Long term follow-up after drug-eluting stent implantation and early experience with endothelial progenitor cell capture stent

De resultaten van drug-eluting stent implantatie op lange termijn en vroegtijdige ervaringen met de endotheliale progenitor cell gecoate stent

Jiro Aoki

Cover illustrations:

Front Cover: Photo of IJsselmeer from Afsluitdijk
Back Cover: Cover page of "Kaitai-shinsyo"
Kaitai-shinsho is the first medical book in Japan. The events leading up to the publication of the work are described in detail in a later work by Gempaku, his Rangaku Kotohajime, where he states that in March 1771. Gempaku, Ryotaku and others observed the dissection of the body of a criminal executed at Honegahara in the Senju district of Edo. Comparing their findings with the Anatomische Tabellen, a Dutch translation of a work on anatomy by the German Johann Adam Kulmus, they were astonished at its exactitude, and undertook to do a Japanese translation, which they achieved after three and a half years of indescribable labor. This translation was published under the title Kaitai-shinsho. The Kaitai-shinsho not only contributed greatly to the advancement of medicine in Japan, it also stimulated a wider interest in Rangaku or Dutch studies, and in this sense too it is a landmark work of classic translation.

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Thesis

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by
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For Asato

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Chapter 1
Introduction and Overview of the Thesis

INTRODUCTION AND OVERVIEW OF THE THESIS

Intracoronary stent replacement is being used increasingly for the treatment of atherosclerotic coronary artery disease and has gained widespread acceptance. Although stent implantation itself has been shown to reduce restenosis compared to balloon angioplasty, in-stent restenosis still occurs in 10-40% of patients.[1,2] In-stent restenosis has long been considered the main limitation hampering the long-term efficacy of coronary stenting. Restenosis after stent occurs secondary to the accumulation of smooth muscle cells and extracellular matrix which consists of proteoglycans, hyaluronan and collagen.[3,4]

To overcome this major limitation, drug-eluting stents were developed. Drug-eluting stents consist of a drug (immunosuppressive, antiproliferative, or anti-inflammatory drug), a polymer, and a stent platform. Several drugs with durable or erodable polymers were tested in clinical trials and showed that drug-eluting stents significantly inhibit neointimal growth compared with bare metal stents.[5-7] Currently, drug-eluting stents have been widely distributed all over the world and become main-stream of percutaneous coronary intervention. However, (1) long-term efficacy and chronic vascular response after drug-eluting stents implantation in humans **(Part 1 of this thesis)** (2) effect of drug-eluting stents for patients with high in-stent resteonsis risk factors, such as diffuse lesion, diabetes mellitus, left main coronary artery lesion, chronic total occlusion or bifurcation lesion **(Part 2 of this thesis)**, have not been fully investigated. Furthermore, problem of stent thrombosis is still observed in drug-eluting stent era. Drug-eluting stents interferes with the natural healing response by preventing or significantly delaying the formation of a functional endothelial lining over stent. The early establishment of a functional endothelial layer after stent implantation may resolve this issue. Recently, the existence of circulating endothelial progenitor cells has been identified as a key factor for re-endothelialization.[8,9] New concept stent using immobilized antibodies targeted at endothelial progenitor cell surface antigens has been developed. (**Part 3 of this thesis**)

Part 1 Long term tissue growth inside and outside drug-eluting stent in humans

In animal models, the inhibition of neointimal hyperplasia after deployment of polymer-coated sirolimus-eluting stents and gelatin coated paclitaxel-eluting stents was not sustained at 90 days due to delayed cellular proliferation. Although long term follow-up after drug-eluting stents implantation shows a sustained clinical benefit in several randomized trials, little is known about neointimal growth and vessel reaction out of the stent beyond the first 6 to 9 months. **In chapter 2**, four-year coronary artery response inside and outside the stent after sirolimus-eluting stent implantation was evaluated by

using serial quantitative IVUS (post-procedure, 4 months, 1 year, 2 years and 4 years) and computer assisted grey-scale value analysis for plaque composition in 23 patients in the Firs-in-man trial. **In chapter 3**, two-year coronary artery response inside and outside the stent after bare metal stents and paclitaxel-eluting stent implantation were evaluated by using serial quantitative IVUS (post-procedure, 6 months and 2 years) in the TAXUS II Study. **In chapter 4**, one-year coronary artery response after various doses and pharmacokinetic release of paclitaxel-eluting stents with an erodable polymer was evaluated by using serial quantitative IVUS (post-procedure, 4 months and 1 year) in the Paclitaxel In-Stent Controlled Elution Study (PISCES). **In chapter 5,** vessel reaction against several kinds of drug-eluting stents (sirolimus, paclitaxel, everolimus and ABT 578-eluting stents were summarized.

Part 2 Efficacy of drug-eluting stent for high risk patients

Many randomized trial showed that sirolimus-eluting stents and paclitaxel-eluting stents are dramatically reduced in-stent restenosis and target lesion revascularization, compared to bare metal stents. However, these trials had exclusion criteria. The efficacy of drug-eluting stents for high risk patients and lesions for restenosis with conventional bare metal stents has not been evaluated in detail. At the Thoraxcenter, Erasmus university, the safety and efficacy of unrestricted utilization of sirolimus and paclitaxel-eluting stents in the real world were analyzed**.** (RESEARCH: Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital Registry and T-SEARCH: Taxus-Stent Evaluated At Rotterdam Cardiology Hospital Registry). In these registries, sub-analyses for "high risk patients" such as patients with diffuse lesion **(chapter 6)**, diabetes mellitus (**chapter 7 and 8)**, chronic total occlusion of left main bifurcation lesion **(chapter 9)**, left main coronary artery lesion **(chapter 10 and 11)**, chronic total occlusion lesion **(chapter 12 and 13)** or bifurcation lesion **(chapter 4 and 15)** were analyzed.

Part 3 Endothelial progenitor cell – alternative to drug-eluting stents

In chapter 16, stent thrombosis is still observed in daily practice, using drug-eluting stents and it is associated with a high morbidity and mortality. EPC capture coating stent using monoclonal anti-human CD34 antibodies has been developed and this device may have the potential to reduce stent thrombosis and in-stent restenosis **(chapter 17)**. **In chapter 18**, the HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth - First In Man) Registry which is the first clinical investigation using this technology, was reported.

Part 4 Future direction to the interventional cardiology

Despite the advances in the treatment of patients with coronary artery disease, sudden cardiac death is still unacceptably prevalent. Patients with ischemic heart disease usually require a combination of therapies (drugs and coronary intervention) and may continue to experience symptoms. Recently, numerous percutaneous interventional treatments and diagnostic tools have been developed to diagnose the vulnerable plaque and to treat the large number of patients with myocardial ischemia. **In chapter 19,** catheter based bypass graft, therapeutic angiogenesis and myogenesis, and the catheter based devices to detect the plaque vulnerability and composition were summarized.

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Part 1

Long term tissue growth inside and outside drug eluting stent in humans

Chapter 2

Evaluation of Four-year Coronary Artery Response After Sirolimus-Eluting Stent Implantation by Using Serial Quantitative IVUS and Computer Assisted Grey-Scale Value Analysis for Plaque Composition

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CLINICAL RESEARCH **Interventional Cardiology**

Evaluation of Four-Year Coronary Artery Response After Sirolimus-Eluting Stent Implantation Using Serial Quantitative Intravascular Ultrasound and Computer-Assisted Grayscale Value Analysis for Plaque Composition in Event-Free Patients

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OBJECTIVES This study sought to evaluate the long-term arterial response after sirolimus-eluting stent implantation.

BACKGROUND Sirolimus-eluting stents are effective in inhibiting neointimal hyperplasia without affecting plaque volume behind the stent struts at six months.

METHODS Serial quantitative intravascular ultrasound and computer-assisted grayscale value analysis over four years were performed in 23 event-free patients treated with sirolimus-eluting stents.

RESULTS In the first two years, the mean plaque volume (155.5 ± 42.8 mm^3 post-procedure and 156.8 ± 57.7 mm^3 at two years, $p = 0.86$) and plaque compositional change expressed as mean percent hypoechogenic tissue of the plaque behind the stent struts (78.9 ± 8.6% post-procedure and 78.2 ± 8.9% at two years, $p = 0.67$) did not significantly change. However, significant plaque shrinking (change in plaque volume = −18.4 mm^3, $p = 0.02$) with an increase in plaque echogenicity (change in percent hypoechogenic tissue = −7.8%, $p < 0.0001$) was observed between two and four years. The mean neointimal volume increased over four years from 0 to 8.4 ± 5.8 mm^3 ($p < 0.0001$). However, no further statistically significant change occurred between two and four years (7.0 ± 6.7 mm^3 vs. 8.4 ± 5.8 mm^3, $p = 0.25$).

CONCLUSIONS Between two and four years after sirolimus-eluting stent implantation, peri-stent tissue shrank with a concomitant increase in echogenicity. These intravascular ultrasound findings suggest that late chronic artery responses may evolve for up to four years after sirolimus-eluting stent implantation. In addition, the fact that the neointima does not significantly change from two to four years may suggest that the biological phenomenon of a delayed healing response has begun to subside. (J Am Coll Cardiol 2005;46:1670–6) © 2005 by the American College of Cardiology Foundation

Polymer-based drug-eluting stents reduce in-stent neointimal hyperplasia in randomized trials and registries (1–3). However, concern exists that the non-erodable polymer, as well as the presence of the drug within the polymer, may exert long-term detrimental biological effects (4,5). Little data are available on long-term arterial responses after either sirolimus-eluting stent (SES) or paclitaxel-eluting stent (PES) implantation. A recent report showed that PES implantation was associated with an increase in plaque volume behind the stent struts at six months (6). Although SES do not affect the plaque volume behind the stent struts at six months, no data at later time points have been reported (7,8). The goal of this study was to evaluate the late progression of the intra-stent neointima as well as the long-term arterial remodeling process and changes in plaque composition inside and outside the stent after SES implantation. To investigate these changes, serial quantitative intravascular ultrasound (IVUS) and computer-assisted grayscale value analyses for plaque compositional imaging over a four-year follow-up period were performed in event-free patients who were treated with SES.

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METHODS

Study population. Thirty patients with de novo coronary artery lesions were treated with a single 18-mm sirolimus-eluting Bx-Velocity stent (Cordis, Miami Lakes, Florida) in São Paulo, Brazil, in the first human study of SES as described elsewhere (9). After the procedure, proper risk factor management was mandated for all patients. Of the 30 patients, 26 patients underwent IVUS examination at four years by protocol, three patients had target vessel revascularization before scheduled four-year follow-up angiography, and one asymptomatic patient refused repeat angiog-

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Abbreviations and Acronyms

ANOVA = analysis of variance
ECG = electrocardiogram/electrocardiographic
IVUS = intravascular ultrasound
PES = paclitaxel-eluting stent
SES = sirolimus-eluting stent

raphy. Of these 26 patients, three were excluded: two patients did not undergo IVUS at two-year follow-up, and plaque behind the stent on the immediate post-procedure IVUS could not reliably be assessed in one patient. Thus, serial coronary angiography and intravascular ultrasound analysis were performed post-procedure, at four-month, one-year, two-year, and four-year follow-up in 23 patients who were event-free throughout the four-year follow-up period.

Serial quantitative IVUS analysis. All follow-up IVUS were performed using an automated pull-back system at 0.5 mm/s and recorded on VHS videotapes. Images were digitized for quantitative analysis. The lumen, stent, and external elastic membrane contours were detected with CURAD QCU analysis software (Curad B.V., Wijk bij Duurstede, the Netherlands) (7). The stented segment and the 5-mm segments proximal and distal to the stent were analyzed. Over the four-year follow-up period, different IVUS catheters and ultrasound consoles were used. Post-procedure, four-month, and one-year follow-up, 20- or 30-MHz non–electrocardiogram (ECG)-gated IVUS were performed. At two-year follow-up, 30- or 40-MHz ECG- or non–ECG-gated IVUS were performed. At four-year follow-up, 30- or 40-MHz non–ECG-gated IVUS were performed. Three IVUS consoles were used (In-Vision [Volcano Therapeutics, Rancho Cordova, California], Clearview, and Galaxy [both Boston Scientific Corp., Natick, Massachusetts]). To analyze and compare the IVUS data consistently, all IVUS examinations were retrospectively ECG-gated using the Intelligate method, which automatically selects the end-diastolic frames from pre-recorded non–ECG-gated IVUS data (10). In addition, an automatic adjustment for 30-MHz Boston Scientific catheters that were connected to a Clearview console was applied as previously described (11).

Image-based plaque characterization (echogenicity). We used a computer-aided, in-house–developed grayscale value analysis program for plaque characterization (12). Based on the mean gray level (brightness) of the adventitia, plaque was classified as more (hyperechogenic) or less bright (hypoechogenic) in relation to the adventitia (Fig. 1A). The volume bounded externally by the surface that lies 0.5 mm outside the media and internally by the surface that lies 0.2 mm outside the media was defined as the adventitia. In cross-sectional images, it appears as a 0.3-mm thick band just outside the media. Upper tissue was defined as tissue that has a mean gray value higher than the mean adventitial intensity plus two times its standard deviation (12). Calcified plaque and stent struts were in this upper tissue range. The percentage of hypoechogenic plaque was calculated for the entire region of interest, excluding upper tissue (Fig. 1B) (12).

Statistical analysis. Continuous variables were expressed as mean values ± standard deviations and compared by means of the paired *t* test. Overall IVUS parameters (volume and echogenicity) across all time points were compared using repeated-measure analysis of variance (ANOVA). Two post-hoc tests (between post-stent and two years, and between two years and four years) were performed with Bonferroni corrections (p value for significance <0.025) for p values <0.05 on ANOVA.

RESULTS

Patient characteristics. Mean age of patients was 57 years, and two-thirds were male (Table 1). The left anterior descending artery was treated in 14 patients, right coronary artery in 6 patients, and left circumflex artery in 3 patients. After stent implantation, risk factor management was instituted in all patients. Aspirin and statins were prescribed in all patients during the four years.

Plaque volume behind the stent struts. Table 2 shows the serial quantitative IVUS data. Plaque volume behind the stent struts did not change significantly in the first two years ($p = 0.86$), but showed a significant change between two and four years because of a decrease in plaque volume behind the stent struts at four years (156.8 ± 57.7 mm^3 vs. 138.4 ± 42.2 mm^3, $p = 0.02$). Although plaque volume at the proximal edge of the stents increased significantly at four-month follow-up compared with post-procedure (32.5 ± 12.2 mm^3 vs. 39.8 ± 15.8 mm^3, $p = 0.005$), it did not differ significantly between post-procedure and four-year follow-up (32.5 ± 12.2 mm^3 vs. 33.0 ± 11.7 mm^3, $p = 0.81$). At the distal edge, no significant changes in plaque volume were observed at any time point ($p = 0.18$).

Neointimal volume. Neointimal volume increased at each measured time point, and was 8.4 ± 5.8 mm^3 at four-year follow-up ($p < 0.0001$). Between post-procedure and two-year follow-up, a significant change in neointimal volume was noted (0 mm^3 vs. 7.0 ± 6.7 mm^3, $p < 0.0001$). However, between two-year and four-year follow-up, the increase in neointimal volume was not statistically different (7.0 ± 6.7 mm^3 vs. 8.4 ± 5.8 mm^3, $p = 0.25$). Figure 2A shows the correlation between neointimal volume and plaque volume behind the stent struts over four years.

Plaque composition. Serial computer-assisted grayscale value analyses for plaque composition are shown in Table 3. With respect to the plaque behind the stent struts, there was a significant decrease in percent hypoechogenic tissue, that is, an increase in percent hyperechogenicity up to four years ($p < 0.0001$). Between post-procedure and two years, there were no significant changes in plaque echogenicity ($78.9 \pm 8.6\%$ vs. $78.2 \pm 8.9\%$, $p = 0.67$). However, between two

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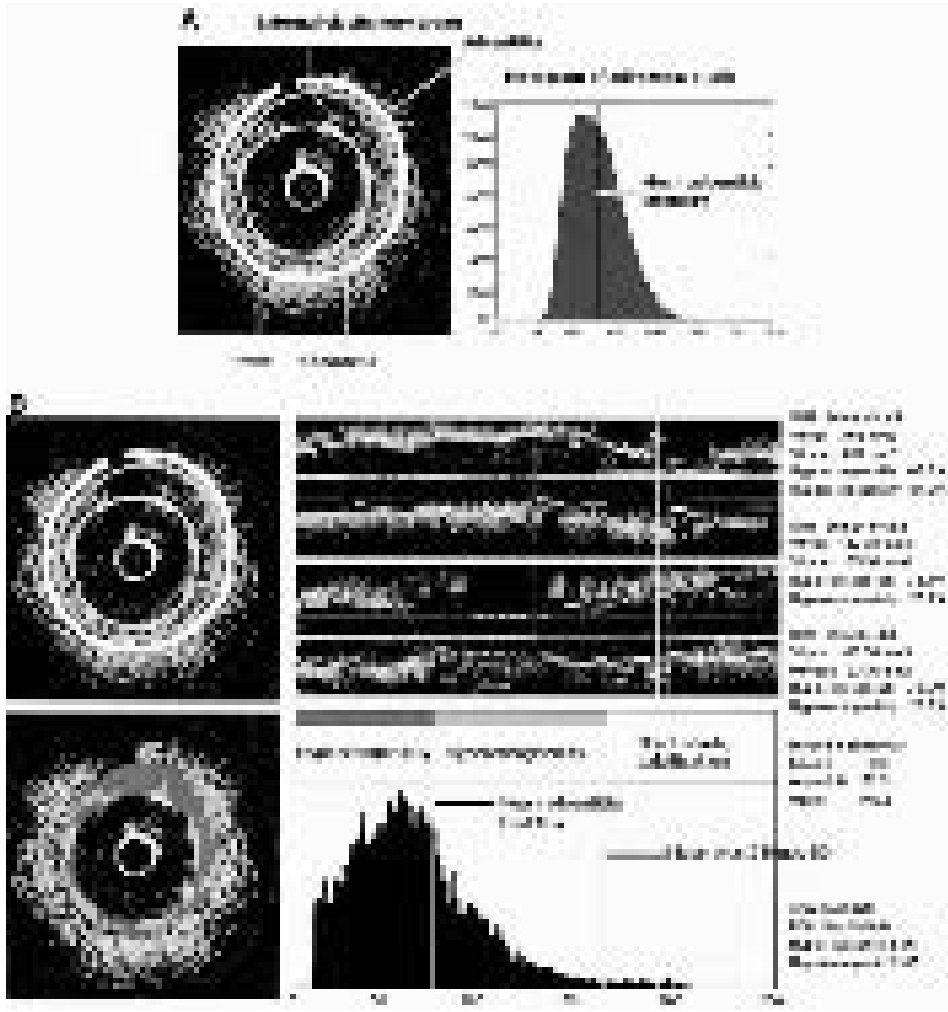

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Figure 1. (A) The adventitia is defined as tissue outside the external elastic membrane contour. For all non-shadowed adventitia pixels, the mean value and standard deviation are calculated. To observe the suitability, a normal distribution curve based on the same mean and standard deviation histogram is created. **(B)** Cross-sectional image of echogenicity and distribution graph of plaque echogenicity behind the stent struts. Hyperechogenic areas are colored **green**. Hypoechogenic areas are colored **red**. ROI = region of interest.

and four years, significant changes were noted (78.2 ± 8.9% vs. 70.4 ± 10.6%, $p < 0.0001$). A similar pattern was observed for plaque at the proximal stent edge with a significant reduction in percent hypoechogenic tissue at four-year follow-up ($p = 0.02$). At the distal stent edge, no significant changes in plaque echogenicity were observed across time points ($p = 0.78$). Figure 3 is a representative example of a patient with plaque shrinkage and reduction of hypoechogenic plaque composition from two-year to four-year follow-up.

Neointimal echogenicity. The echogenicity of the neointima increased over the four-year follow-up period ($p < 0.0001$) (Fig. 2B). On post-hoc testing with Bonferroni corrections, the decrease in hypoechogenicity between four

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Table 1. Patient Characteristics

	n = 23
Age, yrs (mean ± SD)	57 ± 9
Male, %	65.2
Hypertension, %	69.6
Hyperlipidemia, %	47.8
Diabetes mellitus, %	26.1
Family history, %	30.4
Current smoking, %	65.2
Treated vessel	
LAD, %	60.9
LCX, %	13.0
RCA, %	26.1

LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.

months and two years was not significant (74.9 ± 12.7% vs. 66.7 ± 19.1%, p = 0.03), but was significant between two-year and four-year follow-up (66.7 ± 19.1% vs. 57.0 ± 22.6%, p = 0.01).

DISCUSSION

Previous reports have shown that SESs are effective in inhibiting neointimal hyperplasia without affecting total vessel volume or plaque volume behind the stent struts at six months (7,8). In the present study, this pattern of tissue growth inhibition inside and outside the SES was maintained at two years. However, at four-year follow-up, a significant negative remodeling (shrinking) of the plaque behind the stent struts with an increase in hyperechogenicity was observed.

Several studies have shown that plaque echogenicity in the carotid artery is related to the histologic components of plaques and that echolucency (low echogenicity) can predict clinical events (13,14). For coronary plaque studies, plaque echogenicity has also been related to the histologic components of plaque (15–17). Hyperechogenic tissue has been shown to be associated with a predominance of dense fibrous or elastic tissue, whereas hypoechogenic plaque was correlated with predominance of loose fibrous, lipid, or necrotic tissue. Recently, other analysis systems such as IVUS elastography, IVUS palpography, IVUS radiofrequency analysis (so-called virtual histology), and optical coherence tomography have been used to evaluate plaque vulnerability and plaque composition (18–20). However, these methodologic approaches require prospective acquisition of data, for which their respective devices were not available for human use at the time of initial assessment. Plaque echogenicity analysis by computer-assisted grayscale value is currently the only method that has the potential to analyze plaque composition in a retrospective manner.

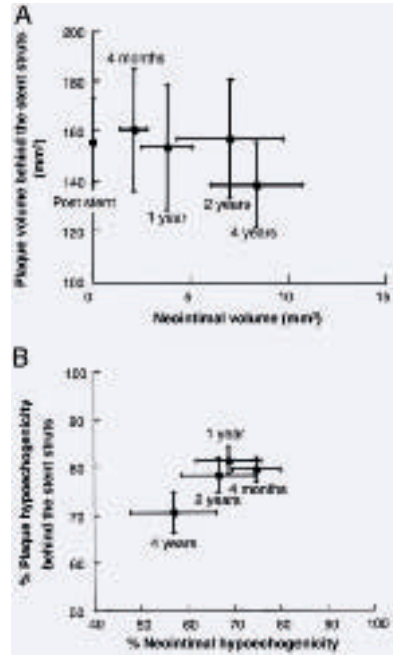


Figure 2. (A) Correlation between neointimal volume and plaque volume behind the stent struts over four years. **(B)** Correlation between neointimal percent hypoechogenicity and plaque percent hypoechogenicity behind the stent struts over four years. **Error bars** indicate 95% confidence interval.

Table 2. Serial Three-Dimensional Intravascular Ultrasound Analysis of Neointima and Plaque Volume

	After Procedure	4 Mo	1 Yr	2 Yrs	4 Yrs	ANOVA* p Value	Post Hoc After Procedure to 2 Yrs	Post Hoc 2 to 4 Yrs
Neointima, mm^3	0	2.1 ± 1.7	3.8 ± 3.3	7.0 ± 6.7	8.4 ± 5.8	<0.0001	<0.0001	0.25
Plaque (stented segment), mm^3	155.5 ± 42.8	160.4 ± 60.4	153.5 ± 61.6	156.8 ± 57.7	138.4 ± 42.2	0.04	0.86	0.02
Vessel (stented segment), mm^3	305.1 ± 53.7	310.8 ± 99.4	305.4 ± 83.8	309.8 ± 84.1	290.5 ± 65.3	0.09	—	—
Plaque (proximal edge), mm^3	32.5 ± 12.2	39.8 ± 15.8	36.5 ± 11.9	37.4 ± 13.0	33.0 ± 11.7	0.006	0.03	0.05
Vessel (proximal edge), mm^3	82.6 ± 21.9	88.6 ± 23.8	80.1 ± 17.2	82.6 ± 22.1	78.3 ± 21.6	0.001	0.98	0.10
Plaque (distal edge), mm^3	26.2 ± 15.4	28.6 ± 11.1	28.6 ± 14.0	31.1 ± 13.4	25.8 ± 11.3	0.18	—	—
Vessel (distal edge), mm^3	63.3 ± 22.0	68.5 ± 20.8	66.5 ± 26.3	67.3 ± 21.8	61.4 ± 22.7	0.07	—	—

*Repeated-measures analysis of variance (ANOVA) was performed among five periods. Post hoc analysis between after the procedure and two years, and between two and four years were performed with Bonferroni corrections (significant level of p value is 0.025).

Table 3. Percent Hypoechogenic Tissue Component in the Plaque and Neointima

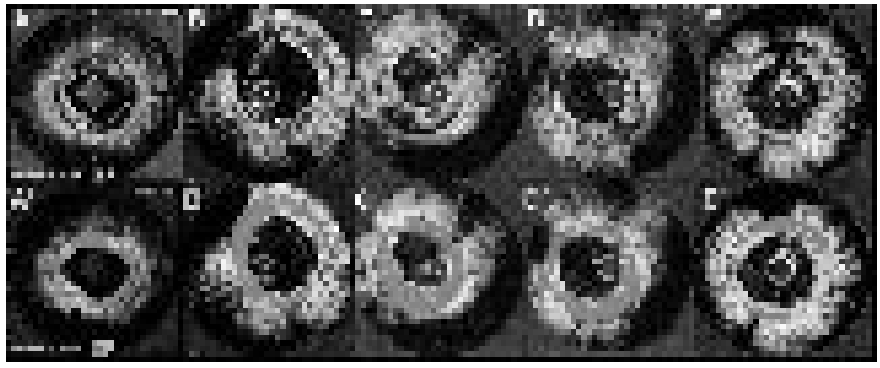
	After Procedure	4 Mo	1 Yr	2 Yrs	4 Yrs	ANOVA* p Value	Post Hoc After Procedure to 2 Yrs	Post Hoc 2 to 4 Yrs
Neointima, %	—	74.9 ± 12.7	68.9 ± 17.1	66.7 ± 19.1	57.0 ± 22.6	0.0001†	0.03‡	0.01
Plaque (stented segment), %	78.9 ± 8.6	79.4 ± 6.7	81.3 ± 7.4	78.2 ± 8.9	70.4 ± 10.6	<0.0001	0.67	<0.0001
Plaque (proximal edge), %	88.7 ± 6.9	87.2 ± 6.5	87.1 ± 6.0	87.7 ± 7.9	81.7 ± 9.3	0.02	0.67	0.008
Plaque (distal edge), %	86.1 ± 9.8	86.8 ± 6.0	87.0 ± 10.4	88.5 ± 9.5	85.9 ± 9.4	0.78	—	—

*Repeated-measures analysis of variance (ANOVA) was performed among five periods. Post-hoc analysis between after the procedure and two years, and between two and four years were performed with Bonferroni corrections (significant level of p value is 0.025). †Repeated-measures ANOVA was performed among four periods, except after the procedure. ‡Post-hoc analysis was performed between four months and two years.

For SES, 80% of the drug load is eluted within 30 days of stent implantation (1). However, concern has arisen about long-term biological reactions to the non-biodegradable polymer (5). Long-term exposure to these polymers may cause chronic inflammation. Complete natural healing (i.e., re-endothelialization and a reduction in proteoglycan content) may take three to six months after bare metal stent implantation (21). In this present study, plaque volume behind the stent struts decreased between two and four years, and this shrinkage was accompanied by a change in plaque echogenicity, suggestive of a change in plaque composition. This may indicate that the peri-stent area has undergone a slower healing process after SES implantation that results in a more fibrous content at four-year follow-up.

In animal experiments, it has been documented that the exuberant proliferative process observed after stenting is largely inhibited in the early stage with SES, but the normal healing process is also delayed with persistence of fibrin deposition and inflammatory cells (22). In humans, one study reported the histologic findings of atherectomy specimens of restenotic lesions after implantation of a paclitaxel derivative-eluting polymer stent in which persistent fibrin accumulation with smooth muscle cells and proteoglycan and collagen type III-rich matrix with inflammation was observed at 12 months (4,5). An autopsy performed on a patient four years after SES implantation showed complete healing, indicating that the delayed healing response had abated, concurring with our findings (23).

In this study, neointimal volume continued to increase over the four-year period. However, the increase between two and four years failed to reach statistical significance (7.0 vs. 8.4 mm^3, $p = 0.25$), and the change in neointimal volume between two years and four years was significantly less than between the post-procedure and two-year measurements (1.4 vs. 7.0 mm^3, $p = 0.04$), which possibly indicates that the delayed tissue proliferation has subsided. Carter et al. (24) reported long-term effects of SES in a porcine coronary model. They found that inhibition of neointimal hyperplasia was not sustained at 90 days compared with the bare metal stent, and the mean neointimal area was similar between 90 days and 180 days. These results differ from observations seen in clinical trials, including this study. Several trials have reported low target vessel revascularization rates up to three years (25). This discrepancy is likely explained by different monocyte and lymphocyte responses to similar concentrations of sirolimus in human and porcine vessels, and the different anatomical



color figures on page 223

Figure 3. A representative example of a patient with plaque compositional changes between two-year and four-year follow-up. **Top row** shows cross-sectional vessel image at **(A)** post-procedure, **(B)** four months, **(C)** one year, **(D)** two years, and **(E)** four years. **Red line** indicates lumen. **Light blue line** indicates stent. **Green line** indicates media. **Dense blue line** indicates adventitia. **Bottom row** shows cross-sectional echogenicity images. Hyperechogenic areas are colored **green**. Hypoechogenic areas are colored **red**. **(A')** Percent plaque behind stent hypoechogenicity was 84.0% post-procedure, **(B')** 85.3% at four months, **(C')** 88.4% at one year, **(D')** 84.2% at two years, and **(E')** 74.8% at four years.

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features of normal porcine coronary arteries versus atherosclerotic human coronary arteries (26).

Furthermore, the increase in neointimal echogenicity as observed in this study would also suggest that a fibrotic process is now operative and predominant. The rate of growth of the neointima has slowed—both features suggest that the completion of the healing process may be expected in the near future.

Study limitations. This study is limited by the sample size of 23 patients. Secondly, patients without events were used for the serial IVUS analysis. Consequently, these results may not apply to all patients treated with SES. Different IVUS catheters and consoles were used over the four-year period, and most data were acquired without ECG gating. These differences may have hampered the consistency of volumetric and echogenic analysis (27). For instance, BSC 30-MHz catheters connected to a Clearview console underestimates true dimensions (11). To correct for these discrepancies, the results from the 30-MHz catheter were adjusted using a previously reported mathematical model (11), and image artifacts resulting from cardiac cycle motion observed in non–ECG-gated images were circumvented by the use of the Intelligate method, which converts non–ECG-gated data to ECG-gated data retrospectively (10,28).

The adventitia was taken as a reference to determine the change in echogenicity occurring in the peri-stent and intrastent tissue. Any alterations to the adventitia (e.g., inflammatory and fibrotic reactions) after stent deployment may alter the echogenicity during the follow-up period. Because any potential increase in echogenicity of the adventitia cannot be totally excluded or measured, the change in echogenicity of the peri-stent and intra-stent tissue may be underestimated and the interference of stent struts with plaque echogenicity may not be completely excluded. Finally, any remaining bias after correction from the use of different IVUS systems cannot be totally excluded in the present study. Despite the inherent limitations, plaque echogenicity analysis by computer-assisted grayscale value is to date the only method with the potential to analyze plaque composition retrospectively.

Conclusions. After SES implantation, negative plaque remodeling and a decrease of hypoechogenic plaque composition were observed at four-year follow-up. In addition, the fact that the neointima does not significantly change from two to four years may suggest that the biological phenomenon of a delayed healing response has begun to subside.

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Chapter 3

Peri-stent remodeling and neointimal suppression two-years after polymer based paclitaxel eluting stents implantation- insight from serial IVUS analysis in the TAXUS II study

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Peristent Remodeling and Neointimal Suppression 2 Years After Polymer-Based, Paclitaxel-Eluting Stent Implantation

Insights From Serial Intravascular Ultrasound Analysis in the TAXUS II Study

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Background—The purpose of this study was to evaluate long-term vascular responses as long as 2 years after implantation of polymer-based, paclitaxel-eluting stents in contrast to uncoated stents.

Methods and Results—TAXUS II is a randomized, double-blind trial comparing slow-release (SR) and moderate-release (MR) TAXUS stents with bare-metal control stents (BMSs). One hundred sixty-one event-free patients (SR, 43; MR, 41; and BMS, 77) underwent serial intravascular ultrasound (IVUS) analysis after the procedure and at 6 months and 2 years. At 2 years, neointimal responses continued to be significantly suppressed in the SR and MR groups when compared with the BMS group (BMS, 1.49 ± 1.12 mm^2; SR, 0.94 ± 0.76 mm^2 [$P=0.004$]; and MR, 1.06 ± 0.90 mm^2 [$P=0.02$]). Between 6 months and 2 years, the BMS group showed compaction of the neointima (Δ, -0.22 ± 1.05 mm^2 [$P=0.08$]). In contrast, both the SR and MR groups exhibited an increase (Δ SR, 0.30 ± 0.76 mm^2 ($P=0.01$); MR, 0.41 ± 0.94 mm^2 [$P=0.009$]). Between 6 months and 2 years, the initial increase in plaque outside the stent regressed in the BMS and SR groups to levels comparable to those after the procedure, whereas expansive remodeling partially regressed in the MR group (Δ between after the procedure and 2 years BMS, -0.34 ± 1.28 mm^2 [$P=0.05$]; SR, -0.02 ± 1.40 mm^2 [$P=0.93$]; MR, 0.32 ± 1.56 mm^2 [$P=0.27$]).

Conclusions—The 2-year follow-up demonstrates that neointimal suppression was dose independent and that this effect was still sustained at 2 years. However, the increase in area outside the stent seen at 6 months regressed to different extents in a dose-dependent manner at 2 years. (***Circulation*. 2005;112:3876-3883.**)

Key Words: stents ■ remodeling ■ restenosis

Both slow-release (SR) and moderate-release (MR) polymer-based, paclitaxel-eluting stents prevent in-stent neointimal growth compared with bare-metal stents (BMSs).[1] In the patient population studied in TAXUS II, these antirestenotic effects were comparable for both dose formulations. However, at 6 months, this inhibition was associated with expansive, peristent remodeling.[2] The extent of peristent remodeling was more pronounced with the MR formulation, implying dose-dependent differences in vascular responses outside but not inside the stent.

Clinical Perspective p 3883

In animal studies, the mechanism of action of drug-eluting stents on neointimal proliferation after stent implantation seems to be partially explained by a delay in vascular responses. For polymer-based, paclitaxel-eluting stents, inhibition of in-stent neointimal growth is associated with a delay in intimal healing up to 28 days, as indicated by initially increased fibrin deposition, inflammation, and delayed endothelialization.[3] By 90 days, peristrut changes associated with paclitaxel were resolving, but in-stent neointimal growth suppression was no longer present.

TAXUS II is an international study of 2 consecutive cohorts designed to evaluate 2 formulations of a polymer-based, paclitaxel-eluting stent. The primary end point in the original protocol was the percent net volume obstruction, providing a unique opportunity to evaluate serial intravascular ultrasound system (IVUS) changes over time.

The objective of this study was to evaluate long-term arterial responses both inside and outside the stent as long as 2 years after implantation of polymer-based, paclitaxel-eluting stents by using serial quantitative IVUS analysis in event-free patients.

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Methods

Patient Selection

The original study design, procedure, and IVUS results have been described previously.[1,2,4] The design of the TAXUS II study is a randomized, double-blind, controlled trial. In brief, 536 patients with single de novo coronary lesions (>50% stenosis on visual assessment) treatable with a single stent (3.0- or 3.5-mm diameter and 15 mm long) were randomly assigned to 2 consecutive, independent cohorts. The first cohort of patients was randomized to be treated with either a control BMS or a TAXUS-NIRx SR formulation stent. A second cohort of patients was randomized to control BMSs versus a TAXUS-NIRx MR formation. The primary end point was met with a significant 66% (SR) and 62% (MR) reduction in 6-month percent net volume obstruction as assessed by IVUS in both groups, without an apparent difference between the SR and MR groups.

