of DES [3-6] despite longer total stent length, multivessel treatment, and a heterogeneous population (Table 5). This incidence complements information already available from the randomized trials regarding the safety of these new devices.

Table 5: Clinical Trials on Drug-Eluting Stents

Trial Name	Number of Patients in Drug-Eluting Arm	Total Stent Length mm (Mean ± SD)	Incidence of Stent Thrombosis in the First 30 Days (%)
SIRIUS (3)	533	23.0 ± 8.6	0.2*
E-SIRIUS (6)	157	21.5 ± 6.7	1.1*
C-SIRIUS (5)	50	23.8 ± 8.4	2.0*
TAXUS-IV (4)	662	21.9 ± 8.1	0.3†
SES group	1,017	42.5 ± 29.6	‡1.0–1.5§
PES group	989	44.2 ± 29.4	‡1.0–1.6§

Abbreviations as in Table 1.

* Definition of stent thrombosis was not stated.

† Stent thrombosis defined as angiographically proven, or cardiac death or myocardial infarction in the first 30 days.

‡ Stent thrombosis defined as angiographically proven.

§ Stent thrombosis defined as angiographically proven, or adjudicated death or myocardial infarction in the first 30 days.

Angiographic ST was associated with a high mortality and morbidity in our study. Within the DES population, 15 patients (75%) experienced a MI as their diagnosis at the second presentation, and 3 (15%) died during the reintervention procedure. The inclusion of possible ST patients increased the mortality to 32%. Given the small number of events, the fact that no deaths occurred in the BMS group was most likely due to chance. These results are in concordance with the results of a large BMS registry. [2]

Previous studies have demonstrated that residual dissection, [1,11] long stents, [1] small final lumen diameter, [1] and use of multiple stents [2] are risk factors for the development of ST. In our series, multiple risk factors were identified in most patients who developed ST. Patients with ST had more multiple lesions treated, smaller minimum stent diameters, and longer stent lengths compared with those without ST; however, these factors were not significant on univariate analysis. What did emerge and which has not been previously reported is that patients undergoing bifurcation stenting had a higher incidence of ST compared with those

without bifurcation stenting. A recent study on bifurcations reported a 3.5% incidence of ST, which is higher than the overall incidence in this population. [14]

Although stent implantation for AMI was not significant on univariate analysis, the interaction of AMI and bifurcation stenting when entered as a covariate for ST on multivariate analysis emerged as a highly significant independent predictor, and bifurcation stenting as a covariate was no longer significant. This result confirms a clinical suspicion in our department regarding the increased risk of ST in patients treated with bifurcation stenting in the setting of AMI.

Mechanical reasons that predispose to ST can be modified by interventional technique. Optimizing stent placement including, if necessary, intravascular ultrasound-guided postdilation, kissing balloon postdilation with bifurcation stenting, and careful inspection for residual dissection after stent implantation, may further reduce the incidence of ST.

Pharmacologic reasons for ST, i.e., inadequate antiplatelet therapy, are patient-specific factors. Recent research literature has focused on "resistance" to either aspirin [15] or to clopidogrel. [16] Currently, most laboratories do not routinely test for antiplatelet resistance. In our series, two patients who had not taken their prescribed clopidogrel after the procedure developed ST.

This report covers ST occurring in the first 30 days after stent implantation only, during which all patients received dual antiplatelet therapy. The duration of clopidogrel therapy differed among the three groups; in part, it reflects uncertainty with regards to re-endothelialization after DES implantation. Late ST has been reported to occur with BMS [17] and with DES, [18] including a reported fatality [19] after clopidogrel discontinuation. At this stage, the incidence of late ST in the DES era is unknown, and further studies are required to clarify this potential late complication.

Comment on sample size and statistical comparisons

Because ST occurs at a low incidence (~1.0 to 1.5%), a small sample size may underestimate or overestimate the true incidence. In a previously published report from our institution, we reported an angiographic incidence of 0.4% in 508 patients. [8] In the present study we extended the population to incorporate the entire period of DES used to date at our institution (n = 2,006) to allow a more accurate analysis of the true incidence of ST in the DES population. Despite having 2,512 patients, the low and small/negligible absolute difference in incidence precludes formal statistical comparisons of ST rates among the three groups because it lacks sufficient statistical power. To achieve adequate power would require sample sizes in the order of >100,000 patients. To date, this study is the largest series of patients reported on in the DES era.

Study limitations

These single-center registry data complement available randomized data, as they reflect the results of unrestricted DES use.

Conclusions

Despite having a more complex cohort with high-risk inclusion criteria, longer stent lengths, and more complex procedural features, the incidence of ST with DES are in the same range as the BMS population observed in our present study. They also are in agreement with previously reported data by others from the BMS era and with those results reported on in the earlier randomized DES trials. Furthermore, the two groups of DES, i.e., SES and PES, share an incidence of ~1.0% to 1.5%. Stent thrombosis is associated with a high morbidity and mortality.

As extensively documented in previous reports with BMS, mechanical reasons were observed to be frequent associations for ST with DES. In this study, bifurcation stenting in the setting of AMI was a highly significant independent predictor for angiographic ST.

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Chapter 19

Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients: an evaluation from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study

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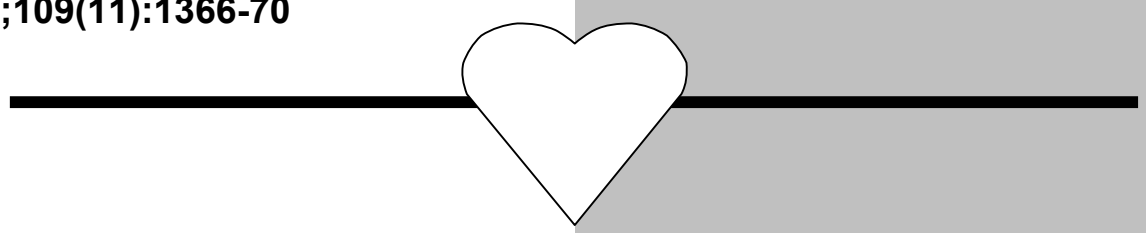
Circulation
2004;109(11):1366-70



Abstract

Background: The factors associated with the occurrence of restenosis after sirolimus-eluting stent (SES) implantation in complex cases are currently unknown.

Methods and Results: A cohort of consecutive complex patients treated with SES implantation was selected according to the following criteria: (1) treatment of acute myocardial infarction, (2) treatment of in-stent restenosis, (3) 2.25-mm diameter SES, (4) left main coronary stenting, (5) chronic total occlusion, (6) stented segment >36 mm, and (7) bifurcation stenting. The present study population was composed of 238 patients (441 lesions) for whom 6-month angiographic follow-up data were obtained (70% of eligible patients). Significant clinical, angiographic, and procedural predictors of post-SES restenosis were evaluated. Binary in-segment restenosis was diagnosed in 7.9% of lesions (6.3% in-stent, 0.9% at the proximal edge, 0.7% at the distal edge). The following characteristics were identified as independent multivariate predictors: treatment of in-stent restenosis (OR 4.16, 95% CI 1.63 to 11.01; P<0.01), ostial location (OR 4.84, 95% CI 1.81 to 12.07; P<0.01), diabetes (OR 2.63, 95% CI 1.14 to 6.31; P=0.02), total stented length (per 10-mm increase; OR 1.42, 95% CI 1.21 to 1.68; P<0.01), reference diameter (per 1.0-mm increase; OR 0.46, 95% CI 0.24 to 0.87; P=0.03), and left anterior descending artery (OR 0.30, 95% CI 0.10 to 0.69; P<0.01).

Conclusions: Angiographic restenosis after SES implantation in complex patients is an infrequent event, occurring mainly in association with lesion-based characteristics and diabetes mellitus.

Introduction

In-stent restenosis is the major limitation hampering the medium-term efficacy of coronary stenting. Several reports have evaluated the impact of baseline and procedural characteristics on the risk of subsequent restenosis after bare metal stent implantation, with a number of high-risk parameters, such as diabetes, lesion length, and vessel size, being consistently identified in most studies.[1–7] Unfortunately, these characteristics are commonly found in the daily practice, where treatment of complex patients frequently appears as a challenging therapeutic dilemma.

Sirolimus-eluting stents (SESs) have been proven to strikingly decrease neointimal growth, leading to a marked reduction in restenosis rates.[8–10] In the RAndomized study with the sirolimus-eluting Bx VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions (RAVEL),[8] no cases of binary angiographic restenosis were seen after SES implantation. Moreover, restenosis was significantly reduced from 36.3% with conventional stents to 8.9% with SESs in the randomized SIRolImUS-eluting Bx velocity balloon expandable stent trial (SIRIUS)[9] and from 42.3% to 5.9% in the E-SIRIUS trial,[10] with diabetes, small vessel size, and long lesions being identified as predictors of post-SES restenosis in the SIRIUS trial.[9] Nevertheless, these randomized studies have been largely restricted to selected patients treated with single-lesion elective stenting. The factors related to angiographic restenosis after SES implantation in highly complex subsets are currently unknown.

SES implantation was recently shown to effectively improve the 1-year clinical outcomes in "real world" practice in patients enrolled in the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) study.[11] In the RESEARCH study, a parallel angiographic substudy was conducted to evaluate the late angiographic findings of complex patients treated with SESs. The present report aimed to evaluate the value of clinical, angiographic, and procedural factors in predicting the risk of binary restenosis in highly complex patients treated with SES implantation in the RESEARCH study.

Methods

Study Design and Patient Population

The design of the RESEARCH study has been reported previously.[11] In brief, SES implantation (Cypher; Johnson & Johnson-Cordis unit, Cordis Europa NV) was introduced as the default strategy for all patients undergoing percutaneous coronary interventions in our institution after April 2002. All procedures were performed according to standard techniques, and the final interventional strategy was left to the discretion of the operator, with the aim of achieving a final residual stenosis <50% by online quantitative coronary angiography in the presence of TIMI (Thrombolysis In Myocardial Infarction) 3 grade flow. The use of periprocedural glycoprotein IIb/IIIa inhibitors and antithrombotic medications was left entirely to the discretion of the attending team.

Patients receiving SESs were considered candidates for angiographic reevaluation if they had at least 1 of the following characteristics: (1) treatment of acute myocardial infarction, (2) treatment of in-stent restenosis, (3) use of a very small SES (2.25-mm nominal diameter), (4) treatment of left main coronary, (5) treatment of chronic total occlusion (>3 months), (6) total adjacent stented segment longer than 36 mm, and (7) bifurcation stenting (SES implanted in both the main vessel and the side branch). Patients with the aforementioned characteristics who had not undergone repeat intervention in the first month and had not presented any formal medical contraindication for angiographic restudy were considered eligible for angiographic follow-up at 6 to 8 months. Coronary angiograms performed prematurely because of clinical indications were used as the follow-up angiography if performed after 4 months or if restenosis was detected. In other cases, a second angiogram was obtained between 6 and 8 months. Importantly, although all patients were approached for angiographic follow-up, patient refusal was not considered as an exclusion criterion to be enrolled in the RESEARCH study. Angiographic restudy was not requested for nonresidents of the Netherlands.

During the first 6 months of enrollment, a total of 362 consecutive patients had at least 1 of the high-risk criteria listed above (57% of all patients treated with SESs in the period). Of these, 2 patients moved to another country, 10 had died within the first 6 months of follow-up, 6 had repeat intervention before 30 days (surgical or percutaneous), and 3 were considered to have a medical contraindication to the angiographic follow-up (1

patient with previous stroke and disabling dementia, 1 with severe allergic contrast reaction at the index procedure, and 1 with end-stage hepatic failure due to autoimmune hepatitis). Of the remaining 341 patients, angiographic reevaluation at 204±34 days was obtained for 238 patients (70% of eligible patients), who compose the present study population.