To further evaluate the natural history of vascular responses to TAXUS, the study protocol was amended to include a 2-year IVUS long-term follow-up. Of the initial 536 patients, 161 patients without any clinical events through the 2-year follow-up and with serial (postprocedure, 6 months, and 2 years) and analyzable IVUS data were selected for this substudy (BMS, 77; SR, 43; and MR, 41). This patient population represents a highly selected subgroup of patients successfully treated with either a BMS, a TAXUS SR stent, or a TAXUS MR stent. Because the 2-year quantitative coronary angiography (QCA) and IVUS substudy was added as an amendment to the original study protocol, it required additional approval from the local regulatory agencies and ethics committees before being implemented at the sites. The 2-year substudy was not approved by the appropriate regulatory authorities or ethics committees at 9 of the 38 sites. As a result, of the original 536 intent-to-treat patients, 154 were not eligible to participate in the 2-year substudy. Additionally, 122 patients did not consent to the 2-year substudy, whereas 30 patients were excluded for clinical reasons, resulting in 230 patients who were eligible to participate in the substudy. In 34 of the 230 patients, IVUS either was not performed or was not of adequate quality to be included in the qualitative and quantitative analysis. An additional 23 patients were excluded because they had either a target-vessel revascularization before 6 months or had a target-vessel revascularization after 6 months but did not have IVUS before the target-vessel revascularization. Finally, 12 patients were excluded from this analysis because paired IVUS data were not available at all 3 time points (postprocedure, 6-month, and 2-year data). Written, informed consent was obtained from all patients.

TAXUS Stent System

The 15-mm NIR Conformer stent of 3.0- or 3.5-mm diameter was used in this study (Boston Scientific Corp and Medinol Ltd). All TAXUS NIRx stents were coated with 1.0 $\mu g/mm^2$ paclitaxel in an SR or MR formulation as previously described.[1] The SR and MR dose formulations are characterized by differences in the amount of drug released during the initial 48-hour burst phase as well as the amount of drug remaining embedded in the polymer at 30 days.

Study Procedure

Stents were implanted after balloon predilatation as described in the initial reports. Per study protocol, all patients were to receive 75 mg/d aspirin indefinitely. Clopidogrel (300 mg) was administered, preferably 48 hours before the procedure, followed by 75 mg once daily for 6 months.

Quantitative IVUS and Angiographic Analysis

The quantitative IVUS and QCA analyses were performed by an independent core laboratory that remains blinded to treatment allocation during the ongoing 5-year follow-up (Cardialysis). Serial IVUS (postprocedure, 6-month, and 2-year follow-up) procedures were performed after administration of 200 μg intracoronary nitroglycerin with an automated pullback at 0.5 mm/s. All IVUS procedures were recorded on VHS videotape, and images were digitized for analysis. A computer-based contour-detection program was used for automated 3-dimensional reconstruction of the stented segment.[5,6] Reconstruction and quantification of 3-dimensional IVUS images have been validated previously.[5] In brief, a series of tomographic images is continuously acquired during an IVUS pullback procedure. With use of a 40-MHz ultrasound probe, 25 frames per second are available from a motorized pullback procedure recorded on videotape. In this study, an average of 714 sections in the stented lesion were obtained per patient. All acquired cross-sectional frames were analyzed by semiautomatic contour tracing in several reconstructed, longitudinally cut planes, as developed and tested in cooperation with Cuard B.V. The applied approach focuses on the tracing of contours in the reconstructed, longitudinally cut planes (L-mode view). The number of L-mode contours to be traced is independent of the number of frames in the analysis. As many as 72 L-mode views at 5° intervals can be selected for display and subsequent analysis. Contours of vessel, lumen, and stent structures can then be traced. Instead of trying to find the structures completely automatically, the program uses starting points as defined by the user, followed by autotracing of the contour segment in either of 2 possible directions. Pieces of the contours can be retraced in a semiautomatic procedure to optimize the interaction between operator and algorithm. In this way, all cross-sectional areas are analyzed, and the 3-dimensional nature of the data set is fully used. The interobserver correlation coefficients for lumen, stent, and vessel volumes resulted in R^2 values of 0.96, 0.99, and 0.99, respectively.

In the stented segment, mean peristent area and mean neointimal area were calculated. Incomplete stent apposition (ISA) was defined as 1 or more stent struts clearly separated from the vessel wall with evidence of blood speckles behind the strut without overlapping side branches.[6–8] ISA was classified into 3 groups. Resolved ISA was defined as ISA that disappeared during follow-up. Persistent ISA was defined as ISA that was evident both after the procedure and at follow-up. Late acquired ISA was defined as ISA that was absent after the procedure but present at follow-up.

Statistical Analysis

The BMS groups of the 2 cohorts were combined because the baseline and 6-month follow-up data showed no significant differences, as previously described.[1] Therefore, 3 groups are reported in this study: The combined BMS, the TAXUS-SR, and the TAXUS-MR groups. Discrete variables are displayed as percentages and were tested with Fisher's exact test. Continuous variables are expressed as mean±SD. When 3 groups were compared, overall probability values were derived from 1-way ANOVA or Fisher's exact test. Comparisons between postprocedure and follow-up data were performed with a 2-tailed, paired *t* test, whereas comparisons between 2 groups were performed with Fisher's least significant difference test. Linear regression was performed to assess the correlation between different IVUS outcomes. A value of $P<0.05$ was considered statistically significant.

Results

Patients and Procedural Characteristics

Table 1 presents the patient and procedural characteristics for the group that had serial (after the procedure, at 6 months, and at 2 years) IVUS examinations compared with the entire TAXUS II study cohort. Comparable baseline demographic and angiographic data with the exception of the prevalence of males ($P=0.03$) indicate that the data in the serial IVUS cohorts are representative of the overall randomized study population.

Area Inside the Stent (Neointimal Area)

As shown in Table 2, the neointimal area at 6 months was significantly suppressed in the SR and MR groups, as detected by serial IVUS when compared with the BMS group (1.71 ± 1.38 mm^2 in the BMS group versus 0.64 ± 0.81 mm^2 in

TABLE 1. Baseline and Procedural Characteristics

	BMS (n=77)	SR (n=43)	MR (n=41)	*P**	All Randomized Patients (N=536)
Age, y	57.2±9.0	59.4±1.3	57.5±10.9	0.50	60.1±10.0
Male, %	85.7	65.1	73.2	0.03	75.6
Current smoker, %	29.9	14.0	24.4	0.14	25.0
Diabetes, %	13.0	9.3	9.8	0.85	14.7
Hypertension, %	46.8	62.8	51.2	0.24	61.4
Hypercholesterolemia, %	72.7	83.7	80.5	0.35	75.9
Unstable angina, %	27.3	27.9	14.6	0.26	34.3
Previous MI, %	50.7	41.9	51.2	0.63	39.7
Target vessel, %					
LAD	52.0	41.9	39.0	0.34	44.6
LCX	11.7	20.9	19.5	0.31	19.6
RCA	36.4	37.2	41.5	0.89	35.8
RVD, mm	2.73±0.50	2.78±0.38	2.76±0.45	0.88	2.75±0.46
Target lesion length, mm	10.5±4.15	10.0±3.69	11.0±6.27	0.68	10.4±4.23
Stent size, mm	3.29±0.25	3.31±0.24	3.23±0.25	0.31	3.26±0.25

MI indicates myocardial infarction; LAD, left anterior descending coronary artery; LCX, left circumflex artery; RCA, right coronary artery; and RVD, reference vessel diameter. Other abbreviations are as defined in text. Values are mean±SD or percentages.

*ANOVA among the 3 groups.

the SR group, $P<0.0001$; 0.66±0.83 mm^2 in the MR group, $P<0.0001$). This reduction relative to the BMS group was also present at 2 years (1.49±1.12 mm^2 in the BMS group versus 0.94±0.76 mm^2 in the SR group, $P=0.004$; 1.06±0.90 mm^2 in the MR group, $P=0.02$). When relative changes within the 3 groups were compared, the BMS group showed compaction of the neointima between 6 months and 2 years, as demonstrated by a trend toward a decrease in neointimal area (Δ, −0.22±1.05 mm^2, $P=0.08$). In contrast, the SR and MR groups both exhibited a significant increase in neointimal area between 6 months and 2 years when compared with controls (SR Δ, 0.30±0.76 mm^2, $P=0.01$ versus BMS; MR Δ, 0.41±0.94 mm^2, $P=0.009$ versus BMS; Table 2). However, according to QCA analyses, the average minimal lumen diameter (MLD) in the SR and MR groups did not decrease from 6 months to 2 years (2.30±0.33 to 2.36±0.28 mm in the SR group; 2.30±0.38 to 2.31±0.35 mm in the MR group; Table 3).

TABLE 2. Quantitative IVUS Data

	BMS (n=77)	SR (n=43)	MR (n=41)	*P**
Neointimal area, mm^2				
6 Months	1.71±1.38	0.64±0.81	0.66±0.83	<0.0001
2 Years	1.49±1.12	0.94±0.76	1.06±0.90	0.006
Difference 2 years−6 months	−0.22±1.05	0.30±0.76	0.41±0.94	0.001
Plaque area outside the stent (peristent area), mm^2				
After procedure	7.97±2.00	8.18±2.11	8.38±2.52	0.71
Difference 6 months−after	0.68±1.19	1.18±1.66	1.52±1.68	0.04
Difference 2 years−6 months	−1.02±0.92	−1.21±1.39	−1.19±1.56	0.74
Difference 2 years−after	−0.34±1.28	−0.02±1.40	0.32±1.56	0.11
Vessel area, mm^2				
After procedure	16.43±3.07	17.25±2.93	16.79±3.36	0.50
Difference 6 months−after	1.03±1.41	1.21±1.84	1.60±1.94	0.34
Difference 2 years−6 months	−1.18±1.23	−1.33±1.74	−1.38±1.78	0.50
Difference 2 years−after	−0.15±1.49	−0.12±1.76	0.21±1.80	0.60

Abbreviations are as defined in text. Values are mean±SD.

*ANOVA among the 3 groups.

TABLE 3. QCA Data

	After Procedure	6 Months	2 Years
BMS (n=77)			
RVD, mm	2.89±0.39	2.64±0.49	2.64±0.46
MLD, mm	2.61±0.35	1.91±0.45	2.05±0.40
DS, %	9.50±5.45	27.19±13.36	21.49±11.41
SR (n=43)			
RVD, mm	2.87±0.30	2.81±0.40	2.78±0.33
MLD, mm	2.59±0.29	2.30±0.33	2.36±0.28
DS, %	9.53±5.44	17.63±8.78	14.64±6.96
MR (n=41)			
RVD, mm	2.89±0.38	2.75±0.37	2.79±0.42
MLD, mm	2.58±0.33	2.30±0.38	2.31±0.35
DS, %	10.24±5.25	16.05±9.59	16.24±9.56

RVD indicates reference vessel diameter; DS, diameter stenosis. Other abbreviations are as defined in text. Values are mean±SD.

Area Outside the Stent (Peristent Area)

Changes up to 6 Months

In the first 6 months, significant increases in mean peristent area (calculated as mean vessel area minus mean stent area), consistent with expansive vessel remodeling, were observed in all 3 groups (Table 2). In the BMS group, the peristent area increased by 8.5%, from 7.97±2.00 to 8.65±1.91 mm^2 (P=0.0001). This contrasted with an increase by 14.4% in the SR group (8.18±2.11 mm^2 after the procedure versus 9.37±2.79 mm^2 at 6 months; P=0.0003) and by 18.1% in the MR group (8.38±2.52 mm^2 after the procedure versus 9.90±2.45 mm^2 at 6 months; P<0.0001).

Changes From 6 Months to 2 Years

From 6 months to 2 years, a significant regression of the peristent area was observed in all 3 groups. In the BMS group, the peristent area decreased by 11.8%, from 8.65±1.91 to 7.63±1.56 mm^2 (P<0.0001). Similarly, the peristent area decreased by 12.9% in the SR group (9.37±2.79 mm^2 versus 8.16±2.09 mm^2; P<0.0001) and by 12.0% in the MR group (9.90±2.45 mm^2 versus 8.70±2.20 mm^2; P=0.0003).

At 2 years, this regression in the BMS and SR groups resulted in absolute peristent areas that were comparable to those observed after the procedure (difference between postprocedure and 2-year measurements, −0.34±1.28 mm^2 in the BMS group and −0.02±1.40 mm^2 in the SR group). In the MR group, regression of the initial increase was incomplete, with a remaining net increase at 2 years with respect to the postprocedure value of 0.32±1.56 mm^2 (Table 2).

Assessment of the peristent area showed that the expansive vessel remodeling observed at 6 months regressed from 6 months to 2 years in all 3 groups. The incidence of this remodeling pattern was observed in the vast majority of patients (67.5% in the BMS, 74.4% in the SR, and 78.0% in the MR groups; Figure 1).

Correlation Between Area Inside the Stent (Neointimal Area) and Area Outside the Stent (Peristent Area)

Figure 2 presents the changes of the area inside the stent versus the correlating changes outside the stent for 2 years to illustrate the natural history of vascular responses around and within the stent. This graph illustrates that for the BMS, there was a reduction in neointimal area as well as a reduction in the peristent area between 6 months and 2 years. For the SR group, the neointimal area increased, yet there was a reduction in peristent area, similar to that seen with the BMS. Finally, for the MR group, the neointima significantly increased between 6 months and 2 years, with a partial decrease in peristent area.

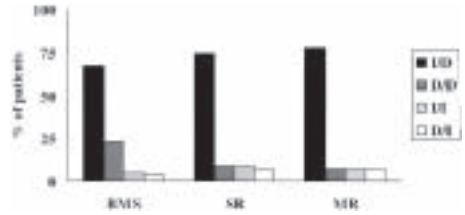

Figure 1. The incidence of increasing (I) or decreasing (D) peristent area up to 2 years after stent implantation within each group. I/D indicates that peristent area (PSA) increased during the first 6 months and decreased from 6 months to 2 years; D/D indicates that PSA decreased up to 2 years; I/I indicates that PSA increased up to 2 years; and D/I indicates that PSA decreased during the first 6 months and increased from 6 months to 2 years. Other abbreviations are as defined in text.

For all 3 groups, there were no correlations between peristent area after the procedure and neointimal area at 6 months (R=−0.016, P=0.70 in the BMS group; R=−0.021, P=0.55 in the SR group; and R=−0.037, P=0.93 in the MR group) and 2 years (R=−0.011, P=0.51 in the BMS group; R=0.11, P=0.037 in the SR group; and R=−0.036, P=0.88 in the MR group). In addition, there were no correlations between relative changes in peristent area and changes in

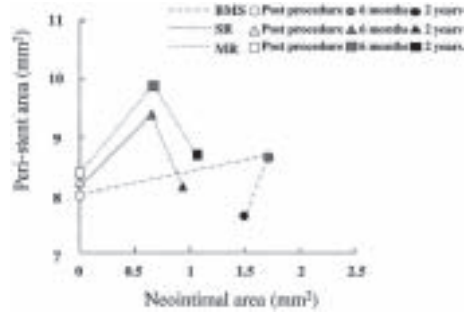

Figure 2. Correlation between neointimal area and peristent area for 2 years. Probability values for peristent area from after the procedure to 6 months are 0.0001 for BMS, 0.0003 for SR, and <0.0001 for MR. Probability values for peristent area from 6 months to 2 years are <0.0001 for BMS, <0.0001 for SR, and 0.0003 for MR. The probability value for neointimal area from after the procedure to 6 months is <0.0001 for all 3 groups, whereas probability values for neointimal area from 6 months to 2 years are 0.08 for BMS, 0.01 for SR, and 0.009 for MR. Abbreviations are as defined in text.

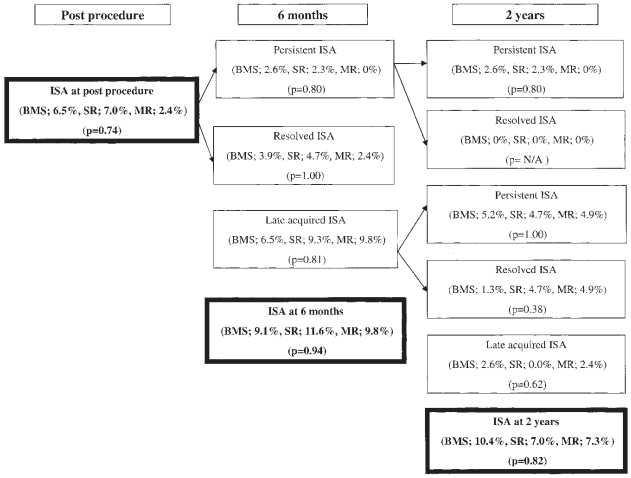

Figure 3. Incidence of ISA for as long as 2 years after stent implantation. Abbreviations are as defined in text.

neointimal area over time at 6 months ($R=-0.013$, $P=0.57$ in the BMS group; $R=0.028$, $P=0.18$ in the SR group; and $R=-0.018$, $P=0.48$ in the MR group) and 2 years ($R=-0.017$, $P=0.72$ in the BMS group; $R=-0.021$, $P=0.54$ in the SR group; and $R=0.021$, $P=0.22$ in the MR group).

Incomplete Stent Apposition

As shown in Figure 3, the incidences of ISA at 2 years were similar among the 3 groups (10.4% in the BMS group, 7.0% in the SR group, and 7.3% in the MR group; $P=0.82$). The incidences of late acquired ISA at 2 years in all groups were lower than at 6 months (2.6% versus 6.5% in the BMS group, 0% versus 9.3% in the SR group, and 2.4% versus 9.8% in the MR group).

Discussion

This article presents the first long-term (up to 2 years) serial IVUS analysis after deployment of BMSs or drug-eluting stents in a series of 161 patients. To assess long-term IVUS outcomes in response to the original study stent implanted during the index procedure, neointimal area analyses had to exclude patients with target-lesion revascularization before the follow-up IVUS examination. Thus, neointimal hyperplasia in the overall population might be underestimated when compared with this analysis. The major findings of this study are as follows: (1) Neointimal suppression is maintained for as long as 2 years in both the SR and MR groups when compared with the BMS group. (2) Whereas the BMS group showed compaction of the neointima over time, there were very modest increases in neointima in the SR and MR groups between 6 months and 2 years, with significant reductions relative to the control. (3) The initial increase in peristent area that coincides with neointimal suppression in both TAXUS groups during the first 6 months regressed completely in the SR group and partially in the MR group during the following 18 months to 2 years.

Change in Plaque Area Outside the Stent

In both paclitaxel groups, a significantly increased peristent area was observed at 6 months. This expansive remodeling regressed at 2 years, resulting in comparable levels of peristent area to the BMS group. One might hypothesize that this could be a result of the "drug effect" associated with a potentially delayed healing process. The mode of action of polymer-based, paclitaxel-eluting stents is believed to be associated with a delay in cellular processes within the vessel wall. This effect is exemplified in animal models by later endothelialization, reduced smooth muscle cell proliferation, and increased fibrin disposition around the stent struts.[3] Long-term follow-up beyond 2 years may provide more insight regarding the possibility of a continued delay versus a persistent alteration of the remodeling processes outside the stent.

Mean peristent area is driven by vessel area minus stent area. Thus, ISA area influences peristent area. The occurrence of late acquired ISA at 6 months that was resolved at 2 years can also explain the plaque remodeling pattern outside the stent in this study. However, the incidences of late acquired ISA at 6 months that were resolved at 2 years were low (1.3% in the BMS, 4.7% in the SR, and 4.9% in the MR groups). In addition, because the change in vessel area was similar to the change in peristent area, plaque remodeling outside the stent can be mainly accounted for by changes in plaque area, not ISA.

The current in vivo findings are limited to areal comparisons between groups and do not account for potentially different cellular compositions of the areas inside and outside the stent among the groups. New IVUS technologies, such as computer-assisted gray-scale value analysis and virtual his-

tology, may offer advances in the detection of plaque composition to help confirm this hypothesis in future studies.[9,10]

Long-Term Effect of Inhibition of Neointimal Growth

Both neointimal area from IVUS analyses and the change in MLD from QCA analyses are parameters of neointimal growth. In the present study, there are apparent discrepancies between the change in neointimal area and the change in MLD from 6 months to 2 years, especially in the TAXUS groups. Although average neointimal area increased in both TAXUS groups from 6 months to 2 years, average MLD did not decrease during the same time period. Neointimal area is calculated by considering neointimal growth in the entire stented segment. The change in MLD is calculated by considering the worst region, regardless of axial location. Thus, MLD does not account for diffuse neointimal growth over the entire length of the stent. These differences demonstrate that neointimal area is a better index of the magnitude and distribution of neointimal growth within the stent segment and may account for some of the discrepancies between the change in neointimal area and the change in MLD in this study.

Carter et al[11] reported that the inhibition of neointimal hyperplasia after deployment of polymer-coated, sirolimus-eluting stents was not sustained at 90 and 180 days owing to delayed cellular proliferation associated with increased levels of proliferative cell nuclear antigen. Farb et al[3] reported that neointimal suppression after deployment of chondroitin sulfate– and gelatin-coated, paclitaxel-eluting stents was also not maintained at 90 days. In this human IVUS study, from 6 months to 2 years, there was a small but significant increase in neointima of unclear clinical significance observed in the TAXUS group. At variance with the animal studies mentioned earlier, the present study of a distinctly different polymer and dose-release formulation shows that a significant effect on neointimal suppression was still present at the 2-year follow-up when compared with the BMS.

In this large IVUS 2-year substudy, neointimal regression in the BMS group confirmed findings previously reported from other long-term follow-up assessments of the natural healing process after stent implantation. Kimura et al[12] reported that mean in-stent luminal diameter as measured by serial QCA analysis was improved from 1.95 to 2.09 mm between 6 months and 3 years. This observation is in agreement with a postmortem human coronary artery analysis.[13] A hypercellular neointima, rich in type III collagen, versican, and hyaluronan but relatively little type I collagen, was observed as long as 18 months after BMS implantation in humans. After 18 months, neointimal tissue regressed because of the replacement of water-trapping proteoglycans (hyaluronan and versican) by decorin and type I collagen. After drug-eluting stent implantation, this pathological change may be delayed owing to chronic vessel responses induced by the presence of a durable polymer that still contains the drug. The histological findings of atherectomy specimens of neointimal tissue after implantation of a paclitaxel derivative–eluting polymer stent showed persistent fibrin accumulation with smooth muscle cells and a proteoglycan- and type III collagen–rich matrix associated with inflammation at 12 months.[14]

Although long-term follow-up after drug-eluting stent implantation has shown a sustained clinical benefit in several randomized trials, little is known about neointimal growth beyond the first 6 to 9 months.[15,16] The longest available angiographic follow-up after drug-eluting stent implantation (sirolimus-eluting stents) is 4 years. From 2 to 4 years, neointimal growth was still observed.[16] When neointimal growth after drug-eluting stent implantation begins to subside is unknown. The issue of a "late catch-up phenomenon" (delayed restenosis), which was observed after brachytherapy, has not been fully investigated with drug-eluting-stents.[17–20] Longer follow-up with serial angiographic and IVUS analyses are needed to resolve this issue.

Interestingly enough, this phenomenon of long-term compaction of the neointima was not observed in the TAXUS arm of this substudy up to 2 years. One might argue that this can also be attributed to the mode of action of paclitaxel, as discussed earlier, resulting in a general delay in vascular responses. In contrast to the findings outside the stent, no potential dose-dependent differences could be identified inside the stent. This raises the interesting question of different dose thresholds and time kinetics for paclitaxel-induced effects on different cellular compartments. Longer-term follow-up studies will be needed to further understand these phenomena.

Change of Plaque Area Outside the Stent and Neointimal Growth

The relation between peristent remodeling and neointimal growth after BMS implantation has been a controversial topic. Nakamura et al[21] reported an inverse correlation between percent peristent volume change and percent intrastent neointimal volume change ($r=-0.517$, $P<0.0001$), whereas Hoffman et al[22] reported a weak positive correlation ($r=0.282$, $P=0.058$)). However, the remodeling of the peristent area observed in the present study had no relation to neointimal growth inside the stent in all groups.

Incomplete Stent Apposition

Regional expansive remodeling has been established as the cause of late ISA after BMS implantation.[23] In this study, plaque outside the stent shrank from 6 months to 2 years. As a result, the incidence of late acquired ISA at 2 years was lower than at 6 months. After drug-eluting stent implantation, the multiple effects of the eluted drugs also influence the phenomenon of ISA; the antiproliferative effect may preclude the growth of tissue in the void between the struts, and the antimetabolic effect may induce either necrosis or apoptosis, which may generate a new empty space between the struts.[6,7] However, the incidences of ISA in both the SR and MR paclitaxel stent groups for 2 years were similar to those observed in the BMS group. In other words, the antiproliferative and antimetabolic effects of the drug did not affect the incidence of ISA at 2 years, and the clinical relevance of ISA is dubious.[8] Previously, one case of ISA at 6 months that

evolved into a coronary aneurysm at 18 months after sirolimus-eluting stent implantation was reported.[7] However, such a phenomenon was not observed in this study.

Limitations

The virtual impossibility of analyzing exactly the same ultrasonic cross sections is a major limitation in serial ultrasound studies. To minimize this limitation, the 3-dimensional IVUS reconstruction with semiautomatic contour tracing in several reconstructed, longitudinally cut planes was adapted for this study.

In addition, this study is a substudy of the TAXUS II trial, which is analyzing outcomes in a highly selected subgroup of event-free patients with focal, de novo lesions, and serial 2-year data were obtained in approximately half of the original 6-month cohort of 314 patients. Although the serial data at 6 months were comparable to the original 6-month cohort data, this selection might theoretically limit transferability to the overall patient cohort.

Conclusions

Increased plaque outside the stent 6 months after paclitaxel-eluting stent implantation regressed completely in the SR group and partially in the MR group by 2 years. Neointimal suppression with both SR and MR paclitaxel-eluting stents was sustained for as long as 2 years. Whereas neointima decreased in the BMS group between 6 months and 2 years, neointima continued to increase in the SR and MR groups without effect on clinical events. Although plaque outside the stent began to shrink by 2 years, longer-term follow-up will be required to establish the natural history of local paclitaxel delivery.

Acknowledgment

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Disclosure

Dr Russell is a full-time employee of and stockholder in Boston Scientific Corp. Dr Koglin is a full-time employee of Boston Scientific Corp. Dr Dudek has a consultant/advisory board position with Boston Scientific Corp and has received fees for speaking at interventional cardiology meetings from Boston Scientific Corp. Dr Banning has received a research grant and other research support from Boston Scientific Corp. Dr Drzewiecki has received a research grant from Boston Scientific Corp. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Although long-term follow-up after drug-eluting stent implantation has shown a sustained clinical benefit in several randomized trials, little is known about neointimal and plaque growth beyond the first 6 to 9 months. In the IVUS analyses of the TAXUS II study, neointimal suppression with both SR and MR paclitaxel-eluting stents was sustained for as long as 2 years. Whereas neointima decreased in the BMS group between 6 months and 2 years, neointima continued to increase in the SR and MR groups without affecting clinical events. Although plaque outside the stent began to shrink by 2 years, a longer-term follow-up will be required to establish the natural history of local paclitaxel delivery. The issue of delayed restenosis, which has been observed after brachytherapy, has not been thoroughly evaluated with drug-eluting stent.

Chapter 4

One-year clinical effect of various doses and pharmacokinetic releases of paclitaxel eluted from an erodable polymer – Insights from the Paclitaxel In-Stent Controlled Elution Study (PISCES)

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Clinical research

EuroIntervention

One-year clinical outcome of various doses and pharmacokinetic release formulations of paclitaxel eluted from an erodable polymer - Insight in the Paclitaxel In-Stent Controlled Elution Study (PISCES)

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KEYWORDS
Stent, Paclitaxel, Elution release kinetics

Abstract

Aims: The one year clinical benefit of various doses and release durations of paclitaxel eluted from an erodable polymer has not been evaluated so far.

Methods and results: Conor paclitaxel-eluting stents have intra-stent wells in which drug and polymer are deposited. Stents with six different release formulations (dose: 10 µg or 30 µg, duration: 5, 10 or 30 days, direction: mural or bidirectional) were implanted in 6 patient cohorts. Clinical follow-up was conducted at 4 and 12 months. Quantitative angiography and IVUS were performed at 4 months, and additional angiographic and IVUS follow-up were performed for groups D5 (10µg/30days/mural) and D6 (30µg/30days/mural), as they had shown the most favorable results at 4 months. At one year, the lowest major adverse cardiac event rates were observed in the slow release (30 day) group (5.1% in D5 and 6.9% in D6). One-year in-stent late loss was 0.52±0.34 mm in D5 and 0.36±0.50mm in D6 (p=0.20) while neointimal area was 0.99±0.54 mm^2 in D5 and 0.77±0.92 mm^2 in D6 (p=0.42). Corresponding in-stent binary restenosis at one year was 0% and 5.6% respectively (p=0.36).

Conclusions: Patients who received the slow release formulation stent had better clinical outcome at one year than those who received the fast release formulation. However, the effect on neointimal suppression requires investigation in a larger population to determine whether the high dose formulation confers an additional clinical benefit.

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Introduction

Drug-eluting stents consist of a drug, a polymer, and a stent platform. Several drugs with durable or erodable polymers have been tested in clinical trials and show that drug-eluting stents significantly inhibit neointimal growth compared to bare metal stents[1-4]. However, the most effective drug dose and pharmacokinetic release formulation have not been evaluated thoroughly in humans.

The Paclitaxel In-Stent Controlled Elution Study (PISCES) has demonstrated that kinetic variations play a key role in the efficacy of a drug-eluting system[5]. At 4 months, the inhibition of in-stent neointimal hyperplasia was better in the slow release groups compared to the fast release groups. The present study evaluates (1) the one-year clinical outcome in all 6 groups and (2) neointimal growth in the two slow release groups, using serial quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) analysis; in order to understand the long-term impact of drug dose and pharmacokinetic release.

Methods

Patient selection

The PISCES trial was a prospective, multi-center, sequentially enrolled, non-randomized, open-label trial in which patients were treated with a Conor paclitaxel-eluting stent in one of six different release formulations, and the results of each group was compared (Table 1). The study device and protocol have been described previously[5,6]. In brief, 191 patients with single *de novo* lesions with a reference diameter of 2.5-3.5 mm and a lesion length that could be covered by a single 17mm stent were enrolled. Conor drug-eluting stents were loaded with 10 or 30 µg of paclitaxel within a bioresorbable polylactide-co-glycolide (PLGA) matrix. The drug and polymer were deposited in the wells. The in-vitro drug release period was either 10 or 30 days. The PLGA polymer is fully erodable and neither polymer nor drug is retained in the stent after several months of implantation.

Follow-up and endpoints

The study protocol required all patients to have follow-up clinic visits with an electrocardiogram (ECG) at one, four and twelve months. An independent clinical event committee adjudicated clinical events and ECGs. Quantitative angiography and IVUS were performed at 4 months. Clopidogrel was discontinued per protocol at 6 months following stent implantation.

Additional angiographic and IVUS follow-up was performed at 12 months in groups D5 and D6 which showed the best results at 4 months (Figure 1)[5,6].

The safety endpoint of the present study is a composite of major adverse cardiac events (MACE) defined as cardiac death, Q-wave or non-Q-wave myocardial infarction, and target lesion revascularization (TLR) at 12 months. If the cause of death was undetermined, it was categorized as cardiac death. Myocardial infarction (MI) was diagnosed by a rise in the creatine kinase level to more than twice the upper normal limit with an increased creatine kinase-MB accompanied by new abnormal Q-waves in the surface electrocardiogram (Q-wave MI) or not (non-Q-wave MI). TLR was defined as revascularization of the stented and the peri-stent segments (5mm proximal and distal). Target vessel revascularization (TVR) was defined as revascularization due to narrowing (>50% diameter stenosis) of any portion of the target vessel outside the peri-stent segment but was not included as an event in the MACE rate.

The efficacy endpoints included the in-stent and peri-stent (in-stent + 5 mm proximal edge + 5 mm distal edge) angiographic late loss and binary restenosis rate as well as percent in-stent volume obstruction as determined by quantitative intravascular ultrasound (IVUS).

Quantitative Coronary Angiography (QCA) evaluation

The quantitative ultrasound and coronary angiographic (QCA) analyses were performed by an independent core laboratory that remained blinded to treatment allocation (Cardialysis, Rotterdam, The Netherlands). Quantitative coronary angiography was performed by means of the CAAS II analysis system (Pie Medical BV, Maastricht, The Netherlands). In each patient, the in-stent and peri-stent segments were analyzed. Binary restenosis was defined in every segment as diameter stenosis >50% at follow-up. Late loss was defined as the difference between MLD post-procedure and MLD at follow-up

Quantitative Intravascular Ultrasound (IVUS)

Post-procedure and follow-up stented vessel segments were examined with intravascular ultrasound (Cardio Vascular Imaging System, CVIS, Sunnyvale CA, U.S.A.) using an automated pullback at 0.5 mm per second. A computer-based contour detection program was applied using CUARD QCU analysis software (Cuard BV, Wijk Bij Duurstede, The Netherlands) for 3-D reconstruction of the stented and adjacent segments[7,8]. The intrastent neointimal area was calculated as the stent area minus lumen area, and plaque area outside the stent was calculated as the vessel area minus stent area. The percentage in-stent volume obstruction was calculated as intrastent neointimal volume/stent volume*100.

Table 1. Release formulations

	D1	D2	D3	D4	D5	D6
Paclitaxel dose (µg/17mm stent)	10	10	10	30	10	30
Duration of elution (days)	5	10	10	10	30	30
Direction of elution	Abluminal and luminal (bidirectional)	Abluminal and luminal (bidirectional)	Abluminal (mural)	Abluminal and luminal (bidirectional)	Abluminal (mural)	Abluminal (mural)
Key	10/5/b	10/10/b	10/10/m	30/10/b	10/30/m	30/30/m

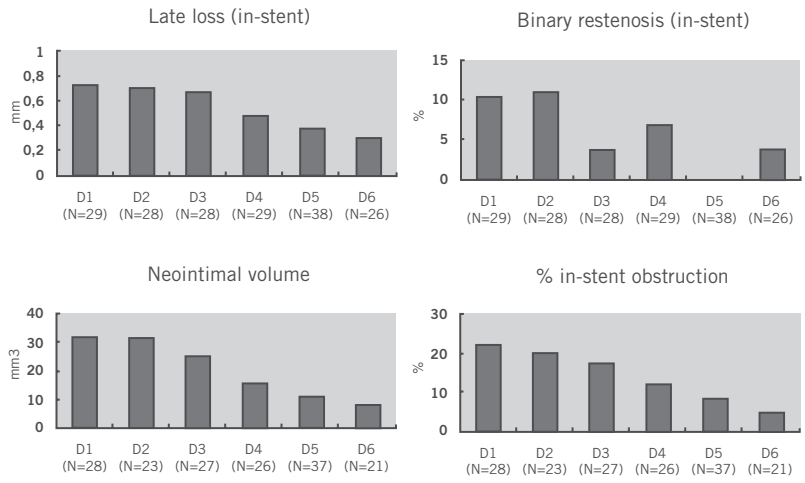

Figure 1: 4-month QCA and IVUS results.

Statistical analysis

The analyses of MACE, angiographic and IVUS parameters were per protocol based, in patients who received the allocated Conor paclitaxel-eluting stents. Continuous variables are expressed as mean±standard deviation. Discrete variables are presented as percentages. For patient demographics, the following tests were applied to calculate the differences among the six groups: F-test from an analysis of variance, two-sample t-test, likelihood ratio chi-square test, Fisher's exact test and Cochran-Mantel-Haenszel test. For QCA and IVUS parameters, continuous variables were compared between groups D5 and D6 with the Student t test, and comparisons between 4 months and 12 months within the same group were performed with a paired *t* test. The Fisher exact test was used for categorical variables. All statistical tests were two-tailed, and p values less than 0.05 were considered statistically significant.

Results

Patient and lesion characteristics

In the PISCES trial, 191 patients were enrolled. The investigational device could not be implanted in four patients. In total, 187 patients were treated with one of the six different formulations of paclitaxel-eluting Conor stents. The average age was 59.1±9.2 years and the prevalence of diabetes was 18.2% in the total population. The baseline demographic and angiographic data was similar among the six groups, except for the incidence of a positive smoking history (Tables 2 and 3).

Clinical events

Clinical follow-up was complete for all patients at one year (Table 4). At four months, the slow release groups had a relatively lower incidence of MACE compared to the fast release groups (2.6% in D5 and 3.4% in D6). This tendency did not change at one year (5.1% in D5 and 6.9% in D6; Figure 2). Between 4 months and 1 year, a MACE occurred in two patients in the slow release groups (D5 and D6): one patient in D5 suffered a non Q-MI due to a non-TVR (maximum CK level of 356 U/L), and one patient in D6 had diffuse in-stent restenosis (binary restenosis of 68%) at 4-month angiographic follow-up with a positive exercise tolerance test. This patient was placed on the waiting list for a repeat intervention. Two weeks after the angiography, she was admitted with a Q-wave MI (maximum CK level of 1687 U/L) and underwent re-catheterization which demonstrated total occlusion at the inlet of the stent. This patient was subsequently treated with a sirolimus-eluting stent. Notwithstanding this patient who had angiographic restenosis, a positive functional test for ischemia but delayed re-intervention at the 4 month follow-up, there were no instances of abrupt, delayed stent thrombosis in the PISCES patients.

Serial QCA analysis

A total of 50 patients (74%) in groups D5 and D6 underwent serial QCA analysis at 4 months and 1 year. The baseline and post-procedure QCA data were similar in the two groups (Table 4). At 4 months, in-stent late loss was not significantly different between

Table 2. Patient characteristics (per protocol)

	D-1 10/5/b N=30	D-2 10/10/b N=29	D-3 10/10m N=30	D-4 30/10/b N=30	D-5 10/30/m N=39	D-6 30/30/m N=29	P-Value comparing 6 groups	P-Value between D5 and D6
Age (mean±SD)	57.4±9.90	61.8±8.9	59.7±9.6	60.2±8.8	56.7±7.6	58.5±10.5	0.23	0.41
Male, %	60.0 (18/30)	72.4 (21/29)	76.7 (23/30)	60.0 (18/30)	82.1 (32/39)	69.0 (20/29)	0.28	0.21
Smoking, %	53.3(16/30)	86.2 (25/29)	76.7 (23/30)	73.3 (22/30)	89.7 (35/39)	72.4 (21/29)	0.01	0.06
Diabetes, %	16.7 (5/30)	17.2 (5/29)	23.3 (7/30)	13.3 (4/30)	10.3 (4/39)	31.0 (9/29)	0.31	0.03
Hypertension, %	40.0 (12/30)	62.1 (18/29)	63.3 (19/30)	56.7 (17/30)	35.9 (14/39)	62.1 (18/29)	0.08	0.03
Dyslipidemia, %	66.7 (20/30)	62.1 (18/29)	73.3 (22/30)	63.3 (19/30)	61.5 (24/39)	65.5 (19/29)	0.93	0.74
Prior MI, %	40.0 (12/30)	44.8 (13/29)	33.3 (10/30)	30.0 (9/30)	41.0 (16/39)	41.4 (12/29)	0.85	0.98
Prior CABG, %	3.3 (1/30)	3.5 (1/29)	0.0 (0/30)	0.0 (0/30)	2.6 (1/39)	6.9 (2/29)	0.59	0.39
Prior PCI	6.7 (2/30)	6.9 (2/29)	10.0 (3/30)	13.3 (4/30)	15.4 (6/39)	17.2 (5/29)	0.71	0.84

Table 3. Lesion and procedural characteristics (per protocol)

	D-1 10/5/b N=30	D-2 10/10/b N=29	D-3 10/10m N=30	D-4 30/10/b N=30	D-5 10/30/m N=39	D-6 30/30/m N=29	P-Value comparing 6 groups	P-Value between D5 and D6
Treated vessel								
LAD	50.0%	41.4%	56.7%	50.0%	48.7%	27.6%	0.30	0.08
LCX	16.7%	20.7%	13.3%	23.3%	23.1%	37.9%	0.30	0.28
RCA	33.3%	37.9%	30.0%	26.7%	28.2%	34.5%	0.94	0.58
ACC/AHA classification								
A/B1/B2	100.0%	100.0%	100.0%	100.0%	94.9%	96.6%	0.34	0.74
C	0.0%	0.0%	0.0%	0.0%	5.1%	3.4%	0.34	0.74
Angiographic features								
Reference vessel diameter, mm	2.76±0.40	2.70±0.52	2.82±0.43	2.64±0.43	2.73±0.41	2.70±0.41	0.71	0.79
Lesion length, mm	9.73±3.68	9.08±3.60	10.60±3.83	10.62±3.09	9.35±3.24	10.31±3.36	0.37	0.24
Minimal lumen diameter, mm	1.10±0.35	1.06±0.38	0.97±0.37	1.05±0.25	1.03±0.28	1.00±0.31	0.70	0.64
Diameter stenosis, %	60.32±9.57	61.02±11.54	65.72±11.77	59.89±7.77	62.05±8.19	63.17±9.63	0.21	0.61
Procedural characteristics								
Stent/patient	1.2±0.38	1.1±0.35	1.1±0.43	1.1±0.25	1.2±0.43	1.0±0.00	0.41	0.13
Stent length, mm	19.03±4.90	18.80±4.80	18.20±3.90	17.60±2.28	18.38±3.88	17.0±0.0 0	0.39	0.13
Stent diameter, mm	3.18±0.24	3.18±0.24	3.25±0.25	3.21±0.25	3.31±0.24	3.25±0.25	0.26	0.44

D5 and D6, although in-stent late loss was lower in D6 than in D5 (0.32±0.40 mm versus 0.40±0.32 mm respectively, p=0.43). From 4 months to 1 year, the late loss increased in both groups but the trend remained in favor of D6; no statistical difference between the two groups could be established although D6 showed a lower in-stent late loss at 1 year (0.52±0.34 mm in D5 and 0.36±0.50 mm in D6, p=0.20). Overall peri-stent binary restenosis at 1 year was observed in one patient in each group (3.1% in D5 and 5.6% in D6, p=1.00).

Serial IVUS analysis

A total of 45 patients (66%) underwent serial IVUS analysis at 4 months and 1 year. The IVUS results showed no statistical differences between groups D5 and D6 (Table 5). The percent in-stent obstruction at 1 year was 12.46±7.60 in D5 and 8.37±9.10 in D6 (p=0.12). However, in D5, the neointimal area increased significantly from 4 months to 1 year (delta=0.38mm^2, p=0.0003) whereas the difference between 4 months and 1 year in D6 failed to be significant (delta=0.21 mm^2, p=0.36, Figure 3).

At 4 months, significant expansive remodeling (an increase in the plaque area outside the stent) was observed in both groups (7.75±1.93 mm^2 vs 9.09±2.45 mm^2, p<0.0001 in D5; 8.04±1.76 mm^2 vs 8.95±1.67 mm^2, p=0.0015 in D6). Between 4 months and 1 year, a significant regression of the expansive plaque area outside the stent was observed in both groups (9.09±2.45 mm^2 vs 8.46±2.15 mm^2, p=0.045 in D5; 8.95±1.67 mm^2 vs 8.37±1.74 mm^2, p=0.0023 in D6).

Discussion

The main findings of this study are the following: first, the slow release (30 day) groups have better clinical outcomes at 1 year compared to the fast release (5 or 10 day) groups. Second, compared to the low dose (10 µg) group, the high dose (30 µg) group had lower late loss and neointimal volume at one year without sta-

Table 4. MACE (Patients with events, per protocol)

	D-1 10/5/b N=30	D-2 10/10/b N=29	D-3 10/10m N=30	D-4 30/10/b N=30	D-5 10/30/m N=39	D-6 30/30/m N=29
Post procedure ~ 4-month						
Cardiac death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Q-wave MI	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)	1 (2.6%)	1 (3.4%)
Non Q-wave MI	1 (3.3%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TLR	5 (16.7%)	4 (13.8%)	2 (6.7%)	1 (3.3%)	0 (0.0%)	1 (3.4%)
TVR	0 (0.0%)	1 (3.4%)	1 (3.3%)	0 (0.0%)	2 (5.1%)	1 (3.4%)
MACE	5 (16.7%)	5 (17.2%)	2 (6.7%)	2 (6.7%)	1 (2.6%)	1 (3.4%)
4-month ~ 12-month						
Cardiac death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Q-wave MI	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.4%)
Non Q-wave MI	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
TLR	0 (0.0%)	1 (3.4%)	2 (6.7%)	1 (3.3%)	0 (0.0%)	1 (3.4%)
TVR	0 (0.0%)	1 (3.4%)	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.4%)
MACE	0 (0.0%)	1 (3.4%)	2 (6.7%)	1 (3.3%)	1 (2.6%)	1 (3.4%)
Post procedure ~ 12-month						
Cardiac death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
Q-wave MI	1 (3.3%)	0 (0.0%)	0 (0.0%)	1 (3.3%)†	1 (2.6%)	2 (6.9%)
Non Q-wave MI	1 (3.3%)	1 (3.4%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)
TLR	5 (16.7%)	5 (17.2%)	4 (13.3%)	2 (6.7%)	0 (0.0%)	2 (6.9%)
TVR	0 (0.0%)	2 (6.9%)	2 (6.7%)?	0 (0.0%)	2 (5.1%)	2 (6.9%)
MACE	5 (16.7%)	6 (20.7%)	4 (13.3%)	3 (10.0%)	2 (5.1%)	2 (6.9%)

*TVR was not included as an event in the MACE rate

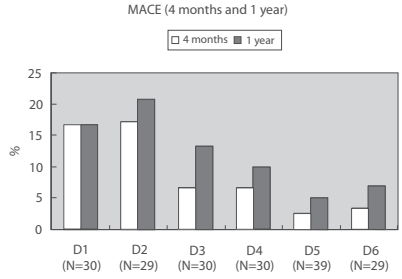

Figure 2: 4-month and 1-year MACE.

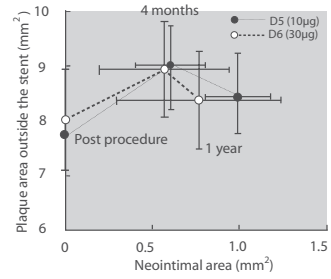

Figure 3. Correlation between neointimal area and peri-stent area over 2 years. Error bars indicate 95% CI.
P values for Neointimal area
D5: Between post procedure and 4 months: <0.0001
Between 4 months and 1 year: 0.0003
D6: Between post procedure and 4 months: 0.029
Between 4 months and 1 year: 0.36
P values for plaque area outside the stent
D5: Between post procedure and 4 months: <0.0001
Between 4 months and 1 year: 0.045
D6: Between post procedure and 4 months: 0.0015
Between 4 months and 1 year: 0.0023

tistically significant difference. Third, between 4 months and 1 year, modest neointimal growth continued in both the low and high dose groups without new instances of in-stent angiographic restenosis or target lesion revascularization, and this neointimal growth was statistically significant in the low dose group only. Fourth, plaque outside the stent increased during the first 4 months following Conor paclitaxel-eluting stent implantation, but by 1 year it had partially regressed in both the low and high dose groups.

Various drug elution processes have reported conflicting clinical results[3,9-12]. In the SCORE trial, QuaDDS stents with a total of 4000 µg paclitaxel and a durable acrylate polymer were found to have an unacceptable safety profile[9]. In the DELIVER trial, the Multi-Link PENTA stent with a coating of 45-150µg paclitaxel (a dose density of 3.0µg/mm^2 stent surface area) without a polymer showed no impact in reducing clinical revascularization or restenosis compared to bare metal stents, presumably due to the rapid elution of the drug[10]. In the ELUTES and ASPECT trials, the high-dose non polymer paclitaxel-eluting stent has the better outcomes compared to the low dose group[11,12]. In the TAXUS IV trial, a slow-release (7.5% at 30 days), polymer-based paclitaxel eluting stent with a total of 106 µg paclitaxel (a dose density of 1.0 µg/mm^2 stent surface area) eluted from a durable polymer showed significantly better inhibition of neointimal growth and clinical outcomes when compared to bare metal stents[3]. In the light of this study and other paclitaxel–eluting stent trials, the drug release profile is a key factor in the clinical efficacy, and drug-eluting stents with a slow release formulation seem to be more efficient. In the present study, the slow release groups demonstrate the best 1-year clinical outcomes, mainly due to better outcomes in the first 4 months. The drug and polymer are completely removed from the wells after several months, thus this novel drug-eluting stent may potentially preclude the chronic vessel reaction usually observed with a durable polymer and persistent drug on the stent[13,14]. Further, there were no instances of late stent thrombosis. Though more data from larger studies is required to draw definitive conclusions, these results support the hypothesis that complete drug elution and polymer resorbtion may confer safety benefits with respect to delayed thrombosis.

In this study, the expansive vessel remodeling observed at 4 months seems similar to the remodeling observed after implantation of Taxus polymeric paclitaxel-eluting stents[15]. The expansive vessel shrinkage observed at 1 year also suggests that the chronic vessel reaction to mechanical injury and biological reaction to the drug and polymer have subsided in that period of time.

However, the chronic vessel reaction inside the stent differs from the reaction observed behind the stent struts. Although this study showed a regression of tissue growth outside the stent between 4 months and 1 year, compaction of neointima was not observed in either the low dose or the high dose group over the same time period. The precise reason for this phenomenon is unclear. One might hypothesize that this could be a result of different tissue composition inside and outside the stent. The tissue growth inside the stent is composed of smooth muscle cells in a proteoglycan rich matrix, whereas the tissue growth behind the stent struts consists of several components: 1) intracellular matrix and cell proliferation such as smooth muscle cells and lymphocyte cells, 2) oedema due to mechanical injury and biological reaction against the drug, polymer and stent, and 3) growth or regression of existing atherosclerotic plaque. Thus, the direction of volumetric change (regression or expansion) from 4 months to 1 year may not be similar inside and outside the stent.

In this study, the actual late loss and neointimal area were smaller in the 30 µg group than in the 10 µg group. These differences were not statistically different and did not influence the clinical outcomes.

Table 5. Serial QCA analysis (post procedure, 4 months and 12 months)

	D5 (10/30/m) N=32	D6 (30/30/m) N=18	P-value
Pre			
Lesion length	9.39±3.37	10.04±2.80	0.49
RVD, mm	2.71±0.43	2.69±0.42	0.84
MLD, mm	1.05±0.29	1.02±0.33	0.73
DS, %	61.5±7.7	62.5±9.2	0.67
Post stenting			
In-stent			
MLD, mm	2.68±0.35	2.51±0.38	0.12
DS, %	12.4±6.5	13.6±6.2	0.56
In-peristent*			
MLD, mm	2.31±0.41	2.18±0.38	0.29
DS, %	22.3±9.1	23.5±8.9	0.65
4-month			
In-stent			
MLD, mm	2.28±0.32	2.19± 0.53	0.53
DS, %	19.9±9.3	21.7±9.7	0.63
Late loss, mm	0.40±0.32	0.32±0.40	0.43
Binary restenosis, %	0.0	5.6	0.36
In-peristent*			
MLD, mm	2.10±0.36	1.97±0.48	0.27
DS, %	25.3±8.7	29.9±13.6	0.20
Late loss, mm	0.21±0.29	0.21±0.39	0.95
Binary restenosis, %	0.0	5.6	0.36
12-month			
In-stent			
MLD, mm	2.16±0.34	2.15±0.65	0.93
DS, %	21.3±10.3	23.2±20.6	0.72
Late loss, mm	0.52±0.34	0.36±0.50	0.20
Binary restenosis, %	0.0	5.6	0.36
In-peristent*			
MLD, mm	2.01±0.35	1.94±0.61	0.69
DS, %	27.5±9.67	29.3±20.8	0.73
Late loss, mm	0.30±0.26	0.24±0.50	0.62
Binary restenosis, %	3.1	5.6	1.00

* In-peristent = In-stent + 5 mm proximal + 5 mm distal

The 10 µg paclitaxel dose may be sufficient to suppress neointimal growth in humans at least for a period of one year. It may also be argued that the sample size is too small to detect a biological difference between the low and the high dose.

In animal studies, paclitaxel polymer coated stents have been found to inhibit in-stent neointimal growth but with signs of delayed intimal healing at 28 days, such as fibrin deposition, inflammation and increased cellular proliferation. By 90 days, local toxicity associated with paclitaxel resolves but in-stent neointimal growth suppression is no longer present[16]. In humans following bare metal stent implantation, the neointima does not keep growing beyond 6 months and

Table 6. Serial IVUS analysis (post procedure, 4 months and 12 months)

	D5 (10/30/m) N=30	D6 (30/30/m) N=15	P-value
Post stenting			
Vessel area, mm²	15.84±3.36	16.00 ±2.80	0.88
Stent area, mm²	8.09±1.81	7.95±1.77	0.81
Plaque area outside the stent, mm²	7.75±1.93	8.04±1.76	0.63
4-month			
Vessel area, mm²	17.31±3.56	17.33±2.74	0.99
Stent area, mm²	8.22±1.86	8.64±1.92	0.49
Lumen area, mm²	7.61±1.87	8.08±1.82	0.43
Neointimal area, mm²	0.61±0.57	0.57±0.74	0.81
Plaque area outside the stent, mm²	9.09±2.45	8.95±1.67	0.85
% in-stent obstruction	7.49±6.92	6.21±7.39	0.57
12-month			
Vessel area, mm²	16.74±3.56	16.73±3.02	0.99
Stent area, mm²	8.21±1.84	8.36±1.83	0.80
Lumen area, mm²	7.23±1.87	7.59±1.46	0.52
Neointimal area, mm²	0.99±0.54	0.77±0.92	0.42
Plaque area outside the stent, mm²	8.46±2.15	8.37±1.74	0.89
% in-stent obstruction	12.46±7.60	8.37 ±9.10	0.12

instead begins to regress due to the replacement of water-trapping proteoglycans (hyaluronan and versican) by decorin and type I collagen[17]. In this study, compaction of neointima was not observed and it is unknown whether neointimal tissue will keep growing or stop beyond one year. Further follow-up is warranted to evaluate the long-term efficacy of these devices and to find the best elution period and drug dose.

Limitations

At one year, 26% and 34% of the patients in the groups of D5 and D6 respectively did not undergo serial invasive QCA or IVUS follow-up evaluation. Following completion of patient enrolment, the protocol was subsequently amended to allow one year angiographic and IVUS follow-up, necessitating a new informed consent. Patients who did not undergo one-year angiography reported no anginal symptoms at one year. The sample sizes for groups D5 and D6 were insufficient to detect a difference in outcome between the low and high doses in the slow release formulation. However, they served as the basis for the development of a large randomized trial (the EuroSTAR trial) which is evaluating both doses (10 µg and 30 µg per 17mm stent) of slow-release paclitaxel using the reservoir-based technology on an ultra-thin cobalt-chromium stent in 270 patients.

Conclusions

The PISCES trial suggests that the pharmacokinetics of drug-eluting stents is important for both neointimal suppression and for clinical outcomes at 1 year. The slow release (30 day) formulation had better clinical outcomes compared to the fast release (5 or 10 day) formulation. The drug dose (10 µg or 30 µg) did not seem to influence the amount of neointimal suppression but the sample sizes in this pilot dose-finding study were insufficient to detect a beneficial difference in dose.

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Chapter 5

Serial Assessment of Tissue Growth Inside and Outside the Stent after Implantation of Drug-Eluting Stent in Clinical Trials. -Does delayed neointimal growth exist?

Aoki J, Abizaid A, Ong AT, Tsuchida K, Serruys PW

Eurointervention. 2005;3:253-255

Editorial

EuroIntervention

Serial assessment of tissue growth inside and outside the stent after implantation of drug-eluting stent in clinical trials. – Does delayed neointimal growth exist?

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Although long term follow-up after drug-eluting stent (DES) implantation shows a sustained clinical benefit in several randomized trials, delayed neointimal growth beyond the first 6 to 9 months has been reported in serial intravascular ultrasound (IVUS) analyses in some trials. The issue of a delayed restenosis which was observed after brachytherapy has not been thoroughly evaluated with DES.

Tissue growth inside the stent (Neointima)

Drug-eluting stents (DES) dramatically reduce neointimal growth at 6 or 9 months compared to bare metal stents (BMS).[1-3] Although long term follow-up after DES implantation shows a sustained clinical benefit in several randomised trials,[4,5] little is known about neointimal growth beyond the first 6 to 9 months. The issue of a "late catch up phenomenon" (delayed restenosis) which was observed after brachytherapy has not been fully investigated with DES.[6]

In porcine models, the inhibition of neointimal hyperplasia after deployment of polymer-coated sirolimus-eluting stents was not sustained at 90 and 180 days due to delayed cellular proliferation, and neointimal suppression after deployment of chondroitin sulfate and gelatin coated paclitaxel-eluting stents was also not maintained at 90 days.[7,8]

In humans, neointimal tissue does not keep growing after BMS implantation. During long-term angiographic follow-up, compaction of neointima has been described in several reports.[9-11] Histological analyses of post-mortem coronary arteries demonstrate that compaction of neointima occurs due to the replacement of water-trapping proteoglycans by decorin and type I collagen.[11] Following DES implantation, neointima continues to grow during the follow-up period in some trials in which serial IVUS analyses were performed (Table 1). A chronic arterial response towards the durable polymer and to the remaining drug within the polymer has been imputed to explain this phenomenon. However, this was also observed with Conor paclitaxel-eluting stents in which neither polymer nor drug is retained at the end of the programmed release period.[12] The precise reason for this observation is thus still unclear, but may be related to the delayed healing response and persistent biological reaction caused by the drug soon after the implantation of DES. In view of the results of animal studies and clinical studies, DES may delay restenosis, instead of halting definitively the process of neointimal hyperplasia. Further follow-up is warranted to evaluate the long-term efficacy of DES.

Tissue growth outside the stent (Vessel remodeling)

Polymer based sirolimus-eluting stents (Cypher) and polymer based paclitaxel-eluting stents (Taxus) are used in daily practice, and several types of drugs and durable or erodable polymers have been tested in clinical trials.[1,3,13,14] After BMS implantation, expansive vessel remodeling (i.e. increasing plaque outside the stent) was reported.[15] In the TAXUS II trial, the increased plaque outside the stent 6 months after BMS implantation had regressed completely at 2 years (Table 2).[16] Thus, it is likely that mechanical injury and biological reaction against the stainless steel stent that may have

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Table 1. Tissue growth inside the stent (Neointimal volume)

		4 or 6 months	1 year	2 years	4 years	p-value*
BMS (N=77)[16], mm^3		28.7±33.2	–	23.9±25.1 – 16.7%	–	0.017
Limus family	Sirolimus (N=23)[17], mm^3	2.1±1.7	3.8±3.3 81.0%	7.0±6.7 233.3%	8.4±5.8 300.0%	<0.0001**
	ABT-578 (N=86)[21]	6.1±7.4	14.2±11.8 132.8%	–	–	N.A.
	Everolimus (N=16)[18], mm^3	9.1±12.2	13.0± 9.0 42.2%	–	–	0.14
Paclitaxel	TAXUS SR (N=43)[16], mm^3	9.4±12.1	–	13.6±11.3 44.7%	–	0.018
	TAXUS MR (N=41)[16], mm^3	10.7±15.8	–	16.9±17.3 57.9%	–	0.013
	Conor (30 day/10 ug) (N=30)[12], mm^3	11.2±11.6	17.7±10.3 58.0%	–	–	0.0004
	Conor (30 day/30 ug) (N=15)[12], mm^3	9.4±11.9	13.8±17.1 46.8%	–	–	0.29

Below percentage line shows relative difference, compared to 4 or 6 months
* Paired *t* -test. ** Repeat variance of analysis (ANOVA)

Table 2. Plaque volume outside the stent (Vessel remodeling)

		Post stenting	4 or 6 months	1 year	2 years	4 years	p-value*
BMS (N=77)[16], mm^3		122.6±32.6	130.6±29.3 6.5%	–	116.6±28.4 –4.9%	–	0.01
Limus family	Sirolimus(N=23)[17], mm^3	155.5±42.8	160.4±60.4 3.2%	153.5±61.6 –1.3%	156.8±57.7 0.8%	138.4±42.2 –11.0%	0.53
	Everolimus(N=16)[18], mm^3	151.8±67.1	159. 5± 64.0 5.1%	152.8± 56.8 –4.2%	–	–	0.1370
Paclitaxel	TAXUS SR(N=43)[16], mm^3	121.9±40.2	135.8±44.0 11.4%	–	114.8±30.7 –5.8%	–	0.002
	TAXUS MR(N=41)[16], mm^3	113.8±30.5	140.7±41.6 22.8%	–	127.3±37.4 11.9%	–	0.0007
	Conor (30 day/10 ug) (N=30)[12], mm^3	135.1±37.1	160.1±46.3 18.5%	153.0±55.7 13.2%	–	–	0.0001
	Conor (30 day / 30 ug) (N=15)[12], mm^3	136.6±29.6	154.1±33.0 12.8%	144.5±26.9 5.5%	–	–	0.002
CD34 antibody coating							
	EPC capture coating (N=16)[20], mm^3	163.0±56.6	165.0±62.9 1.2%	–	–	–	0.37

Below percentage line shows relative difference, compared to 4 or 6 months
*Paired *t* –test, comparison between post stenting and 4 or 6 month follow–up

induced the inflammation, had subsided by 2 years. After sirolimus and everolimus-eluting stents implantation, increasing plaque area outside the stent was insignificant in both the First In Man (sirolimus)[17] and SPIRIT FIRST (everolimus) trials[18], whereas a significantly increasing plaque area behind the stent was observed with paclitaxel-eluting stents in the TAXUS II[15] and PISCES trials[19], and tissue growth exceeded the vessel reaction observed with BMS in both trials. The EPC capture stents induce the rapid establishment of a functional endothelial layer early in the healing response and the mean plaque volume outside the stent was similar immediately post procedure and at 6-month follow-up, demonstrating that overall expansive remodeling did not occur with this device.[20]

The vessel reaction outside the stent differs from the reaction observed inside the stent, and the different drugs, polymers, and pharmacokinetics result in various effects on tissue growth not only in the intrastent neointima but also on vessel remodeling outside the stent. Interestingly, the timing of regression of the plaque outside the stent was also different. For sirolimus-eluting stents, significant expansive plaque outside the stent was not observed during follow-up and shrinkage of plaque outside the stent occurred at 4 years.[17] For paclitaxel-eluting stents, complete regression of expansive plaque outside the stent was observed at 2 years in the slow release group in TAXUS II trial, and partial regression was observed at 1 year in the PISCES and at 2 years in the moderate release group in the TAXUS II trial.[12,16] The exact reason for these variant vascular responses is unknown. The tissue growth outside the stent may be more complex and heterogeneous, compared to tissue growth inside the stent. The tissue growth inside the stent consists of smooth muscle cell and a

proteoglycan rich matrix, whereas the tissue growth outside the stent consists of several components; 1) cell proliferations and intracellular matrix, 2) oedema caused by mechanical injury and chemical injury due to drug, polymer and stent, 3) growth or regression of existing atherosclerotic plaque. Studies involving larger sample sizes and more detailed analyses with novel *in vivo* techniques of tissue characterisation may be necessary to assess and better understand the process of vessel remodeling after DES implantation.

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Part 2

Efficacy of drug eluting stent for high risk patients

Chapter 6

"Full Metal Jacket" (stented length ≥ 64 mm) Using Drug-Eluting Stents for De Novo Coronary Artery Lesions

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A Heart J. 2005;150:994-999

''Full metal jacket'' (stented length ≥64 mm) using drug-eluting stents for de novo coronary artery lesions

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Background Stented segment length was a predictive factor for restenosis in the bare metal stent era. The objective of the study was to evaluate the medium-term clinical outcome and the potential for adverse effects when very long segments (ie, ≥64 mm of stented length) are treated by drug-eluting stent (DES) implantation, an approach colloquially referred to as a ''full metal jacket.''

Methods Since April 2002, we have used DES as the default stent for all percutaneous coronary interventions. From our prospective institutional database we identified 122 consecutive patients, with de novo coronary lesions, in whom a coronary artery was treated with at least 64 mm of overlapping DES: 81 patients were treated with sirolimus-eluting stents and 41 with paclitaxel-eluting stents.

Results The mean number of stents per lesion was 3.3 ± 1.1, and the median stented length was 79 mm (range 64-168 mm). Periprocedural Q-wave myocardial infarction (MI) occurred in 2 patients (1.6%) and subacute stent thrombosis in 1 patient (0.8%). During 1-year follow-up, 5 patients (4.1%), including 3 patients treated for acute MI with cardiogenic shock, died and 10 patients (8.2%) had nonfatal MI (creatine kinase–MB >3 times). The 1-year target vessel revascularization rate was 7.5% and the overall incidence of major adverse cardiac events was 18%. Outcomes in sirolimus-eluting stents and paclitaxel-eluting stents groups did not differ statistically.

Conclusions The use of DES for the treatment of diffuse lesions was associated with a low rate of repeat revascularization, irrespective of stent type. No safety concerns were raised at medium-term follow-up. (Am Heart J 2005;150:994-9.)

In the bare metal stent era, the length of a stented segment was an independent predictor of in-stent restenosis.[1-3] Recent randomized trials, in low-risk patient/lesion cohorts, showed that drug-eluting stents (DES) reduce the need for repeat intervention compared with bare metal stents.[4-7] Drug-eluting stents are rapidly replacing bare metal stents and there has been a tendency toward longer stented segment lengths, given the full lesion coverage from a proximal to a distal "angiographically normal" segment to avoid stent gaps and the incomplete coverage of lesions which have been associated with restenosis after DES implantation.[5,8] However, the clinical effect of very long and overlapping DES implantation in the so-called full metal jacket approach and the potential effects of increased metal and local drug exposures are unknown. In this report, we investigate the clinical outcome after very long sirolimus-eluting stent (SES) and paclitaxel-eluting stent (PES) implantations in a consecutive group of 122 patients (124 lesions) who were treated with at least 64 mm of DES without any gap in the same vessel.

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Methods

Patient selection and procedure

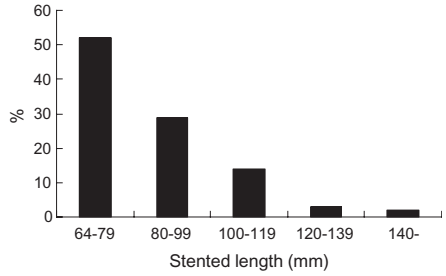
Since April 2002, we have adopted a policy of universal DES implantation for all percutaneous coronary interventions requiring stents at our center, irrespective of clinical presentation or lesion morphology. Sirolimus-eluting stents were exclusively used until March 2003. Since March 2003, PES has been exclusively used. In total, 122 consecutive

Table I. Patient characteristics

	All (n = 122)	SES (n = 81)	PES (n = 41)
Age (y)	63 ± 11	62 ± 12	63 ± 11
Male (%)	75	69	88*
Hypertension (%)	42	43	39
Hyperlipidemia (%)	67	62	76
Current smoking (%)	25	26	24
Diabetes mellitus (%)	19	20	17
Prior MI (%)	44	43	46
Prior CABG (%)	5	5	5
Prior PCI (%)	19	17	22
Multivessel disease (%)	70	70	68
Unstable angina (%)	26	31	17
AMI (%)	11	11	12
AMI with shock (%)	3	2	5

CABG, Coronary artery bypass graft surgery; *PCI*, percutaneous coronary intervention; *AMI*, acute MI.
*$P < .05$ for the comparison between SES and PES groups.

Figure 1



The distribution of stented length.

patients were treated with at least 64 mm of DES without any gap in the same vessel for diffuse coronary lesions, chronic total occlusion, or extensive dissections; this represents 7% of our patients treated exclusively with DES in the same period. The longest available individual stent length was 33 mm in SES and 32 mm in PES. We defined a full metal jacket as 64 mm of continuous stent, calculated as the total of the 2 longest PES lengths.

All interventions were performed using standard techniques. Written informed consent was obtained from all patients as part of the prospective consecutive database. Periprocedural use of glycoprotein IIb/IIIa and intravascular ultrasound (IVUS) was at the discretion of the operator. All patients received a loading dose of 300-mg clopidogrel followed by a daily dosage of 75 mg for 6 months, in addition to life-long aspirin therapy.

End point definition and clinical follow-up

Patients were followed up prospectively and major adverse cardiac events (MACEs) were evaluated. Major adverse cardiac event was defined as death, nonfatal myocardial infarction (MI), or target vessel revascularization (TVR). Myocardial infarction was defined as a creatine kinase–MB (CK-MB) level that was >3 times the upper limit of normal, based on the recommendations in the American College of Cardiology/American Heart Association guidelines.[9] For patients who presented with an acute coronary syndrome and elevated baseline enzyme, a diagnosis of periprocedural MI required a fall and rise of CK-MB of 50% above the previous level.[10] Target vessel revascularization was defined as a reintervention in the treated vessel. Stent thrombosis was angiographically documented as a complete occlusion or a flow-limiting thrombus of a successfully stented segment. Information regarding repeat interventions was prospectively collected by means of an electronic database. Survival status was assessed by written inquiries to the Civil Registry. Questionnaires to assess clinical status were sent to all living patients. The patient, referring physician, and peripheral hospitals were directly approached whenever necessary for additional information. Follow-up angiography was planned only in patients who were enrolled during the first 6 months (n = 38).

Statistical analysis

Continuous variables were expressed as mean ± SD. Discrete variables were presented as percentages. Continuous variables were compared with Student *t* test or Wilcoxon ranked scores when applicable. The Fisher exact test was used for categorical variables. The cumulative incidence of adverse events was calculated according to the Kaplan-Meier method and differences were assessed using the log-rank test. All statistical tests were 2-tailed, and $P < .05$ was considered statistically significant. Patient, lesion, and procedural characteristics associated with 1-year MACE on univariate analysis (P value for selection <.2) were tested for their multivariate predictive value (tested values were cardiogenic shock, female sex, multivessel disease, bifurcation stenting, and use of IIb/IIIa inhibitors). The final model was built by backward stepwise variable selection with entry and exit criteria set at the $P = .05$ and $P = .1$ levels, respectively.

Results

Patient characteristics

Of the 122 consecutive patients, 81 patients (82 lesions) were treated with SES (SES group) and 41 patients (42 lesions) were treated with PES (PES group). Patient characteristics are reported in Table I; 19% had diabetes and 39% underwent the index procedure for an acute coronary syndrome. There were no statistical differences between groups, apart from a higher proportion of men in the PES group. Figure 1 presents the distribution of stented length in this study.

Procedural characteristics

Lesion and procedural characteristics are presented in Table II. The mean number of stents implanted per lesion was 3.3 ± 1.1 (range 2-7 stents), and the median

Table II. Lesion and procedural characteristics

	All (n = 124)	SES (n = 82)	PES (n = 42)
Treated vessel			
LAD (%)	25	29	17
LCX (%)	12	16	5
RCA (%)	63	55	79*
Lesion type			
B1 (%)	1	1	0
B2 (%)	2	2	0
C (%)	98	96	100
CTO (%)	40	38	43
Total occluded length (mm ± SD)	23.2 ± 10.9	22.9 ± 11.2	23.7 ± 10.6
Stent number/vessel	3.3 ± 1.1	3.1 ± 1.0	3.7 ± 1.1*
Mean stent diameter (mm)	2.9 ± 0.3	2.7 ± 0.2	3.0 ± 0.3*
Median stent length/vessel (mm) (range)	79 (64-168)	77 (64-140)	84 (64-168)*
Bifurcation stenting (%)	13	15	10
Use of IIb/IIIa inhibitor (%)	37	38	36
Pre-RD (mm)	2.61 ± 0.55	2.55 ± 0.52	2.74 ± 0.60
MLD (mm)	0.44 ± 0.52	0.46 ± 0.52	0.40 ± 0.51
DS (%)	82.3 ± 20.6	80.8 ± 21.6	85.2 ± 18.4
Post-RD (mm)	2.73 ± 0.49	2.67 ± 0.47	2.86 ± 0.51*
MLD (mm)	2.26 ± 0.46	2.20 ± 0.42	2.37 ± 0.52*
DS (%)	17.4 ± 10.9	17.4 ± 10.8	17.2 ± 11.4

LAD, Left descending coronary artery; *LCX*, left circumflex coronary artery; *RCA*, right coronary artery; *CTO*, chronic total occlusion; *RD*, reference diameter; *MLD*, minimal lumen diameter; *DS*, diameter stenosis.
*$P < .05$ comparison between SES and PES groups.