Quantitative Coronary Angiography

Quantitative coronary angiographic analysis was performed as described previously with a validated computer-based edge-detection system (CASS II, Pie Medical).[12] Interpolated reference diameter, minimal luminal diameter, and diameter stenosis were obtained at baseline, after stenting, and at follow-up. In-stent restenosis was defined by diameter stenosis >50% and was classified as in-stent if inside the stent or in-segment if located within the stented segment plus the 5-mm segments distal or proximal to the stent margins.[9] Restenosis at an ostial location (within 3 mm of the vessel origin) was classified as in-stent unless clearly located outside the limits of the SES.[13]

Statistical Analysis

Continuous variables are presented as mean±SD and were compared with Student's unpaired *t* test. Categorical variables are presented as counts and percentages and compared with the Fisher exact test. Demographic, clinical, procedural, and angiographic variables were tested in univariate and multivariate logistic analyses for their value in predicting binary restenosis. All variables shown in Tables 1 and 2□ were considered in multivariate logistic regression analyses regardless of their univariate findings. The final model was built iteratively and evaluated for lack of fit with the Hosmer-Lemeshow test. Global predictive accuracy was assessed by means of the C-index (area under the receiver operating characteristic curve). Finally, an internal validation was performed with a bootstrap technique.[14] The model was repeatedly applied to 1000 replicated bootstrap samples, and the C-index for each individual sample was calculated. The C-index obtained from each bootstrap sample was then subtracted from the initial C-index value of the original population. The average of the differences was considered as a measure of optimism in the model fit. Finally, a corrected C-index was

Table 1: Clinical Characteristics of 238 Patients Treated With SES Implantation

Characteristic		No.
Male gender		73
Age, y		60 ± 12
Height, cm		172 ± 9
Weight, kg		82 ± 14
Hypercholesterolemia		58
Hypertension		56
Diabetes mellitus		22
Insulin-dependent diabetes		6
Non-insulin-dependent diabetes		16
Previous myocardial infarction		32
Previous bypass surgery		11
Previous percutaneous intervention		28
Vessel disease	1-vessel disease	40
	2-vessel disease	35
	3-vessel disease	25
Clinical presentation	Stable angina	54
	Unstable angina	21
	Acute myocardial infarction	26
Periprocedural IIb/IIIa inhibitor		27

Values are percentages or mean±SD

*Total cholesterol >200 mg/dL or receiving lipid-lowering treatment

Table 2: Procedural and Angiographic Characteristics of 441 Lesions Treated With SES Implantation

Characteristics		No.
Treated vessel	Left main coronary	3
	Left anterior descending	43
	Left circumflex	22
	Right coronary artery	30
	Bypass graft	3
Lesion type	A	6
	B1	23
	B2	43
	C	28
Chronic total occlusion >3 months		8
Moderate/severe angiographic calcification		7
Ostial location		22
Bifurcation treatment		22
Treatment of in-stent restenosis		13
No. of stents implanted		1.41 ± 0.81
Overlapping stents		39
Total stented length, mm		26.0 ± 20.3
Stented length >36 mm		17
Use of 2.25-mm SES		18
Reference diameter, mm		2.50 ± 0.61
Preprocedure minimal luminal diameter, mm		0.69 ± 0.54
Preprocedure diameter stenosis, %		72.2 ± 20.0
Lesion length, mm		16.1 ± 11.8
Postprocedure minimal luminal diameter, mm		2.13 ± 0.58
Postprocedure diameter stenosis, %		17.2 ± 11.1
Follow-up minimal luminal diameter, mm		2.10 ± 0.69
Follow-up diameter stenosis, %		22.8 ± 19.9
Late loss, mm		0.04 ± 0.49
Binary restenosis	In-stent	6.3
	Proximal edge	0.9
	Distal edge	0.7

Values are percentages or mean±SD

*SES implantation in both the main vessel and the side branch

calculated by subtracting the average of the optimism estimates from the original C-index. The bootstrap correction has been described as a nearly unbiased internal validation, which penalizes for any model overfitting.[14] Presented 95% CIs of all multivariate estimates were derived from the bootstrap analysis.

Results

Among the 238 patients (441 lesions) included in this analysis, 13 (6%) had left main coronary stenting, 35 (15%) had at least 1 chronic total occlusion, 45 (19%) received sirolimus stents to treat at least 1 restenotic lesion, 50 (21%) had bifurcation stenting, 62 (26%) were in the acute phase of a myocardial infarction, 68 (28%) had at least one 2.25-mm SES implanted, and 83 (35%) had very long stenting (>36 mm) in at least 1 vessel (Tables 1 and 2). On average, 1.41±0.81 stents were implanted per lesion, and 39% of lesions had at least 2 stents that overlapped. Most lesions were classified as American College of Cardiology/American Heart Association type B2 or C (71%); 22% received bifurcation stenting (stent implanted in both the main vessel and the side branch); 8% were chronic total occlusions (duration >3 months); and 3% were located in the left main

coronary. Mean vessel size was 2.50±0.61 mm (range 1.00 to 4.59 mm), and the average stented length was 26.0±20.3 mm (range 8 to 117 mm).

At the follow-up angiogram, 7.9% of lesions had binary in-segment restenosis. Of these, 6.3% were located inside the stent (in-stent), 0.9% were located in the proximal edge, and the remaining 0.7% occurred at the distal edge. Because of the limited number of lesions with edge restenosis (7 observations), additional analyses were performed for all lesions grouped as in-segment restenosis.

Table 3: Clinical, Procedural, and Angiographic Univariate Predictors of In-Segment Restenosis After SES Restenosis

	OR	95% CI	p
Bypass graft	4.61	1.39 – 15.33	0.01
Treatment of in-stent restenosis	3.66	1.68 – 7.96	<0.01
Previous bypass surgery	3.24	1.42 – 7.41	<0.01
Bifurcation stenting (side branch position)	2.77	1.15 – 6.33	0.02
Ostial location	2.66	1.30 – 5.46	<0.01
Diabetes mellitus	2.54	1.24 – 5.21	0.01
No. of stents implanted	1.62	1.19 – 2.22	<0.01
Postprocedure diameter stenosis (per 10% increase)	1.55	1.14 – 2.10	<0.01
Total stented length (per 10-mm increase)	1.30	1.14 – 1.48	<0.01
Preprocedure minimal luminal diameter	0.46	0.22 – 0.95	0.04
Postprocedure minimal luminal diameter	0.39	0.20 – 0.76	<0.01
Left anterior descending artery	0.37	0.16 – 0.82	0.02
Acute myocardial infarction	0		<0.01

Table 4: Clinical, Procedural, and Angiographic Multivariate Predictors of In-Segment Restenosis After SES Restenosis*

	OR	95% CI	p
Treatment of in-stent restenosis	4.16	1.63 – 11.01	<0.01
Ostial location	4.84	1.81 – 12.07	<0.01
Diabetes mellitus	2.63	1.14 – 6.31	0.02
Total stented length (per 10-mm increase)	1.42	1.21 – 1.68	<0.01
Reference diameter (per 1.0-mm increase)	0.46	0.24 – 0.87	0.03
Left anterior descending artery	0.30	0.10 – 0.69	<0.01

*Intercept coefficient, -2.34.

Table 5: Actual Rates of Post-SES In-Segment Restenosis According to the Presence of High-Risk Characteristics*

	In-Segment Restenosis Rate, %
Treatment of in-stent restenosis	19.6
Ostial location	14.7
Diabetes mellitus	14.3
Stented length >26 mm†	13.9
Reference diameter <2.17 mm‡	10.3
Non-LAD location	10.8

LAD indicates left anterior descending artery.

*Presence of multivariate independent predictors.

†Higher tercile for stented length.

‡Lower tercile for reference diameter.

The Figure shows the univariate relationship between demographic, angiographic, and procedural characteristics and the incidence of post-SES restenosis, and significant univariate parameters are shown in Table 3. In the multivariate analysis, the following variables were identified as independent predictors of restenosis: treatment of in-stent restenosis, ostial location, presence of diabetes mellitus, total stented length, reference diameter, and left anterior descending artery location (Table 4). The final multivariate model fit the data well (Hosmer-Lemeshow test P=0.94; χ^2=2.93; df=8) and had a good predictive accuracy (C-index 0.83), which was virtually unchanged after the bootstrap correction (corrected C-index 0.82). Actual restenosis rates for patients with "high-risk" characteristics (derived from the multivariate model) are shown in Table 5.

Discussion

The present study reported on the predictors of angiographic restenosis after SES implantation in complex patients. Overall, our series included patients with smaller vessels and longer lesions than in other trials conducted to date.[8–10] Moreover, a considerable proportion of patients had previous in-stent restenosis, bifurcation stenting, chronic total occlusions, thrombus-containing lesions, and calcified vessels, conditions that were formally excluded from previous trials. Nevertheless, binary restenosis after SES implantation in such a complex patient population was detected in only a minority of cases (7.9% of lesions). The expected restenosis rate for de novo lesions included in the present report would range from 40.1% to 43.0% if treated with bare metal stents, as calculated from prediction equations derived from previous meta-analysis with conventional stents.[3,6]

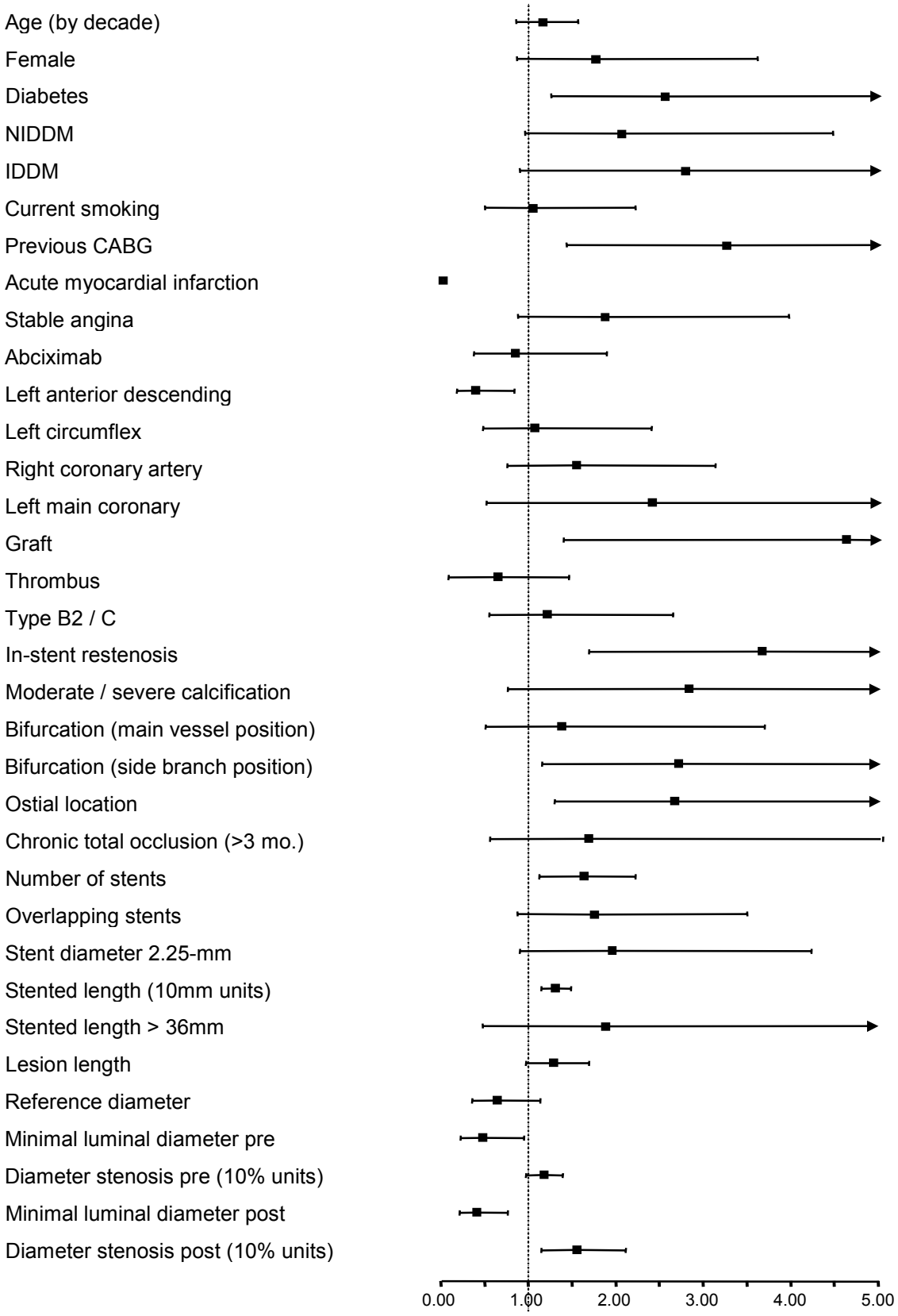
In the SIRIUS trial, small vessel size, long lesion length, and diabetes were shown to significantly increase the incidence of restenosis after SES.[9] These characteristics were confirmed as predictors of post-SES restenosis in the present study, which additionally extended the list of independent parameters to include ostial location and treatment of in-stent restenosis (as negative factors) and left anterior descending artery location (as a protective factor). Interestingly, most characteristics identified as predictors of post-SES restenosis have long been recognized as major predictors of restenosis after balloon angioplasty or conventional bare stent implantation.[1–7,15–17] It seems intuitive to assume that the increased incidence of restenosis after SES implantation in patients with these risk factors may reflect an extreme background tendency to tissue reaction and neointimal growth, which was not sufficiently inhibited by the antiproliferative action of the drug.

Restenosis after SES has been shown to be associated with incomplete lesion coverage in some cases, as detected by intravascular ultrasound.[13] In the present study, lesions involving ostial sites had a higher risk of restenosis, which may be related, at least in part, to technical difficulties in stent positioning and vessel scaffolding at the ostium. We may speculate that the presence of "traditional" risk factors for restenosis may potentially act as a predisposing factor that will lead to restenosis in case a subtle device-related or procedure-related local failure is eventually superimposed. Unfortunately, small gaps between stents and minor ruptures in the metallic stent mesh or in the polymer integrity are not detectable by conventional coronary angiography[13] and could not be evaluated in the present report.

The treatment of in-stent restenosis with SES was associated with a more than 4-fold increase in the risk of restenosis after adjustment for other independent variables. Although SES implantation has been associated with low rates of repeat restenosis after treatment of noncomplex in-stent restenosis,[18,19] the efficacy of this device for more complicated cases remains to be established.[20,21] Redilation of restenotic lesions (ie, exposure to "double injury") has been shown to trigger a peculiar local vascular response, distinct from that observed after the first dilation.[22] Modifications in the reparative mechanisms, especially after endovascular brachytherapy,[20] may decrease the responsiveness of restenotic lesions to the antiproliferative drug.