Table III. Thirty days and 1 year clinical outcomes cumulative events rate estimated by Kaplan-Meier

	All (n = 122)	SES (n = 81)	PES (n = 41)	P*
30 d				
Death (%)	1.6	1.2	2.4	.63
MI (%)	5.8	6.2	4.9	.77
TVR (%)	1.7	2.5	0	–
Death, MI (%)	7.4	7.4	7.3	.97
MACE (%)	8.2	8.6	7.3	.79
1 year				
Death (%)	4.1	2.5	7.3	.20
MI (%)	10.0	11.2	7.4	.53
TVR (%)	7.5	7.5	7.6	.96
Death, MI (%)	12.3	12.3	12.2	.98
MACE (%)	18.0	18.5	17.1	.87

TVR, target vessel revascularization; *MACE*, major adverse cardiac events.
*Comparison between SES and PES groups (log rank).

Table IV. Paired quantitative angiographic analysis (mandatory angiographic follow-up group)

SES (n = 38)	Pre	Post	Follow-up
RD (mm)	2.56 ± 0.53	2.68 ± 0.44	2.76 ± 0.37
MLD (mm)	0.43 ± 0.58	2.24 ± 0.38	2.13 ± 0.58
DS (%)	81.9 ± 24.6	16.2 ± 9.4	23.4 ± 19.5
Late loss (mm)			0.12 ± 0.58
Binary restenosis rate (%)			5.3

RD, reference diameter; *MLD*, minimal lumen diameter; *DS*, diameter stenosis.

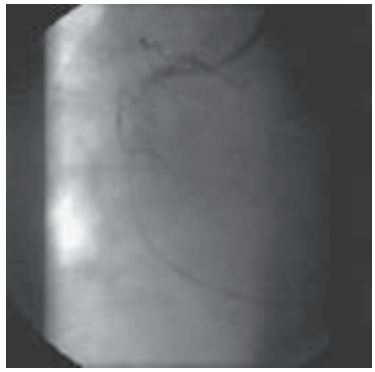
total stented length was 79 mm (range 64-168 mm). Glycoprotein IIb/IIIa inhibitors were used in 37% of patients. In the PES group, the mean stent diameter was larger (3.0 ± 0.3 vs 2.7 ± 0.2 mm, $P < .001$), with longer median stented length (77 vs 84 mm, $P = .03$), compared with the SES group.

Clinical outcome

Complete clinical follow-up information was available for all patients. Table III shows 30-day clinical outcomes as estimated by the Kaplan-Meier method. A periprocedural MI occurred in 5 patients (4.0%). Each CK-MB level was 191, 141, 82, 338, and 159 U/L (normal upper limit of CK-MB is 23 U/L in our institute). Among these patients, 2 patients (1.6%) had Q-wave MI. The causes of periprocedural MI were side-branch occlusion (1 patient), distal embolism (1 patient), distal dissection (1 patient), and dissection of other treated lesion (2 patients). Subacute stent thrombosis occurred in 1 patient (0.8%) in the SES group.

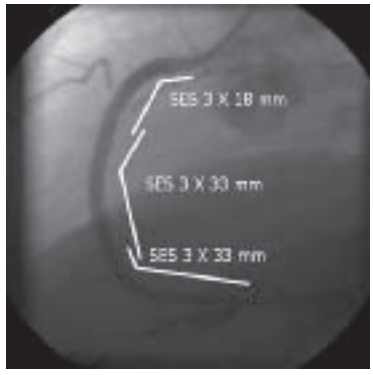
One-year clinical outcomes, estimated by the Kaplan-Meier method, are presented in Table III. Five patients (4.1%) died during the first year, 2 received SES, and 3 received PES. In the SES group, 1 patient who received SES for acute MI with cardiogenic shock died the next day from cardiogenic shock and the other died of a pulmonary embolism 275 days after the procedure. In the PES group, 1 patient who presented with acute MI

Figure 2



Baseline angiography showing diffuse right coronary artery disease.

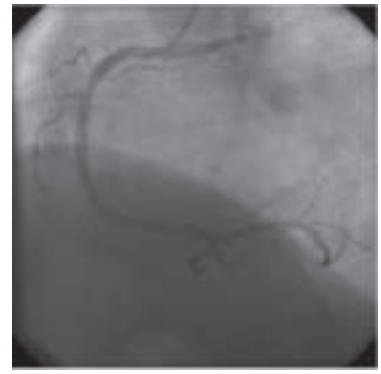
Figure 3



The patient was successfully treated with 3 Cypher stents (total length was 84 mm).

with cardiogenic shock died 6 days later from ongoing heart failure. The second patient underwent an unsuccessful percutaneous coronary intervention 55 days after the initial procedure to treat another lesion, requiring emergent coronary artery bypass surgery and died 1 day after surgery. The remaining patient died of congestive heart failure 244 days after the initial procedure. This patient had already suffered MIs twice before the index procedure and had severe left ventricular dysfunction.

Figure 4



Follow-up angiography (216 days after the index procedure) documenting the absence of in-stent restenosis.

The overall TVR rate was 7.5% and the incidence of MACE was 18.0% at 1 year. There were no statistically significant differences between the SES and the PES groups. Multivariate predictors of 1-year MACE were cardiogenic shock (hazard ratio 8.96, 95% CI 2.11-28.66, P = .0006) and female sex (hazard ratio 2.71, 95% CI 1.06-6.02, P = .02). Mean late loss was 0.12 $\pm$ 0.58 mm in 38 patients who were consecutively enrolled in the first 6 months of our experience and who, for this reason, underwent mandatory follow-up angiography (Table IV).

Figures 2-4 are a representative example of a patient successfully treated with 3 stents (SES) with a total stent length of 84 mm.

Discussion

In this study, median stented length was 79 mm (range 64-168 mm). The incidence of subacute stent thrombosis was 0.8% (1 patient) and the TVR rate was 7.5% at 1 year. Of the 6 patients who had in-stent restenosis within 1 year, 5 (83.3%) patients had focal restenosis easily treated with repeat coronary stenting (mean stent length 20.0 $\pm$ 8.9 mm).

In the bare metal stent era, the stented length is an important predictor of in-stent restenosis. However, there are no precious reports regarding full metal jacket. The results of this present study are promising when compared with published data on bare metal stents with long stented lengths or multiple stenting despite significantly longer lengths in this study (Table V).[11-14] A group of 21 consec-

Table V. One year TLR or TVR and MACE rate in this study, compared data from patients with long length or multiple bare metal stenting

Trial	n	Stented length (mm)	No. of stents/lesion	TLR/TVR (1 y) (%)	MACE (1 y) (%)
Kornowski et al[11]	117	28 ± 5	–	14.5/–	18.7
Kornowski et al[12]	117	–	3.3	13.3/–	24.5
ADVANCE trial stent group[13]	145	26.1 ± 7.7	1-3	–/17.9	23.4
TULIP trial angiographic-guided group[14]	71	35 ± 11	1.1 ± 0.4	23/–	27
TULIP trial IVUS-guided group[14]	73	42 ± 11	1.4 ± 0.6	10/–	12
Historical BMS (≥64 mm)	21	79 (64-115)*	3.5 ± 1.0	–/21.6	38.1
This study	122	79 (64-168)*	3.3 ± 1.1	–/7.5	18.0

TLR, target lesion revascularization; *TVR*, target vessel revascularization; *MACE*, major adverse cardiac events.
*Median (range).

utive patients from our institution, treated with at least 64 mm of continuous bare metal stents (BMS) in the same vessel from the immediate period preceding the introduction of DES, is included as a comparison (unpublished data). The 1-year TVR rate in the BMS group was approximately 3 times higher than the DES population from this study.

Concerns have been raised regarding the clinical impact of high local drug concentration in the tissue wall caused by long stented lengths and overlapped stents (eg, the development of coronary aneurysms).[15,16] We did not observe aneurysm formation in patients who underwent follow-up angiography beyond 6 months. Nor was there any evidence of systemic complications, related to the use of multiple DES, in our patient cohort up to 1 year.

A limitation of treating diffuse coronary disease with long stented lengths in the bare metal stent era was a high incidence of periprocedural MI; this was documented in several stent trials that enrolled patients with long lesions.[11,13,17] In the ADVANCE study, 21.4% had elevated CK-MB, with 7.1% >5 times elevated in the bail out stenting group.[13] The definition of MI after percutaneous coronary interventions differed among studies.[18-20] Even in case of not long length stenting, reports in the literatures indicated that 8.5% had elevated CK-MB (>5 times[17] or >3 times[21]) after stent implantation. If an MI is defined as a CK-MB of >5 times the upper limit of normal, the incidence of periprocedural MI was 3.3% in our study. Based on our results, DES use does not increase the incidence of periprocedural MI compared with published bare metal stent data.

SES and PES were used in this study in consecutive periods. This study is limited by its single-arm design and moderate sample size, and follow-up angiography was performed in one third of patients, precluding reporting of quantitative angiographic variables and our main purpose was not to compare the clinical effect of 2 different types of DES. Procedural characteristics were not similar between both groups (in the PES group, the mean stent diameter was larger and the median stented length was longer compared with the SES group). However, we found that despite extremely long stent lengths, the incidence of TVR was quite low for both SES and PES. Percutaneous coronary intervention using DES therefore seems to be a feasible, effective, and safe option for the treatment of patients with diffuse coronary disease.

Conclusion

Stented length of ≥64 mm with DES for de novo coronary artery lesions was safe. Drug-eluting stents had similar clinical results with low TVR rates. The use of DES for the treatment of diffuse coronary lesions is a feasible percutaneous alternative.

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Chapter 7

The Efficacy of Sirolimus-Eluting Stents versus Bare Metal Stents for Diabetic Patients Undergoing Elective Percutaneous Coronary Intervention

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Original Contribution

The Efficacy of Sirolimus-eluting Stents Versus Bare Metal Stents in Diabetic Patients Undergoing Elective Percutaneous Coronary Intervention

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ABSTRACT: Background. Diabetes mellitus is a well-known risk factor for future adverse cardiac events after coronary intervention with conventional metal stents. In this study, the impact of sirolimus-eluting stents (SES) were evaluated in a consecutive group of diabetic patients undergoing elective percutaneous coronary treatment and compared to a population treated with bare metal stents.

Methods and Results. From April 2002, a policy of routine SES implantation has been instituted in our hospital. During 1 year of enrollment, a total of 112 consecutive diabetic patients with de novo coronary lesions were electively treated with SES (SES group). A similar group for comparison comprised 118 consecutive patients treated with bare metal stents in the preceding period (the pre-SES group). After 1-year follow-up, the cumulative rate of major adverse cardiac events (death, myocardial infarction, and any repeat revascularization) was 17.3% in the SES group versus 30.2% in the pre-SES group (hazard ratio, 0.54 [95% confidence interval, 0.32–0.91]; p = 0.02), mainly due to a marked reduction in the need for repeat revascularization (10.2% versus 23.5%; hazard ratio, 0.40 [95% confidence interval, 0.21–0.78]; p = 0.007).

Conclusions. Routine utilization of SES for diabetic patients significantly reduces the rate of adverse cardiac events at 1 year compared to bare metal stents.

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Key words: diabetes, stent, revascularization

Several clinical studies have demonstrated that diabetes mellitus is an important predictor of angiographic restenosis and late mortality after conventional balloon angioplasty.[1,2] Stent implantation has been shown to improve the clinical outcomes for diabetic patients,[3] however, patients with diabetes mellitus still continue to have increased clinical events and restenosis after coronary stenting.[4–6] Endothelial dysfunction, increased platelet reactivity and thrombogenicity, and dysregulation of growth factors may contribute to the exaggerated neointimal hyperplasia occurring in diabetic patients.[7,8]

Recently, drug-eluting stents have been shown to prevent neointimal hyperplasia and dramatically reduce the restenosis rate in elective patients with *de novo* lesions.[9,10] Sub-studies of the RAVEL, SIRIUS, and TAXUS IV trials have indicated that drug-eluting stents significantly decreased the risk of restenosis in diabetics.[11–13] However, the impact of drug-eluting stents outside the context of randomized trials is presently unknown.

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Methods

Patient population. Since April 2002, we have adopted a policy of DES implantation for all percutaneous coronary interventions requiring stents at our center, irrespective of clinical presentation or lesion morphology. Sirolimus-eluting stents (SES) were exclusively used until March 2003. From April 2002 to March 2003 (11 months), 112 consecutive diabetic patients with *de novo* lesions were electively treated solely with SES (SES group) and composed the present study population. Diabetic status was assessed as documented on the medical report or by the utilization of insulin or oral hypoglycemic drugs. Elective cases were defined as patients without recent (< 2 weeks) acute myocardial infarction. A control group for comparison comprised 118 consecutive diabetic patients with *de novo* lesions, electively treated with bare stents in the 12 months immediately before the introduction of SES (pre-SES group).

All patients received aspirin lifelong and clopidogrel for 1 month in the pre-SES group and for at least 3 months in the SES group. The use of glycoprotein IIb/IIIa inhibitors was at the discretion of the operator. Angiographic success was defined as residual stenosis < 30% by visual analysis in the presence of TIMI 3 grade flow. Written informed consent was obtained from all patients.

Endpoint definitions and follow-up. The primary outcome was the occurrence of major adverse cardiac events (MACE), defined as: 1) death (cardiac and non-cardiac); 2) non-fatal myocardial infarction; or 3) any repeat revascularization. Myocardial infarction (MI) was diagnosed by a rise in the creatine kinase level to more than twice the upper normal limit together with an increase in creatine kinase-MB. Cardiac enzymes were routinely measured after the procedure for all in-hospital patients maintained in our hospital. In most of the peripheral hospitals, cardiac markers were not collected routinely, unless a post procedure myocardial infarction was suspected.[14] In total, post procedural cardiac enzymes were measured in 150 patients (65%). Repeat revascularization was defined as all repeat surgical or percutaneous intervention, including revascularization

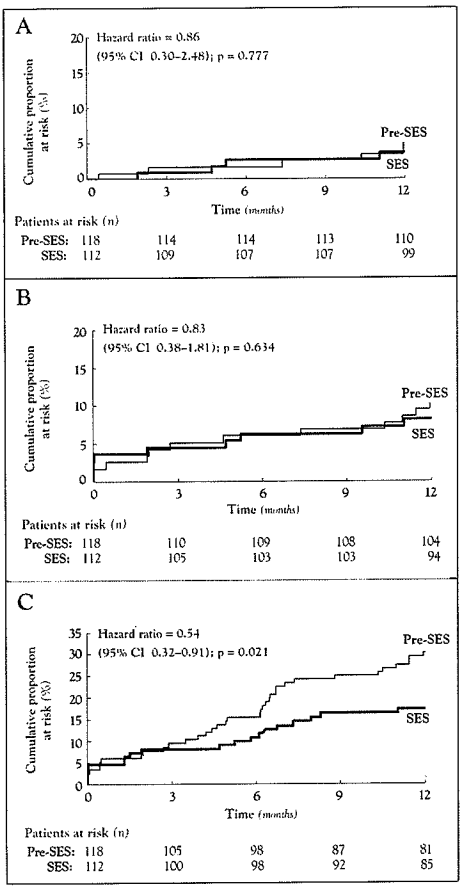

Figure 1. *The cumulative incidence of major adverse cardiac events in the SES group and pre-SES group at 1 year.* **(A)** *Cumulative incidence of death.* **(B)** *Cumulative incidence of death or myocardial infarction.* **(C)** *Cumulative incidence of death, myocardial infarction, or repeat revascularization.*

procedures performed to address segments not treated in the index procedure. Clinically-driven repeat revascularization was defined as any intervention (target lesion, target vessel, and non-index vessel) motivated by a significant luminal stenosis (> 50% diameter stenosis) in the presence of anginal symptoms and/or proven myocardial ischemia by non-invasive testing. Stent thrombosis was angiographically documented as a complete occlusion (TIMI flow 0 or 1) or a flow-limiting thrombus (TIMI flow 1 or 2) of a previously successfully treated artery.

Information regarding repeat interventions was prospectively collected by means of an electronic database. Survival status was assessed by written inquiries to the Civil Registry. Questionnaires

Table 1. Baseline characteristics of patients.

	Pre-SES group (n = 118)	SES group (n = 112)	p-value
Age (*years, mean ± SD*)	64 ± 11	63 ± 10	0.52
Male (%)	64	67	0.68
Hypertension (%)	64	72	0.16
Hypercholesterolemia (%)	66	71	0.48
Family history (%)	23	24	0.88
Current smoking (%)	25	19	0.34
Multivessel disease (%)	62	71	0.16
Previous MI (%)	32	32	1.0
Unstable angina (%)	42	37	0.42
Hb A1C (%)	7.4 ± 1.6	7.2 ± 1.4	0.56
Ccr (*ml/min*)	85 ± 38	89 ± 35	0.36
BMI (kg/m^2)	28 ± 4	29 ± 4	0.32
Previous angioplasty (%)	31	25	0.38
Previous CABG (%)	20	13	0.16
Statin (%)	62	70	0.27
Use of insulin (%)	25	33	0.19

MI = myocardial infarction; Ccr = creatinine clearance; BMI = body mass index; CABG = coronary artery bypass surgery.

Table 2. Angiographic and procedural characteristics of patients.

	Pre-SES group (n = 118)	SES group (n = 112)	p-value
Treated vessel			
LAD, %	55	62	0.35
LCX, %	37	37	1.0
RCA, %	38	40	0.79
LMS, %	6	6	1.0
Bypass graft, %	9	5	0.20
Lesion morphology			
A (%)	20	17	0.73
B1 (%)	40	40	1.0
B2 (%)	46	49	0.69
C (%)	40	40	1.0
Bifurcation stenting (%)	7	18	0.01
Number of treated lesions	2.0 ± 1.1	2.0 ± 1.0	0.96
Stents/patient	2.1 ± 1.4	2.4 ± 1.6	0.10
Mean stent diameter (*mm*)	3.2 ± 0.5	2.8 ± 0.2	< 0.0001
Total stent length per patient (*mm*)	38 ± 29	47 ± 33	0.03
Individual stent length ≥ 33 mm (%)	16	42	< 0.0001
Individual stent diameter ≤ 2.5 mm (%)	12	27	0.007
GP IIb/IIIa inhibitor (%)	31	13	0.001
Angiographic Success (%)	93	94	1.0

LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery; LMS = left main stem.

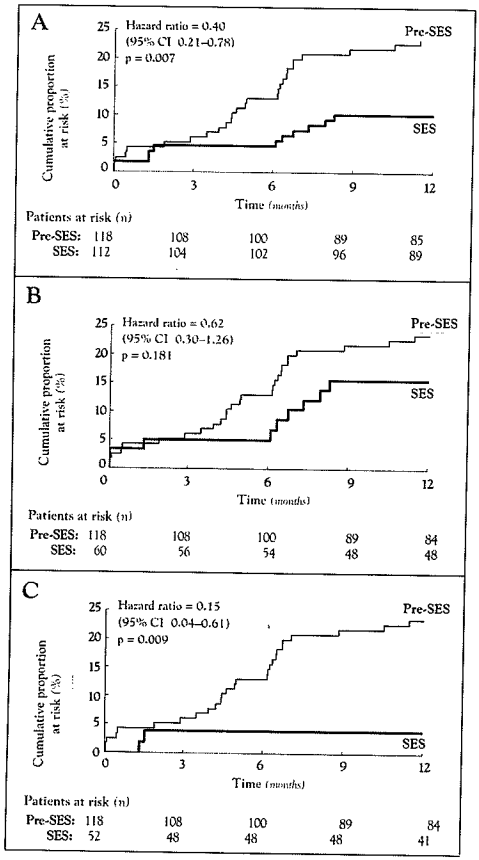

Figure 2. *The cumulative incidence of repeat revascularization in the SES group and pre-SES group at 1 year.* **(A)** *Comparison of patients in the SES group (all 11-month enrollment) and patients in the pre-SES group.* **(B)** *Comparison of patients assigned to selected mandatory angiographic follow-up in the SES group (first 6-month enrollment) and patients in the pre-SES group.* **(C)** *Comparison of patients assigned to only clinical follow-up in the SES group (last 5-month enrollment) and patients in the pre-SES group.*

to assess clinical status were sent to all living patients. The patient, referring physician, and peripheral hospitals were directly approached whenever necessary for additional information.

Angiographic follow-up. Patients treated during the first 6 months of utilization of SES were approached for late angiographic re-evaluation according to the following "complex" characteristics: SES implanted in bifurcations, left main coronary, chronic total occlusions, very small vessels (2.25 mm stent diameter), and long stented length (> 36 mm). In total, 29 of the 60 patients enrolled in the first 6 months (48% of the patients treated in this period) had angiographic re-study between 6 and 9 months of follow-up. For the remaining patients in the pre-SES group and the last subgroup of patients treated with SES (i.e. last 5 months enrollment), follow-up angiography was obtained as clinically indicated by symptoms or documentation of myocardial ischemia.

Statistical analysis. Continuous variables were compared with the Student's t-test, and the Fisher's exact test was used for categorical variables. The cumulative incidence of adverse events was calculated according to the Kaplan-Meier method, and Cox proportional hazard models were used to assess risk reduction of adverse events. All statistical tests were two-tailed, and p values less than 0.05 were considered statistically significant.

Results

Patient characteristics. The baseline, angiographic, and procedural characteristics are presented in Tables 1 and 2. There were no statistical differences between the 2 groups with respect to the baseline and angiographic characteristics. Patients in the SES group had a longer stented length and were treated with stents of smaller diameters. The use of glycoprotein IIb/IIIa inhibitors was less frequent in the SES group than in the pre-SES group (13% versus 31%, $p = 0.001$).

30-day and 1-year clinical outcomes. At 30 days, there were no significant differences in the frequency of major adverse cardiac events between the 2 groups. The 30-day incidence of any MACE was 5.9% in the pre-SES group and 4.5% in the SES group ($p = 0.61$). Angiographically documented stent thrombosis occurred in 1 patient (0.8%) in the pre-SES group and 2 patients (1.8%) in the SES group ($p = 0.77$).

The cumulative incidence of major cardiac events at 1 year is shown in Table 3. Both the cumulative incidence of death, and the composite of death or non-fatal MI were not statistically different between the 2 groups (Figure 1A, 1B). However, the incidence of overall MACE was significantly lower in the SES group than in the pre-SES group (17.3% versus 30.2%, respectively; hazard ratio = 0.54 [95% confidence interval = 0.32–0.91]; $p = 0.03$), mainly due to a decrease in the incidence of repeat revascularization in the SES group (10.2% versus 23.5% in the pre-SES group; hazard ratio = 0.40 [95% confidence interval = 0.21–0.78]; $p = 0.007$) (Figures 1C and 2A).

To better evaluate the impact of protocol-mandated angiographic follow-up on the clinical outcomes, patients treated with SES in the first 6-month enrollment period (48% had elective control angiography), and those treated with SES in the last 5 months were separately compared to the pre-SES group. The 1-year incidence of repeat revascularization in patients included in the first half of the SES group was 15.6%, compared with 23.5% in the pre-SES group (hazard ratio = 0.62 [95% confidence interval = 0.30–1.26]; $p = 0.18$). Conversely, patients treated in the last phase of the SES period had significantly less re-interventions than patients treated with bare stents (3.9% versus 23.5%, respectively; hazard ratio = 0.15 [95% confidence interval = 0.04–0.61]; $p = 0.009$) (Figure 2B, 2C).

Table 3. The 1-year cumulative rate of major adverse cardiac events.

	Pre-SES group	SES group	Hazard ratio (95% CI)	p-value
Death (%)	5.2	3.6	0.86 (0.30–2.48)	0.78
Death or myocardial infarction (%)	10.3	8.2	0.83 (0.38–1.81)	0.63
Target vessel revascularization (%)	19.3	7.4	0.42 (0.20–0.92)	0.03
Repeat revascularization (%)				
Pre-SES group versus all SES group	23.5	10.2	0.40 (0.21–0.78)	0.007
Pre-SES group versus first 6-month enrollment SES group*	23.5	15.6	0.62 (0.30–1.26)	0.18
Pre-SES group versus last 5-month enrollment SES group**	23.5	3.9	0.15 (0.04–0.61)	0.009
Any event (%)	30.2	17.3	0.54 (0.32–0.91)	0.02

Selected mandatory angiographic follow-up group.
**Only clinical follow-up group.*

Patients with insulin-requiring diabetes mellitus (IRDM). In this study, 37 patients with IRDM were treated with SES and 29 patients with IRDM were treated with BMS. The 1-year cumulative MACE rate was 26.3% in the SES group, and 35.5% in the BMS group, which was not statistically significant (hazard ratio = 0.63 [95% confidence interval = 0.27–1.44], $p = 0.28$).

Discussion

The present study shows that, in comparison to bare metal stents, utilization of sirolimus eluting stents for diabetic patients treated in the daily practice was safe and effective in reducing major cardiac events at 1 year, mainly due to a marked decrease in the incidence of repeat intervention.

In our series, the SES-treated cohort was composed by two groups prospectively evaluated according to different followed-up strategies. Specifically, a subset of diabetic patients enrolled in the first half of the SES phase underwent protocol-mandated late angiographic re-study, while patients treated in the last half had only clinically driven angiographic re-evaluation. This contrasted with the pre-SES control group, where only clinically driven angiographic follow-up was obtained for the entire group. The different follow-up strategy applied for the two SES subgroups could have accounted for the marked difference in outcomes seen between these subsets. High prevalence of silent ischemia in diabetic patients might decrease the incidence of clinically driven repeat revascularization, and the increase in the incidence of re-intervention due to the so-called "oculo-stenotic reflex" is a well-known phenomenon occurring among patients undergoing protocol-mandated angiographic follow-up.[15,16] In the BENESTENT II trial, the one-year incidence of repeat revascularization in the stented group was 18.3% with angiographic follow-up, compared with 7.8% without angiographic follow-up.16 In our series, the effect of the angiographic follow-up on repeat interventions was clearly observed in the SES group: patients in the SES subgroup with re-study had a rate of repeat intervention of 15.6%, while in patients without re-study the incidence of re-intervention was 3.9%. It is worth noting that, although not assessed in the present study, diabetics may be more prone to be influenced by a potential "oculo-stenotic reflex." The presence of diffuse coronary artery disease, incomplete relief of symptoms related to microcirculation disease, and extra-cardiac co-morbidities, features commonly seen in this high-risk group of patients, may lead to a more aggressive treatment strategy by the time of the repeat catheterization.

Previous randomized trials have shown the effect of drug-eluting stents for diabetic patients with relatively simple lesions.[12,13] In the RAVEL trial, sirolimus-eluting stents effectively inhibited neointimal hyperplasia in diabetic patients.[13] Similarly, in the SIRIUS trial, SES implantation for diabetic patients was associated with reduction of 9-month MACE from 25.0% with bare metal stent to 9.2%.[17] The present study assessed the impact of routine utilization of drug-eluting stents for diabetics treated in daily practice. Despite of the fact that our patients had more complex lesion types and were treated with longer stent lengths and smaller stent diameters than previous randomized trials,[9,18] SES implantation was associated with an overall 60% risk reduction of any repeat revascularization in the present study. Furthermore, it must be recognized that this risk reduction may actually be an underestimate due to the unbalanced frequency of angiographic follow-up between patients treated with SES and patients treated with bare metal stents.

Insulin-requiring diabetes mellitus (IRDM) is associated with a high adverse cardiac event rate after coronary stenting in the diabetic population.[4-6] The efficacy of the DES for patients with IRDM requires further evaluation. In the SIRIUS trial, the 9-month MACE rate for patients with IRDM who were treated with SES were not significantly different from patients with IRDM who were treated with bare metal stents (MACE; 15.8% versus 22.7%; $p = 0.58$).[17] This result is in agreement with our study. A randomized trial enrolling more patients is required to further evaluate this issue.

In our study, the vast majority of diabetic patients had multi-vessel coronary disease. Diabetic patients with multi-vessel disease have been shown to be at high risk for future cardiac events. Moreover, the best therapeutic approach for these patients is still a matter of ongoing debate. Previous randomized trials of diabetics have shown lower mortality rates following bypass surgery than after balloon angioplasty.[19,20] However, more contemporary

studies with coronary stents have failed to show any difference in mortality between the surgical and percutaneous treatments.[21-23] In these studies, both modalities differed mainly with regards to an excessive incidence of repeat revascularization after stenting, a complication frequently related to the occurrence of late restenosis. According to the analysis of diabetic patients in the ARTS trial, the 1-year incidence of repeat revascularization was 22.3% in the stented group and 3.1% in the CABG group.[21] The significantly lower incidence of repeat revascularization in SES-treated patients compared to the bare stent group indicates the promising role of SES for the management of diabetics with advanced atherosclerotic disease. Two clinical trials (the FREEDOM trial and the BARI-2D) are currently ongoing to further evaluate the value of sirolimus-eluting stents in this scenario.[24]

This study is limited by its non-randomized, single-center design and moderate sample size. It is, however, the first study to evaluate the efficacy of drug-eluting stents for diabetic patients outside the context of randomized trials.

Conclusions

Routine utilization of sirolimus-eluting stents for diabetic patients effectively reduced the incidence of adverse cardiac events at 1 year compared to bare metal stents. Sirolimus-eluting stent implantation seems to be a promising strategy for diabetic patients treated in daily practice.

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Chapter 17

How to Accelerate the Re-endothelialization of Stents

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How to accelerate the endothelialization of stents

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Summary

Coronary artery stenting is currently the most frequently performed percutaneous coronary intervention for the treatment of coronary artery disease. The endothelium is a single layer of endothelial cells lining the vascular wall and plays an integral part in maintaining vascular homeostasis. Stenting however causes significant injury to the vascular wall and endothelium, resulting in inflammation, repair and the development of neointimal hyperplasia. The ability of the endothelium to repair itself depends on both the migration of surrounding mature endothelial cells, and the attraction and adhesion of circulating endothelial progenitor cells (EPCs) to the injured region, which then differentiate into endothelial-like cells.

Current therapies with drug-eluting stents interrupt the natural response to damage. Accelerating the reendothelialization of the damaged arterial segment following stent implantation is an attractive form of therapy as it is seen as hastening the natural process of repair. It potentially has the benefit of reducing the amount of neointimal hyperplasia and stent thrombosis. Studies have been performed to identify agents that augment the mobilisation and recruitment of EPCs to the injured area (statins, exercise, estrogen and cytokines). Other studies have looked at seeding stents with endothelial cells or EPCs. The most current approach is to coat anti-CD34 antibodies on a stent surface to attract circulating EPCs to the stent which then differentiate into endothelial-like cells. This approach is currently being tested in safety and feasibility clinical studies. Arch Mal Cœur 2005 ; 98 : 123-6.

Résumé

L'insertion d'une endoprothèse coronaire est l'intervention percutanée effectuée le plus souvent pour le traitement de la maladie coronaire. L'intima consiste en une seule couche de cellules endothéliales tapissant la paroi vasculaire et jouant un rôle intégral dans la maintenance de l'homéostasie vasculaire. L'insertion d'un stent traumatise la paroi vasculaire et l'endothélium, et engendre une inflammation, une réparation et le développement d'une hyperplasie intimale. La capacité de l'endothélium à se réparer dépend de la migration des cellules endothéliales matures avoisinantes et aussi de l'attraction et de l'adhésion des cellules endothéliales procréatrices circulantes (EPCs) vers la région traumatisée, celles-ci prenant ensuite la forme de cellules endothéliales.

Les traitements actuels avec des stents actifs interrompent la réponse naturelle envers le traumatisme. L'accélération de l'endothélialisation des segments artériels endommagés après l'insertion d'une endoprothèse est une forme de thérapie attractive car elle semble promouvoir le processus naturel de réparation. Cela a l'avantage potentiel de réduire la réaction d'hyperplasie intimale et de thrombose du stent. Des études ont été faites pour identifier les facteurs susceptibles d'augmenter la mobilisation et le recrutement des PCEs vers la région endommagée (statines, exercice, estrogène et cytokines). D'autres études ont examiné l'intérêt des stents imbibés de cellules endothéliales ou de PCEs. L'approche actuelle la plus courante est d'enrober les stents d'anticorps anti-CD34 pour attirer les PCEs circulantes qui peuvent ensuite se différencier en cellules de type endothélial. Cette approche est en cours d'évaluation dans des études cliniques de sécurité et de faisabilité. Arch Mal Cœur 2005 ; 98 : 123-6.

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Coronary artery stenting has been definitively proven to be superior to balloon angioplasty in most types of coronary lesions and is currently the most frequently performed percutaneous coronary intervention for the treatment of coronary artery disease [1, 2]. The long-term success of coronary stenting is limited by the development of restenosis, caused by the development of an exuberant neointima in response to the vessel wall injury caused by the implantation of a

stent. The current generation of coronary stents, coated with antiproliferative agents, reduce restenosis by interrupting the vessel wall response to injury [3, 4], which may result in a delay in endothelialization. A potentially viable alternative for the reduction of neointimal hyperplasia is to limit the response to injury by accelerating the reendothelialization of stents and the associated vessel wall.

This review will describe the function of endothelial cells and the origin of endothelial-like cells from endothelial progenitor cells (EPCs), primitive cells originating from the bone marrow. Methods of augmenting the recruitment of EPCs and the mobilisation of these cells from their origin to the vessel wall are elucidated. Finally, experiments involving stent-based therapies are described.

BACKGROUND

Endothelial cells and abnormalities

The endothelium is a monolayer of endothelial cells lining the lumen of blood vessels. It functions as a protective biocompatible barrier between tissue and circulating blood. It serves as a selective sieve to facilitate the bi-directional passage of macromolecules and blood gases between tissues and blood. Vascular homeostasis is maintained through the balanced release of autocrine and paracrine substances from these cells.

Endothelial cell dysfunction disrupts this balance, predisposing the vessel wall to vasoconstriction, leukocyte adherence, platelet activation, mitogenesis, prooxidation, thrombosis, impaired coagulation, inflammation, atherosclerosis and neointimal formation [5, 6].

Vascular injury from stent implantation

Stent implantation results in substantial injury to the vessel wall. In particular, when stenting is accompanied by damage to the tunica media or penetration of the stent into a lipid core, increased arterial inflammation is induced which is associated with increased neointimal growth [7]. Chronic inflammation is augmented by the presence of a foreign body (stent) and arterial injury. Vascular smooth muscle cell (VSMC) migration, proliferation, and matrix protein production contributes to neointimal growth which occur as part of the healing process of the damaged arterial wall.

In-stent restenosis may be therefore viewed as an exaggerated response to the healing process. As a result, intense effort has been made to understand the mechanisms that govern VSMC proliferation and to develop therapies to inhibit excessive VSMC growth. The repair of the disrupted endothelium involves both the migration of surrounding mature endothelial cells into the injured area and the attraction of circulating immature cells called endothelial progenitor cells to the site, which then differentiate into endothelial-like cells (see below) [8].

Current therapies

Currently available drug eluting stents (DES) utilize agents such as rapamycin (a cytostatic immunomodulatory compound) and paclitaxel (a chemotherapeutic agent); both of which have been shown to reduce the incidence of restenosis after stenting [9, 10]. Following DES implantation, the fate of the endothelium is uncertain with evidence to suggest that paclitaxel and sirolimus delay reendothelialization [11, 12]. As such, prolonged antiplatelet therapy is currently recommended following the implantation of DES.

Alternative hypothesis

As an alternative hypothesis, some groups have suggested that neointimal hyperplasia is at least in part a result of delayed or belated reendothelialization [13]. Animal studies have repeatedly shown that extensive endothelial denudation of the arterial wall promotes neointimal thickening. The understanding that certain functions of the endothelium including barrier regulation of the permeability, thrombogeneticity, leukocyte adherence, and production of growth-inhibitory molecules are critical to the prevention of the development of neointimal growth [14].

Endothelial progenitor cells

EPCs belong to a family of progenitor cells, primitive bone marrow cells that have the capacity to proliferate, migrate and differentiate into various mature cell types. EPCs in particular, possess the ability to mature into endothelial-like cells [15]. The first evidence for the presence of EPCs in the adult circulation emerged when mononuclear blood cells from healthy human volunteers were shown to acquire an endothelial cell-like phenotype in vitro and to incorporate into capillaries in vivo [16]. These putative EPCs were characterized via their expression of CD34 and vascular endothelial growth factor receptor-2 (VEGFR-2). Subsequent studies confirmed that CD34+ cells isolated from bone marrow or umbilical cord blood also had the capacity to differentiate into mature endothelial-like cells [17, 18]. EPCs are considered to be part of the mononuclear- macrophage system and reside predominantly in the bone marrow and possibly in the spleen [19]. A small number (0.01%-0.3% of circulating mononuclear cells) are present in the peripheral circulation [20]. The lifetime of circulating EPCs in vivo under physiological or pathological conditions is unknown.