Curiously, lesions located in the left anterior descending artery had a decreased restenosis rate in the present series. Whether this factor represents a true protective characteristic has to be further investigated in future studies. Although post-SES restenosis was not detected in any patient admitted with acute myocardial infarction, this characteristic was not included in our final multivariate model, which suggests that perhaps acute myocardial infarction at admission per se was not an important factor affecting restenosis in the present study

Figure: Univariate OR of binary angiographic in-segment restenosis after SES restenosis according to demographic, clinical, procedural, and angiographic characteristics. NIDDM indicates non–insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; pre, preprocedure; and post, postprocedure.



population. Post-SES restenosis in the present study was almost entirely restricted to the segment inside the stent (≈80% of restenoses). This finding represents a major difference from previous trials with SES, in which restenosis more frequently occurred at the stent edges.[9,10] In the RESEARCH study, all operators were strongly advised to actively cover the entire injured vessel area and to avoid both residual dissection at stent borders and gaps between stents. In addition, the stent placement strategy aimed to cover the treated segment "from healthy tissue to healthy tissue," to avoid having the free borders of the stents terminate in grossly diseased segments. However, it remains speculative whether these procedural strategies might have had any impact in reducing the incidence of restenosis at the stent edges.

Study Limitations

The present report may suffer from its relatively limited study population, which was restricted to complex patients who fulfilled predefined criteria to be included in this angiographic substudy. Therefore, our results cannot be directly extrapolated to the entire cohort of consecutive patients treated in the RESEARCH study, and further analyses are needed to fully assess the angiographic outcomes of subsets not included in the present study. Ten patients with early death could not be restudied at 6 months, and a higher rate of angiographic follow-up (≈70% in this study) would be desirable for a comprehensive evaluation. However, the present study was designed to enroll all unselected patients treated in our institution, and patient refusal for angiographic follow-up did not preclude enrollment in the RESEARCH study. Obviously, this real-life scenario differs substantially from that of randomized trials and limits the compliance to angiographic restudy.

Conclusions

Angiographic restenosis after SES implantation in complex patients is an infrequent event (7.9% of lesions), occurring mainly in association with local, lesion-based characteristics and diabetes mellitus.

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Chapter 20

The unrestricted use of paclitaxel- versus sirolimus-eluting stents for coronary artery disease in an unselected population: one-year results of the Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry

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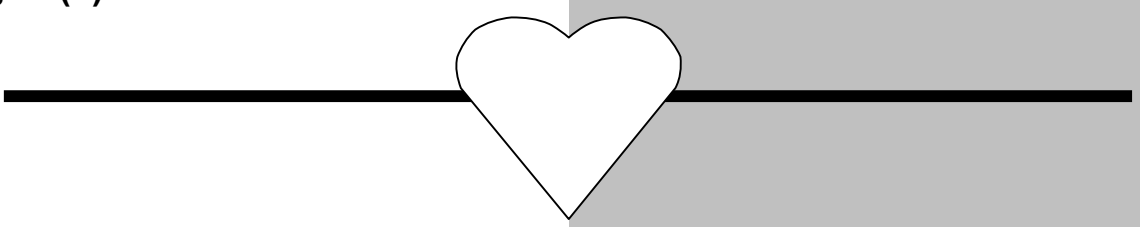
Journal of the American College of Cardiology
2005; 45(7):1135-41



Abstract

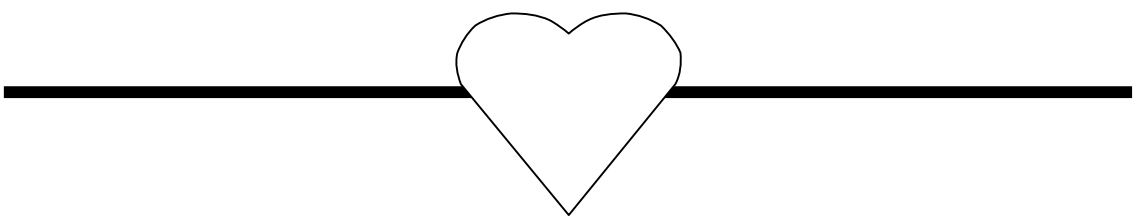
Objectives: We investigated the efficacy of paclitaxel-eluting stents (PES) compared to sirolimus-eluting stents (SES) when used without restriction in unselected patients.

Background: Both SES and PES have been separately shown to be efficacious when compared to bare stents. In unselected patients, no direct comparison between the two devices has been performed.

Methods: Paclitaxel-eluting stents have been used as the stent of choice for all percutaneous coronary interventions in the prospective Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry. A total of 576 consecutive patients with de novo coronary artery disease exclusively treated with PES were compared with 508 patients treated with SES from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry.

Results: The PES patients were more frequently male, more frequently treated for acute myocardial infarction, had longer total stent lengths, and more frequently received glycoprotein IIb/IIIa inhibitors. At one year, the raw cumulative incidence of major adverse cardiac events was 13.9% in the PES group and 10.5% in the SES group (unadjusted hazard ratio [HR] 1.33, 95% confidence interval [CI] 0.95 to 1.88, p = 0.1). Correction for differences in the two groups resulted in an adjusted HR of 1.16 (95% CI 0.81 to 1.64, p = 0.4, using significant univariate variables) and an adjusted HR of 1.20 (95% CI 0.85 to 1.70, p = 0.3, using independent predictors). The one-year cumulative incidence of clinically driven target vessel revascularization was 5.4% versus 3.7%, respectively (HR 1.38, 95% CI 0.79 to 2.43, p = 0.3).

Conclusions: The universal use of PES in an unrestricted setting is safe and is associated with a similar adjusted outcome compared to SES. The inferior trend in crude outcome seen in PES was due to its higher-risk population. A larger, randomized study enrolling an unselected population may assist in determining the relative superiority of either device.



Introduction

Sirolimus-eluting stents (SES, Cypher, Cordis, Johnson and Johnson, Miami Lakes, Florida) [1] and paclitaxel-eluting stents (PES, TAXUS, Boston Scientific Corp., Natick, Massachusetts) [2] have both been independently shown to reduce the need for repeat intervention when compared to bare-metal stents (BMS) in separate randomized clinical trials. The Food and Drug Administration approvals for these devices were granted in 2003 and 2004, respectively, and it is estimated that drug-eluting stents (DES) currently comprise 70% of the stent market in the U.S. The randomized controlled trials on which approval was granted enrolled highly selected patients with single lesions that could be covered with one DES and were compared against BMS which is not representative of daily clinical practice.

Our group has previously published the results of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry, which demonstrated that routine implantation of SES resulted in a reduction in major adverse cardiac events (MACE), principally driven by a reduction in target vessel revascularization (TVR) when compared with a historical BMS control group. [3] The PES were commercialized subsequent to SES, based on the results of randomized controlled trials. [4,5] The beneficial effect of PES in patients treated in daily practice remains to be defined. The aim of this study was to report the one-year outcomes of unrestricted/universal use of PES in patients with de novo coronary artery lesions and to compare its efficacy against our historical SES cohort. [3]

Methods

Study design and patient population

The Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry is a prospective single-center registry with the main purpose of evaluating the safety and efficacy of PES implantation for consecutive unselected patients treated in daily practice. Its conceptual design and methodology are similar to that of the RESEARCH registry [6] and follows the dynamic registry design described by Rothman and Greenland. [7]

Since February 16, 2003, when PES was granted Conformité Européenne approval, it replaced SES as the default stent for every percutaneous coronary intervention. Up until 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). This comprised 83.7% of all patients with de novo disease who received coronary stents. In this period, only 12 patients received BMS exclusively (11 were due to requirement for stents >3.5mm, 1 patient had elevated liver enzymes that precluded long-term clopidogrel therapy). Patients treated with PES and BMS in the same procedure (20 patients), those treated with PES and SES (20 patients), those treated with SES only (15 patients), and patients enrolled in other drug-eluting trials (44 patients) were not included in the present report. The PES are available in diameters of 2.25 mm, 2.5 mm, 3.0 mm, and 3.5 mm and in lengths of 8 to 32 mm in 4-mm increments for each available diameter.

This PES group was compared with a control group that comprised the active arm of the RESEARCH registry, that is the 508 patients with de novo disease treated solely with SES (SES group). Thus, the report consists of 1,084 patients treated with DES, differentiated by the type of drug coating on the stent, either sirolimus or paclitaxel.

Procedures and postintervention medications

Interventions were performed according to current standard procedures, with the final interventional strategy (including direct stenting, postdilation, periprocedural glycoprotein IIb/IIIa inhibitor, and use of intravascular ultrasound) left entirely up to the operator's discretion. [6] Angiographic success was defined as residual stenosis ≤30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. Patients were advised to maintain lifelong aspirin (at least 80 mg/day) and were pretreated with 300 mg clopidogrel. Postprocedural clopidogrel treatment differed between the two groups. Patients treated with PES were prescribed at least six months of clopidogrel (75 mg/day), based on existing data from randomized, controlled trials. [5] For patients treated with SES, clopidogrel was prescribed for at least three months, unless one of the following was present (in which case clopidogrel was maintained for at least six months): multiple SES implantation (≥3 stents), total stent length ≥36 mm, chronic total occlusion, and bifurcations.

End point definitions and clinical follow-up

The primary outcome was the occurrence of MACE, defined as a composite of: 1) all cause death, 2) nonfatal myocardial infarction (MI), or 3) TVR. Myocardial infarction was diagnosed by a rise in the creatine kinase-MB fraction (CK-MB) of more than three times the upper limit of normal according to American Heart Association/American College of Cardiology guidelines. [8] In patients who underwent coronary artery bypass surgery during the follow-up period, a periprocedural MI was diagnosed by a rise in the CK-MB level of five times the upper limit of normal. [9] For patients who presented with an acute MI, a diagnosis of re-MI in the acute phase required a fall and rise of CK-MB of 50% above the previous level. [10] Target lesion revascularization was defined as a repeat intervention (surgical or percutaneous) to treat a luminal stenosis within the stent or in the 5-mm distal or proximal segments adjacent to the stent. Target vessel revascularization was defined as a re-intervention driven by any lesion located in the same epicardial vessel. Thrombotic stent occlusion 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 successfully treated artery. A committee of three cardiologists (A.O., J.A., and E.M.F.) reviewed all MACE.

All patients underwent clinical follow-up. Information about the in-hospital outcomes was obtained from our institutional electronic clinical database and by review of the hospital records for those discharged to referring hospitals (patients were referred from a total of 14 local hospitals). Postdischarge survival status was obtained from the Municipal Civil Registries at 1, 6, and 12 months. All repeat interventions (surgical and percutaneous) and re-hospitalizations were prospectively collected during the follow-up. Questionnaires regarding adverse events, anginal status, and medication use were sent to all living patients at 6 and 12 months. Referring physicians and institutions were contacted for additional information if required.

In both groups, follow-up coronary angiography was clinically driven by symptoms or signs suggestive of myocardial ischemia or mandated by the operator at the end of the index procedure predominantly for complex procedures. In the PES group, three specific subgroups were restudied: left main stem stenting, crush-bifurcation procedures, and patients who were concomitantly in a vulnerable plaque study involving non-treated vessels (in total, 27% [n = 154] of PES patients underwent re-study during follow-up, including 14% [n = 81] that were clinically driven). In the SES group, the following “complex patient” subgroups were re-studied: bifurcation lesions, left main stem stenting, chronic total occlusions, very small vessels, long stent length (36 mm), and acute MI (in total, 40% [n = 204] of SES patients were re-studied, including 8% [n = 40] that were clinically driven). Because of the well-known effect of angiographic re-evaluation in increasing the incidence of repeat revascularization, [11] all re-interventions were retrospectively adjudicated and classified as either clinically driven or non-clinically driven. Clinically driven repeat revascularization was defined as any intervention motivated by a significant luminal stenosis (≥50% diameter stenosis) in the presence of anginal symptoms and/or proven myocardial ischemia in the target vessel territory by noninvasive testing.

Statistical analysis

Continuous variables are presented as mean ± standard deviation, and were compared using the Student unpaired *t* test. Categorical variables are presented as counts and percentages and compared by means of the Fisher exact test. All statistical tests were two-tailed. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. 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. Separate Cox regression analyses were performed to identify independent predictors of adverse events, using clinical, angiographic, and procedural variables contained in Table 1 and Table 2. The Cox proportional hazards regression models were used to control for differences between groups, and the final results are presented as adjusted hazard ratios (HRs).

Table 1: Baseline Characteristics

	SES group (n = 508)	PES group (n = 576)	p value
Male, %	68	74	0.04
Age, yrs ± SD	61 ± 11	62 ± 11	0.4
Diabetes, %	18	18	0.8
Non–insulin-dependent, %	12	13	0.5
Insulin-dependent, %	6	5	0.7
Hypertension, %	41	42	0.9
Hypercholesterolemia, %	56	62	0.03
Current smoking, %	31	29	0.6
Previous myocardial infarction, %	30	35	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	

PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent.

[] Relative to patients with acute myocardial infarction.

Table 2: Procedural Characteristics

	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 artery, %	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	4.0 ± 2.0	6 ± 0	< 0.05
Bifurcation stenting, %	16	16	0.9
No. of stented segments ± SD	2.0 ± 1.0	1.7 ± 0.9	< 0.001
No. of stented vessels ± SD	1.3 ± 0.6	1.3 ± 0.6	0.8
No. 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 stent length >33 mm, %	45	48	0.5
Angiographic success of all lesions, %	97	97	0.9

Abbreviations as in Table 1.