As described above, the intact endothelium plays a vital role in maintaining vascular equilibrium. Repair of damaged endothelium is therefore vital in restoring this equilibrium. Recently it has been shown that at sites of endothelial cell damage (carotid artery) the mobilization and incorporation of bone marrow derived EPCs modulates reendothelialization [21, 22]. Impaired mobilization or depletion of EPCs may contribute to endothelial dysfunction [23]. Patients with cardiovascular disease have been shown to have lower levels of circulating EPCs compared to healthy patients [23].

ACCELERATING THE ENDOTHELIALIZATION OF STENTS

Augmentation of EPC recruitment and mobilisation

In separate experiments, predominantly in animal models, attempts have been made to elucidate the mechanisms surrounding EPC recruitment and mobilization. In vivo insults such as limb ischaemia or coronary thrombosis, burn injury or coronary bypass surgery rapidly enhance the number of circulating EPCs [24-26]. The studies described below refer to additional attempts to augment the recruitment and mobilization of EPCs.

HMG-CoA reductase inhibitors or statins have been the most widely studied agent and have been shown in numerous studies to enhance EPC mobilization [27, 28] and to also improve endothelial function independent of cholesterol reduction [29]. Furthermore, statins have been shown to accelerate reendothelialization after vascular injury (through the increased expression of the main fibronectin receptor, integrina s5b1) [21, 22] and cause a dose-dependent significant reduction in neointimal thickening in a rat model [21].

In a mouse model, physical activity was shown to increase the production and circulating numbers of EPCs via a partially nitric oxide-dependent anti-apoptotic effect [30]. Within the same study, the authors demonstrated that in patients with stable coronary artery disease, moderate exercise training for 28 days led to a significant increase in circulating EPCs and reduced EPC apoptosis.

In another study, the same group showed that the intravenous infusion of autologous spleen derived mononuclear cells or in vitro cultured EPCs resulted in significantly enhanced reendothelialization associated with diminished neointimal formation following endothelial cell damage in the carotid artery of splenectomized mice [31].

They also showed that in a separate experiment, estrogen increased bone marrow derived EPC production by decreasing the apoptosis rate (mediated by the caspase-8 pathway), leading to decreased neointimal formation in injured carotid arteries in mice [32].

The use of cytokines to mobilize EPCs has been well studied in the ischaemia/infarction model. VEGF [33] and GM-CSF [34] have both been shown in animal models to accelerate reendothelialization and reduce vascular inflammatory processes after arterial wall injury.

Studies involving coronary stents

In animal studies in 1988 our group showed it was possible to seed stainless steel self-expandable stents with endothelial cells derived from human umbilical cord veins in vitro [35]. The stents were then implanted in porcine femoral arteries and when explanted at 1 week demonstrated complete covering of the stent struts by endothelium. More recently, others have reported the results of EPC seeded stents in an in-vitro study. After 7 days of culture, EPCs seeded on stents had migrated from the stent struts, proliferated and endothelialized both the luminal surface of hybrid vascular medial tissue and the stent struts [36].

Clinical trials

To date, no human trials have been published with regard to the use of endothelial cells or endothelial progenitor cells and stent implantation. A novel approach has been to seed anti-CD34 antibodies onto a stent surface (Genous, Orbus International B.V., The Netherlands). CD34 is a surface cell receptor found on circulating EPCs. In theory, upon stent implantation, peripherally circulating EPCs attach to the antibodies on the stent surface and then differentiate into mature endothelial-like cells, thus covering the stent surface. This has been successfully tested in animal models and as part of a single-centre "First-In-Man" trial entitled HEALING-1, our institution has successfully implanted these stents in 16 patients. Follow-up is still incomplete and results of this trial are still pending at the time of writing. HEALING-2, a European multicentre trial has been planned to follow.

CONCLUSION

In conclusion, methods to accelerate the endothelialization of stents might provide an attractive option for they attempt to accelerate a natural process, with the possibility of reducing both stent thrombosis and restenosis. To do so requires consideration of the various steps involved. First attempts at coating the stent with endothelial stents were shown to be possible, but required endothelial cells to be harvested and expanded ex-vivo. The discovery of circulating endothelial progenitor cells opened the door to new methods. Seeding the stents with EPCs also requires harvesting of these cells. In a parallel stream, researchers have identified separate mechanisms to accelerate endothelialization through the mobilization of EPCs in animal models (statin therapy, exercise, estrogen and cytokines). The latest, and possibly the most attractive attempt, has been to capture circulating EPCs from the peripheral blood by coating coronary stents with anti-CD34 antibodies. These antibodies will attract and bind circulating EPCs (which possess the surface cell receptor CD34), and result in the coverage of the stent with EPCs which then proliferate and differentiate into mature endothelial-like cells. Clinical trials are underway and the results are awaited.

KEY WORDS : stents, endothelium, endothelial progenitor cells, statins.

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Chapter 8

Outcomes of Unrestricted Utilization of Paclitaxel versus Sirolimus-Eluting Stents in 293 Unselected Consecutive Diabetic Patients

Ong AT, Aoki J, Hoye A, van Mieghem CA, Rodriguez Granillo GA, Valgimigli M, Tsuchida K, Sonnenschein K, Regar E, van der Giessen WJ, de Jaegere PP, Sianos G, McFadden EP, de Feyter PJ, van Domburg RT, Serruys PW.

Am J Cardiol. 2005;96:358-362

Comparison of Short- (One Month) and Long- (Twelve Months) Term Outcomes of *Sirolimus*- Versus *Paclitaxel*-Eluting Stents in 293 Consecutive Patients With Diabetes Mellitus (from the RESEARCH and T-SEARCH Registries)

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This study evaluated and compared the efficacy of sirolimus-eluting stents (n = 145 patients) with that of paclitaxel-eluting stents (n = 148 patients) in 293 consecutive unselected patients who had diabetes mellitus. Baseline clinical characteristics and presentations were similar: mean age of 64 years, 50% presented with unstable angina or myocardial infarction, and 66% had multivessel disease. Angiographic and procedural characteristics differed, with more complex lesions and more vein grafts managed in the paclitaxel-eluting stent group. Overall mean stented length was 46 ± 32 mm. There were no differences in unadjusted outcomes by stent type (1-year major adverse cardiac event rates of 20.4% for sirolimus-eluting stents vs 15.6% for paclitaxel-eluting stents, p = 0.12) or when adjusted for multivariate predictors (adjusted hazard ratio 0.68, 95% confidence interval 0.37 to 1.24, p = 0.21). Independent predictors of outcome in patients who had diabetes mellitus were stenting of the left main artery, stenting of the left anterior descending artery, creatinine clearance, and female gender. Patients who required insulin had a significantly higher, crude major adverse cardiac event rate at 1 year compared with those who used oral agents, but this rate became nonsignificant when adjusted for independent predictors of outcome. **(Am J Cardiol 2005;96:358–362)**

The Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) and Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registries are identical sequential prospective registries that were specifically set up to evaluate the universal utilization of sirolimus- and paclitaxel-eluting stents (SESs and PESs, respectively) in an unrestricted population.[1,2] The present study evaluated short- (1 month) and long-term (12 months) efficacies of SESs and PESs in patients with diabetes mellitus (DM).

• • •

We performed a prospective cohort study to investigate the outcomes of drug-eluting stent implantation in patients who had DM. Since April 2002, our institution has adopted a policy of universal drug-eluting stent implantation for all patients who undergo percutaneous coronary intervention that requires stenting. All patients are prospectively entered into a dedicated database. The initial results of this approach have been published elsewhere.[1,2] Until February 2003, SESs (Cypher, Cordis, a Johnson & Johnson Company, Miami Lakes, Florida) were exclusively used; subsequently, PESs (Taxus, Boston Scientific Corp., Natick, Massachusetts) became the default stent.

Follow-up was complete for 98% of patients. Survival status was obtained from municipal civil registries at 1, 6, and 12 months. All repeat interventions (surgical and percutaneous) and rehospitalizations were prospectively collected during follow-up. Questionnaires concerning 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. Written informed consent was obtained from every patient.

From April 2002 to December 2003, 293 unselected consecutive patients who had DM and de novo coronary artery disease were treated exclusively with drug-eluting stents; 145 patients received SESs and 148 received PESs. The 2 groups were sequential and are part of the RESEARCH and T-SEARCH prospective registries, respectively. Patients who have DM constitute 18% of the patient population treated percutaneously at our institution and were defined by

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therapy; those on oral medications were classified as requiring noninsulin and those on insulin therapy as requiring insulin.

All interventions were performed according to current standard procedures using routine high-pressure balloon inflations, with the final interventional strategy (including direct stenting, postdilatation, use of periprocedural glycoprotein IIb/IIIa inhibitors, and use of intravascular ultrasound) at the operator's discretion.[3] Angiographic success was defined as a residual stenosis ≤30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction grade 3 flow. All patients were advised to maintain lifelong use of aspirin (≥80 mg/day). All patients were pretreated with 300 mg of clopidogrel. Postprocedurally, patients who received PESs were prescribed ≥6 months of clopidogrel (75 mg/day),[4] and those who received SESs were prescribed clopidogrel for ≥3 or 6 months depending on the complexity of the procedure.[1]

The primary outcome was the occurrence of major adverse cardiac events, defined as a composite of all-cause death, nonfatal myocardial infarction, or target vessel revascularization. Myocardial infarction was diagnosed by an increase in creatine kinase-MB fraction of >3 times the upper limit of normal.[5] In patients who underwent coronary artery bypass surgery during follow-up, periprocedural myocardial infarction was diagnosed by an increase in creatine kinase-MB level of 5 times the upper limit of normal.[6] For patients who presented with an acute myocardial infarction, a diagnosis of repeat myocardial infarction in the acute phase required a decrease and then increase in creatine kinase-MB of 50% above the previous level.[7] Target lesion revascularization was defined as a repeat intervention (surgical or percutaneous) to control 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 reintervention that was influenced by any lesion in the same epicardial vessel. Angiographic stent thrombosis was defined as an angiographically documented complete occlusion (Thrombolysis In Myocardial Infarction grade 0 or 1 flow) or a flow-limiting thrombus (Thrombolysis In Myocardial Infarction grade 1 or 2 flow) in a previously successfully stented artery in the first 30 days. Suspected stent thrombosis was defined as unexplained sudden death or nonfatal myocardial infarction that was unrelated to a periprocedural complication without repeat angiography. Two independent cardiologists (AO and JA) reviewed all major adverse cardiac events.

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 were compared by Fisher's exact test. All statistical tests were 2-tailed. Cox's proportional hazards analysis was performed to identify independent predictors of major adverse cardiac events using significant univariate variables and clinically important variables listed in Tables 1 and 2 (tested variables were age, gender, insulin requirement, creatinine clearance,

Table 1
Baseline clinical characteristics

Variable	SES Group (n = 145)	PES Group (n = 148)	p Value
Men	66%	67%	0.8
Age (yrs)	62.6 ± 10.2	64.6 ± 10.3	0.08
Non–insulin-requiring DM	73%	77%	0.4
Insulin-requiring DM	27%	23%	0.4
Hypertension	68%	70%	0.7
Hypercholesterolemia*	66%	85%	<0.001
Current smoking	23%	20%	0.7
Previous myocardial infarction	37%	42%	0.5
Previous coronary angioplasty	23%	21%	0.8
Previous coronary bypass grafting	10%	14%	0.5
Single-vessel coronary disease	34%	31%	0.7
Multivessel coronary disease	66%	69%	0.7
Clinical presentation			0.4
Stable angina pectoris	49%	56%	
Unstable angina pectoris	38%	34%	
Acute myocardial infarction	13%	10%	
Hemoglobin-A1c (%)	7.3 ± 1.3	7.6 ± 1.5	0.09
Creatinine clearance (ml/min)	87.6 ± 33.0	80.8 ± 33.4	0.10
Body mass index (kg/m^2)	28.4 ± 4.1	27.9 ± 3.8	0.3

Values are means ± SD or percentages.
* Defined as a fasting cholesterol level >5.5mmol/L or use of lipid-lowering therapy.

Table 2
Angiographic and procedural characteristics

Variable	SES Group (n = 145)	PES Group (n = 148)	p Value
Treated coronary vessel*			
Left anterior descending artery	60%	48%	0.05
Left circumflex artery	40%	34%	0.3
Right artery	32%	42%	0.11
Left main artery	8%	8%	1.0
Bypass graft	3%	10%	0.02
Lesion type†			
A	17%	8%	0.02
B1	37%	24%	0.02
B2	45%	47%	0.7
C	47%	56%	0.13
No. of coronary vessels treated			0.5
1	61%	64%	
2	35%	28%	
3	4%	8%	
Multivessel treatment	39%	36%	0.6
Bifurcation stenting	19%	14%	0.4
No. of stented vessels	1.4 ± 0.6	1.4 ± 0.7	0.9
No. of implanted stents	2.4 ± 1.5	2.3 ± 1.4	0.6
Total stented length per patient (mm)	45.3 ± 32.1	48.5 ± 33.8	0.4
Nominal stent diameter ≤2.5 mm	40%	47%	0.2
Chronic total occlusion (>3 mos)	14%	12%	0.6
Glycoprotein IIb/IIIa inhibitor use	18%	28%	0.04
Angiographic success of all lesions	94%	97%	0.4

Values are means ± SD or percentages.
* Expressed as percentage of patients with vessel type treated. Total exceeds 100%.
† Expressed as percentage of patients with lesion type. Total exceeds 100%.

Table 3
Major adverse cardiac events in the first month after stent implantation

Patients With Events at 0–1 month	SES Group (n = 143)	PES Group (n = 148)	p Value*
Death	5 (3.4%)	5 (3.4%)	1.0
Nonfatal myocardial infarction	5 (4.1%)	3 (2.0%)	0.3
Target lesion revascularization	5 (3.4%)	1 (0.7%)	0.1
Target vessel revascularization†	5 (3.4%)	3 (2.0%)	0.5
Any event	14 (9.7%)	9 (6.1%)	0.3
Angiographically proved stent thrombosis	3 (2.1%)	1 (0.7%)	0.4
Suspected stent thrombosis	1 (0.7%)	2 (1.4%)	1.0
Total stent thrombosis	4 (2.8%)	3 (2.0%)	0.7

* By Fisher's exact test.
† Includes target lesion revascularization.

presenting symptoms, lesion type, multivessel disease, bifurcation stenting, stenting of the left main artery, stenting of the left anterior descending artery, stent type, number of stents, total stent length, and minimum stent diameter). Stent type and requirement for insulin were forced into the model, whereas other variables were entered in a forward stepwise method (entry and removal criteria of 0.05 and 0.10, respectively). The cumulative incidence of adverse events was estimated according to the Kaplan-Meier method.

Baseline clinical characteristics were similar for the 2 groups with the exception of hypercholesterolemia (Table 1). Sixty-six percent were men and 25% required insulin. Multivessel coronary disease was present in 66% of patients, and 50% presented with an acute coronary syndrome (unstable angina or acute myocardial infarction). Mean hemoglobin A1c levels were 7.6 ± 1.5% in the PES group and 7.3 ± 1.3% in the SES group. More patients in the PES group were classified as having hypercholesterolemia (defined as a fasting serum cholesterol level >5.5mmol/L or use of lipid-lowering therapy at the time of the procedure) due to the more widespread use of lipid-lowering agents in the latter period.

Significant differences were noted in terms of angiographic and procedural characteristics (Table 2). In the PES group, more patients received treatment in a bypass graft (10% vs 3% in the SES group, p = 0.02) and fewer patients received treatment in the left anterior descending artery (48% vs 60% respectively, p = 0.05). The use of glycoprotein IIb/IIIa inhibitors was greater in the PES group (28% vs 18%, p = 0.04). More complex lesions were treated in the PES group, with fewer type A or B1 lesions treated (p = 0.02). Multivessel treatment was performed in 40% of patients. Total stented length was similar in the 2 groups (48.5 ± 33.8 mm in the PES group and 45.3 ± 32.1 mm in the SES group, p = 0.4), as was the number of stents implanted (2.3 ± 1.3 vs 2.4 ± 1.5 stents, respectively, p = 0.6).

In the first month after stent implantation, there were 10 deaths that were equally divided between groups (Table 3). Three deaths were clinically suspected to be due to stent thrombosis (Table 3). There were 8 myocardial infarctions, 5 in the SES group and 3 in the PES group. Of the 6 target lesion revascularizations, 4 were for stent thrombosis and 2 were the result of a procedural complication that required urgent coronary surgery. In total, 4 patients (2.8%) in the SES group and 3 (2.0%) in the PES group had suspected or

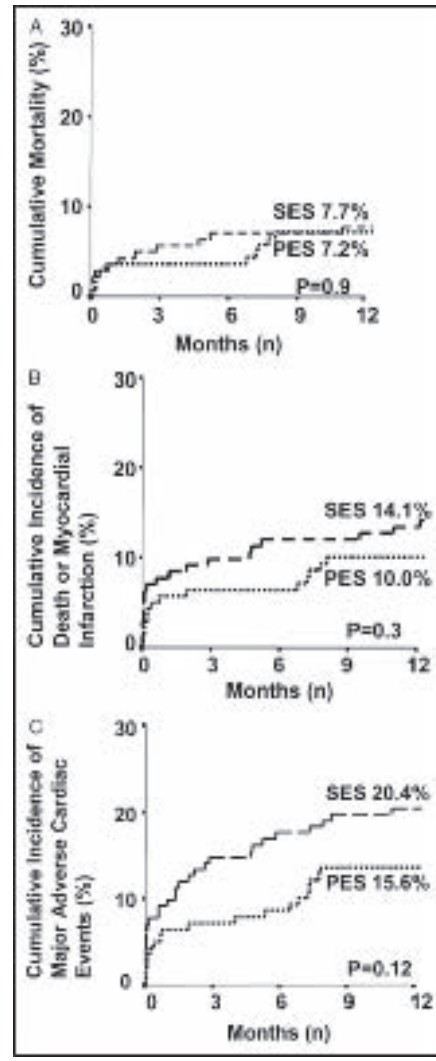

Figure 1. Event curves at 1 year for cumulative risks of *(A)* death, *(B)* death or myocardial infarction, and *(C)* death, myocardial infarction, or target vessel revascularization.

proved stent thrombosis (p = 0.7). A major adverse cardiac event occurred in 9.7% of patients in the SES group and 6.1% of patients in the PES group within the first 30 days.

At 1 year, there were no differences in the incidence of death between groups (SES 7.7%, PES 7.2%, p = 0.9; Figure 1). The incidence of death or myocardial infarction was also similar (SES 14.1%, PES 10.0%, p = 0.3). The composite end point of death, myocardial infarction, or target vessel revascularization was also nonsignificantly different (SES 20.4%, PES 15.6%, p = 0.12), with a trend favoring PES. Incidences of target lesion revascularization were 8.8% in the SES group and 5.7% in the PES group (p = 0.08; Figure 2

When patients were classified by insulin requirement, patients who required insulin (n = 72) developed more events compared with those who did not require insulin (n = 221, crude major adverse cardiac events 27.4% vs 14.6%, respectively, p = 0.008; Figure 3). Hemoglobin A1c levels were higher in the insulin-requiring DM group than in the non–insulin-requiring DM group, although not significantly (7.6% vs 7.2%, p = 0.4).

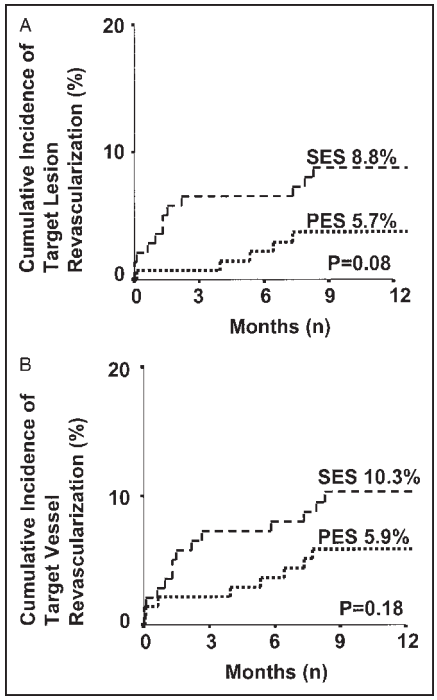

Figure 2. One-year cumulative risks of *(A)* target lesion revascularization and *(B)* target vessel revascularization.

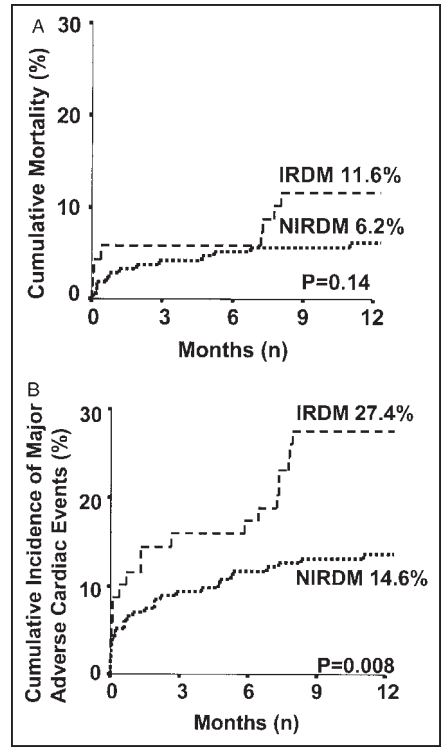

Figure 3. Cumulative risks of *(A)* death and *(B)* major adverse cardiac events stratified by diabetic type. IRDM = insulin-requiring DM; NIRDM = non–insulin-requiring DM.

Table 4
Multivariate predictors of major adverse cardiac events at one year (Cox's proportional hazards model)

Variable	Adjusted HR	95% CI	p Value
Stenting of left anterior descending artery	2.79	1.44–5.39	0.002
Stenting of left main artery	2.78	1.24–6.25	0.013
Creatinine clearance (/ml/min increment)	0.99	0.98–1.00	0.03
Women	1.90	1.02–3.53	0.04
Use of PES	0.68	0.37–1.24	0.21
Use of insulin	1.48	0.80–2.74	0.22

CI = confidence interval; HR = hazard ratio.

Stenting of the left anterior descending artery, stenting of the left main coronary artery, and female gender were independently associated with worse outcomes, whereas better renal function (defined as milliliter-per-minute incre-

ment in creatinine clearance) was associated with improved outcomes (Table 4). Insulin requirement, significant in univariate analysis, became nonsignificant in the multivariate model (adjusted hazard ratio 1.48, 95% confidence interval 0.80 to 2.74, p = 0.22), and no significant differences were noted with stent type (adjusted hazard ratio 0.68, 95% confidence interval 0.37 to 1.24, p = 0.21).

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The major finding of this study is that unrestricted use of PESs in a universal drug-eluting stent environment is associated with a nonsignificantly lower incidence of major adverse cardiac events at 1 year compared with SESs (adjusted hazard ratio 0.68, 95% confidence interval 0.37 to 1.24, p = 0.21). Patients with DM and who required insulin had a significantly higher crude incidence of major adverse cardiac events compared with those who did not require insulin in a combined drug-eluting population; this significance became nonsignificant after adjustment for multivariate predictors.

Mortality rate at 1 year between groups in our study was similar (7.7% in SES group and 7.2% in PES group, p = 0.9). It is difficult to compare between studies; however, as a guide, this result lies between that reported in the stent arm of the randomized Arterial Revascularization Therapy Study (6.3%)[8] and a multivessel report from the database of the Cardiovascular Research Foundation (14% to 15%),[9] with the caveat that baseline demographics were different. For a population that had DM, the use of glycoprotein IIb/IIIa inhibitors in this study was very low; more frequent use may have improved mortality rates.[10]

This study has described the experience of a single-center registry of drug-eluting stents in a moderate number of patients. Routine angiographic follow-up was not performed, thus precluding an assessment of restenotic rates. The low use of glycoprotein IIb/IIIa inhibitors is a limitation but was a reflection of the "real-world" practice of the operators. The results of this study should be viewed as an exploratory analysis that reported outcomes after the unrestricted use of drug-eluting stents in the real world in patients who had DM.

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Chapter 9

Sirolimus-eluting stent implantation for chronic total occlusion of the left main coronary artery

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IT FITS! (Intelligence Transfer: From Images to Solutions)

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

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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 LMCA who was successfully treated with bifurcation stenting with sirolimus-eluting stents.
(J Interven Cardiol 2005;18:65–69)

Introduction

Chronic total occlusion of the left main coronary artery (LMCA) is an 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 LMCA 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 months 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 (Fig. 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 (Fig. 2). The patient rejected coronary artery bypass grafting, but consented to undergo attempted revascularization with percutaneous coronary intervention.

A 6F introducer sheath was inserted in the right femoral artery. In addition, a 5F introducer sheath was inserted in the left femoral artery to enable simultaneous right and left coronary injections. In the absence

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All authors have read and approved submission of the manuscript. There is no conflict of interest for any author.

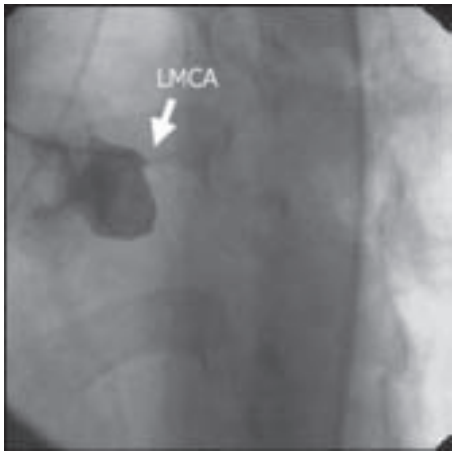

Figure 1. Left coronary artery angiogram, revealing total occlusion of the left main stem artery.

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 6F 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 into the LCX was attempted. Unfortunately, this was complicated by catheter/wire-induced dissection from the LMCA to the mid-LCX (Fig. 3), and the wire was withdrawn. The LAD/distal LMCA was stabilized through stent implantation with a 3.0 × 23 mm SES (Cypher, Cordis), which was then post-dilated with a 3.5 mm balloon (U-pass, Cordis) giving a good result (Fig. 4). After several attempts, a 0.0014″ Shinobi wire was eventually successfully crossed, via the SES struts, into the true lumen of the LCX. After sequential predilatation using a 2.0 mm balloon (Stomer, Medtronic), both the lesion and the mid-LCX dissection (Fig. 5) were treated with implantation of a 2.5 × 33 mm SES deployed from LCX ostium. The final angiogram showed good result with TIMI III flow in both the LAD and the LCX (Fig. 6).[18]

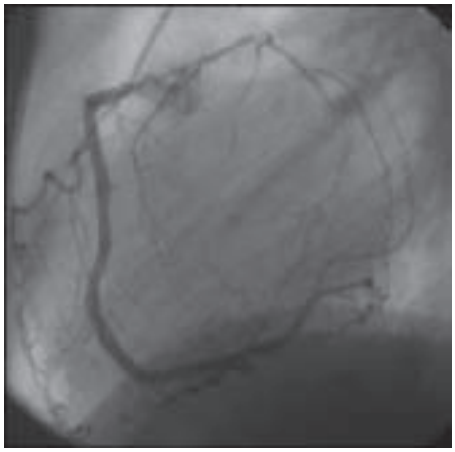

Figure 2. Right coronary angiogram demonstrating grade III retrograde collaterals arising from the right coronary artery to both the left anterior descending and the left circumflex arteries.

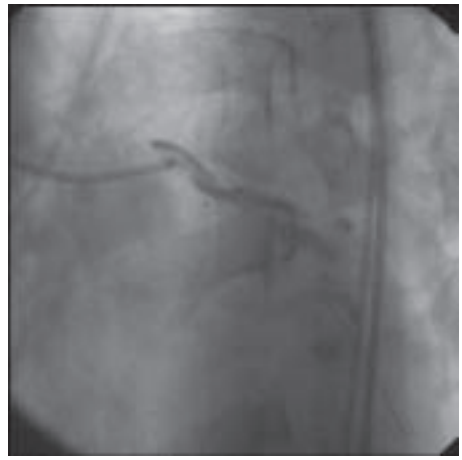

Figure 3. Left coronary angiogram showing the dissection of the left main stem artery to the mid-circumflex artery.

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

Discussion

Chronic total occlusion (CTO) of the LMCA is rare. In patients who are investigated in the catheter

SES FOR CTO OF LMCA

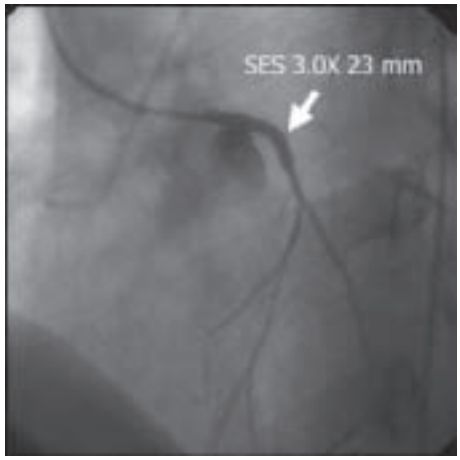

Figure 4. Left coronary angiogram following stent deployment with a 3.0 × 23 mm sirolimus-eluting stent in the left main stem/left anterior descending artery.

laboratory, its prevalence varies from 0.04% to 0.4%.[1–4] CABG has been considered to be the treatment of choice in LMCA disease, especially 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 has been shown to be 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 LMCA.[19] There are two 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] 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 the 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

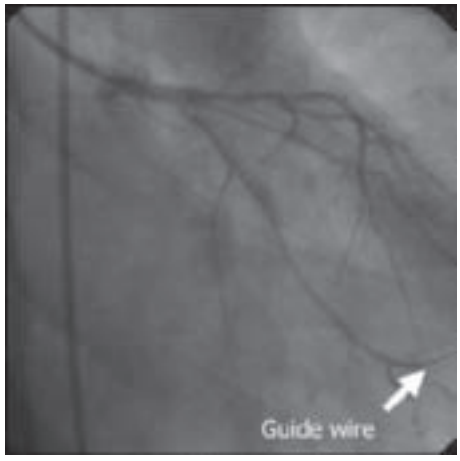

Figure 5. Left coronary angiogram showing that a wire has successfully crossed through the stent struts and into the true lumen of the distal left circumflex artery. The region of dissection can clearly be seen in the proximal and mid parts of the vessel (contrast staining).

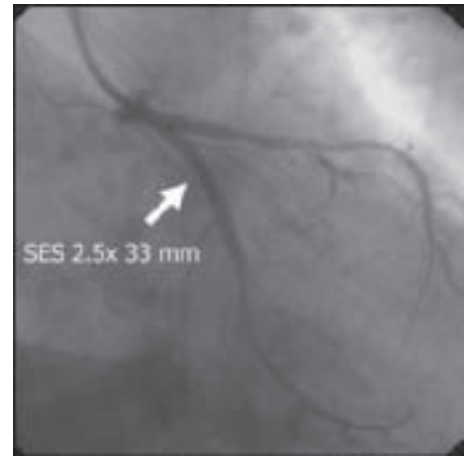

Figure 6. The final angiogram following additional stent implantation with a 2.5 × 33 mm sirolimus-eluting stent up to the ostium of the circumflex artery, showing a good result in both the left anterior descending and the left circumflex arteries.

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, with zero percent mortality and 4% target vessel revascularization.[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 an 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. Further data are 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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EDITOR'S RESPONSE

In the current case presentation, Dr. Aoki offers a glimpse at one of the still untapped frontiers in interventional cardiology. Percutaneous management of left main coronary lesions has remained undesirable because of the immediate technical difficulties and the subsequent risk of potentially fatal restenosis. The present case was particularly difficult because the left main was chronically occluded into both the left anterior descending and the left circumflex coronary arteries. The double catheter approach with simultaneous injection into the right coronary artery and the left main greatly facilitated distal guidewire placement. Achieving distal guidewire access was the greatest technical challenge of this particular case. Once distal access was attained, angiographic success was all but assured. While I believe that the angiographic results should have been confirmed with intravascular ultrasound to ensure adequate stent apposition within this critical area, this case represents a therapeutic victory over extreme lesion complexity with excellent angiographic and clinical results. Such cases should only be performed in high-volume centers with highly experienced coronary interventionalists.

However, the acute results in left main coronary stenting are only part of the battle. The largest hurdle in the management of these lesions is avoiding restenosis and its risk for death. The use of drug-eluting stents in the left main coronary artery may offer a solution. Arampatzis et al. studied the use of sirolimus-coated stents in 16 consecutive patients undergoing elective left main stenting in a single center.[1] Half of the patients had lesions involving the left anterior descending/left circumflex bifurcation. Nine patients had unprotected left main stenoses. There were no deaths reported during 1 year of follow-up. Peri-procedural non-Q-wave myocardial infarction occurred in one patient. Of the 12 patients who underwent angiographic follow-up at 6 months, only one demonstrated restenosis requiring repeat percutaneous intervention. No other major adverse coronary events occurred in the entire cohort during the year following left main intervention. Although the patient in the current case presentation did not undergo angiographic follow-up, he remained clinically stable and free of angina for 9 months. This case, therefore, succeeded in illustrating the potential of the left main coronary stenting in the drug-eluting stent era. I agree with the authors that this is an area of interventional cardiology that requires immediate investigation to fully understand its applications and its limitations.

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Chapter 10

Short-and long-term clinical outcome after drug-eluting stent implantation for the percutaneous treatment of left main coronary artery disease: insight from the rapamycin-eluting and taxus stent evaluated at Rotterdam cardiology hospital registries

Valgimigli M, van Mieghem CA, Ong AT, Aoki J, Rodriguez Granillo GA, McFadden EP, Kappetein AP, de Feyter PJ, Smith PC, Regar E, van der Giessen WJ, Sianos G, de Jaegere PP, van Domburg RT, Serruys PW.

Circulation. 2005;111:1383-1189

Interventional Cardiology

Short- and Long-Term Clinical Outcome After Drug-Eluting Stent Implantation for the Percutaneous Treatment of Left Main Coronary Artery Disease

Insights From the Rapamycin-Eluting and Taxus Stent Evaluated At Rotterdam Cardiology Hospital Registries (RESEARCH and T-SEARCH)

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Background—The impact of drug-eluting stent (DES) implantation on the incidence of major adverse cardiovascular events in patients undergoing percutaneous intervention for left main (LM) coronary disease is largely unknown.

Methods and Results—From April 2001 to December 2003, 181 patients underwent percutaneous coronary intervention for LM stenosis at our institution. The first cohort consisted of 86 patients (19 protected LM) treated with bare metal stents (pre-DES group); the second cohort comprised 95 patients (15 protected LM) treated exclusively with DES. The 2 cohorts were well balanced for all baseline characteristics. At a median follow-up of 503 days (range, 331 to 873 days), the cumulative incidence of major adverse cardiovascular events was lower in the DES cohort than in patients in the pre-DES group (24% versus 45%, respectively; hazard ratio [HR], 0.52 [95% CI, 0.31 to 0.88]; $P=0.01$). Total mortality did not differ between cohorts; however, there were significantly lower rates of both myocardial infarction (4% versus 12%, respectively; HR, 0.22 [95% CI, 0.07 to 0.65]; $P=0.006$) and target vessel revascularization (6% versus 23%, respectively; HR, 0.26 [95% CI, 0.10 to 0.65]; $P=0.004$) in the DES group. On multivariate analysis, use of DES, Parsonnet classification, troponin elevation at entry, distal LM location, and reference vessel diameter were independent predictors of major adverse cardiovascular events.

Conclusions—When percutaneous coronary intervention is undertaken at LM lesions, routine DES implantation, which reduces the cumulative incidence of myocardial infarction and the need for target vessel revascularization compared with bare metal stents, should currently be the preferred strategy. **(*Circulation*. 2005;111:1383-1389.)**

Key Words: stents ■ angioplasty ■ arteries

Despite the recognition that coronary revascularization, in selected patients with multivessel disease, can presently be accomplished by either a surgical or a percutaneous approach with no significant difference in long-term mortality,[1,2] coronary artery bypass grafting (CABG) is still considered the treatment of choice in patients with left main (LM) disease.[3] Several trials have reported on the safety and feasibility of stent implantation to treat LM stenosis.[4,5] However, particularly in this subset of patients, restenosis remains a major, and potentially fatal, complication, precluding more widespread use of percutaneous coronary intervention (PCI).[4,6] In the first observational report of patients treated with a sirolimus-eluting stent (SES) for LM disease, a low rate of binary restenosis and a favorable clinical outcome were reported.[7] However, the benefit of drug-eluting stents (DES) on the short- and long-term incidence of major adverse cardiovascular events in this setting, compared with bare metal stents (BMS), remains largely unknown.