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

Results

Baseline and procedural characteristics

The PES patients were more often male, had more MI as their presenting symptom, more cardiogenic shock, more complex lesions treated, longer total stent lengths, and more frequently received glycoprotein IIb/IIIa inhibitors (Table 1 and Table 2). Fewer PES patients had a history of previous bypass surgery, and fewer segments per patient were stented, although the number of vessels treated per patient was identical. Other baseline and procedural characteristics were similar.

Clinical outcome

First 30 days

No significant differences were noted between groups with respect to the incidences of death, death or MI, TVR, or MACE in the first month (Table 3). Mortality in the first 30 days was 2.1% in the PES group and 1.6% in the SES group (p = 0.7). In both groups, most deaths occurred in patients with cardiogenic shock. Angiographically proven stent thrombosis occurred in six patients in the PES group, four of whom were treated for AMI, the other two presented with unstable angina. Two patients with AMI also underwent bifurcation stenting, as did one with unstable angina. In total, three patients with bifurcation stenting experienced stent thrombosis. In the SES group, two patients were diagnosed with stent thrombosis. One patient died as a result of stent thrombosis in the PES group.

Table 3: Major Adverse Cardiac Events in the First Month Following Stent Implantation

0 to 1 Month	SES group (n = 508)	PES group (n = 576)	p value□
Death, n (%)	8 (1.6)	12 (2.1)	0.7
Nonfatal myocardial infarction, n (%)	12 (2.4)	17 (3.0)	0.6
Target lesion revascularization, n (%)	6 (1.2)	7 (1.2)	1.0
Target vessel revascularization, n (%)†	6 (1.2)	13 (2.3)	0.2
Any event, n (%)	23 (4.5)	34 (5.9)	0.3
Stent thrombosis, n (%)‡	2 (0.4)	6 (1.0)	0.3

Abbreviations as in Table 1.

□ By Fisher exact test.

† Includes target lesion revascularization.

‡ Angiographically documented stent thrombosis requiring repeat intervention.

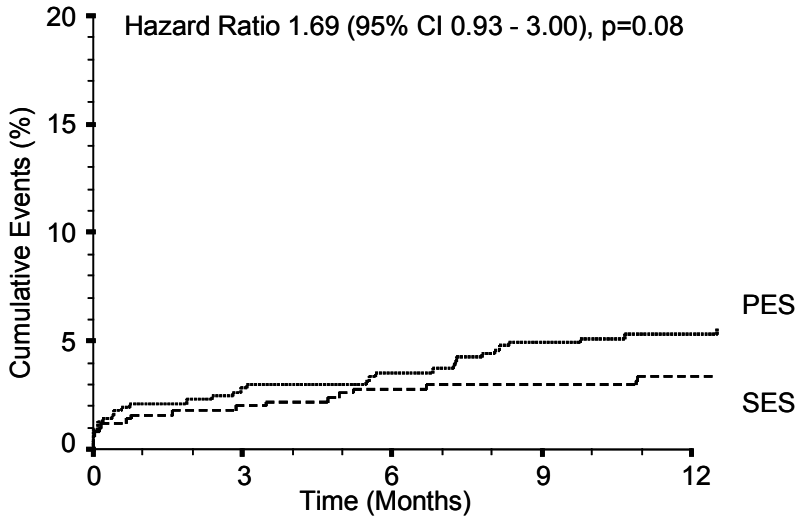
One year

The MACE components are presented in Figure 1 and Figure 2. At one year, 5.3% of patients in the PES group and 3.4% in the SES group had died (HR 1.69, 95% confidence interval [CI] 0.93 to 3.00, p = 0.08). In total, 8.8% of patients in the PES group versus 7.0% in the SES group had either died or suffered a nonfatal re-MI (HR 1.28, 95% CI 0.84 to 1.95, p = 0.3). The incidence of TVR was similar in the SES and PES groups: 7.3% versus 5.1% (HR 1.31, 95% CI 0.81 to 2.13, p = 0.3). Clinically driven TVR was reduced by a similar magnitude in both groups, specifically 3.7% versus 5.4%, respectively (HR 1.38, 95% CI 0.79 to 2.43, p = 0.3). Post-hoc analysis of clinically driven TVR demonstrates that confidence limits crossed unity, with point estimates close to unity in the subgroups analyzed (Fig. 3). Regarding the primary end point of MACE (the composite of death, MI, or TVR), Kaplan-Meier estimates were 13.9% in the PES group versus 10.5% in the SES group (unadjusted HR 1.33, 95% CI 0.95 to 1.88, p = 0.10).

Figure 1: Unadjusted Kaplan-Meier event curves at one year.

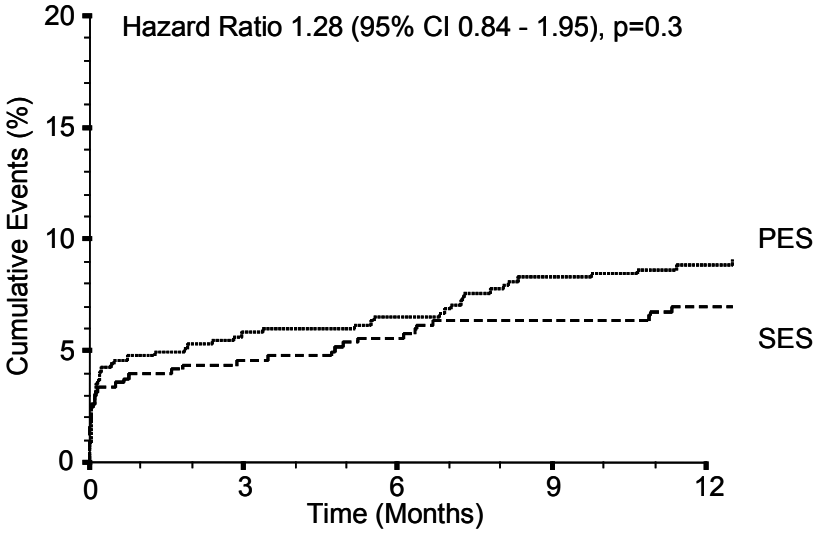
CI = confidence interval; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent.

A: Cumulative risk of death.



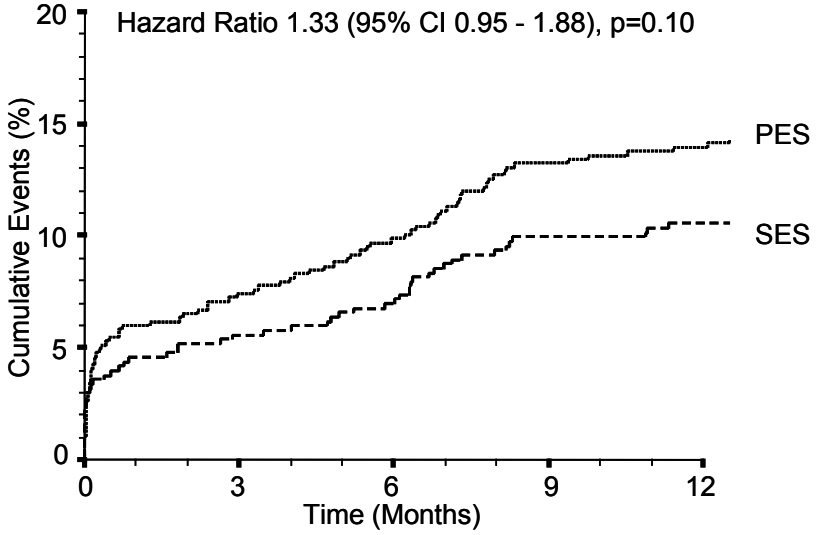
Patients At Risk (n)					
PES	576	550	546	538	500
SES	508	493	489	488	442
Events (%, 95% CI)					
PES			3.5 (2.0-5.1)		5.3 (3.5-7.1)
SES			2.8 (1.3-4.2)		3.4 (1.8-5.0)

B: Cumulative risk of death or myocardial infarction.



Patients At Risk (n)					
PES	576	534	530	520	484
SES	508	480	475	471	429
Events (%, 95% CI)					
PES			6.5 (4.4-8.6)		8.8 (6.5-11.1)
SES			5.6 (3.6-7.6)		7.0 (4.7-9.2)

C: Cumulative risk of death, myocardial infarction, or target vessel revascularization.

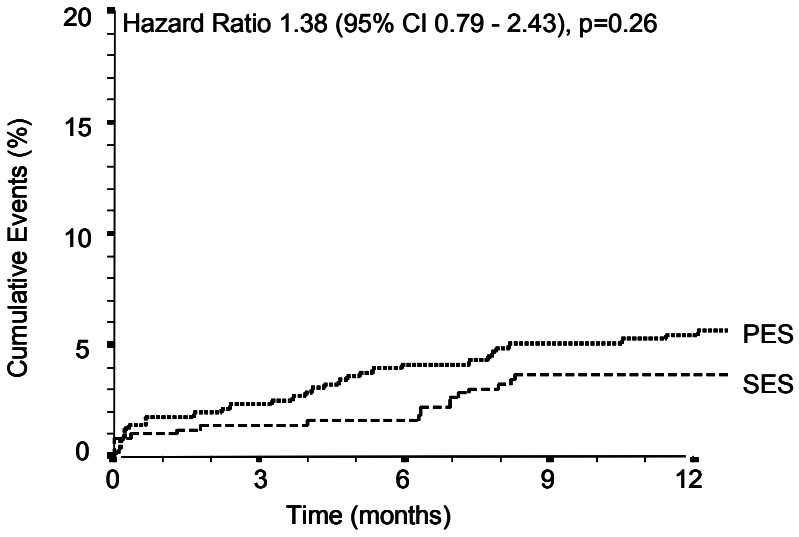


Patients At Risk (n)					
PES	576	525	511	492	456
SES	508	475	468	453	409

Events (%, 95% CI)		
PES	9.9 (7.4-12.3)	13.9 (11.1-16.8)
SES	7.2 (4.9-9.4)	10.5 (7.9-13.2)

Figure 2: Unadjusted one-year cumulative risk of clinically driven target vessel revascularization.

Abbreviations as in Figure 1.

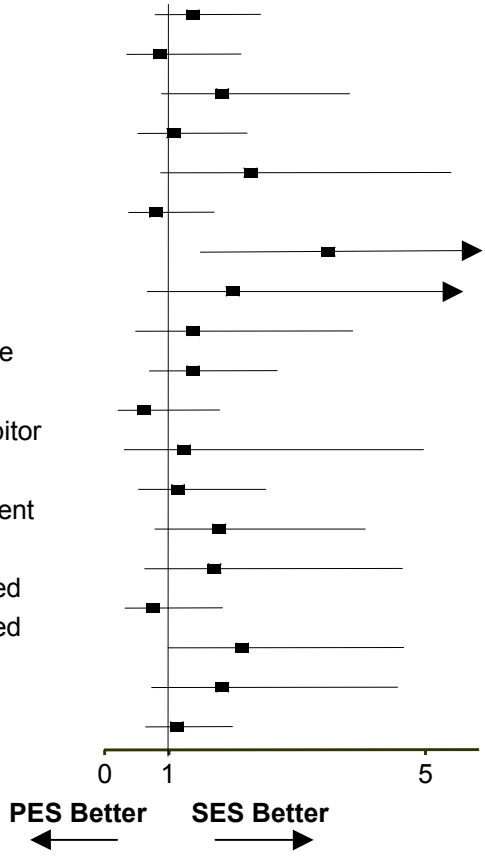


Patients At Risk (n)					
PES	576	541	524	513	495
SES	508	486	481	470	430

Events (%)		
PES	4.1 (2.5-5.8)	5.4 (3.5-7.3)
SES	1.6 (0.5-2.7)	3.7 (2.0-5.3)

Figure 3: Hazard ratios (HR) of stent type at one-year follow-up for clinically driven target vessel revascularization in subgroups of patients according to baseline and procedural characteristics.
MI = myocardial infarction; other abbreviations as in Figure 1.

Subgroup	HR	95% CI	p value
All patients	1.38	(0.79-2.43)	0.3
Age > 65	0.87	(0.35-2.13)	0.7
Age ≤ 65	1.84	(0.89-3.82)	0.1
Male	1.08	(0.52-2.22)	0.8
Female	2.28	(0.88-5.40)	0.1
Stable angina	0.80	(0.38-1.71)	0.6
Unstable angina	3.49	(1.11-10.96)	0.03
Acute MI	2.0	(0.41-9.61)	0.4
1 vessel disease	1.38	(0.49-3.87)	0.5
Multivessel disease	1.38	(0.7-2.69)	0.4
Diabetes mellitus	0.62	(0.22-1.80)	0.4
Use of IIb/IIIa inhibitor	1.24	(0.31-4.97)	0.8
1 vessel treatment	1.15	(0.53-2.51)	0.7
Multivessel treatment	1.79	(0.79-4.06)	0.2
Bifurcation	1.72	(0.63-4.64)	0.3
> 2 stents implanted	0.76	(0.32-1.84)	0.5
≤ 2 stents implanted	2.15	(0.99-4.66)	0.06
Lesion type A/B1	1.84	(0.74-4.57)	0.2
Lesion type B2/C	1.13	(0.64-1.99)	0.7



There were two cases of late (>6 months to 1 year) stent thrombosis documented angiographically in the PES group. In one, it occurred eight months after the index procedure while the patient was on antiplatelet monotherapy with aspirin. The second occurred 11 months after the index procedure after the patient had temporarily suspended antiplatelet therapy (aspirin) for noncardiac surgery.