The purpose of the present study was to investigate, in this subset of patients undergoing revascularization in a tertiary referral center, the differential impact of DES as opposed to conventional BMS on the occurrence of short- and long-term major cardiovascular events.

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Methods

Study Design and Patient Population

Since April 16, 2002, SES (Cypher, Johnson & Johnson, Cordis unit) have been used as a default strategy for every PCI at our institution as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. From the first quarter of 2003, paclitaxel-eluting stents (PES) (Taxus, Boston Scientific Corporation) became commercially available, replacing SES as the strategy of choice in every PCI because of cost-effectiveness considerations, as part of the Taxus Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry. As a policy, all elective patients presenting with significant (>50% by visual estimation) LM disease, referred to our institution for coronary revascularization, are evaluated by both interventional cardiologists and cardiac surgeons, and the decision to opt for PCI or surgery is reached by consensus on the basis of a comprehensive evaluation of the following items: suitable anatomy and lesion characteristics for stenting and size and quality of vessels distal to the disease and of arterial and/or venous conduits for grafting. Finally, patient and/or referring physician preferences for a percutaneous approach, with both aware of the procedural risks and contraindications to surgery on the basis of the presence of comorbidity as evaluated by a cardiac surgeon, are also considered.

From April 16, 2002, to December 31, 2003, a total of 95 consecutive patients were treated exclusively with ≥1 DES in the LM as part of an elective or nonelective revascularization procedure and constitute the DES group of the present report. Fifty-two patients in the first cohort (of whom procedural details and medium-term follow-up were previously reported for 31[7]), received SES exclusively (available, at that time, in diameters from 2.25 to 3.00 mm), whereas in the following group of 43 patients, PES (available in diameters from 2.25 to 3.5 mm) were implanted. A control group for comparison was composed of 86 consecutive patients who received conventional BMS (available in diameters from 2.5 to 5.00 mm) for LM treatment in the period immediately before the introduction of SES. The following BMS were used: BX Sonic or BX Velocity in 35% (Cordis, Johnson & Johnson Company), R-Stent in 29% (Orbus Medical Technologies), Multi-Link Penta in 28% (Guidant Corp), Multi-Link Tetra in 8% (Guidant Corp), and other stents in 4%. Therefore, the total study population comprised all 181 consecutive patients who underwent percutaneous LM treatment from April 2001 to December 2003 with either BMS or DES in the 2 study phases, respectively. To stratify the study population into high– and low–surgical risk groups, the Parsonnet surgical risk score was calculated for each patient.[8] A score >15 was used to identify patients at high risk, as previously suggested.[6,9] Protected LM segment was defined as the presence of at least 1 patent arterial or venous conduit to at least 1 left coronary segment. Nonelective treatment was defined as a procedure performed on referral before the beginning of the next working day.[10]

This protocol was approved by the hospital ethics committee and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from every patient.

Procedures and Postintervention Medications

All interventions were performed according to current standard guidelines, and the final interventional strategy, including the use of glycoprotein IIb/IIIa inhibitors, was left entirely to the discretion of the operator, except for the stent utilization. Angiographic success was defined as residual stenosis <30% by visual analysis in the presence of Thrombolysis in Myocardial Infarction (TIMI) 3 flow grade. All patients were advised to maintain the use of aspirin lifelong. One-month clopidogrel treatment (75 mg/d) was recommended for patients treated in the pre-DES phase. For patients treated with either SES or PES, clopidogrel was prescribed for 6 months.

End Point Definitions and Clinical Follow-Up

The primary outcome was the occurrence of major adverse cardiac events, defined as (1) death, (2) nonfatal myocardial infarction (MI), or (3) target vessel revascularization. Patients with >1 event have been assigned the highest ranked event, according to the previous list. All deaths were considered to be of cardiac origin unless a noncardiac origin was established clinically or at autopsy. MI was diagnosed by a rise in the creatine kinase level to more than twice the upper normal limit with an increased creatine kinase-MB fraction. Target vessel revascularization was defined as a repeated 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, including the ostium of the left anterior descending artery (LAD) and/or circumflex artery. Information about in-hospital outcomes was obtained from an electronic clinical database for patients maintained at our institution and by review of 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. Information on occurrence of MI or repeated interventions at follow-up was collected by consulting our institutional electronic database and by contacting referring physicians and institutions and all living patients.

Statistical Analysis

Continuous variables are shown as mean±SD and were compared by Student unpaired *t* test. Categorical variables are presented as counts and percentages and were compared with the Fisher exact test. Survival curves were generated by the Kaplan-Meier method, and survival among groups was compared with the log-rank test. Cox proportional hazards models were used to assess risk reduction of adverse events. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Univariate analysis was performed with the consideration of all variables reported in Tables 1 and 2. Multivariate analyses, with consideration of all variables with a value of $P<0.10$, were performed to identify independent predictors of adverse events. Probability was significant at a level of <0.05. All statistical tests were 2-tailed. Statistical analysis was performed with the use of Statistica 6.1 (Statsoft Inc).

Results

Baseline and Procedural Characteristics

Baseline and procedural characteristics are shown in Table 1 and Table 2. The 2 groups were well matched for all baseline characteristics, including comorbidities. Overall, the average left ventricular ejection fraction was slightly >40%, and approximately half of the patients in both groups were admitted with acute coronary syndromes. Acute MI was the indication to the procedure in 19%; 10% of the patients presented with severe hemodynamic compromise at entry. The distal LM was involved in two thirds of cases in both groups, whereas patients treated with DES had significantly more 3-vessel disease, more bifurcation stenting, a higher number of stents, and greater total stent length per patients. The nominal stent diameter, as a result of limited size availability, was on average smaller in the DES group, which explains the more common practice of postdilatation in this group of patients. Procedural success was 99% in patients receiving DES: in 1 patient who presented with acute MI and shock, a final TIMI 1 flow grade was obtained, and the patient died 3 hours after the procedure. The procedural success was 98% in patients treated in the pre-DES phase: in 2 patients with acute MI and TIMI 0 flow grade in the left coronary artery, the LM and proximal LAD were stented, and subsequently CABG was performed because of residual critical stenosis in the left circumflex artery.

TABLE 1. Baseline Characteristics of the Study Population

Variables	Pre-DES Group (n=86)	DES Group (n=95)	P
Age, y *	66±10	64±12	0.18
Men, %*	62	66	0.53
Body mass index, kg/m^2*	26±4	27±4	0.31
Diabetes, %*	22	30	0.23
Non–insulin-dependent, %	17	20	0.71
Insulin-dependent, %	5	10	0.17
Hypertension, %*	57	53	0.65
Hypercholesterolemia, %	55	56	0.88
Current smoking, %	19	18	0.8
Creatinine, μmol/L*	102±80	95±31	0.36
LVEF, %*	42±13	41±14	0.85
Medical history, %			
Protected LM	22	16	0.17
PCI	35	28	0.42
MI	41	38	0.58
Transient ischemic attack/stroke	8	11	0.81
Heart failure*	16	20	0.36
Severe COPD*†	5	8	0.38
Peripheral arterial disease*	24	22	0.86
Carotid artery disease*	6	6	0.98
Clinical presentation, %			
Stable angina	50	48	0.8
Unstable angina	33	33	1
Acute MI*	17	20	0.70
Cardiogenic shock at entry*	9	12	0.66
Parsonnet score	16±11	19±12	0.17

LVEF indicates left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease.

*Parameters included in the Parsonnet classification.

†Resulting in functional disability or hospitalization, requiring chronic bronchodilator therapy, or forced expiratory volume in 1 second <75% of predicted.[8]

Thirty-Day Outcomes

There were no significant differences between the DES and the pre-DES groups in the incidence of major adverse cardiovascular events during the first 30 days (Table 3). In the DES group, all deaths except 3 occurred in patients presenting with ST-segment elevation acute MI and cardiogenic shock at entry. In all these patients except 4 with severe peripheral artery disease, an intra-aortic balloon was placed during PCI. In the elective population, a total of 2 deaths occurred; both patients presented with unstable angina with mild troponin elevation and were refused by surgeons because of old age (84 years), low left ventricular ejection fraction (≤30%), and diabetic chronic renal insufficiency in 1 patient and diffuse 3-vessel disease associated with small-caliber vessels in the second. In this second patient the right coronary artery was occluded. The reason for death was pulmonary infection, which developed 19 days after the procedure in the first patient, and cardiogenic shock, which developed during the intervention, resistant to hemodynamic support (left ventricular assist device) in the other patient. In the pre-DES group, all 6 deaths occurred in patients with ST-segment elevation acute MI, of whom 4 were in cardiogenic shock at entry. No documented thrombotic stent occlusion occurred in the first 30 days or thereafter.

TABLE 2. Angiographic and Procedural Characteristics of the Study Population

Variables	Pre-DES Group (n=86)	DES Group (n=95)	P
Lesion location, %			
Ostium	18	27	0.20
Body	40	37	0.31
Distal	66	65	0.9
Pure LM disease, %	2	3	1
LM plus 1-vessel disease, %	29	17	0.4
LM plus 2-vessel disease, %	42	21	<0.001
LM plus 3-vessel disease, %	27	59	0.003
Right coronary artery >70% stenosis, %	27	53	0.02
Right coronary artery occlusion, %	13	19	0.43
No. of implanted stents	1.2±0.5	1.4±0.6	0.01
Nominal stent diameter, mm	3.6±0.5	3.1±0.32	<0.001
Total stent length per patient, mm	20±9	24±13	0.02
Predilatation, %	67	71	0.62
Cutting balloon, %	5	6	0.94
Rotational atherectomy, %	1	3	0.8
Directional atherectomy, %	6	0	0.007
Postdilatation, %	58	80	0.01
Larger balloon inflated, mm	4±0.6	3.9±0.4	0.07
Maximal pressure, atm	17±2	17±3	0.85
Bifurcation stenting, %	10	26	0.02
Culotte*	11	36	0.4
T technique*	88	44	0.35
Crush*	0	12	0.56
Kissing technique*	0	8	0.91
Intravascular ultrasonography, %	23	27	0.36
Glycoprotein IIb/IIIa inhibitors, %	26	28	0.83
Intra-aortic balloon pump, %	16	15	0.88
Left ventricular assist device, %	0	2	0.52
Minimal lumen diameter, mm, preintervention	1.05±0.59	1.09±0.44	0.58
Minimal lumen diameter, mm, postintervention	2.97±0.6	2.83±0.49	0.09
Reference vessel diameter, mm, postintervention	3.37±0.6	3.25±0.5	0.2

*Relative to patients with bifurcation stenting.

Long-Term Outcome

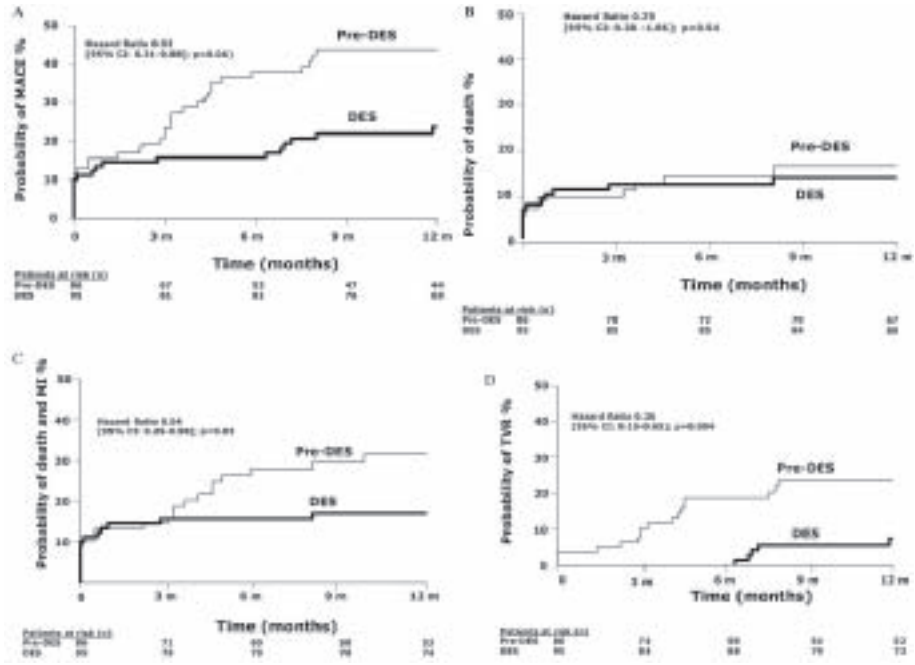
After a median follow-up of 503 days (range, 331 to 873 days), the cumulative incidence of major adverse cardiovascular events (death, MI, or target vessel revascularization) was significantly lower in the DES patients than in the pre-DES patients (24% versus 45%, respectively; hazard ratio

TABLE 3. Thirty-Day Outcomes

Variables	Pre-DES Group (n=86)	DES Group (n=95)	*P**
Death, n (%)	6 (7)	10 (11)	0.60
Nonfatal MI, n (%)	8 (9)	4 (4)	0.24
Death or nonfatal MI, n (%)	14 (16)	14 (15)	0.84
Target vessel revascularization, n (%)	2 (2)	0 (0)	0.22
Repeated PCI	1 (1)	0 (0)	
CABG	1 (1)	0 (0)	
Any event, n (%)	16 (19)	14 (15)	0.56
Stent thrombosis, n (%)†	0 (0)	0 (0)	1

*By Fisher exact test.
†Angiographically documented.

[HR], 0.52 [95% CI, 0.31 to 0.88]; $P=0.01$) (Figure, A). Mortality was similar in the DES (14%) and pre-DES cohort (16%; HR, 0.79 [95% CI, 0.38 to 1.66]; $P=0.54$) (Figure, B), whereas there was a significant reduction in both the rate of MI (4% versus 12%, respectively; HR, 0.22 [95% CI, 0.07 to 0.65]; $P=0.006$) and composite death/MI (Figure, C) as well as in the need for target vessel revascularization (6% versus 23%, respectively; HR, 0.26 [95% CI, 0.10 to 0.65]; $P=0.004$) (Figure, D) in the DES group. Seventy-four percent of the deaths were cardiac, whereas 3 of 13 in the DES group and 4 of 14 in the pre-DES phase were attributed to extracardiac reasons. In Table 4, the baseline and procedural characteristics of those patients in the DES group who underwent target vessel revascularization during follow-up are reported. In all cases, the lesion was located in the distal LM, in 50% of cases diabetes was present, and all except 1 were women. In 3 cases, in-stent restenosis occurred; in 2 patients intimal hyperplasia developed at the distal edge of the stent, whereas in 1 patient severe ostial side branch restenosis (circumflex artery) necessitated reintervention. In all cases, restenosis was focal (<10 mm in length) and was successfully treated with repeated PCI. In the pre-DES group, 13 cases of pure in-stent restenosis, of which 3 were focal, were treated with PCI (9 patients) or CABG (4 patients). In 2 patients, diffuse intimal hyperplasia associated with progression of atherosclerotic disease in other vessels was treated with CABG, and in 5 patients (3 with ST-segment elevation acute MI as the indication for LM intervention), staged reintervention with CABG (in 4 patients) and PCI (in 1 patient) was performed because revascularization remained incomplete at the time of the index procedure.



One-year adverse events in patients treated with BMS before the introduction of DES (pre-DES group) and in patients treated exclusively with DES implantation (DES group). Cumulative risk of major adverse cardiovascular events (MACE) (A), death (B), death or MI (C), and target vessel revascularization (TVR) (D) is shown.

TABLE 4. Characteristics of Patients in the DES Group Who Underwent Target Vessel Revascularization During Follow-Up

	Patient No.					
	1	2	3	4	5	6
Age, y	66	77	36	70	52	56
Gender	F	F	F	M	F	F
Diabetes	Yes	No	No	Yes	No	Yes
Lesion location	Distal	Distal	Distal	Distal	Distal	Distal
Severe calcification	Yes	No	No	No	No	No
Stent type	SES	SES	PES	PES	PES	PES
Stent No.	2	2	1	2	1	2
Total stent length, mm	16	36	20	48	16	36
Bifurcation stenting	No	Yes	No	Yes	No	Yes
Technique	...	Crush	...	Culotte	...	Culotte
Postdilatation	Yes	Yes	Yes	Yes	Yes	Yes
Final kissing	No	No	No	Yes	No	No
Gap between stents	No	No	No	No	No	No
Stent underexpansion	Yes	No	No	No	No	No
Restenosis location	In-stent	In-stent*	RS	In-stent	DER	DER*
Revascularization type	PCI	PCI	PCI	PCI	PCI	PCI
QCA after PCI						
Reference vessel diameter, mm	3.74	3.27	3.53	2.65	2.44	2.76
Minimal lumen diameter, mm	2.12	1.06	3.34	2.49	1.94	2.32
Lesion length, mm	13.4	19.7	13.5	21.3	8.9	18.9
QCA at follow-up						
Reference vessel diameter, mm	3.87	3.43	3.21	2.32	1.82	2.36
Minimal lumen diameter, mm	1.23	0.57	0.98	0.99	0.6	0.71
Restenosis length, mm	5.8	9.06	3.6	5.48	7.72	9.5

QCA indicates quantitative coronary angiography; In-stent, restenosis located within the stent margins; RS, restenosis located in the side branch (the ostium of the circumflex artery); and DER, distal edge restenosis located within the 5-mm segment distal to the stent.

*More than 1 focal site.

Predictors of Adverse Events

The Parsonnet score, ranging from 2.5 to 55.5 (mean value, 18±2; interquartile range, 16.5) was 16±11 and 19±12 in the pre-DES and DES groups, respectively (P=0.17) (Table 1), with a trend toward a higher rate of patients considered at high surgical risk (58% versus 46%, respectively; P=0.13) in the DES compared with the pre-DES cohort.

On univariate analysis, Parsonnet classification, use of intra-aortic balloon pump, presence of shock at entry, lesion located in the distal LM, nonelective PCI, troponin elevation at entry, TIMI flow grade before and after PCI, reference vessel diameter, left ventricular ejection fraction, and the use of DES were identified as significant predictors of adverse events. On multivariate analysis, Parsonnet classification, troponin elevation at entry, lesions located at distal site, reference vessel diameter, and the use of DES were independent predictors of major adverse cardiovascular events (Table 5).

Discussion

Despite the feasibility and the high procedural success rate of percutaneous LM intervention, the long-term incidence of adverse events in the pre-DES "era" was often reported to be unacceptably high in this subset of patients.[4,6] This reflected the inclusion of high-risk patients, such as those not considered "good surgical candidates," as well as the dramatic impact of treated vessel failure in this specific anatomic context. In consecutive patients receiving elective BMS for unprotected LM treatment, the 3-year cumulative incidence of death was recently reported to be ≈16%.[6] In that series, 28% of the population was at high surgical risk. More than 50% of our study population was at high surgical risk according to the Parsonnet classification, thus explaining the relatively high rate of adverse events we observed. In this setting, when patients treated with DES were compared with those treated with BMS, a marked benefit with respect to the rate of major adverse cardiac events, as evidenced by a 47% relative risk reduction, emerged in the former. This was mainly due to the difference in the incidence of MI (67% relative risk reduction) and target vessel revascularization (65% relative risk reduction), with no effect on mortality. The higher prevalence of 3-vessel disease and bifurcation stenting in the DES group makes the observed benefit even more convincing. The difference in the incidence of events between

TABLE 5. Univariate and Multivariate Cox Proportional Hazards Analysis

Variables	*P*	Hazard Ratio (95% CI)	χ^2
Univariate analysis			
Distal LM disease	0.003	2.7 (4.8–1.53)	13.3
DES use	0.019	0.54 (0.9–0.32)	5.48
Nonelective PCI	0.0047	2.1 (3.5–1.3)	8
Intra-aortic balloon pump use	0.0002	2.9 (4.9–1.7)	14
LVEF, %	0.00001	0.95 (0.97–0.93)	20
Parsonnet score	>0.00001	1.07 (1.09–1.05)	44
Reference vessel diameter	0.00001	0.36 (0.58–0.32)	19
Shock at entry	>0.00001	4.48 (7.9–2.5)	21
TIMI flow before PCI	0.03	0.75 (0.96–0.58)	4.3
TIMI flow after PCI	0.03	0.58 (0.85–0.39)	4.7
Troponin T >0.02 μg/L at entry	0.0002	3.15 (5.26–1.9)	18
Multivariate analysis 1			
Distal LM disease	0.0007	2.94 (5.5–1.57)	76
DES use	0.00009	0.33 (0.57–0.19)	
LVEF, %	0.09	0.98 (1.001–0.95)	
Parsonnet score	0.0009	1.04 (1.07–1.01)	
Reference vessel diameter	0.005	0.51 (0.79–0.33)	
Troponin T >0.02 μg/L at entry	0.02	2.3 (4.4–1.2)	
Multivariate analysis 2			
Distal LM disease	0.00017	3.3 (6.1–1.7)	68
DES use	0.00018	0.35 (0.6–0.20)	
LVEF, %	0.00013	0.95 (0.98–0.94)	
Reference vessel diameter	0.0011	0.48 (0.74–0.30)	
Shock at entry	0.006	3.49 (8.6–1.4)	
Troponin T >0.02 μg/L at entry	0.016	2.27 (4.2–1.17)	

Multivariate analysis model 1 was performed with all major adverse cardiovascular event predictors on univariate analysis; in multivariate analysis model 2, the Parsonnet score was removed because of colinearity between the variables included in the model and those used in the calculation of the score, such as left ventricular ejection fraction (LVEF), use of intra-aortic balloon pump, and presence of shock.

the 2 groups emerged slowly after the procedure, with no clear advantage at 30 days, possibly reflecting the specific mechanism of action of DES on intimal hyperplasia.

The overall advantage of DES remained significant after adjustment for the Parsonnet score, the anatomic site of obstruction, and troponin status at entry. Therefore, our data suggest that when percutaneous treatment of LM coronary artery disease is undertaken, DES should be used as the default strategy.

The LM bifurcation was frequently involved (>60%) in our series, and even when the obstruction was more proximally located and did not directly involve the LAD or left circumflex artery ostia, its treatment often required the management of LM bifurcation. To date, the results of SES implantation to treat bifurcated lesions have been relatively disappointing, with high rates of restenosis in the side branch.[11] Our present findings are in keeping with these previous observations, confirming that in the DES era distal LM location is an independent predictor of adverse events at follow-up. Furthermore, because the strategy and technical aspects of bifurcation management were left entirely to the preference of treating physicians, no clear conclusions can be drawn in this regard.

Inconsistent findings have been reported thus far with regard to the effect of DES on long-term cumulative incidence of MI. In the first randomized clinical trials comparing SES or PES with BMS, no difference in the incidence of MI was observed.[12,13] Second-generation randomized trials assessing the benefit of DES in patients selected to be at intermediate risk for in-stent restenosis or all-inclusive registries reported trends toward MI reduction in the DES group, but none of them reached statistical significance.[14,15] Recently, a clear reduction in the cumulative incidence of MI in the DES group was reported in the SES-SMART trial, in which a selected group of high-risk patients has been evaluated.[16] Similarly, in our patient population, a reduced incidence of MI was observed in the DES group. Of note, 2 and 1 cases of MI in the pre-DES phase were related to target vessel revascularization and not related to target vessel revascularization, respectively. Whether this difference between studies is the reflection of a type II error in studies enrolling patients at low or intermediate risk remains unclear, but when the retrospective nature of our investigation is considered, data from prospective studies are needed to confirm our findings.

Limitations of the Study

The present study is a single-center experience from a tertiary referral center and lacks the clear advantages of a multicenter randomized study. In keeping with the aim of our investigation, an "all-comers" population has been enrolled, clearly resulting in a heterogeneous group of patients. Further studies, with larger sample sizes, are required to investigate the differential impact of DES versus BMS in prespecified subgroups, stratified according to clinical presentation (stable versus unstable) or protected versus unprotected type of treatment.

Despite the fact that the study was conducted over a relatively short period, we cannot exclude the possibility that improvements in technique or differences in drug prescription could have partially accounted for the difference observed in terms of major adverse cardiovascular events between groups. However, conducting randomized trials that seek to assess the efficacy of DES versus BMS in this specific subset of patients seems unlikely, and our understanding of the benefit of drug-coated stents to treat this group of patients will probably also rely in the near future on well-conducted registries that are able to record and monitor our daily clinical practice.

Conclusions

The use of DES as a default strategy to treat LM disease was associated with a significant reduction in adverse events. The effectiveness of DES persisted even after adjustment for clinical and procedural variables, including the Parsonnet

surgical risk score. Our findings apply to a selected group of patients referred for percutaneous LM treatment and suggest that in this setting routine DES implantation, by reducing the cumulative incidence of major adverse cardiovascular events, should be currently regarded as the strategy of choice. Until new evidence is provided by randomized clinical trials directly comparing the surgical and percutaneous approaches, CABG should remain the preferred revascularization treatment in good surgical candidates presenting with LM coronary artery disease.

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Chapter 11

Sirolimus- versus Paclitaxel-Eluting stent implantation for the percutaneous treatment of left main coronary artery disease. A combined RESEARCH and TSEARCH Long-term Analysis

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CLINICAL RESEARCH **Interventional Cardiology**

Sirolimus-Eluting Versus Paclitaxel-Eluting Stent Implantation for the Percutaneous Treatment of Left Main Coronary Artery Disease

A Combined RESEARCH and T-SEARCH Long-Term Analysis

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OBJECTIVES The purpose of this study was to investigate the long-term clinical and angiographic profile of sirolimus-eluting stent (SES) versus paclitaxel-eluting stent (PES) in patients undergoing percutaneous intervention for left main (LM) coronary disease.

BACKGROUND The long-term clinical and angiographic impact of SES as opposed to PES implantation in this subset of patients is unknown.

METHODS From April 2002 to March 2004, 110 patients underwent percutaneous intervention for LM stenosis at our institution; 55 patients were treated with SES and 55 with PES. The two groups were well balanced for all baseline characteristics.

RESULTS At a median follow-up of 660 days (range 428 to 885), the cumulative incidence of major adverse cardiovascular events was similar (25% in the SES group vs. 29%, in the PES group; hazard ratio 0.88 [95% confidence interval 0.43 to 1.82]; $p = 0.74$), reflecting similarities in both the composite death/myocardial infarction (16% in the SES group and 18% in the PES group) and target vessel revascularization (9% in the SES group and 11% in the PES group). Angiographic in-stent late loss (mm), evaluated in 73% of the SES group and in 77% of the PES group, was 0.32 ± 74 in the main and 0.36 ± 0.59 in the side branch in the SES group vs. 0.46 ± 0.57 ($p = 0.36$) and 0.52 ± 0.42 ($p = 0.41$) in the PES group, respectively.

CONCLUSIONS In consecutive patients undergoing percutaneous LM intervention, PES may perform closely to SES both in terms of angiographic and long-term clinical outcome. (J Am Coll Cardiol 2006;47:507–14) © 2006 by the American College of Cardiology Foundation

Routine drug-eluting stent (DES) implantation, by reducing the need for target vessel revascularization (TVR) and angiographic restenosis, has been recently proposed as the preferred strategy in poor surgical candidates undergoing percutaneous left main coronary artery (LM) intervention (1–3).

The longest average follow-up available for this treatment is currently one year, and whether sirolimus-eluting stent (SES) or paclitaxel-eluting stent (PES) is performing better in these patients is unknown (1–3).

Similarly, even for more conventional lesions, the differential safety and efficacy profile of these two DES options is largely debated (4–8). When taken together, current evidence possibly suggests that in more complex lesion/patient subsets, SES performs better and more safely than PES (4–7,9).

The percutaneous management of LM lesions is a challenging intervention, where bifurcated vessels, extensive wall calcification, and poor hemodynamic tolerance often coexist during treatment.

The purpose of the present study was to investigate, in a high-risk subset of patients undergoing revascularization in a tertiary referral center, the differential long-term impact of SES compared with PES in terms of clinical and angiographic outcome. Intravascular ultrasound analysis has also been carried out at follow-up to quantity neointimal hyperplasia volume.

METHODS

Study design and patient population. Since April 16, 2002, SES (Cypher; Johnson & Johnson-Cordis, Warren, New Jersey) has been used as a default strategy for every PCI at our institution as part of the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. From the first quarter of 2003, PES (Taxus; Boston Scientific Corp., Natick, Massachusetts) became commercially available, replacing SES as the strategy of choice in every PCI,

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Abbreviations and Acronyms

BMS = bare-metal stent
BR = binary restenosis
CX = left circumflex coronary artery
DES = drug-eluting stent
IVUS = intravascular ultrasound
LAD = left anterior descending coronary artery
LL = late loss
LM = left main coronary artery
MACE = major adverse cardiac events
MI = myocardial infarction
MLD = minimal luminal diameter
PES = paclitaxel-eluting stent
RCA = right coronary artery
SES = sirolimus-eluting stent
TVR = target vessel revascularization

as part of the Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry. As a policy, all elective patients presenting with significant (>50% by visual estimation) LM disease, referred to our institution for coronary revascularization, are evaluated both by interventional cardiologists and by cardiac surgeons, and the decision to opt for PCI or surgery is reached by consensus as previously described (1).

From April 16, 2002, to March 6, 2004, a total of 110 consecutive patients were treated exclusively with one or more DES in the LM as part of an elective or nonelective revascularization procedure and constitute the patient population of the present report. Fifty-five patients first received exclusively SES, available at that time in diameters from 2.25 to 3.00 mm, and then 55 patients received PES, available in diameters from 2.25 to 3.5 mm. To ensure comparability between the two study groups, the Parsonnet surgical risk score, based on both clinical presentation profile and comorbidities, and the William Beaumont Hospital simplified scoring system were calculated for each patient (10,11). Nonelective treatment was defined as a procedure carried out on referral before the beginning of the next working day (12).

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

Procedures and postintervention medications. All interventions were performed according to current standard guidelines, and, except for the stent utilization, the final interventional strategy was left entirely to the discretion of the operator. Angiographic success was defined as residual stenosis <30% by visual analysis in the presence of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. All patients were advised to maintain aspirin lifelong, and clopidogrel was prescribed for 6 months in both groups.

End point definitions and clinical follow-up. The occurrence of major adverse cardiac events, defined as death, nonfatal myocardial infarction, or target vessel revascularization, was recorded. Patients with more than one event were assigned the highest ranked event, according to the previous list. End point definitions were previously reported (1). In order to make the clinical follow-up of the two sequential cohorts of patients comparable, clinical outcome of the SES cohort was censored at two years.

Quantitative angiographic and intravenous ultrasound analysis. Quantitative analyses of all angiographic data were performed with the use of edge-detection techniques (CAAS II; Pie Medical, Maastricht, the Netherlands). A value of 0 mm was assigned for the minimal luminal diameter (MLD) in cases of total occlusion at baseline or follow-up. Binary restenosis (BR) was defined as stenosis of >50% of the luminal diameter in the target lesion. Acute gain was defined as the MLD after the index procedure minus the MLD at baseline angiography. Late loss (LL) was defined as the MLD immediately after the index procedure minus the MLD at angiographic follow-up. Quantitative angiographic measurements of the target lesion were obtained in the in-lesion zone (including the stented segment as well as the margins 5 mm proximal and distal to the stent). Intravascular ultrasound (IVUS) analysis was performed after administration of 200 μg of intracoronary nitroglycerin, with an automated pullback at 0.5 mm/s. All IVUS procedures were recorded on VHS videotape, and

Table 1. Baseline Characteristics of the Study Population

Variables	SES Group (n = 55)	PES Group (n = 55)	p Value
Age (yrs)*	64 ± 12	63 ± 12	0.54
Males (%)*	64	58	0.84
Body mass index (kg/m^2)*	23 ± 4	25 ± 5	0.31
Diabetes (%)*	34	24	0.29
Hypertension (%)*	54	53	>0.99
Hypercholesterolemia (%)	58	56	>0.99
Current smokers (%)	16	20	0.8
Creatinine (μmol/l)*	96 ± 32	100 ± 80	0.68
LV ejection fraction (%)*	44 ± 16	44 ± 12	0.95
Medical history (%)			
Protected left main	18	15	0.80
PCI	31	33	>0.99
Myocardial infarction	38	47	0.44
TIA/stroke	9	11	0.74
Heart failure*	16	16	>0.99
COPD severe*†	4	5	>0.99
Peripheral arterial disease*	22	16	0.63
Carotid artery disease*	9	5	0.71
Clinical presentation (%)			
Stable angina	49	45	0.86
Silent ischemia	0	4	0.12
Unstable angina	33	33	>0.99
Acute myocardial infarction*	15	18	0.72
Cardiogenic shock at entry*	9	9	>0.99
Parsonnet score	20 ± 13	17 ± 11	0.27
William Beaumont Hospital score‡	7.7 ± 4.28	7.36 ± 4.7	0.73

*Parameter included in the Parsonnet classification. †Resulting in functional disability, hospitalization, requiring chronic bronchodilatator therapy, or FEV1 <75% of predicted. ‡Based on age >65 years, creatinine elevation, multivessel disease, and occurrence of myocardial infarction within the previous 14 days.

COPD = chronic obstructive pulmonary disease; LV = left ventricular; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent; TIA = transient ischemic attack.

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images were digitized for analysis. A computer-based contour detection was performed with Qurad QCU analysis software (Curad, Wijk Bij Duurstede, the Netherlands) as previously described (13). Intimal hyperplasia volume was calculated as stent volume minus luminal volume. Percentage intimal hyperplasia was defined as intimal hyperplasia volume divided by stent volume.

Statistical analysis. The sample size was calculated on the assumption that average late loss in the SES and PES group would be around 0.15 mm and 0.35 mm, respectively, based on previous findings. To detect this effect size with a sigma value of 0.3, 85% power, and a type I error (alpha) of 0.05, 32 patients per group were required. Continuous variables are shown as mean ± standard deviation (SD) and were compared using Student unpaired *t* test. Categorical variables are presented as counts and percentages and compared with the Fisher exact test. Survival curves were generated by the Kaplan-Meier method, and survival among groups was compared using the log rank test. Cox proportional hazards models were used to assess risk reduction of adverse events. Multivariable analysis, considering all variables reported in Tables 1 and 2 with a p value of less than 0.10, was performed to adjust for possible confounders and identify whether the stent received was an independent predictor of adverse events. Probability was significant at a level of <0.05. All statistical tests were two-tailed. Statistical analysis was performed with Statistica 6.1 software (Statsoft, Tulsa, Oklahoma).

RESULTS

Baseline and procedural characteristics. Baseline and procedural characteristics are shown in Tables 1 and 2. The two groups were well matched for all baseline characteristics. In both cohorts, half of the patients presented with a left ventricular ejection fraction of 45% or less or with acute coronary syndrome as indication to treatment, and 9% of the patients presented with severe hemodynamic compromise at entry. The distal LM was overall involved in two-thirds of cases. In the SES group, nominal stent diameter was smaller—reflecting the unavailability of stent bigger than 3.0 mm during the study period—and cumulative stent length tended to be shorter than in the PES group. Bifurcation stenting was equally employed in both groups with a clear preference for T-stenting and for culotte technique in the SES and PES groups, respectively.

Thirty-one patients (56%) in the SES and 25 (45%) in the PES group received intervention in one or more non-LM lesion(s) during index procedure (p = 0.18). Complete

Table 2. Angiographic and Procedural Characteristics of the Study Population

Variables	SES Group (n = 55)	PES Group (n = 55)	p Value
Lesion location (%)*			
Ostium	27	22	0.51
Body	29	24	0.54
Distal	64	76	0.28
Pure left main disease (%)	5	5	>0.99
LM plus 1-vessel disease (%)	18	18	>0.99
LM plus 2-vessel disease (%)	20	24	0.82
LM plus 3-vessel disease (%)	57	53	0.87
Right coronary artery >70% stenosis (%)	69	64	0.88
Right coronary artery occlusion (%)	24	20	0.82
Number of implanted stents	1.43 ± 0.53	1.50 ± 0.6	0.49
Nominal stent diameter (mm)	3.00 ± 0.25	3.29 ± 0.28	<0.001
Total stent length per patient (mm)	23 ± 11	27 ± 13	0.07
Predilation (%)	71	60	0.15
Cutting balloon (%)	7	7	>0.99
Rotational atherectomy (%)	2	4	>0.99
Directional atherectomy (%)	0	0	>0.99
Postdilatation (%)	82	72	0.15
Bigger balloon inflated (mm)	3.75 ± 0.48	3.70 ± 0.5	0.48
Maximal pressure (atm)	18 ± 5	19 ± 3	0.55
Bifurcation stenting (%)	29	33	0.84
Culotte	0	20	0.009
T-technique	20	5	0.05
Crush	7	4	0.67
Kissing technique	2	4	>0.99
Intravascular ultrasonography (%)	33	27	0.53
IIb/IIIa inhibitors (%)	33	27	0.68
Intra-aortic balloon pump (%)	20	18	>0.99
Left ventricle assist device (%)	5	0	0.24
Temporary pacing during procedure (%)	7	9	>0.99

*Location of disease was not mutually exclusive among LM segments.
LM = left main coronary artery; other abbreviations as in Table 1.