Predictors of adverse events

To assess the independent predictors of MACE at one year, two separate multivariate analyses were performed. First, a model was built using all baseline and procedural characteristics shown in Table 1 and Table 2. Forward stepwise regression was performed with entry and stay criteria of 0.05 and 0.10, respectively. The following variables were significant: cardiogenic shock, female gender, multivessel disease, diabetes mellitus, left main stenting, bifurcation stenting, and lesion type B2/C (Table 4). A second model built using the same variables with the end point of TVR at one year revealed bifurcation stenting was the only significant independent predictor of TVR.

Adjustment for differences between groups

The Cox regression models were 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 from Table 4 (see Table 5). All previously significant variables remained significant except for lesion type B2/C. The adjusted HR for use of PES became even less significant, decreasing from 1.33 (95% CI 0.95 to 1.88, p = 0.10) to 1.20 (95% CI 0.85 to 1.70, p = 0.3), after controlling for the increased complexity in the PES group.

Table 4: Multivariate Predictors of Major Adverse Cardiac Events at One Year (Cox Proportional Hazards Model)

	HR	95% CI	p value
Major adverse cardiac events			
Cardiogenic shock (stable angina as reference variable)	4.54	2.44–8.48	< 0.001
Female gender	1.72	1.22–2.43	0.002
Multivessel disease	1.74	1.19–2.55	0.005
Diabetes mellitus	1.65	1.12–2.42	0.01
Left main stenting	1.96	1.10–3.48	0.02
Bifurcation stenting	1.59	1.06–2.38	0.03
Lesion type B2 or C	1.85	1.01–3.40	0.047
Target vessel revascularization			
Bifurcation stenting	2.77	1.68–4.57	< 0.001

CI = confidence interval; HR = hazard ratio.

 Major adverse cardiac events: death, myocardial infarction, or target vessel revascularization.

Table 5: Hazard Ratios by Stent Type of Major Adverse Cardiac Events After Adjustment

	HR	95% CI	p value
MACE†			
Unadjusted	1.33	0.95–1.88	0.10
Adjusted for significant predictors of MACE	1.20	0.85–1.70	0.3
Adjusted for significant univariate variables‡	1.16	0.81–1.64	0.4
TVR			
Unadjusted	1.31	0.81–2.13	0.26
Adjusted for significant predictors of TVR	1.33	0.82–2.15	0.25

Abbreviations as in Table 4.

 Stent type coded as: 0 = sirolimus-eluting stent, 1 = paclitaxel eluting stent.

† Major adverse cardiac events: death, myocardial infarction, or target vessel revascularization (TVR).

‡ Significant univariate variables for major adverse cardiac event (MACE) were the significant predictors plus total stent length and number of stents implanted.

A second model was then built forcing stent type and significant univariate variables (independent predictors plus total stent length and number of stents), and the adjusted outcome of MACE at one year was similar between SES and PES (adjusted HR 1.16, 95% CI 0.81 to 1.64, p = 0.4). Finally, stent type was also not a significant predictor of TVR when adjusted for bifurcation stenting (adjusted HR 1.33, 95% CI 0.82 to 2.15, p = 0.25).

Discussion

The major finding of this report is that the unrestricted use of PES in de novo lesions is associated with a nonsignificant difference in outcome compared to SES, both unadjusted and when controlled for significant baseline and procedural characteristics. The trend toward an inferior crude outcome with PES was due to the more complex characteristics of the group.

The two sequential registries were separated by a four-month interval. Several differences in baseline characteristics were noted. More MIs including patients in cardiogenic shock were treated in the T-SEARCH registry because of the implementation of a local pre-hospital protocol that triaged more patients to primary percutaneous coronary intervention. More complex lesions were treated in the T-SEARCH registry, with a shift from type A/B1 to B2/C lesions, with more stents being implanted in the T-SEARCH registry. This in part reflects the increased complexity of cases being performed with time and as operators and referring physicians becoming more aware and familiar with DES.

The primary end point of this trial was overall MACE, and the results for this comparison are presented both unadjusted and following adjustment for significant predictive variables (Table 5). With the commercialization of PES, our institution switched completely from SES to PES, precluding randomization. Therefore, it was intuitive to present the data as such and imperative to statistically correct by using significant predictive variables to account for the increased complexity seen in the PES group. To preserve the prospective, consecutive, and unselected nature of both registries, and the requirement to control for multiple significant variables, the Cox regression model was used. Our results demonstrate that, following adjustment, the HR was closer to unity compared to the crude result, further confirming the increased complexity in the PES group.

The multivariate analysis (Table 4) for independent predictors of MACE is unique as it is an analysis of 1,084 DES patients treated in an unrestricted setting. In a total cohort of DES patients, cardiogenic shock, female gender, multivessel disease, diabetes mellitus, left main stenting, bifurcation stenting, and treatment of a complex lesion significantly predicted an adverse outcome. From this list, patients who possess these characteristics should undergo more regular clinical surveillance.

The major advantage of DES has been to reduce the need for repeat revascularization. [1-3] In our study, the incidence TVR at one year with PES was not significantly different from the results obtained with SES. Furthermore, when the adjusted end point of clinically driven TVR was used (Fig. 2), similar outcomes were reproduced, thus confirming that both drug-eluting systems serve to reduce clinical restenosis in an unselected population.

A nonsignificantly higher incidence of angiographic stent thrombosis in the first 30 days was noted in the PES cohort (1.0% in SES vs. 0.4% in PES, p = 0.3). However, it is important to emphasize that, owing to the infrequent occurrence of this event, large numbers of patients are required to assess this complication properly. We have shown that in a larger population, the incidence rates in both DES were in the same range: 1.0% (95% CI 0.6% to 1.9%) in PES and 1.0% (95% CI 0.5% to 1.8%) in SES. [12]

At the time the T-SEARCH registry was conducted, TAXUS II [5] and the Randomized Comparison of a Sirolimus-Eluting Stent with a Standard Stent for Coronary Revascularization (RAVEL) [13] were the two published trials available with one-year MACE results from the eluting stent arms of 10.9% (slow-release arm) and 5.8%, respectively. Based on those results, the group sample sizes of our study would have been adequately powered to show a difference.

Subsequent to that, the results of larger trials of both devices—TAXUS IV and Sirolimus-Eluting Stent in Coronary Lesions (SIRIUS)—were published and demonstrated a smaller difference (8.4% vs. 7.1%, respectively). The population of this registry is an all-inclusive unrestricted one, a sample that is representative of the population seen in a tertiary catheterization laboratory. Therefore, this population is directly comparable to daily practice and the results do not require extrapolation as for randomized trials. The results of this registry complement published randomized trials.

Conclusions

The universal use of PES in an unrestricted setting is safe, and associated with a non-significant adjusted difference in outcome at one year compared to SES, with a trend toward worse outcomes in the PES cohort, in part owing to its higher-risk profile. Both DES reduce the need for repeat intervention in the real world setting of complex patient and procedural characteristics.

References

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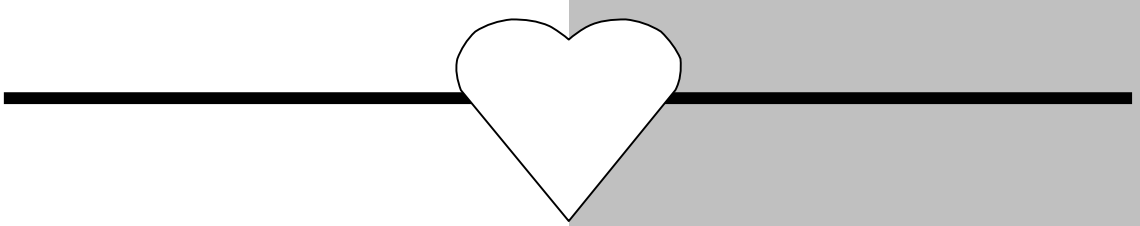
Part 4

SUMMARY AND CONCLUSIONS



Chronic total occlusions

The number of patients undergoing coronary revascularization is rising, and there has been an increase in the proportion of patients being treated with percutaneous intervention compared with coronary artery bypass surgery *(Chapter 3).* In keeping with this, between 1992 and 2002 there was a steady rise in the number of percutaneous interventions for chronic total occlusions (CTOs) carried out at the Thoraxcenter. However, despite the evolution of specialized technologies, the success rate for CTO recanalization remained fairly constant, with an overall success rate of 65%. Successful recanalization of a CTO has important implications with, at 5 years, a significantly higher rate of survival compared with those following an unsuccessful recanalization attempt.

Until the introduction of drug-eluting stents, intra-coronary radiation therapy was the gold standard for the treatment of in-stent restenosis, with relatively low rates of recurrence at 6 months. However, long-term follow-up has since demonstrated that these patients are at risk of late recurrence of stenosis. In addition, impairment of re-endothelialization following radiation therapy increase the risk of vessel occlusion due to thrombosis. We evaluated all patients treated with intra-coronary radiation therapy at the Thoraxcenter, and found that over a mean follow-up of 40.3 months, there was a high rate of vessel occlusion (12.3%) *(Chapter 4)*, Prolongation of dual anti-platelet therapy to 6 months duration was insufficient to protect against the development of occlusion, which was associated with significant morbidity.

Several angiographic features have been identified as predictors for successful recanalization, and the presence or absence of these can influence the decision regarding whether percutaneous revascularization is attempted or the patient is referred directly for bypass surgery. We evaluated the role of pre-operative non-invasive imaging with multi-slice computed tomographic (MSCT) coronary angiography to predict the outcome of attempted CTO recanalization and therefore identify those patients most likely to benefit from attempted percutaneous revascularization *(Chapter 5).* By multivariate analysis of the clinical, angiographic and MSCT features, we found three independent predictors of angioplasty failure: the presence of a blunt stump by angiography, length of occlusion >15mm (demonstrated on MSCT), and severe calcification (demonstrated on MSCT). This suggests therefore that MSCT can be helpful in the therapeutic decision-making for patients who have CTO.

Importantly, a failed CTO recanalization attempt can be associated with a significant procedural-related complication rate including a 1% risk of death *(Chapter 3).* New technologies must therefore focus on a safe approach to successful recanalization. One novel technology dedicated to CTO recanalization is the SafeCross™ system (*Chapters 6, 7 and 8)*. This system combines guidance to help steer the wire, with the capability to penetrate through the occlusion with radiofrequency ablation. Near infra-red light is emitted and the system uses optical coherence reflectometry to determine the position of the wire tip in relation to the vessel wall. The ablation is only enabled when the system detects that the wire is intraluminal and heading in a correct direction away from the vessel wall. In our experience, we found the system to be a useful adjunct, with successful recanalization achieved in 52% CTO cases that had previously had an unsuccessful attempt using conventional means. Importantly, there were no complications related to use of the device. The device was successfully used even in a heavily calcified occlusion of the ostium of the left anterior descending artery (*Chapter 7).* The most common reason for unsuccessful CTO recanalization is failure to cross the lesion with a guidewire. This can be improved with technologies such as the SafeCross™ system, however subsequent failure commonly reflects the inability to cross the occlusion with a balloon. The rotablator can be a useful adjunctive device in this situation to facilitate subsequent dilatation and stent implantation *(Chapter 8)*.

Prior to the introduction of drug-eluting stents, the majority of major adverse cardiac events following successful CTO recanalization are related to the need for repeat intervention *(Chapter 3).* In large randomised studies, drug-eluting stents have been shown to reduce the rate of restenosis and the need for target vessel revascularization compared with bare metal stents when used in relatively simple lesions. Patients with more complex lesions such as CTOs were excluded from these studies. We evaluated whether sirolimus- and paclitaxel-eluting stents were also effective in improving outcomes for patients with a CTO *(Chapters 9 and 10).* At 1 year, patients treated with a sirolimus-eluting stent had a significantly higher rate of survival-free of major adverse cardiac events compared with patients treated with bare metal stents (96.4% versus 82.8%, $p<0.05$).