Table 3. 30-Day and Long-Term Outcomes

Variables	SES Group	PES Group	p Value*
30-day outcome			
Whole population	(n = 55)	(n = 55)	
Death, n (%)	7 (13)	3 (5)	0.32
Nonfatal MI, n (%)	2 (4)	2 (4)	>0.99
Death or nonfatal MI, n (%)	9 (16)	5 (9)	0.40
TVR, n (%)	1 (2)	0 (0)	>0.99
Any event, n (%)	10 (18)	5 (9)	0.27
Stent thrombosis, n (%)†	0 (0)	0 (0)	
Elective population	(n = 43)	(n = 43)	
Death, n (%)	2 (5)	0 (0)	0.49
Nonfatal MI, n (%)	2 (5)	2 (5)	>0.99
Death or nonfatal MI, n (%)	4 (9)	2 (5)	0.68
TVR, n (%)	1 (2)	0 (0)	>0.99
Any event, n (%)	5 (12)	2 (5)	0.44
Stent thrombosis, n (%)†	0 (0)	0 (0)	>0.99
Long-term outcome			
Whole population	(n = 55)	(n = 55)	
Death, n (%)	6 (11)	7 (13)	0.70
Nonfatal MI, n (%)	2 (4)	4 (7)	0.25
Death or nonfatal MI, n (%)	9 (16)	10 (18)	0.90
TVR, n (%)	5 (9)	6 (11)	0.67
Any event, n (%)	14 (25)	16 (29)	0.74
Stent thrombosis, n (%)†	0 (0)	0 (0)	>0.99
Elective population	(n = 43)	(n = 43)	
Death, n (%)	2 (5)	2 (5)	0.98
Nonfatal MI, n (%)	2 (5)	4 (9)	0.22
Death or nonfatal MI, n (%)	4 (9)	6 (14)	0.51
TVR, n (%)	5 (12)	5 (12)	0.82
Any event, n (%)	9 (21)	11 (25)	0.55
Stent thrombosis, n (%)†	0 (0)	0 (0)	>0.99

*By Fischer exact test for 30-day outcome and by log rank test for long-term outcome.
†Angiographically documented.
MI = myocardial infarction; TVR = target vessel revascularization; other abbreviations as in Table 1.

revascularization was achieved in 27 (49%) patients in the SES and 36 (65%) in the PES group (p = 0.17).

Overall procedural success was 98%. In one patient receiving SES, presenting with acute MI and shock, a final TIMI flow grade 1 was obtained. An abrupt irreversible occlusion of the circumflex occurred in one PES patient after deployment of a stent in the left main and proximal left anterior descending coronary artery (LAD).

Thirty-day outcomes. There were no significant differences between the SES and PES groups in the incidence of major adverse cardiac events (MACE) (death, target vessel revascularization, or myocardial infarction [MI]) during the first 30 days (Table 3). Eight deaths occurred in 10 patients presenting with ST-segment elevation acute myocardial infarction and cardiogenic shock at entry. One elective patient, undergoing LM treatment under left ventricular assist device due to end-stage heart disease, died 2 days after for cardiogenic shock, while the second elective patients died for non-cardiovascular reasons after 19 days. No documented thrombotic stent occlusion occurred in the first 30 days or thereafter.

Long-term clinical outcome. After a median follow-up of 660 days (range 428 to 885 days), the cumulative incidence

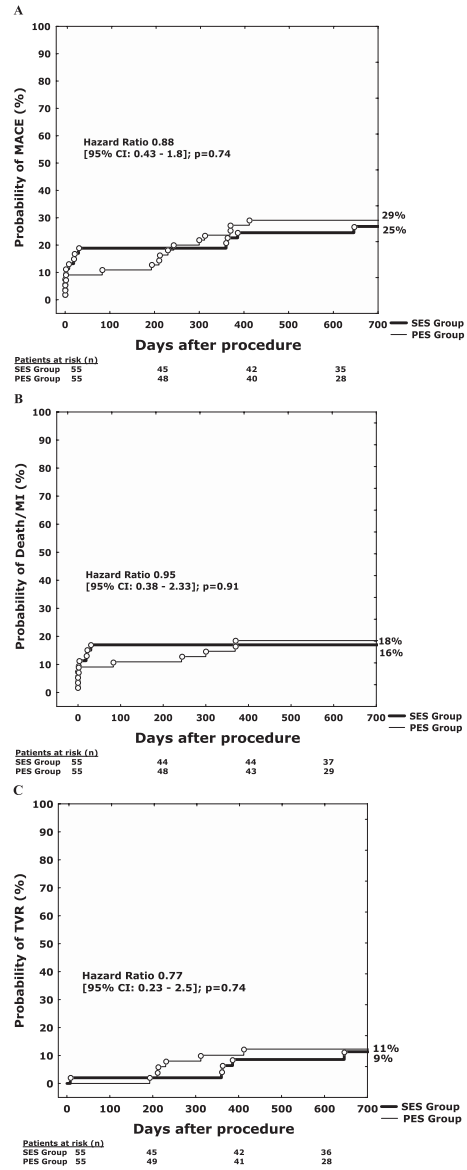

Figure 1. Adverse events in patients treated with sirolimus-eluting stent (SES group) and in patients treated exclusively with paclitaxel-eluting stent implantation (PES group). **(A)** Cumulative risk of major adverse events (MACE); **(B)** death or myocardial infarction (MI); and **(C)** target vessel revascularization (TVR). CI = confidence interval.

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of MACE did not significantly differ in the SES compared to the PES patients (25% vs. 29%, respectively; hazard ratio [HR] 0.88 [95% confidence interval (CI): 0.43 to 1.82]; p = 0.74) (Fig. 1A). The composite death/MI was 16% in the SES and 18% in the PES group (HR 0.95 [95% CI: 0.38 to 2.33]; p = 0.90) (Fig. 1B), and cumulative incidence of TVR was 9% in the SES and 11% in the PES group (HR 0.77 [95% CI: 0.23 to 2.56]; p = 0.66) (Fig. 1C).

In the elective patient population (43 patients in each group), the cumulative incidence of MACE was similar in the SES (21%) and PES groups (25%; HR 0.77 [95% CI 0.32 to 1.8]; p = 0.55). The composite of death/MI was 9% in the SES and 14% in the PES group (HR 0.66 [95% CI 0.19 to 2.3]; p = 0.52), and the need for TVR was 12% in both groups (HR 0.87 [95% CI 0.24 to 3]; p = 0.8).

The cumulative incidence of MACE was similar in patients receiving single-vessel stenting (24% in the SES and 27% in the PES group) and those treated with bifurcation stenting (31%, HR 1.38 [95% CI 0.47 to 4]; p = 0.55; and 33%, HR 1.22 [95% CI 0.45 to 3.3]; p = 0.69; respectively.

After adjustment for nominal stent diameter and total stent length at multivariable Cox regression analysis, SES implantation as opposed to PES failed to emerge as an independent predictor of MACE (HR 0.79 [95% CI 0.5 to 1.5]; p = 0.66). The same remained true after forcing the Parsonnet score into the model.

Angiographic outcome. Thirty-five patients in the SES (73% of eligible patients) and 38 patients in the PES group (77% of those eligible) underwent angiographic follow-up. Data regarding the quantitative coronary angiography for main and side branches are presented in Tables 4 and 5, respectively.

MAIN BRANCH. In the SES and PES groups, the main treated branch circumflex was LM-LAD in 22 (63%) and 21 (55%) patients, respectively followed by LM-circumflex in 6 (17%) and 8 (21%), LM alone in 5 (14%) and 6 (16%), and LM-intermediate branch in 2 (6%) and 3 (8%), respectively. In unprotected patients in the SES and PES groups, LM-LAD was the main treated branch in 77% and in 63%, respectively, followed by LM alone in 15% and 17%, LM-circumflex in 8% and 14%, and LM-intermediate branch in 0% and 6%, respectively.

Baseline and follow-up angiographic variables did not differ in the two study groups. No difference was noted in terms of BR in the two groups as the result of a similar in-stent and in-lesion LL (Table 4).

SIDE BRANCH. All baseline angiographic variables were well matched between SES and PES groups in the side branches receiving stent. At follow-up, both LL and BR were similar in the two study groups. For those side branches that did not undergo stenting as part of LM treatment, despite a bigger reference vessel diameter in the SES than in the PES group, the pattern of LL was around zero in both groups (Table 5).

Table 4. Quantitative Coronary Angiography Analysis of the Main Branch

Variables	SES Group (n = 35)	PES Group (n = 38)	p Value
Before procedure			
RVD (mm)	3.20 ± 0.57	3.2 ± 0.73	0.82
MLD (mm)	1.26 ± 0.74	1.38 ± 0.49	0.62
Diameter stenosis (%)	60 ± 24	59 ± 16	0.85
Lesion length (mm)	9.5 ± 3.34	10 ± 4.44	0.56
After procedure			
In-stent			
RVD (mm)	3.10 ± 0.5	3.2 ± 0.6	0.43
MLD (mm)	2.76 ± 0.5	2.81 ± 0.5	0.32
Acute luminal gain (mm)*	1.50 ± 0.78	1.43 ± 0.75	0.66
Diameter stenosis (%)	10.7 ± 10	10.8 ± 9	0.97
In-lesion			
RVD (mm)	2.86 ± 0.6	2.77 ± 0.66	0.54
MLD (mm)	2.47 ± 0.54	2.46 ± 0.58	0.61
Acute luminal gain (mm)*	1.21 ± 0.84	1.10 ± 0.83	0.54
Diameter stenosis (%)	13 ± 10	11 ± 9	0.45
Follow-up			
In-stent			
RVD (mm)	3.19 ± 0.6	3.01 ± 0.6	0.31
MLD (mm)	2.44 ± 0.85	2.35 ± 0.6	0.60
Diameter stenosis (%)	21.3 ± 25	22.8 ± 19	0.76
Late loss (mm)†	0.32 ± 74	0.46 ± 0.57	0.36
Binary restenosis, n (%)‡	3 (9)	5 (13)	0.71
Reocclusion, n (%)§	2 (6)	0 (0)	0.24
In-lesion			
RVD (mm)	3.00 ± 0.66	2.89 ± 0.66	0.41
MLD (mm)	2.24 ± 0.83	2.2 ± 0.63	0.77
Diameter stenosis (%)	22 ± 24	22 ± 19	0.97
Late loss (mm)†	0.22 ± 0.73	0.25 ± 0.46	0.86
Binary restenosis, n (%)‡	3 (9)	4 (11)	>0.99
Reocclusion, n (%)	2 (6)	0 (0)	1

*Difference between MLD after procedure and MLD before procedure. †Difference between MLD at follow-up and MLD after procedure. ‡All non-occlusive restenosis were focal (length <10mm). §All two restenotic reocclusions occurred in protected LM lesions.

MLD = minimal lumen diameter; PES = paclitaxel-eluting stent; RVD = reference vessel diameter; SES = sirolimus-eluting stent.

COMBINED ANALYSIS. When both main and side branches were evaluated on a patient basis, in-lesion BR occurred in 7 (20%) and 12 (32%) patients in the SES and PES groups, respectively (p = 0.44). All cases of nonocclusive restenosis were focal (length <10 mm).

IVUS analysis. Overall, 46 patients (18 in the SES and 28 in the PES group) underwent IVUS investigation at follow-up. Their baseline and procedural characteristics did not differ from those receiving angiographic examination without IVUS (data not shown). In 11 patients in the SES and 16 in the PES group, LM-LAD was evaluated; the study vessel was LM-CX in 4 SES and 7 PES and LM alone in 3 SES and 5 PES patients. In two patients per group, stent malapposition was noted. As shown in Table 6 the degree of neointimal hyperplasia did not differ between the two study groups.

DISCUSSION

Since their introduction to the market, DES use has steadily increased. Depending on the health care system, they are

Table 5. Quantitative Coronary Angiography Analysis in the Side Branches

	Stented Branches			Nonstented Branches		
Variables	**SES Group**	**PES Group**	**p Value**	**SES Group**	**PES Group**	**p Value**
Before procedure	n = 12	n = 15		n = 21	n = 23	
RVD (mm)	2.63 ± 0.67	2.70 ± 0.61	0.69	2.44 ± 0.72	2.00 ± 0.55	0.02
MLD (mm)	1.16 ± 0.52	1.27 ± 0.77	0.69	1.68 ± 72	1.47 ± 0.67	0.31
Diameter stenosis (%)	56 ± 21	54 ± 24	0.61	27 ± 28	26 ± 25	0.96
Lesion length (mm)	10 ± 4	11 ± 8	0.76	5.7 ± 3	4.9 ± 2.1	0.30
After procedure						
RVD (mm)	2.73 ± 0.79	2.85.0 ± 0.57	0.65	2.26 ± 0.7	2.00 ± 0.6	0.12
MLD in-stent (mm)	1.95 ± 0.43	2.32 ± 0.45	0.041	—	—	
MLD in-lesion (mm)	1.9 ± 0.38	2 ± 0.55	0.46	1.7 ± 0.58	1.48 ± 0.69	0.27
ALG in-stent (mm)	0.79 ± 0.57	1 ± 0.6	0.62	—	—	
ALG in-lesion (mm)	0.72 ± 0.55	0.75 ± 0.76	0.89	0.01 ± 0.66	0.009 ± 0.5	0.97
Diameter stenosis (%)	25 ± 18	18 ± 11	0.17	23 ± 25	20 ± 23	0.66
Follow-up						
RVD (mm)	2.70 ± 0.54	2.56 ± 0.60	0.40	2.30 ± 0.69	2.00 ± 0.55	0.20
MLD in-stent (mm)	1.6 ± 0.45	1.8 ± 0.49	0.35	—	—	
MLD in-lesion (mm)	1.54 ± 0.58	1.62 ± 0.65	0.73	1.83 ± 0.63	1.40 ± 0.77	0.059
Diameter stenosis (%)	39 ± 23	29 ± 25	0.24	21 ± 14	33 ± 32	0.13
LL in-stent (mm)	0.36 ± 0.59	0.52 ± 0.42	0.41	—	—	
LL in-lesion (mm)	0.33 ± 0.42	0.39 ± 0.62	0.78	0.13 ± 0.44	0.07 ± 0.62	0.23
BR in-stent, n (%)*	3 (25)	3 (20)	>0.99	—	—	
BR in-lesion, n (%)*	3 (25)	2 (13)	0.63	1 (5)	6 (26)	0.10
Reocclusion, n (%)	2 (6)	0 (0)	0.24	0 (0)	2 (9)	0.49

*All non-occlusive restenosis were focal (length <10 mm).
ALG = acute luminal gain; BR = binary restenosis; LL = late loss; other abbreviations as in Table 4.

now partially or almost completely replacing bare-metal stents (BMS) during coronary intervention.

Recently, some concerns for the consequences of using these devices liberally have been raised, which emphasizes the need to scrutinize those patient/lesion subsets that were excluded from landmark randomized trials, particularly beyond conventional eight to nine months' follow-up (14–17). Yet in both controlled and observational studies, a potential differential efficacy and safety profile between SES and PES has been observed, especially in patient populations considered to be at higher risk for adverse events. Thus, current available evidence reinforces the idea that it would be improper to attribute a class effect to DES and that a high-risk patient population should be better evaluated to further compare the safety/efficacy profile of these two stents.

The percutaneous management of LM lesions is a challenging intervention, where bifurcated vessels, extensive wall calcification, and poor hemodynamic tolerance often coexist during treatment as natural extensions of the anatomic characteristics of the lesions (18,19). Moreover, percutaneous LM intervention, being usually reserved to poor surgical candidates, is often undertaken in patients with low ejection fraction or renal dysfunction, which are known predictors of adverse events even in patients receiving DES (16).

Table 6. Quantitative Intravascular Ultrasound (IVUS) Results

IVUS Variables	SES Group n = 18	PES Group n = 28	p Value
IVUS volumes (mm^3)			
Luminal	237 ± 183	250 ± 167	0.80
Vessel	473 ± 371	528 ± 351	0.63
Stent	256 ± 194	267 ± 174	0.81
Intimal hyperplasia	19.3 ± 26	28 ± 60	0.44
Intimal hyperplasia/10 mm*	6.3 ± 9	9.6 ± 13	0.74
Percentage intimal hyperplasia (%)	7.5 ± 8	10 ± 14	0.68

*Calculated as intimal hyperplasia volume divided by the length of the region of interest expressed in mm (24 ± 19 in the SES and 29 ± 19 in the PES group; p = 0.49), multiplied by 10.
PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent.

The main results of our analysis show that, as predicted by the risk status of the patients, the overall event rate was higher than that previously reported for non-LM lesions. However, the safety/efficacy profile of the two DES evaluated was apparently maintained at long-term follow-up, with PES performing closely to SES in terms of both clinical and angiographic outcome.

This statement is based on the following findings:

1. The great majority of events occurred in both groups within one year, considering either the whole (86% in the SES and 81% in the PES) or the elective population (78% in the SES and 73% in the PES group). No early or late angiographically confirmed stent thrombosis has been observed, with only one sudden death occurring in an 86-year-old woman affected by a hematological malignancy seven months after the index procedure.
2. The short- and long-term clinical event rate in the two study groups was not different, and at multivariable analysis the stent implanted failed to emerge as an independent predictor of adverse events.
3. Angiographic and IVUS investigation demonstrated that late loss and neointimal hyperplasia volume were similar in the two groups of patients. The angiographic

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outcome of the nonstented side branches was also remarkably similar between the two groups.

Among these observations, the last one was unexpected and deserves special attention.

In all major randomized controlled trials evaluating the benefit of SES versus BMS, the average in-stent LL for SES was reported to be constantly equal to or below 0.20, whereas the same figure for PES, based on PES versus BMS studies, was around two times higher. The Prospective, Randomized, Multi-Center, Comparison of the Cypher Sirolimus-Eluting and the Taxus Paclitaxel-Eluting Stent Systems (REALITY) study showed a difference between these two DES in terms of angiographic end points that was even bigger, with a mean in-stent LL of 0.9 in SES and 0.31 in the PES group (5). Conversely, in the current investigation we failed to show any difference between the two stents in terms of in-stent or in-segment LL or BR, either in the main branch or in the stented side branches. Interestingly, this was confirmed by the IVUS analysis. Although the difference was more striking for SES, the LL in both groups were actually much higher than the figures expected. The explanation for this discrepancy can only be speculative for the moment and it may suggest that angiographic response to DES is lesion/patient-specific. Data so far available in the literature are inconclusive in this regard. Park et al. (2) recently reported an average late loss of 0.05 mm in 102 patients receiving SES for the treatment of unprotected left main disease, whereas the same figure in 85 LM patients at higher risk status, treated with either PES or SES, was cumulatively reported to be 0.58 mm (3). Unfortunately, in that study no distinction between SES and PES was made (3).

The lack of availability of SES sizes bigger than 3.0 mm during the study period, which imposed an aggressive overdilation strategy to match LM reference diameter, might have theoretically played a role. However, this technical issue was at least partially encountered in the series reported by Park et al. (2) as well.

Alternatively, this difference between studies could possibly reflect a selection bias, with patients at higher clinical risk based on previous cardiovascular history and comorbidities being more prone to develop a more aggressive intimal proliferation after DES. To investigate this possibility in an exploratory fashion (this analysis was not prespecified for the current study), we pooled the LL for both main branch and all stented side branches as the outcome variable in a linear regression model. At univariate analysis including all variables reported in Tables 1 and 2 we found protected status to be the strongest predictor for high LL ($\beta = 0.47$ [95% CI 0.24 to 0.7]; $p = 0.001$; adjusted $R^2 = 0.39$). Accordingly, we observed that in patients receiving unprotected LM intervention (n = 59) LL was cumulatively lower (0.31 ± 0.41 vs. 0.63 ± 72; $p = 0.037$) than in patients receiving protected treatment (n = 14), and, of note, all occlusive binary restenosis occurred in the protected group of patients.

Interestingly, none of the variables reported in Tables 1 and 2 differed significantly between patients receiving protected versus unprotected LM intervention, with the overall Parsonnet score being 16 ± 7.5 in protected versus 18 ± 10 in unprotected patients ($p = 0.4$).

The observed difference in LL between protected versus unprotected LM intervention might possibly outline a role for shear stress as potential modulator of vessel response to DES, as recently suggested by our group (20). This analysis was exploratory in nature and clearly beyond the scope of the current investigation. However, it underscores the need to consider DES performance in the context of the patient population in which the device was actually tested.

Taken together, our observations suggest that DES may perform more effectively in good than in poor surgical candidates, which reinforces the interest in assessing the value of this treatment as compared with conventional surgical approach in a properly designed randomized trial.

Study limitations. The present study is a single-center experience from a tertiary referral center and lacks the clear advantages of a multicenter randomized study. In particular, despite the fact that the study was conducted over a relatively short period, we cannot exclude the possibility that improvements in technique or differences in drug prescription could have partially confounded our main results.

Accordingly, the results of our study are encouraging, but they cannot be conclusive. Studies with bigger sample sizes and more prolonged clinical follow-ups are clearly required to rule out the occurrence of less common device-related side effects.

Clinical implications of the combined RESEARCH and T-SEARCH analysis. In the overall results of the unselected RESEARCH versus T-SEARCH comparison, a shift toward more complex lesions has been noted from SES to PES cohort (8). This difference was not confirmed in our current analysis, which focused on LM lesions cumulatively treated over a longer period of time: more patients in the SES group received concomitant intervention in non-LM lesions and fewer reached complete revascularization than in the PES cohort. However, the stent length was greater in the PES group. When this finding is combined with the observed shift from T-stenting in the SES period to culotte in the PES period as bifurcation technique, it may suggest that operators have become progressively more familiar with DES over time and that full lesion coverage with DES had been more frequently performed in the PES than in the SES group. The impact of these confounders on our final result remains incompletely understood.

When taken together, the combined RESEARCH and T-SEARCH analysis may reinforce the concept that in an uncontrolled setting such as our clinical practice, the coronary device in itself should probably be regarded among the principal but clearly not as the only component of the long-term procedural success in the DES era. Rather, the two

drug-eluting stents available on the market should always be put in the context of the characteristics of the treated patients and the operator's experience to better forecast their effect on short- and long-term outcome.

Conclusions. After a median follow-up of two years, no late serious adverse events, possibly suggesting a time-dependent change in the therapeutic profile of the investigated devices, were observed.

In a consecutive group of patients undergoing percutaneous LM intervention, PES may perform closely to SES in terms of both clinical and angiographic outcome.

A multinational multicenter randomized study is currently ongoing to estimate the clinical value of PES-supported LM intervention with respect to conventional surgical treatment.

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Chapter 12

Significant reduction in restenosis after the use of sirolimus-eluting stents in the treatment of chronic total occlusions

Hoye A, Tanabe K, Lemos PA, Aoki J, Saia F, Arampatzis C, Degertekin M, Hofma SH, Sianos G, McFadden E, van der Giessen WJ, Smits PC, de Feyter PJ, van Domburg RT, Serruys PW.

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

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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. (J Am Coll Cardiol 2004;43:1954–8) © 2004 by the American College of Cardiology Foundation

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).

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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

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Abbreviations and Acronyms

BMS	= bare metal stent
CTO	= chronic total occlusion
MACE	= major adverse cardiac events
PCI	= percutaneous coronary intervention
RESEARCH	= Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital registry
SES	= sirolimus-eluting stent
TVR	= target vessel revascularization

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 Tables 1 and 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.

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).

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

Table 1. Baseline Patient Demographics

	Bare Stents n = 28	SES n = 56	p Value
Mean age (yrs)	59.8 ± 11.1	60.2 ± 10.0	0.9
Male gender (%)	85.7	71.4	0.2
Current smoker (%)	35.7	26.8	0.5
Diabetes mellitus (%)	7.1	14.3	0.4
Hypertension (%)	39.3	39.3	1.0
Hypercholesterolemia (%)	57.1	55.4	1.0
Previous myocardial infarction (%)	46.4	55.4	0.6
Previous PCI (%)	21.4	12.5	0.3
Previous CABG (%)	0	0	–
Glycoprotein IIb/IIIa inhibitor usage (%)	25.0	21.4	1.0
Presence of multivessel disease (%)	60.7	46.3	0.3
PCI in at least one additional (nonoccluded) major epicardial vessel during the index procedure (%)	28.6	42.6	0.2

CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention; SES = sirolimus-eluting stents.

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Table 2. Baseline Procedural Characteristics

	Bare Stents n = 29	SES 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
Postprocedure vessel 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; QCA = quantitative coronary angiography; RCA = right coronary artery; SES = sirolimus-eluting stents.

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.

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

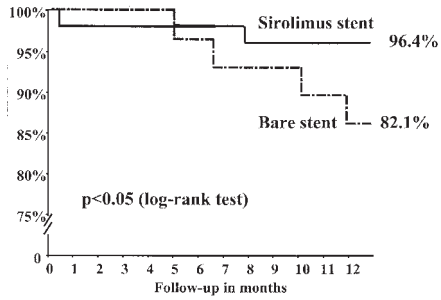

Figure 1. Kaplan-Meier curves for survival-free of death, acute myocardial infarction, or target vessel revascularization.

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

Table 3. Postprocedural and Six-Month Follow-Up Quantitive Angiographic Data for the Sirolimus-Eluting Stent (Patient Number n = 33)

	Proximal 5 mm	In-Stent	Distal 5 mm
Postprocedure			
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
Six-month follow-up			
Mean 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

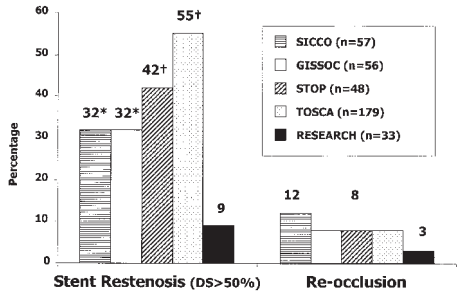

Figure 2. The percentage binary restenosis rate (>50% diameter stenosis) and reocclusion rate of Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital registry (RESEARCH) compared with published data from the patients treated with stent implantation in the randomized trials Stenting in Chronic 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). DS = diameter stenosis. *$p < 0.05$ compared with the results of RESEARCH; †$p < 0.01$ compared with the results of RESEARCH.

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.

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Chapter 13

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

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Clinical research

EuroIntervention

Drug-eluting stent implantation for chronic total occlusions: comparison between the Sirolimus- and Paclitaxel-eluting stent

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KEYWORDS
Occlusion, stents, restenosis

Abstract

Aims: 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.

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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, additional 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 predefined 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 having been treated with drug-eluting

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

SES: sirolimus-eluting stents, PES: paclitaxel-eluting stents, LAD: left anterior descending artery, LCX: circumflex artery, RCA: right coronary artery

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 854 IU/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.

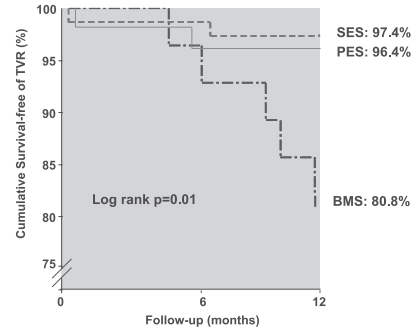

Figure 1. Kaplan-Meier estimates of the cumulative survival-free of target vessel revascularization following stent implantation in a chronic total occlusion for patients treated with sirolimus-eluting (SES), paclitaxel-eluting (PES), or bare metal stent (BMS) implantation.

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.

Discussion

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 6 months.

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 utilised.

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Chapter 14

Restenosis rates following bifurcation stenting with sirolimus-eluting stents for de novo narrowings

Tanabe K, Hoye A, Lemos PA, Aoki J, Arampatzis CA, Saia F, Lee CH, Degertekin M, Hofma SH, Sianos G, McFadden E, Smits PC, van der Giessen WJ, de Feyter P, van Domburg RT, Serruys PW.

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

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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. © **2004 by Excerpta Medica, Inc.**

(Am J Cardiol 2004;91:115–118)

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 revascu-

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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).

larization. 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 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
Postprocedure	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
Postprocedure		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.

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.

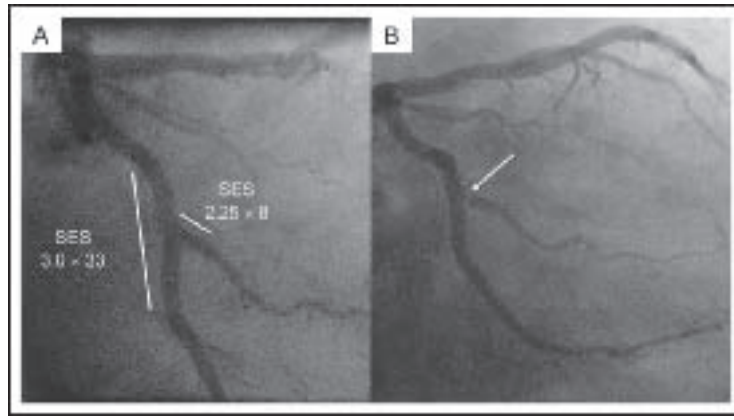

FIGURE 1. A 3.0 × 33 mm SES was implanted in the circumflex artery, and a 2.25 × 8 mm SES was implanted in the side branch (obtuse marginal) with T-stenting technique *(A)*. At 6-month angiographic follow-up, restenosis occurred at the ostium of the side branch *(arrowhead) (B)*.

• • •

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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Treatment of de novo bifurcation lesions: comparison of Sirolimus- and Paclitaxel-eluting stents

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KEYWORDS
Drug eluting stent, bifurcation lesions, Sirolimus, Paclitaxel.

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 6 months was obtained in 99% patients with survival-free of major adverse cardiac events (MACE) of 93.7% for SES versus 85.8% for PES, p=0.05. By multivariate analysis, factors predictive for MACE were age, diabetes mellitus, previous CABG, multivessel disease, treatment for acute myocardial infarction, and treatment with PES. Survival-free of target lesion revascularization (TLR) was 95.7% for SES versus 86.8% for PES, p=0.01, 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.

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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[2,3,4,5,6]. 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).

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 2.25 mm to 3.00 mm and lengths from 8 mm to 33 mm. PESs were available in diameters from 2.25 mm to 3.5 mm 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 300 mg clopidogrel, and received life-long aspirin together with 75 mg 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

FIGURE 1.

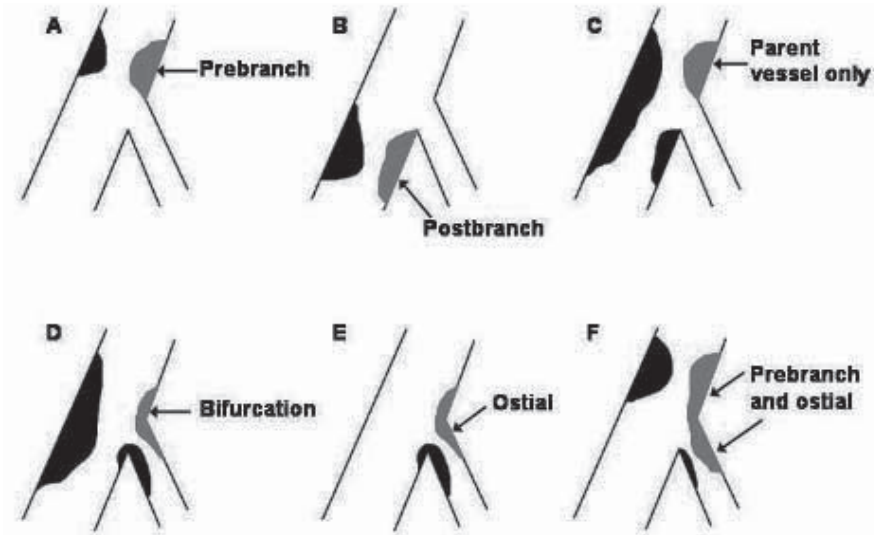

Fig. 1: The Duke classification of bifurcation lesions.

European Community and the Declaration of Helsinki. All patients signed a written informed consent

Follow-up: Clinical follow-up was obtained using telephone calls and questionnaires, and 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. All tests were two-tailed, and a p value of <0.05 was considered as significant. Logistic regression models were established to investigate independent predictors of MACE (death, AMI, or TVR), and target lesion revascularization. Variables entered were age, gender, diabetes mellitus, hypertension, hypercholesterolemia, smoking, multivessel disease, prior AMI, prior CABG, clinical presentation, use of a glycoprotein IIb/IIIa inhibitor, target vessel, bifurcation anatomy, stent type, stenting technique, diameter of stent, total length of stents, and use of kissing balloon post-dilatation. Odds ratio with corresponding 95% confidence intervals are reported.

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. Angiographically documented stent thrombosis occurred in 2 patients treated with SES (1.4%) and 3 patients treated with PES (2.9%), p=0.4 (Table 3). All episodes of stent thrombosis were subacute (within 30 days following stent implantation), and were treated percutaneously, all patients survived. The cumulative incidence of major adverse cardiac events at 6-months for the SES and PES groups are presented in Table 4, and the survival-free of MACE at 6-months is illustrated in figure 3. The independent predictors for MACE and TLR by multivariate analysis 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 6-months, survival-free of TLR was 95.7% for SES versus 86.8% for PES, p=0.01 (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%).

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 age, diabetes mellitus, multivessel disease, previous CABG, treatment in the setting of acute myocardial infarction, and therapy with PES. Target lesion revascularization (TLR) at 6-months was higher in the PES group than the SES group, with a survival-free of TLR of 86.8% versus 95.7% respectively, p=0.01. By multivariate analysis, the use of PES was the only factor predictive for 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 pre-

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

SES: Sirolimus-eluting stents, PES: Paclitaxel-eluting stents, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention.

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.

FIGURE 2.

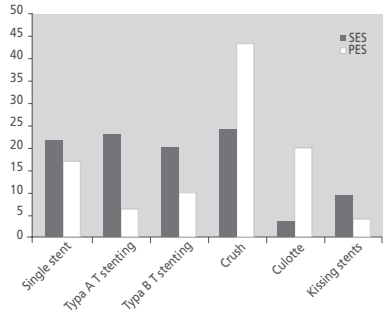

Fig. 2: The type of stenting strategy employed for the Sirolimus-eluting (SES) and Paclitaxel-eluting stent (PES).

FIGURE 3.

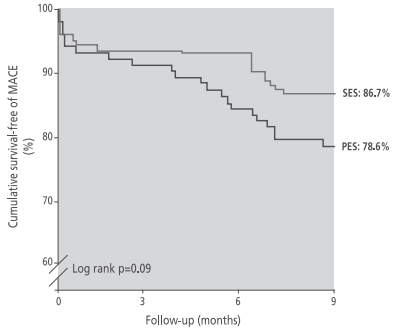

Fig. 3: Kaplan-Meier curves for survival-free of major adverse cardiac events (MACE) for the Sirolimus-eluting (SES) and Paclitaxel-eluting stent (PES).

FIGURE 4.

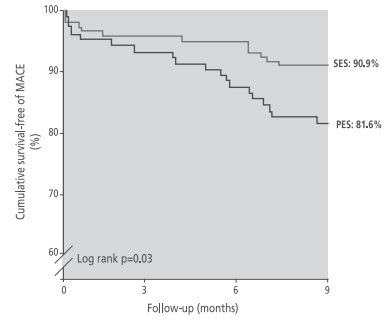

Fig. 4: Kaplan-Meier curves for survival-free of target lesion revascularization (TLR) for the Sirolimus-eluting (SES) and Paclitaxel-eluting stent (PES).