Furthermore, follow-up angiography at 6-months showed that the sirolimus-eluting stent effectively suppressed neointimal proliferation, and was associated with a low late lumen loss of just 0.13 ± 0.46mm. We subsequently also evaluated the clinical outcomes of patients treated with paclitaxel-eluting stents *(Chapter 10).* Following therapy of a CTO of >3 months duration, the cumulative survival-free of target vessel revascularization was 97.4% for patients treated with sirolimus-eluting stents, 96.4% for paclitaxel-eluting stents, and significantly lower at 80.8% for bare metal stents (p=0.01). These data demonstrate efficacy of both the sirolimus- and paclitaxel-eluting stents in reducing restenosis and the need for repeat reintervention compared with bare metal stents. This improvement in outcomes means an expansion in the complexity of those lesions deemed suitable for percutaneous intervention. Chronic total occlusion of the left main stem is a very rare lesion, but we demonstrate that in contemporary practice, it can be successfully treated with drug-eluting stent implantation *(Chapter 11).*

Bifurcations

A variety of techniques have been proposed to treat bifurcation lesions *(Chapters 12 and 13).* However, when bare metal stents are utilised, techniques involving stenting of the side branch are associated with a higher rate of restenosis compared with strategies whereby only the main vessel is stented. We evaluated the efficacy of drug-eluting stents in consecutive patients treated for at least one bifurcation lesion *(Chapter 14).* In these patients, the side branch was stented in addition to the main vessel as it seemed intuitive when using these stents to cover the entire lesion. At 6 months, the incidence of major adverse cardiac events was 10.3%, which is lower than that documented in published data of bare metal stents. The incidence of target lesion revascularization was 8.6%. Follow-up angiography demonstrated restenosis rates of the main vessel and side branch of 9.1% and 13.6% respectively, with an overall restenosis rate of 22.7%. The majority of restenoses of the side branch occurred at the ostium following T-stenting. Indeed, the restenosis rate in the side branch following T-stenting was 16.7% whilst that following other stenting techniques was 7.1%. The major problem with T-stenting relates to the degree of angulation between the main vessel and side branch. If this angle approximates 90˚, precise stent positioning in both vessels can completely cover the lesion. However, the majority of bifurcation lesions have an angle of <70˚. We hypothesised that the side branch restenoses seen in our study might relate to inadequate or incomplete coverage of the ostium thereby reducing the efficacy of the drug-eluting stent. This led to a shift away from a strategy of T-stenting, towards methods which ensure complete coverage – the crush and Culotte techniques of stenting *(Chapter 15).* However, despite the change in stenting technique, the choice of strategy was not an independent predictor for either major adverse cardiac events or the need for target lesion revascularization. It is unlikely that any single strategy will be optimal for all bifurcations due to the diversity of these lesions with differences of vessel size, angulation, and plaque distribution.

Following stenting of bifurcation lesions, we found a difference in outcomes with respect to stent type in favour of fewer repeat target lesion revascularization in the sirolimus-eluting stent group as compared with those treated with paclitaxel-eluting stents *(Chapter 15).* However, this result must be taken with caution in view of the lack of randomisation of the data. Indeed, in *chapter 20*, we show that for the total populations treated with drug-eluting stent implantation, stent type (sirolimus-eluting versus paclitaxel-eluting) was not an independent predictor of either major adverse cardiac events or the need for target vessel revascularization.

The crush technique of bifurcation stenting is a new strategy that ensures complete lesion coverage, and was introduced specifically to be used with drug-eluting stents. We evaluated the outcomes of 231 consecutive patients treated using this technique for 241 de novo bifurcation lesions *(Chapter 16).* The rate of in-hospital major adverse cardiac events was 5.2%. At 9-months, the incidence of possible post-procedural stent thrombosis was of concern, with 10 (4.3%) patients having had a possible event. The rate of survival-free of target lesion revascularization was 90.3%, and survival-free of major adverse cardiac events was 83.5%. Therapy of the left main stem was an independent predictor for adverse events, and further research is needed before this technique can be routinely recommended in this group. Angiographic follow-up demonstrated a mean late loss of 0.30±0.64mm and 0.41±0.67mm for the main vessel and side branch respectively, with binary restenosis rates of 9.1% and 25.3%. Kissing balloon post-dilatation significantly reduced the side branch late

lumen loss (0.24±0.50mm versus 0.58±0.77mm, p<0.001) and binary restenosis rates (9.6% versus 41.3%, p<0.0001), and should therefore be carried out routinely in all cases to reduce the rate of restenosis.

The Culotte technique of bifurcation stenting is also a strategy that ensures complete lesion coverage. However, the technique fell out of favour because of high restenosis rates following bare metal stent implantation. We evaluated the outcomes of a series of patients treated with this technique using drug-eluting stents and showed promising clinical and angiographic outcomes (*Chapter 17)*. These results warrant the re-evaluation of the Culotte technique utilizing drug-eluting stents, in the setting of large randomized studies.

Chronic total occlusions, bifurcations, and the RESEARCH and T-SEARCH Registries

From April 2002, drug-eluting stents were used as the default strategy for all patients undergoing percutaneous coronary intervention. Initially, patients were treated with the sirolimus-eluting stent, then during the first quarter of 2003, our strategy switched to using paclitaxel-eluting stents in all patients. These patients comprise the RESEARCH and T-SEARCH Registries respectively. All consecutive patients were enrolled irrespective of clinical presentation and lesion characteristics, and the incidence of major adverse cardiac events was prospectively evaluated during follow-up.

By multivariate analysis, the treatment of chronic total occlusions was not found to be an independent predictor of stent thrombosis, restenosis, or adverse cardiac events including target vessel revascularization. However, our data show that in the era of drug-eluting stents, percutaneous coronary intervention of bifurcation lesions is associated with an increased risk of adverse events. Drug-eluting stents impair the process of re-endothelialization compared with bare metal stents, and there are concerns that this might lead to an increased risk of stent thrombosis. We evaluated >2,500 consecutive patients, and show that in unselected patient populations treated with either sirolimus-eluting or paclitaxel-eluting stents, the incidence of stent thrombosis at 30 days is within the range seen following bare stent implantation *(Chapter 18).* The only independent predictor for stent thrombosis was bifurcation stenting in the setting of acute myocardial infarction. This emphasises the importance of optimal pharmacotherapy in this group, and suggests that it may be preferable to use a single stent strategy for bifurcation lesions treated in this setting.

During the first 6 months of the RESEARCH Registry, patients treated for complex disease were invited back for follow-up coronary angiography. These were patients treated for acute myocardial infarction, in-stent restenosis, left main stem stenting, chronic total occlusion, bifurcation stenting, those who received a 2.25mm stent, and those treated with a stented segment length >36mm. Bifurcation stenting (side branch position) was a univariate predictor of restenosis (OR 2.77; 95% CI: 1.15-6.33, p=0.02), though this was no longer a predictor on multivariate analysis *(Chapter 19).*

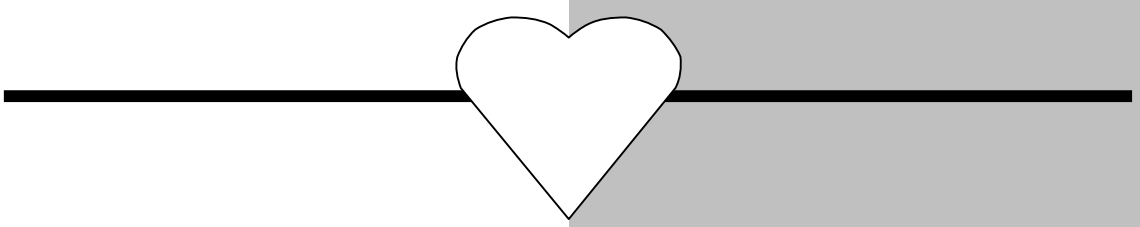
We subsequently evaluated the clinical outcomes of all patients treated with drug-eluting stents for de novo lesions *(Chapter 20).* Use of the paclitaxel-eluting stent was associated with a non-significant difference in outcome compared with the sirolimus-eluting stent. However, when the entire population was evaluated for predictors of adverse outcomes, bifurcation stenting was an independent predictor of major adverse cardiac events (HR 1.59; 95%CI: 1.06-2.38, p=0.03), and was the only independent predictor of target vessel revascularization (HR 2.77; 95%CI: 1.68-4.57, p<0.001).

Conclusions

In the therapy of chronic total occlusions and bifurcation lesions, sirolimus- and paclitaxel-eluting stents are effective in reducing restenosis compared with bare metal stents. Successful chronic total occlusion therapy infers a significant improvement in long-term survival, and therefore justifies an aggressive strategy of recanalization. However, failed recanalization may be associated acutely with an adverse event, and new technologies must focus on a safe approach to successful recanalization.

The most effective strategy of stenting of bifurcation lesions is currently undefined, and further randomised studies are warranted taking into account factors such as vessel size, angulation between the main vessel and side branch, and plaque distribution at baseline. In contemporary coronary interventional practice utilizing drug-eluting stents, bifurcation lesions continue to pose a problem in terms of being associated with an increased risk of major adverse cardiac events and target vessel revascularization.

Samenvatting en Conclusies



Chronische totale occlusies

Het aantal patienten dat een coronaire revascularisatie ondergaat neemt gestaag toe en deze tendens is grotendeels toe te schrijven aan de toename van het aantal percutane coronaire interventies ten nadele van coronaire bypass operaties (hoofdstuk 3). In analogie hiermee was er in het Thoraxcentrum tussen 1992 en 2002 eveneens een duidelijke toename in het aantal percutane interventies voor chronische totale occlusies (CTO's). Hoewel er in deze periode een belangrijke technologische vooruitgang is geweest, bleef de kans op succesvolle recanalisatie relatief constant, namelijk om en bij de 65%. Een succesvolle recanalisatie van een CTO heeft nochtans belangrijke prognostische implicaties: deze patienten hebben een betere 5-jaarsoverleving in vergelijking met de groep waarbij recanalisatie niet lukt.

Tot de introductie van drug-eluting-stents was intracoronaire brachytherapie de aangewezen therapie voor de behandeling van in-stent-restenose aangezien met deze therapie de kans op recidief restenose relatief laag was 6 maanden behandeling. Lange-termijn resultaten hebben evenwel aangetoond dat patienten behandeld met brachytherapie een hoger risico vertonen op het ontwikkelen van laattijdige restenose. Bovendien verhoogt brachytherapie de kans op coronaire thrombose doordat het interfereert met het normale re-endothelialisatieproces. In hoofdstuk 4 rapporteren we de resultaten van alle patienten die in het Thoraxcentrum behandeld werden met coronaire brachytherapie: na een gemiddelde follow-up van 40.3 maanden was er een hoge mate van bloedvatocclusie (12.3%). Combinatietherapie met 2 klassen van bloedplaatjesaggregantia gedurende een periode van 6 maanden heeft bovendien geen beschermend effect tegen het ontstaan van bloedvatocclusie, hetgeen gepaard gaat met een belangrijke morbiditeit.

Er zijn verschillende angiografische karakteristieken gekend die het succes van een recanalisatie voorspellen. Het aan- of afwezig zijn van deze kenmerken beinvloedt mee de beslissing om een patient voor percutane coronaire revascularisatie dan wel voor coronaire bypass chirurgie te verwijzen. In hoofdstuk 5 beschrijven we de toegevoegde waarde van niet-invasieve beeldvorming met multi-slice computer tomografie (MSCT) van de coronaire bloedvaten als voorbereidend onderzoek voor het uitvoeren van de revascularisatie. We hebben de rol van MSCT onderzocht voor het voorspellen van de kans op succes van een percutane coronaire interventie van een CTO en met andere woorden nagegaan welke patienten een redelijk hoog slaagpercentage hebben. Multivariaat analyse van klinische, angiografische en MSCT kenmerken leverde 3 onafhankelijke variabelen op die geassocieerd zijn met een lage slaagkans van de percutane interventie: de aanwezigheid van een abrupt stopbeeld op het conventionele angiogram, een geoccludeerd bloedvat segment van >15mm (MSCT variabele) evenals een sterk verkalkt segment van de coronair arterie (MSCT variabele). Deze bevindingen suggereren dat MSCT mogelijk een rol heeft bij de beslissing om een patient met een CTO al dan niet via percutane weg te behandelen.

In hoofdstuk 3 beschrijven we dat een niet succesvolle percutane recanalisatiepoging voor een CTO kan gerelateerd zijn aan majeure complicaties waaronder een mortaliteitsrisico van 1%. Nieuwe technologische verbeteringen zijn bijgevolg noodzakelijk om de recanalisatiepoging succesvoller en tegelijkertijd veiliger te maken. Een van deze nieuwe technieken voor de behandeling van CTO's is het SafeCross™ system (hoofdstuk 6 tot en met 8*)*. Dit systeem combineert 2 eigenschappen: (1) het biedt ondersteuning bij het maneuvreren van de draad, en (2) door middel van radiofrekwentie ablatie is het mogelijk hard materiaal te doorbreken. Het systeem maakt gebruik van optical coherence tomografie om de positie van de draadtip in relatie tot de bloedvatwand te bepalen. Ablatie is enkel mogelijk wanneer de tip van de draad centraal in het bloedvat wordt gedetecteerd en in de juiste richting, weg van de bloedvatwand, opschuift. Onze ervaring met dit systeem is gunstig aangezien het toeliet 52% van de patiënten, die reeds een eerste niet-succesvolle percutane revascularisatiepoging achter de rug hadden, deze keer met succes te behandelen. Belangrijk te vermelden is dat er bij gebruik van dit systeem geen complicaties optraden. Zelfs bij een ernstig verkalkte occlusie vanaf de oorsprong van de LAD (left anterior descending arterie) was het SafeCross™ systeem succesvol (hoofdstuk 7). De voornaamste reden voor het niet slagen van een recanalisatiepoging van een CTO is de onmogelijkheid om met een draad de occlusie te passeren. Het SafeCross™ systeem biedt wat dit betreft een hogere slaagkans. Casussen die dan nog niet lukken zijn gewoonlijk gerelateerd aan de ballon die de occlusie niet kan passeren. Rotablatie kan in deze situatie zinvol zijn aangezien het de ballondilatatie en vervolgens de stentplaatsing vergemakkelijkt (hoofdstuk 8).

In de periode voor de introductie van drug-eluting stents, was het merendeel van de majeure cardiale events na succesvolle recanalisatie van een CTO te wijten aan de noodzaak tot herinterventie (hoofdstuk 3). In grote gerandomiseerde studies werd aangetoond dat het gebruik van drug-eluting stents bij de behandeling van relatief eenvoudige lesies de incidentie van restenose en de noodzaak tot herinterventie van het behandelde bloedvat (ook wel 'target vessel' revascularisatie genoemd) in belangrijke mate hebben gereduceerd in vergelijking met niet-gecoate stents (ook wel 'bare metal stents' genoemd). Patienten met complexe lesies zoals CTO's werden evenwel niet geincludeerd in deze studies. In hoofdstuk 9 en 10 beschrijven we of drug-eluting stents, met name sirolimus-eluting en paclitaxel-eluting stent, ook de outcome verbeteren van patienten met CTO's. Patienten die behandeld werden met een sirolimus-eluting stent hadden 1 jaar na de interventie een significant hogere overleving vrij van majeure cardiale events in vergelijking met de controlegroep waarin 'bare metal stents' werden gebruikt (96.4% versus 82.8%, $p<0.05$). Bovendien bleek uit de controle angiografie 6 maanden na de interventie dat sirolimus-eluting stents effectief de ontwikkeling van neointimahyperplasie onderdrukken hetgeen resulteerde in een 'late lumen loss' van slechts 0.13 ± 0.46mm. In hoofdstuk 10 beschrijven we de klinische outcome van patienten die met een paclitaxel-eluting stent werden behandeld. Na behandeling van een CTO van minstens 3 maanden oud, was het percentage patienten waarbij geen nieuwe herinterventie van het behandelde bloedvat meer noodzakelijk was significant hoger in de drug-eluting stent groep (97.4% voor sirolimus, 96.4% voor paclitaxel) in vergelijking met de 'bare metal stent' groep (80.8%) (P-waarde= 0.01). Deze bevindingen bewijzen de efficientie van zowel de sirolimus- als paclitaxel-eluting stent wat betreft afname van restenose en de nood tot herinterventie in vergelijking met b'are metal stents'. Deze duidelijke verbetering in outcome, ook na behandeling van meer complexe lesies, laat een verruiming toe van de indicaties voor percutane coronaire interventies. Een chronische totale occlusie van de linker hoofdstam is een uitzonderlijk gegeven: in hoofdstuk 11 illustreren we dat dit type lesie tegenwoordig succesvol kan behandeld worden mits gebruik gemaakt wordt van een drug-eluting stent.

Bifurcaties

De aanpak van coronaire bifurcatie lesies is niet uniform en verklaart het grote aantal percutane behandelingsmethoden (hoofdstuk 12 en 13). Wanneer 'bare metal stents' worden gebruikt voor de behandeling van het zijvat, blijkt de incidentie van restenose hoger te zijn in vergelijking met een meer eenvoudige behandelingsstrategie waarbij enkel het hoofdvat gestent wordt. In hoofdstuk 14 rapporteren we de efficientie van drug-eluting stents in een consecutieve groep van patienten waarbij percutane interventie van minstens 1 bifurcatielesie noodzakelijk was. In deze groep patienten werd afgezien van het hoofdvat systematisch ook het zijvat gestent aangezien het intuitief gezien beter lijkt om gans de lesie te overdekken met een drug-eluting stent. Na 6 maanden was de incidentie van majeure cardiale events 10.3%, een duidelijke afname in vergelijking met gepubliceerde data met 'bare metal stents'. De incidentie van 'target lesie' revascularisatie was 8.6%. Bij controle angiografie werd restenose gedocumenteerd bij 22.7% der patienten: 9.1% vertoonde restenose in het hoofdvat, 13.6% in het zijvat. Restenose van het zijvat deed zich voornamelijk voor ter hoogte van het ostium, met name bij patienten behandeld volgens de T-stent techniek: in deze groep patienten kwam restenose voor bij 16.7% der patienten, in tegenstelling tot andere behandelingsstrategieen waar restenose voorkwam bij 7.1% der patienten. Het belangrijkste probleem van de T-stent techniek is gerelateerd aan de hoek tussen het hoofd- en zijvat. Een hoek van 90 graden laat een accurate positionering van de stent toe waarbij de lesie volledig overdekt wordt. In het merendeel der bifurcatielesies bedraagt de hoek evenwel minder dan 70 graden. Onze hypothese was dat het optreden van restenose van de zijtak in de beschreven groep patienten mogelijks gerelateerd is aan inadekwate of onvolledige overdekking van het ostium waardoor de effectiviteit van drug-eluting stents afneemt. Deze bevinding heeft ertoe geleid dat T-stenting minder gebruikt wordt ten voordele van behandelingsmethoden die per definitie het ostium van het zijvat mee overdekken, met name de Crush en Culotte techniek (hoofdstuk 15). Deze verandering in behandelingsmethode was evenwel geen onafhankelijke predictor voor majeure cardiale events of 'target lesie' revascularisatie. Het is onwaarschijnlijk dat 1 bepaalde behandelingsstrategie optimaal is voor ieder type bifurcatie lesie als gevolg van de grote verscheidenheid aan bifurcatiepathologie: belangrijke elementen hierin

zijn de verschillen in grootte van het bloedvat, de grootte van de hoek tussen hoofd- en zijvat, en de distributie van de plaque.

Na stenting van bifurcatie lesies vonden wij een verschil in outcome in functie van het type drug-eluting stent dat werd gebruikt: 'target lesie' revascularisatie was minder frekwent bij patiënten behandeld met een sirolimus-eluting stent in vergelijking met patiënten behandeld met een paclitaxel-eluting stent (hoofdstuk 15). Dit verschil moet evenwel kritisch bekeken worden aangezien het geen gerandomiseerde studie betrof. In hoofdstuk 20 tonen we namelijk aan dat in de totale populatie die met een drug-eluting stent werd behandeld, het type drug-eluting stent (sirolimus- versus paclitaxel-eluting stent) geen onafhankelijk predictor was voor wat betreft majeure cardiale events of de nood voor 'target vessel' revascularisatie.

Bifurcatiestenting volgens de Crush techniek is een nieuwe behandelingsmethode die specifiek geïntroduceerd werd voor gebruik met drug-eluting stents en maakt het mogelijk de lesie in hoofd- en zijvat volledig te overdekken. Hoofdstuk 16 beschrijft de outcome van 231 consecutieve patiënten, met in totaal 241 de novo bifurcatie lesies, die volgens de Crush methode werden behandeld. In-hospitaal majeure cardiale events deden zich voor bij 5.2% der patienten. De resultaten na een gemiddelde follow-up van 9 maanden waren de volgende: 1/ 10 patienten (4.3% der studiepopulatie) ontwikkelden mogelijks een subacute of laattijdige stent thrombose, een zorgwekkende bevinding; 2/ de overleving vrij van 'target lesion' revascularisatie was 90.3%, en de overleving vrij van majeure cardiale events was 83.5%; 3/ Crush stenting van de hoofdstam was een onafhankelijke predictor voor het optreden van cardiale events: deze bevinding vereist verder onderzoek vooraleer Crush stenting kan worden aanbevolen als een routinetechniek voor de behandeling van een significante hoofdstamlesie; 4/ follow-up door middel van angiografie toonde aan dat de gemiddelde 'late loss' voor het hoofd- en zijvat respectievelijk 0.3±0.64mm en 0.41±0.67mm was en de incidentie van restenose respectievelijk 9.1% en 25.3%; 5/ 'Kissing balloon' postdilatatie reduceerde op significante wijze 'late lumen loss' (0.24±0.50mm versus 0.58±0.77mm, $p<0.001$) evenals de incidentie van restenose (9.6% versus 41.3%, $p<0.0001$) van het zijvat, en zou om die reden systematisch moeten worden gebruikt ter reductie van de incidentie van restenose.

Bifurcatiestenting volgens de Culotte techniek is een ander type strategie die eveneens zorgt voor een volledige overdekking van de lesie. Wegens een hoge incidentie van restenose bij patiënten behandeld met 'bare metal stents' werd deze techniek evenwel minder populair. Hoofdstuk 17 beschrijft een serie patiënten behandeld met drug-eluting stents volgens de Culotte techniek waarbij de klinische en angiografische outcome veelbelovend was. Deze resultaten creëeren de noodzaak de Culotte techniek in de setting van drug-eluting stents te herevalueren in grote gerandomiseerde studies.

Chronische totale occlusies, bifurcaties, en de RESEARCH en T-SEARCH registraties

Sedert april 2002 worden in het Thoraxcentrum te Rotterdam drug-eluting stents gebruikt als standaard behandeling bij alle patiënten die een percutane coronaire interventie ondergaan. Tot het eerste kwartaal van 2003 werden alle patiënten behandeld met een sirolimus-eluting stent en vervolgens werd overgeschakeld op paclitaxel-eluting stents. Deze patiënten maken deel uit van respectievelijk de RESEARCH en T-SEARCH registratie. In deze registraties werden systematisch alle patiënten geincludeerd ongeacht de klinische presentatie of lesie karakteristieken. In beide registraties wordt de incidentie van majeure cardiale events prospectief geëvalueerd.

Uit multivariaat analyse blijkt dat het gebruik van drug-eluting stents voor chronisch totale occlusies geen onafhankelijke predictor is voor stent thrombose, restenose of het optreden van cardiale events, inclusief de nood aan 'target vessel' revascularisatie. De registratiegegevens tonen evenwel aan de percutane behandeling van bifurcatielesies geassocieerd is met een hoger risico op cardiale events. Drug-eluting stents verstoren het normale re-endothelialisatieproces in vergelijking met 'bare metal stents', en hebben aanleiding gegeven tot de bezorgdheid dat dit kan leiden tot een hoger risico op stent thrombose. In een serie van meer dan 2500 consecutieve patienten hebben we aangetoond dat in een niet-geselecteerde patientenpopulatie die behandeld werden met een sirolimus- of paclitaxel-eluting stent, de incidentie van stent thrombose gedurende de eerste 30 dagen na de behandeling vergelijkbaar is met de incidentie bij gebruik van 'bare metal stents' (hoofdstuk 18). De enige onafhankelijke predictor voor het optreden van stent thrombose was bifurcatiestenting

bij patiënten behandeld voor een acuut myocardinfarct. Deze bevinding benadrukt het belang van optimale medicamenteuse therapie in deze patientengroep en suggereert dat bij de behandeling van bifurcatielesies in de setting van een acuut myocardinfarct een eenvoudige strategie waarbij enkel het hoofdvat gestent wordt te verkiezen is.

Gedurende de eerste 6 maanden van de RESEARCH registratie werden alle patiënten die behandeld werden voor complexe lesies uitgenodigd voor een controle angiografie. Het betrof patiënten behandeld wegens een acuut myocardinfarct, in-stent restenose, stenting van de hoofdstam, chronische totale occlusies, bifurcatiestenting, vernauwingen van kleine bloedvaten waarbij een 2.25mm stent gebruikt werd, of patiënten waarbij het gestente bloedvat segment meer dan 36mm betrof. Bifurcatiestenting was een predictor voor het optreden van restenose op niveau van het zijvat bij univariaat analyse (OR 2.77; 95% CI: 1.15-6.33, p=0.02), doch niet bij multivariaat analyse (hoofdstuk 19).

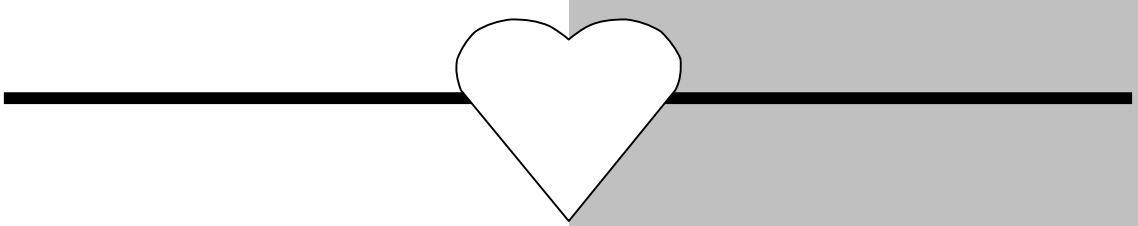
Hoofdstuk 20 beschrijft de klinische outcome van alle patiënten die behandeld werden met een drug-eluting stent voor de novo lesies. Het gebruik van een paclitaxel-eluting stent was geassocieerd met een niet-significant verschil in outcome in vergelijking met de sirolimus-eluting stent. Bifurcatiestenting was evenwel een onafhankelijke predictor van majeure cardiale events (HR 1.59; 95% CI: 1.06-2.38, p=0.03), en de enige onafhankelijke predictor voor wat betreft ‘ target vessel’ revascularisatie (HR 2.77; 95% CI: 1.68-4.57, p<0.001).

Conclusies

Voor de behandeling van chronische totale occlusies en bifurcatielesies zijn de sirolimus- en paclitaxel-eluting stent effectief in vergelijking met ‘bare metal stents’ voor wat betreft reductie van restenose. Succesvolle behandeling van een chronische totale occlusie gaat gepaard met een significante verbetering van de overleving op lange termijn en rechtvaardigt bijgevolg een agressieve recanalisatiestrategie. Een niet-succesvolle recanalisatiepoging kan in de acute fase evenwel geassocieerd zijn met een majeur event en maakt het noodzakelijk nieuwe technologiëen te ontwikkelen die op een veilige manier de kans op succes verhogen.

De meest effectieve strategie bij de behandeling van bifurcatielesies is tot op heden niet gekend. Gerandomiseerde studies die rekening houden met de grootte van het bloedvat, de hoek tussen hoofd- en zijvat, en de distributie van de plaque zijn noodzakelijk om hierin duidelijkheid te verschaffen. Ook in de huidige praktijk van interventiecardiologie waarbij gebruik gemaakt wordt van drug-eluting stents, is het behandelingsresultaat van bifurcatie lesies niet optimaal aangezien dit type lesies geassocieerd blijft met een verhoogd risico op majeure cardiale events en ‘target vessel’ revascularisatie.

Acknowledgements



It seemed like a goal that was perhaps just that step too ambitious. But you don't get anywhere if you don't try. When I decided on a career in cardiology, it became apparent that there were going to be several hurdles. Firstly, it is a very popular medical speciality and entrance into training is highly competitive. Secondly, some colleagues suggested that it was "not a good career choice" for a female. Still, I stuck to my guns and must thank the support I received from several cardiologists in Sheffield, particularly David Oakley and Julian Gunn. I started training in Hull in 1998 on a career path destined for life as a general cardiologist in a district general hospital. However, I discovered I really enjoyed operating and my trainers suggested that I should consider formal training in coronary intervention. I leapt at the opportunity and must thank all the guidance I received at the time from the interventional cardiologists in Hull – Mike Norell, Farqad Alamgir, John Caplin, and Gerry Kaye.

I was determined to have a career in Interventional Cardiology in a tertiary referral hospital setting and soon realised that to achieve this, I needed to do something to "stand out from the rest." Thoraxcenter, Rotterdam. Professor Patrick Serruys. "I'll never get accepted there". I cautiously wrote the letter and was pleased to receive a fairly optimistic response inviting me for an interview. As many Fellows before me have experienced, that first encounter was extremely nerve wracking – but needn't have been. For such a well renowned and intelligent man I discovered that Professor Serruys was actually nice, indeed quite charming!

I was invited to start work in September 2002, but there was one small problem. I wanted to further my training in intervention and work in the cath lab – "you must be fluent in Dutch". No problem I thought? I was terrible at languages at school and knew that the language center is one part of my brain that does not function very well. Maybe it's because I'm English - we're not a country known for our language skills but after all, doesn't everyone in the world speak English?

On my first day in September, I will admit to being nervous – I have always been quite shy amongst people that I don't know very well. However, everyone was really welcoming, and I even discovered a couple of fellow "ex-pats" working in the lab. Each member of the cath lab team quickly earnt my respect. Not only because they all spoke impeccable English – but mainly because of their expertise and dedication. I hope I don't forget anyone. I thank the nurses for their patience – Marjo, Jeanine, Tieneke, Marielle, Marianne, Elza, Caroline, Kim, Denis, Helen, Nuhren, Marieke, Marianne, Stijn, Nico, Dick, and Samantha and Fiona my fellow English workers. I learnt a great deal from each of the technicians – Gio, Emile, Jurgen, Anne-marie, John, Ben, Maaike, Elco, and Max. When I arrived, I didn't even know how to move the intensifier, let alone move the table in the right direction! I must thank Paul and Arno – you bridged the language gap on many occasions and worked very hard completing mountains of paperwork, "persuading" the ethics committee, and patiently obtaining informed consent. Paul, I hope my British successors will be able to keep you supplied with your custard powder and burger relish! There are many more members of the team who keep the whole system running and deserve a great deal of recognition – Anja, Elles, Edith, Laetitia, Mieke, Marijke, Sjaan. I must also thank Ron van Domburg for his statistical expertise, and Jan Tuin for the hours spent making images and editing movies (compensated by a good taste in music). To develop a center of excellence takes great teamwork and dedicated members of staff. I feel privileged to have been accepted as a part of this, albeit for a relatively brief 2-year period.

I will always remember that first day when I started clinical duties working in the lab with Professor Serruys. I couldn't put it off – I needed to speak Dutch with enough clarity to be understood and provide the patients with proper informed consent. I had been given some cassette tapes to learn Dutch "easily". No chance. I was destined for a baptism of fire on my first day. I did my best but got some very strange looks from the patients. Thank goodness for the help from the nursing staff of the wards, and the Dutch Fellows especially Ben Gho, Eric Duckers, Michelle Michels, Kadir Caliskan, and Robert Jan van Geuns.

Each of the seniors shared with me their many and varied “tips and tricks” and I learnt from them all. Professor Patrick Serruys, an astonishing individual, intellectual, creative, technically brilliant, and extremely hard-working. If I only learnt one word in Dutch it was “uitstekend” – Professor you are truly uitstekend. The hours we spent attempting chronic occlusions, usually successfully of course – in the words of Freddie Mercury “We are the Champions”. Professor Pim de Feyter, you are a true gentleman, and great to work with. Wim van der Giessen, thankyou for all your support, and congratulations on your “Professorship”, your wickedly dry sense of humour was typically “English” at times. George Sianos, you are an extremely competent operator and became a good teacher equipped with your large armory of strategies to overcome any obstacle. I know – “push the guide”. Eugene McFadden, not quite British (and proud of it), you learnt a great deal of Dutch – certainly better than mine, I’m sure this was to ensure you were up to date with all the gossip. I will always appreciate your patience and great ability to stay cool and calm under pressure, we all respect your skill and competence. I hope that you are enjoying you new life in Ireland (even though it’s a non-smoking country), and remember how to be a general cardiologist. How are your ECHO skills? Thanks also to Pieter Smits, Evelyn Regar, Martin van der Ent, and Sjoerd Hofma, I wish you all luck in your future careers.

One of the most valuable experiences of being at the Thoraxcenter is being part of the team of Fellows from around the world. I made friends with people that I’m sure I would never have met otherwise - a truly cultural experience! We had tremendous team spirit and comradeship that was matched only by the work that was produced. The list of fellows and nationalities is varied – Pedro (Brazil), Francesco and Marco (Italy), Akis (Greece), Muzaffer (Turkey), Andrew (Australia), Kengo, Jiro and Keiichi (Japan), Gaston (Argentina), Carlos and Nico (Belgium), Vijay (India), Ronald (Singapore), Hector (Mexico). Pedro was the key to the entire operation, one of the most thoughtful and intellectual people I will ever meet. Pedro, I owe you a great deal. You tolerated the European climate remarkably well, but I’m sure you are enjoying life back in warmer climates (remember that the British are obsessed with the weather and it was a stable part of lunchtime conversation). As a group we worked hard but enjoyed the occasional night out – pizza on a Wednesday, Francesco, what is rucola? The occasional drink of course – though don’t even think of trying to keep up with the big Greek guy. Akis, surprisingly dextrous, mildly eccentric, obsessed with cinema, I have never seen a bottle of Jack Daniels disappear so quickly! You could be forgiven for thinking that these three comprise the three musketeers, in fact they were more like the “three tenors”. I remember one night, working very late to submit abstracts, when I was “serenaded” by Pedro, Francesco, and Akis. Perhaps the fluorescent lighting had made them go a little crazy. I suppose there was a weak resemblance to what might be termed music but take it from me – singing is not one of your talents. I never spent much time in the Z building – Muzaffer and Kengo seemed to be always working. Muzaffer you make a great cup of Turkish coffee. Kengo, Jiro, and Keiichi – the Japanese Fellows, you are all truly inspiring with your dedication, patience and generosity of spirit. I look forward to visiting you in Japan in the near future. Gaston, you made us all feel very old! You have achieved alot already in your career, good luck with the rest of your training. Hector, it was a shame that we didn’t really get the opportunity to work together - good luck with continuing on the CTO road.

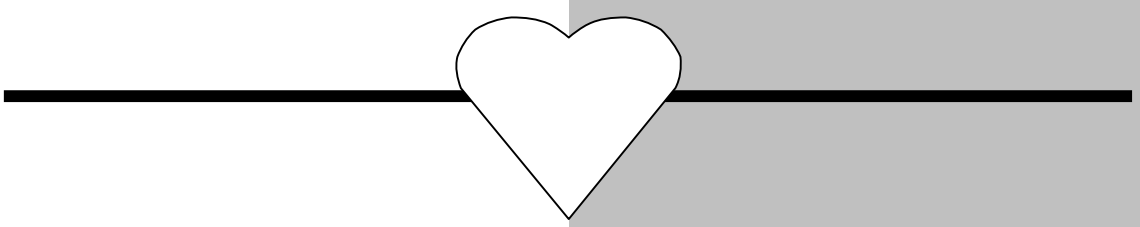
A special mention for my paranymphs – Carlos and Nico the two Belgian guys, and my honourary paranymph Andrew. Andrew, you made my life in Rotterdam much more pleasant - even offering to bring me chicken soup when I was ill in bed! You put me to shame – in 2 years, you visited more places in Europe than I have travelled to in my entire life! You and May were so welcoming and great hosts, it is just a shame you live so far away. It is a pity that you can’t attend the defense, but it was a good excuse being back in Australia. Crazy Andrew did agree to travel on a plane for 3 days just to attend the 1 hour defense and then leave immediately afterwards to get back to work in Oz! The voice of reason (mine) stepped in to advise against the risk of DVT! Nico – thanks for stepping in at the last minute! That CT paper will always be memorable not least

because of the time it took to finally complete it – thank goodness Pedro was able to help with the stats! Carlos, you are a great guy and I hope that we stay in touch. You were absolutely invaluable when making contact with all those bifurcation patients, a very time consuming and rather unrewarding job, I was really grateful. Also the samenvatting en conclusies – I'm afraid my Dutch wasn't quite good enough to even think about attempting such a translation, and it must have taken ages. To all the fellows, it was a privilege to work with each and every one of you. You and your families will always be welcome to visit me in the UK – there is a lot more to the UK than just London, the North of England is a great place.

I would like to thank all the thesis committee members for their presence at this thesis, it is indeed an honour for me – Professor de Feyter, Professor van der Giessen, Professor van der Steen, Professor Pattynama, Professor Piek, Professor di Mario, Professor Sivanathan, and of course Professor Serruys.

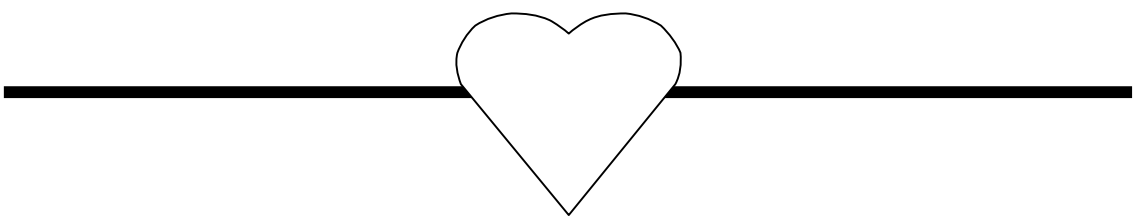
Many people think that I made some sort of sacrifice to come to the Thoraxcenter, and it is true that there are short-term financial disadvantages. But the people who make the real sacrifices are the family members. I know that the 2-years I spent away were much more difficult for my husband Phil than for me. I came home as often as I could and can fondly remember spending precious weekends together - I think they're what kept us both sane. Phil, I will always be grateful to you for your support and for taking good care of Fluffy!

Curriculum Vitae

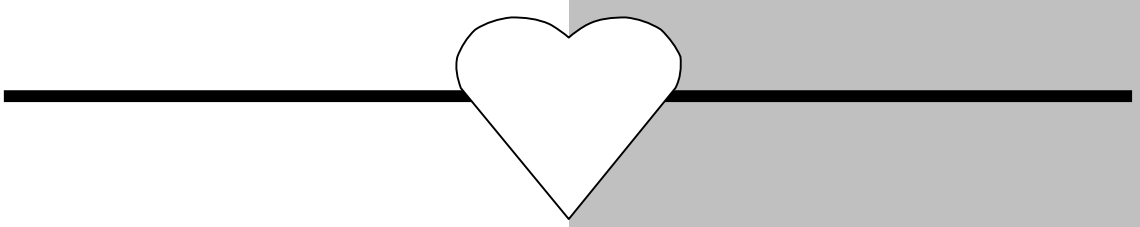


Angela Hoye was born on 30th September 1970 in Nottingham, England. Following schooling in Guildford, she went to the University of Sheffield in 1988, and graduated with the degree of Batchelor of Medicine and Surgery in 1993. She undertook training in general internal medicine in Sheffield, and successfully gained full Membership of the Royal College of Physicians (UK) in 1996. Following junior positions in cardiology, she started formal cardiology training on the East Yorkshire rotation in January 1998. In September 2002, she started a clinical and research fellowship in the catheterisation laboratory of the Thoraxcenter, Erasmus Medical Centre in Rotterdam, under the supervision of Prof Patrick Serruys. In 2004, she returned to England and completed her cardiology training in January 2005. She is currently working as an Interventional Cardiologist in the University Hospitals of Hull, East Yorkshire.

Angela Hoye is a member of the British Cardiac Society, the British Cardiovascular Interventional Society, and the Royal College of Physicians (London).



List of Publications



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