Table 4. Cumulative incidence of major adverse cardiac events at 6-months for the Sirolimus- and Paclitaxel-eluting stents

	SES n=144	PES n=104	p value (log rank)
Death (%)	1.4	3.2	0.4
Death or AMI (%)	4.9	7.1	0.5
Death, AMI, or TLR (%)	6.3	13.2	0.08
Death, AMI, or TVR (%)	6.3	14.2	0.05

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 6 months

	Odds ratio	95% confidence intervals
MACE		
Age	1.02	1.01 to 1.05
Prior CABG	2.75	1.1 to 7.2
Diabetes mellitus	2.15	1.2 to 4.0
Multivessel disease	1.36	1.0 to 1.9
Presentation with acute myocardial infarction	2.35	1.1 to 5.0
Therapy with Sirolimus-eluting stent	0.71	0.4 to 1.0
TLR		
Therapy with Sirolimus-eluting stent	0.45	0.19 to 0.95

MACE: major adverse cardiac event; CABG: coronory artery bypass graft surgery; TLR: target lesion revascularization

Table 3. Demographic of the 5 patients angiographically documented stent thrombosis

Age, sex	Stent type	Target vessel	Time to thrombosis, days	Diabetes mellitus	Use of GP IIb/IIIa inhibitor	Clinical presentation at index	Stenting strategy	Kissing balloon post-dilatation
74yr F	SES	LAD	1	N	N	SA	Crush	Y
57yr M	SES	LAD	18	Y	Y	AMI	Type B "T"	N
66yr M	PES	LCx	7	N	N	UA	Crush	N
46yr F	PES	LAD	6	N	N	AMI	Crush	N
51yr F	PES	LCx	4	N	Y	AMI	Type B "T"	Y

SES: Sirolimus-eluting stent; PES: Paclitaxel-eluting stent; LAD: left anterior descending; LCx: left circumflex; SA: stable angina; AMI: acute myocardial infarction; UA: unstable angina.

dictor for either MACE or the need for TLR. The current study is limited by the lack of angiographic follow up, so cannot fully evaluate restenosis which, particularly when occurring in the side branch, may be clinically silent.

Currently, there is only one published randomized evaluation of drug-eluting stents for bifurcation lesions[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 demonstrate an improvement in the restenosis rates compared with historical data of bare metal stenting.

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%[2,3,4,5,6]. 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, multivariate 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]. 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). The same authors[15] examined stent implantation in the pig model and found that more tissue prolapse occurred following implantation of a stent with an open cell design. 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]. In the same randomized studies, evaluation of the drug-eluting stent cohorts showed a mean in-stent late loss of 0.17 ± 0.45mm in SIRIUS, and 0.39 ± 0.50mm in TAXUS-IV, perhaps suggesting the SES is more efficacious at inhibiting the development of neointimal hyperplasia than the PES.

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 1300 patients with multivessel disease, randomized to either SES or PES implantation. Initial results were recently presented at the American College of Cardiology meeting in 2005[19]. There was no significant difference with respect to the overall rates of MACE between the stent types (9.2% for SES versus 10.6% for PES, p=0.41). However, in keeping with the difference in the degree of platelet activation related to stent design[15], the rate of stent thrombosis was higher for the PES group (1.8% versus 0.4%, p=0.0196). Furthermore, all angiographic parameters with respect to efficacy of suppression of neointimal growth were better following SES implantation. The in-stent late loss was 0.09 ± 0.43mm for the SES, versus 0.31 ± 0.44mm for the PES, p<0.001. Such a difference may potentially be clinically relevant when treating complex lesions such as bifurcations, particularly when vessels with a small diameter are stented. Patients with bifurcation lesions were not excluded from this study, and a more detailed analysis of subgroups such as those treated for a bifurcation lesion is awaited.

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 low rates of major adverse cardiac events at 6-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 with drug-eluting stents remains unclear.

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Part 3
Endothelial progenitor cell – alternative to drug-eluting stents

Chapter 16

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

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Thirty-Day Incidence and Six-Month Clinical Outcome of Thrombotic Stent Occlusion After Bare-Metal, Sirolimus, or Paclitaxel Stent Implantation

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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. (J Am Coll Cardiol 2005;45:947–53) © 2005 by the American College of Cardiology Foundation

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).

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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 pre-

Abbreviations and Acronyms

AMI = acute myocardial infarction
BMS = bare-metal stents
CI = confidence interval
DES = drug-eluting stents
MI = myocardial infarction
OR = odds ratio
PES = paclitaxel-eluting stents
SES = sirolimus-eluting stents
ST = stent thrombosis
TIMI = Thrombolysis In Myocardial Infarction

scribed 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

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.

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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.

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.

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).

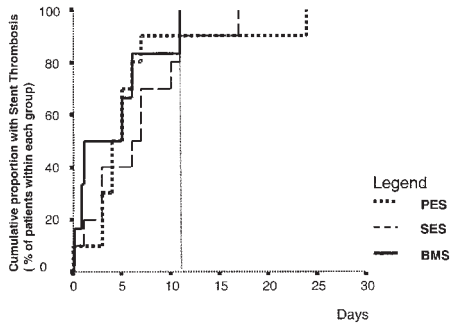

Figure 1. Cumulative incidence of angiographic stent thrombosis stratified by groups against time. **Vertical line** = day 11 on horizontal axis. BMS = bare-metal stents; PES = paclitaxel-eluting stents; SES = sirolimus-eluting stents.

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

Table 3. Detailed Description of Drug-Eluting Stent Patients With Angiographic 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**	**7**	**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-AMI	AP	AMI	UAP post-AMI
Glycoprotein IIb/IIIa 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 bifurcation stenting	–	–	–	–	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
Reintervention										
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.

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.

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

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.

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Table 3 Continued

11 PES 0.04	12 PES 4	13 PES 7	14 PES 6	15 PES 3	16 PES 4	17 PES 24	18 PES 5	19 PES 5	20 PES 3	Mean ± SD, % 6.3 ± 5.7
59	50	67	47	61	52	60	54	65	31	59.7 ± 11.9
M	M	M	F	M	F	M	M	M	M	13 M:7 F
–	–	–	–	+	–	–	–	–	–	30%
–	–	–	+	+	+	–	+	–	+	30%
–	–	+	–	+	–	+	–	+	–	45%
–	–	+	–	–	–	–	–	–	+	25%
AMI	AMI	AP	AMI	AP	AMI	AP	AMI	AP	AP	
–	–	–	Y	–	–	–	Y	Y	–	30%
RCA	LAD	OMCX	LAD/DIAG	LCx	LCx/OMCx	LCx	LAD/Diag	LAD/IM/LCx	LAD	
B2	B2	C	C	B2	C	C	C	C	B2	
–	–	crush	crush	–	t-stent	–	crush	culotte crush	–	40%
–	–	N	N	–	N	–	N	Y	–	
3	3.5	2.5	2.5	2.5	2.25	2.25	2.75	2.25	3	2.7 ± 0.3
28	24	32	36	20	44	32	36	140	84	41.2 ± 27.8
1	1	2	2	1	2	2	2	8	4	2.2 ± 1.5
AMI	AMI	AMI	AMI	AMI	UAP	UAP	AMI	AMI	AMI	AMI = 75%
–	–	Y	–	Y	–	Y	–	–	–	Yes = 35%
–	–	–	–	–	–	–	–	–	–	
–	–	SB	SB	–	SB	MB+SB	SB	MB+SB	–	
–	–	–	–	Y	–	–	–	–	–	10%
Y	Died	Y	Y	Y	Y	Y	Y	Died	Died	Death = 15%

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.

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

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§

*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.
Abbreviations as in Table 1.

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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.

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 17

How to Accelerate the Re-endothelialization of Stents

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Arch Mal Coeur Vaiss 2005; 98:123-126

How to accelerate the endothelialization of stents

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Summary

Coronary artery stenting is currently the most frequently performed percutaneous coronary intervention for the treatment of coronary artery disease. The endothelium is a single layer of endothelial cells lining the vascular wall and plays an integral part in maintaining vascular homeostasis. Stenting however causes significant injury to the vascular wall and endothelium, resulting in inflammation, repair and the development of neointimal hyperplasia. The ability of the endothelium to repair itself depends on both the migration of surrounding mature endothelial cells, and the attraction and adhesion of circulating endothelial progenitor cells (EPCs) to the injured region, which then differentiate into endothelial-like cells.

Current therapies with drug-eluting stents interrupt the natural response to damage. Accelerating the reendothelialization of the damaged arterial segment following stent implantation is an attractive form of therapy as it is seen as hastening the natural process of repair. It potentially has the benefit of reducing the amount of neointimal hyperplasia and stent thrombosis. Studies have been performed to identify agents that augment the mobilisation and recruitment of EPCs to the injured area (statins, exercise, estrogen and cytokines). Other studies have looked at seeding stents with endothelial cells or EPCs. The most current approach is to coat anti-CD34 antibodies on a stent surface to attract circulating EPCs to the stent which then differentiate into endothelial-like cells. This approach is currently being tested in safety and feasibility clinical studies. Arch Mal Cœur 2005 ; 98 : 123-6.

Résumé

L'insertion d'une endoprothèse coronaire est l'intervention percutanée effectuée le plus souvent pour le traitement de la maladie coronaire. L'intima consiste en une seule couche de cellules endothéliales tapissant la paroi vasculaire et jouant un rôle intégral dans la maintenance de l'homéostasie vasculaire. L'insertion d'un stent traumatise la paroi vasculaire et l'endothélium, et engendre une inflammation, une réparation et le développement d'une hyperplasie intimale. La capacité de l'endothélium à se réparer dépend de la migration des cellules endothéliales matures avoisinantes et aussi de l'attraction et de l'adhésion des cellules endothéliales procréatrices circulantes (EPCs) vers la région traumatisée, celles-ci prenant ensuite la forme de cellules endothéliales.

Les traitements actuels avec des stents actifs interrompent la réponse naturelle envers le traumatisme. L'accélération de l'endothélialisation des segments artériels endommagés après l'insertion d'une endoprothèse est une forme de thérapie attractive car elle semble promouvoir le processus naturel de réparation. Cela a l'avantage potentiel de réduire la réaction d'hyperplasie intimale et de thrombose du stent. Des études ont été faites pour identifier les facteurs susceptibles d'augmenter la mobilisation et le recrutement des PCEs vers la région endommagée (statines, exercice, estrogène et cytokines). D'autres études ont examiné l'intérêt des stents imbibés de cellules endothéliales ou de PCEs. L'approche actuelle la plus courante est d'enrober les stents d'anticorps anti-CD34 pour attirer les PCEs circulantes qui peuvent ensuite se différencier en cellules de type endothélial. Cette approche est en cours d'évaluation dans des études cliniques de sécurité et de faisabilité. Arch Mal Cœur 2005 ; 98 : 123-6.

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Coronary artery stenting has been definitively proven to be superior to balloon angioplasty in most types of coronary lesions and is currently the most frequently performed percutaneous coronary intervention for the treatment of coronary artery disease [1, 2]. The long-term success of coronary stenting is limited by the development of restenosis, caused by the development of an exuberant neointima in response to the vessel wall injury caused by the implantation of a

stent. The current generation of coronary stents, coated with antiproliferative agents, reduce restenosis by interrupting the vessel wall response to injury [3, 4], which may result in a delay in endothelialization. A potentially viable alternative for the reduction of neointimal hyperplasia is to limit the response to injury by accelerating the reendothelialization of stents and the associated vessel wall.

This review will describe the function of endothelial cells and the origin of endothelial-like cells from endothelial progenitor cells (EPCs), primitive cells originating from the bone marrow. Methods of augmenting the recruitment of EPCs and the mobilisation of these cells from their origin to the vessel wall are elucidated. Finally, experiments involving stent-based therapies are described.

BACKGROUND

Endothelial cells and abnormalities

The endothelium is a monolayer of endothelial cells lining the lumen of blood vessels. It functions as a protective biocompatible barrier between tissue and circulating blood. It serves as a selective sieve to facilitate the bi-directional passage of macromolecules and blood gases between tissues and blood. Vascular homeostasis is maintained through the balanced release of autocrine and paracrine substances from these cells.

Endothelial cell dysfunction disrupts this balance, predisposing the vessel wall to vasoconstriction, leukocyte adherence, platelet activation, mitogenesis, prooxidation, thrombosis, impaired coagulation, inflammation, atherosclerosis and neointimal formation [5, 6].

Vascular injury from stent implantation

Stent implantation results in substantial injury to the vessel wall. In particular, when stenting is accompanied by damage to the tunica media or penetration of the stent into a lipid core, increased arterial inflammation is induced which is associated with increased neointimal growth [7]. Chronic inflammation is augmented by the presence of a foreign body (stent) and arterial injury. Vascular smooth muscle cell (VSMC) migration, proliferation, and matrix protein production contributes to neointimal growth which occur as part of the healing process of the damaged arterial wall.

In-stent restenosis may be therefore viewed as an exaggerated response to the healing process. As a result, intense effort has been made to understand the mechanisms that govern VSMC proliferation and to develop therapies to inhibit excessive VSMC growth. The repair of the disrupted endothelium involves both the migration of surrounding mature endothelial cells into the injured area and the attraction of circulating immature cells called endothelial progenitor cells to the site, which then differentiate into endothelial-like cells (see below) [8].

Current therapies

Currently available drug eluting stents (DES) utilize agents such as rapamycin (a cytostatic immunomodulatory compound) and paclitaxel (a chemotherapeutic agent); both of which have been shown to reduce the incidence of restenosis after stenting [9, 10]. Following DES implantation, the fate of the endothelium is uncertain with evidence to suggest that paclitaxel and sirolimus delay reendothelialization [11, 12]. As such, prolonged antiplatelet therapy is currently recommended following the implantation of DES.

Alternative hypothesis

As an alternative hypothesis, some groups have suggested that neointimal hyperplasia is at least in part a result of delayed or belated reendothelialization [13]. Animal studies have repeatedly shown that extensive endothelial denudation of the arterial wall promotes neointimal thickening. The understanding that certain functions of the endothelium including barrier regulation of the permeability, thrombogeneticity, leukocyte adherence, and production of growth-inhibitory molecules are critical to the prevention of the development of neointimal growth [14].

Endothelial progenitor cells

EPCs belong to a family of progenitor cells, primitive bone marrow cells that have the capacity to proliferate, migrate and differentiate into various mature cell types. EPCs in particular, possess the ability to mature into endothelial-like cells [15]. The first evidence for the presence of EPCs in the adult circulation emerged when mononuclear blood cells from healthy human volunteers were shown to acquire an endothelial cell-like phenotype in vitro and to incorporate into capillaries in vivo [16]. These putative EPCs were characterized via their expression of CD34 and vascular endothelial growth factor receptor-2 (VEGFR-2). Subsequent studies confirmed that CD34+ cells isolated from bone marrow or umbilical cord blood also had the capacity to differentiate into mature endothelial-like cells [17, 18]. EPCs are considered to be part of the mononuclear- macrophage system and reside predominantly in the bone marrow and possibly in the spleen [19]. A small number (0.01%-0.3% of circulating mononuclear cells) are present in the peripheral circulation [20]. The lifetime of circulating EPCs in vivo under physiological or pathological conditions is unknown.

As described above, the intact endothelium plays a vital role in maintaining vascular equilibrium. Repair of damaged endothelium is therefore vital in restoring this equilibrium. Recently it has been shown that at sites of endothelial cell damage (carotid artery) the mobilization and incorporation of bone marrow derived EPCs modulates reendothelialization [21, 22]. Impaired mobilization or depletion of EPCs may contribute to endothelial dysfunction [23]. Patients with cardiovascular disease have been shown to have lower levels of circulating EPCs compared to healthy patients [23].

ACCELERATING THE ENDOTHELIALIZATION OF STENTS

Augmentation of EPC recruitment and mobilisation

In separate experiments, predominantly in animal models, attempts have been made to elucidate the mechanisms surrounding EPC recruitment and mobilization. In vivo insults such as limb ischaemia or coronary thrombosis, burn injury or coronary bypass surgery rapidly enhance the number of circulating EPCs [24-26]. The studies described below refer to additional attempts to augment the recruitment and mobilization of EPCs.

HMG-CoA reductase inhibitors or statins have been the most widely studied agent and have been shown in numerous studies to enhance EPC mobilization [27, 28] and to also improve endothelial function independent of cholesterol reduction [29]. Furthermore, statins have been shown to accelerate reendothelialization after vascular injury (through the increased expression of the main fibronectin receptor, integrina s5b1) [21, 22] and cause a dose-dependent significant reduction in neointimal thickening in a rat model [21].

In a mouse model, physical activity was shown to increase the production and circulating numbers of EPCs via a partially nitric oxide-dependent anti-apoptotic effect [30]. Within the same study, the authors demonstrated that in patients with stable coronary artery disease, moderate exercise training for 28 days led to a significant increase in circulating EPCs and reduced EPC apoptosis.

In another study, the same group showed that the intravenous infusion of autologous spleen derived mononuclear cells or in vitro cultured EPCs resulted in significantly enhanced reendothelialization associated with diminished neointimal formation following endothelial cell damage in the carotid artery of splenectomized mice [31].

They also showed that in a separate experiment, estrogen increased bone marrow derived EPC production by decreasing the apoptosis rate (mediated by the caspase-8 pathway), leading to decreased neointimal formation in injured carotid arteries in mice [32].

The use of cytokines to mobilize EPCs has been well studied in the ischaemia/infarction model. VEGF [33] and GM-CSF [34] have both been shown in animal models to accelerate reendothelialization and reduce vascular inflammatory processes after arterial wall injury.

Studies involving coronary stents

In animal studies in 1988 our group showed it was possible to seed stainless steel self-expandable stents with endothelial cells derived from human umbilical cord veins in vitro [35]. The stents were then implanted in porcine femoral arteries and when explanted at 1 week demonstrated complete covering of the stent struts by endothelium. More recently, others have reported the results of EPC seeded stents in an in-vitro study. After 7 days of culture, EPCs seeded on stents had migrated from the stent struts, proliferated and endothelialized both the luminal surface of hybrid vascular medial tissue and the stent struts [36].

Clinical trials

To date, no human trials have been published with regard to the use of endothelial cells or endothelial progenitor cells and stent implantation. A novel approach has been to seed anti-CD34 antibodies onto a stent surface (Genous, Orbus International B.V., The Netherlands). CD34 is a surface cell receptor found on circulating EPCs. In theory, upon stent implantation, peripherally circulating EPCs attach to the antibodies on the stent surface and then differentiate into mature endothelial-like cells, thus covering the stent surface. This has been successfully tested in animal models and as part of a single-centre "First-In-Man" trial entitled HEALING-1, our institution has successfully implanted these stents in 16 patients. Follow-up is still incomplete and results of this trial are still pending at the time of writing. HEALING-2, a European multicentre trial has been planned to follow.

CONCLUSION

In conclusion, methods to accelerate the endothelialization of stents might provide an attractive option for they attempt to accelerate a natural process, with the possibility of reducing both stent thrombosis and restenosis. To do so requires consideration of the various steps involved. First attempts at coating the stent with endothelial stents were shown to be possible, but required endothelial cells to be harvested and expanded ex-vivo. The discovery of circulating endothelial progenitor cells opened the door to new methods. Seeding the stents with EPCs also requires harvesting of these cells. In a parallel stream, researchers have identified separate mechanisms to accelerate endothelialization through the mobilization of EPCs in animal models (statin therapy, exercise, estrogen and cytokines). The latest, and possibly the most attractive attempt, has been to capture circulating EPCs from the peripheral blood by coating coronary stents with anti-CD34 antibodies. These antibodies will attract and bind circulating EPCs (which possess the surface cell receptor CD34), and result in the coverage of the stent with EPCs which then proliferate and differentiate into mature endothelial-like cells. Clinical trials are underway and the results are awaited.

KEY WORDS : stents, endothelium, endothelial progenitor cells, statins.

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Chapter 18

Endothelial Progenitor Cell Capture By Stents Coated With Antibody Against CD34-The HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man) Registry

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Endothelial Progenitor Cell Capture by Stents Coated With Antibody Against CD34

The HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man) Registry

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OBJECTIVES This study was designed to evaluate whether rapid endothelialization of stainless steel stents with a functional endothelium prevents stent thrombosis and reduces the restenotic process.

BACKGROUND A "pro-healing" approach for prevention of post-stenting restenosis is theoretically favored over the use of cytotoxic or cytostatic local pharmacologic therapies. It is believed that the central role of the vascular endothelium is to maintain quiescence of the underlying media and adventitia.

METHODS Sixteen patients with de novo coronary artery disease were successfully treated with implantation of endothelial progenitor cell (EPC) capture stents.

RESULTS Complete procedural and angiographic success was achieved in all 16 patients. The nine-month composite major adverse cardiac and cerebrovascular events (MACCE) rate was 6.3% as a result of a symptom-driven target vessel revascularization in a single patient. There were no other MACCE despite only one month of clopidogrel treatment. At six-month follow-up, mean angiographic late luminal loss was 0.63 ± 0.52 mm, and percent stent volume obstruction by intravascular ultrasound analysis was 27.2 ± 20.9%.

CONCLUSIONS This first human clinical investigation of this technology demonstrates that the EPC capture coronary stent is safe and feasible for the treatment of de novo coronary artery disease. Further developments in this technology are warranted to evaluate the efficacy of this device for the treatment of coronary artery disease. (J Am Coll Cardiol 2005;45:1574–9) © 2005 by the American College of Cardiology Foundation

The emergence of drug-eluting stents has dramatically reduced the incidence of in-stent restenosis (1,2). This therapy interferes with the natural healing response by preventing or significantly delaying the formation of a functional endothelial lining over the stent (3).

Recently, the existence of circulating endothelial progenitor cells (EPCs) has been identified as a key factor for re-endothelialization (4). The early establishment of a functional endothelial layer after vascular injury has been shown to assist in the prevention of neointimal proliferation and thrombus formation (5,6). The EPC capture stents have been developed using immobilized antibodies targeted at EPC surface antigens. The HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man) registry is the first clinical investigation using this technology.

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METHODS

Patient selection. The HEALING-FIM registry is a single-center, prospective, non-randomized registry trial. Patients were eligible if they were between ages 18 and 85 years and had a diagnosis of stable or unstable angina or silent ischemia. Additional eligibility criteria were the presence of a single primary target lesion in a native coronary artery that was 2.5 to 3.5 mm in diameter that could be covered by a single trial stent (13 mm or 18 mm length), a stenosis of 51% to 99% of the luminal diameter as estimated visually, and a flow rate of grade 1 or higher according to the classification of the Thrombolysis In Myocardial Infarction (TIMI) trial. Patients were not eligible for enrollment if they had an evolving myocardial infarction; stenosis of the left main coronary artery; a lesion located at an ostial location; a calcified lesion that could not be completely dilated before stenting; angiographically visible thrombus within the target lesion; a left ventricular ejection fraction of <30%; or an intolerance of aspirin, clopidogrel, ticlopidine, heparin, stainless steel, or contrast material. The trial was reviewed and approved by the ethics review committee, and written informed consent was obtained from all patients.

Study device: EPC capture stent. The EPC antibody surface consists of a covalently coupled polysaccharide

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Abbreviations and Acronyms

EPC	= endothelial progenitor cell
HAMA	= human antimurine antibody
HEALING-FIM	= Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth-First In Man
IVUS	= intravascular ultrasound
MACCE	= major adverse cardiac and cerebrovascular events
MI	= myocardial infarction
SMC	= smooth muscle cell
TIMI	= Thrombolysis In Myocardial Infarction

intermediate coating with murine monoclonal anti-human CD34 antibodies, attached to a stainless steel stent (R stent, OrbusNeich, Fort Lauderdale, Florida) (Fig. 1). This antibody specifically targets CD34+ cells (endothelial progenitor cells are CD34 positive) in the vascular circulation. This device was supplied in aqueous sodium azide solution as a preservative to maintain bioactivity and required hand crimping by the operator onto a percutaneous transluminal coronary angioplasty balloon catheter before implantation.

Study procedures. Lesions were treated according to local standard interventional techniques. Specifically, the decision to predilate or direct stent was at the investigator's discretion, and post-dilation was performed as required to ensure that the residual stenosis was <20% by visual assessment, with a TIMI flow grade rate 3. In case of a dissection or incomplete coverage of the lesion, implantation of additional EPC capture R stents was permitted.

Intravenous boluses of heparin were administered to maintain an activated clotting time >300 s during the implantation. Treatment with aspirin, at a dose of at least 80 mg/day, was initiated at least 12 h before the procedure and continued for one month. In addition, a loading dose of 300 mg of clopidogrel was administered before the procedure, followed by 75 mg daily for 28 days. Glycoprotein IIb/IIIa inhibitors were used at the operator's discretion. Angiographic success was defined as the successful implantation of the study device, with a stenosis of <20% of the vessel diameter with TIMI flow grade 3.

Follow-up. All patients were scheduled for a clinical follow-up at one, six, and nine months following the implantation procedure to assess the anginal status and the occurrence of major adverse cardiac and cerebrovascular events (MACCE). An electrocardiogram was obtained at each visit, and an angiographic and intravascular ultrasound (IVUS) study was performed at a mean of 185 ± 14 days.

Quantitative angiographic and IVUS analysis. Coronary angiograms were obtained in multiple views after an intracoronary injection of nitrates. Offline quantitative analyses of preprocedural, postprocedural, and six-month follow-up angiographic data were performed. Restenosis was defined as a reduction of 50% or more of the luminal diameter. Late luminal loss was defined as the difference between the minimal luminal diameter after procedure and at six months. The target lesion was defined as the stented

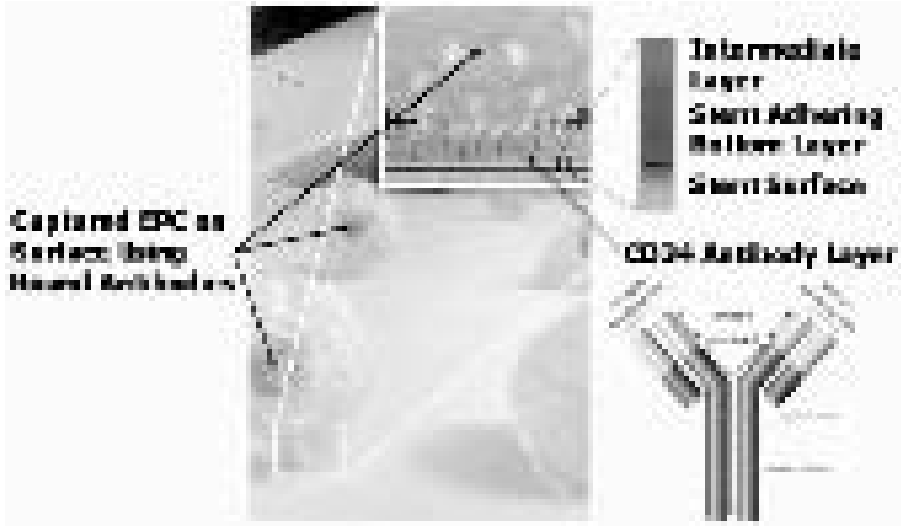

Figure 1. Endothelial progenitor cell (EPC) capture coating technology.
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segment plus the 5-mm segments proximal and distal to the stented segment.

Intravascular ultrasound was performed with an automated pullback at 0.5 mm/s to examine the target lesion at postprocedure and six-month follow-up. Lumen, stent, and external elastic membrane contours were detected with the use of CUARD QCU analysis software (CUARD BV, Wijk Bij Duurstede, the Netherlands), applying a three-dimensional reconstruction as described elsewhere (7).

Study end points. The primary safety end point of this study was the absence of stent thrombosis up to six months. The second end point was a composite of MACCE, defined as cardiac death, stroke, Q-wave or non–Q-wave myocardial infarction (MI), and target vessel revascularization. Stroke was defined as a focal neurologic deficit resulting from a vascular cause involving the central nervous system. Q-wave MI was defined as development of new abnormal Q waves not present on the patient's baseline. Non–Q-wave MI was defined as a creatine kinase of more than twice the upper limit of normal with an abnormal level of the MB isoenzyme of creatine kinase. The efficacy end point was late luminal loss as determined by quantitative coronary angiography and % stent volume obstruction by IVUS at six months. Stent thrombosis was angiographically documented as a complete occlusion (TIMI flow grade 0 or 1) or a flow-limiting thrombus (TIMI flow grade 1 or 2) of a previously successfully treated artery.

Detection of human antimurine antibody (HAMA). Human antimurine antibody testing was not added to the study until several patients had already returned for follow-up. Testing with baseline data was conducted on 4 of 16 patients. The HAMA was determined by a commercially available enzyme-linked immunosorbent assay kit (MEDAC, Hamburg, Germany) (8). A positive assay was defined as ≥10 ng/ml. Significant levels of HAMA were defined as ≥150 ng/ml.

Histology. One specimen was retrieved by directional atherectomy (Flexi-cut, Guidant Europe SA, Diegem, Belgium), fixed in 4% buffered formaldehyde with metal stent fragments removed and embedded in paraffin.

Sections were stained with hematoxylin eosin and an elastin stain (Resorcin Fuchsin) for general assessment of the tissue. Cellular characterization was performed with immunocytochemistry, using antibodies against smooth muscle (specific alpha-actin), leukocytes (CD45), macrophages (mac 387), proliferation cells (Mib 1), and EPC (CD34). All antibodies except anti-CD34 were obtained from DAKO (DakoCytomation, Produktionsvej, Denmark).

Statistical analysis. Because of the size of the patient population in this nonrandomized registry, no formal statistical analysis was conducted to determine the efficacy of the device. Continuous variables are expressed as mean ± SD. Comparisons between postprocedure and six-month follow-up values were performed with a two-tailed paired *t* test. A p value <0.05 was considered statistically significant.

Table 1. Baseline Characteristics and Procedural Outcomes, Patients (n = 16)

Men	11 (69%)
Age (yrs)	68 ± 10
Diabetes	5 (31%)
Hypertension	12 (75%)
Hypercholesterolemia	12 (75%)
Family history	6 (38%)
Current smoking	4 (25%)
Unstable angina	8 (50%)
Target coronary artery	
LAD	8 (50%)
RCA	5 (31%)
LCX	3 (19%)
Lesion type	
A	8 (50%)
B1	6 (38%)
B2	2 (13%)
C	0 (0%)
Angiographic features	
Lesion length (mm)	10.6 ± 4.0
Reference vessel diameter (mm)	2.63 ± 0.30
Minimal luminal diameter (mm)	0.95 ± 0.33
Diameter stenosis (%)	63.7 ± 11.9
Procedural outcomes	
Mean stent diameter (mm)	3.3 ± 0.3
Mean stent length (mm)	18.4 ± 6.4
Overlapping stenting	2 (13%)
Post dilation	8 (50%)
Direct stenting	2 (13%)
Use of glycoprotein IIb/IIIa inhibitor	3 (19%)
Angiographic success	16 (100%)

LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery.

RESULTS

Baseline characteristics and procedural outcome. Overall, 16 patients were enrolled in the HEALING-FIM registry between May and November 2003. Table 1 presents the baseline characteristics and procedural outcomes for this patient population. A second overlapping stent was implanted in two patients to treat a dissection following implantation of the first stent.

Clinical outcome. Table 2 provides an overview of the MACCE at one and nine months. There was no subacute thrombosis or MACCE in the first month after implantation. During the first nine months, MACCE occurred in a patient with insulin-dependent diabetes with diabetic nephropathy. This patient (#12) was admitted with a non–ST-segment elevation MI (maximum creatinine kinase level was 524 U/l) at six months after the index procedure and underwent recatheterization that demonstrated focal in-stent restenosis with TIMI flow grade 3 and no visible contrast detect, which could have been caused by stent thrombosis. No MACCE was reported in other patients.

Six-month angiographic and IVUS results in stented segment. Scheduled coronary angiography at six months was performed in 15 patients (93.8%). The patient who refused angiography was asymptomatic. At six months, mean late luminal loss was 0.63 mm on quantitative

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Table 2. Clinical Outcomes at 1 Month and 9 Months

Death	
Within 1 month	0%
9 months	0%
Stroke	
Within 1 month	0%
9 months	0%
Q-wave MI	
Within 1 month	0%
9 months	0%
Non–Q-wave MI	
Within 1 month	0%
9 months	6.3% (1/16)
TVR	
Within 1 month	0%
9 months	6.3% (1/16)
MACCE	
Within 1 month	0%
9 months	6.3% (1/16)
Stent thrombosis	
Within 1 month	0%
9 months	0%

MACCE = major adverse cardiac and cerebrovascular events; MI = myocardial infarction; TVR = target vessel revascularization.

coronary angiography and percent stent volume obstruction was 27.2% on IVUS (Table 3). Binary restenosis occurred in two patients (13.3%). Restenosis was focal in one patient and diffuse in the other. In the case of the patient with diffuse restenosis (case #4), the patient had no symptoms and a percent diameter stenosis was 58% at six months. This patient did not undergo repeat revascularization. Focal restenosis occurred in an insulin-dependent patient (case #12). This patient was subsequently treated with directional coronary atherectomy and implantation of a paclitaxel-eluting stent. Intravascular ultrasound analysis revealed incomplete stent apposition in one patient (6.3%), which had resolved at six months. Furthermore, no late-acquired incomplete stent apposition was observed for the entire patient population.

Table 3. Serial Quantitative Analysis of the Stented Segment by QCA and IVUS (n = 15)

	Post	6-Month Follow-Up	p Value
QCA			
RVD (mm)	2.71 ± 0.31	2.69 ± 0.32	0.738
MLD (mm)	2.47 ± 0.29	1.84 ± 0.56	0.0004
%DS	8.5 ± 3.4	32.1 ± 16.7	0.0001
Stent thrombosis (%)		0%	
Late loss (mm)		0.63 ± 0.52	
Loss index		0.45 ± 0.39	
Binary restenosis		13.3% (2/15)	
IVUS			
Vessel volume (mm^3)	336.5 ± 86.7	339.9 ± 88.9	0.583
Stent volume (mm^3)	173.5 ± 44.9	175.0 ± 42.6	0.715
Plaque behind stent volume (mm^3)	163.0 ± 56.6	165.0 ± 62.9	0.371
Neointima volume (mm^3)		51.7 ± 47.8	
% in-stent obstruction		27.2 ± 20.9	
In-stent malapposition	6.7% (1/15)	0%	

DS = diameter stenosis; IVUS = intravascular ultrasound; MLD = mean luminal diameter; QCA = quantitative coronary angiography; RVD = revascularized vessel diameter.

Histology of the atherectomy specimen. Histologic analysis showed tissue consisting of a mixture of myxoid and fibrous material with variable cell density. Some of the fibrous pieces showed a paucity of cells. The myxoid fragments consisted of smooth muscle cells (SMCs) within variable amounts of proteoglycan (Figs. 2A to 2C). Some thrombus remnants were seen and assessed to be several days old (Figs. 2D and 2E, no SMCs, only some nuclei), presumably related to the small MI. The atherectomy specimens included metal stent fragments. That indicates that the plaques behind the stent struts were included in the specimens. There were large areas of calcification in both the fibrous and myxoid tissue (Fig. 2F), presumably old plaque, as these were also observed with IVUS. Immunocytochemistry (Figs. 2C and 2E) shows that most cells were SMC-alpha-actin positive. Mib-1 (proliferation), Mac387 (macrophages), and CD34 were negative. There were only a few CD45-positive cells (leukocytes).

HAMA test results. The HAMA testing was conducted on a subset of the population (last four consecutive patients). A positive assay due to the treatment with the study device was not observed in these patients.

DISCUSSION

This study is the first clinical experience with implantation of a bioengineered stent. The results of the HEALING-FIM registry show that the EPC capture stent is safe and feasible: with no stent thrombosis (30 days or 6 months), and MACCE occurred in only one patient (6.3%), despite only 30 days of clopidogrel therapy.

This clinical registry was preceded by several experimental studies. In an in vivo study, at 1 h after deployment the EPC capture stent showed a >90% cell coverage, while the bare stainless steel stents were almost completely devoid of cells. Histologic analysis at 31 days showed that percent area luminal stenosis was significantly reduced with the EPC capture stents compared with stainless steel stents (15.49 ± 4.54% vs. 23.96 ± 7.70%, p = 0.01) (9).

These preclinical and preliminary clinical results have to be interpreted carefully, considering the recent emergence of new technologies such as drug-eluting stents. Drug-eluting stents inhibit the inflammatory and proliferative process of the normal healing response, including the formation of a confluent endothelial layer on the stent (3). The EPC capture stents induce the rapid establishment of a functional endothelial layer early in the healing response. In this registry, the atherectomy specimen indicated a well-healed artery with minimal inflammation.

Of note, the neointimal hyperplasia in the EPC capture coating stents was not significantly reduced when compared with the usual late loss seen after conventional bare metal stent implantation. It has been argued that EPC capture coating covers only the stent struts, and theoretically no

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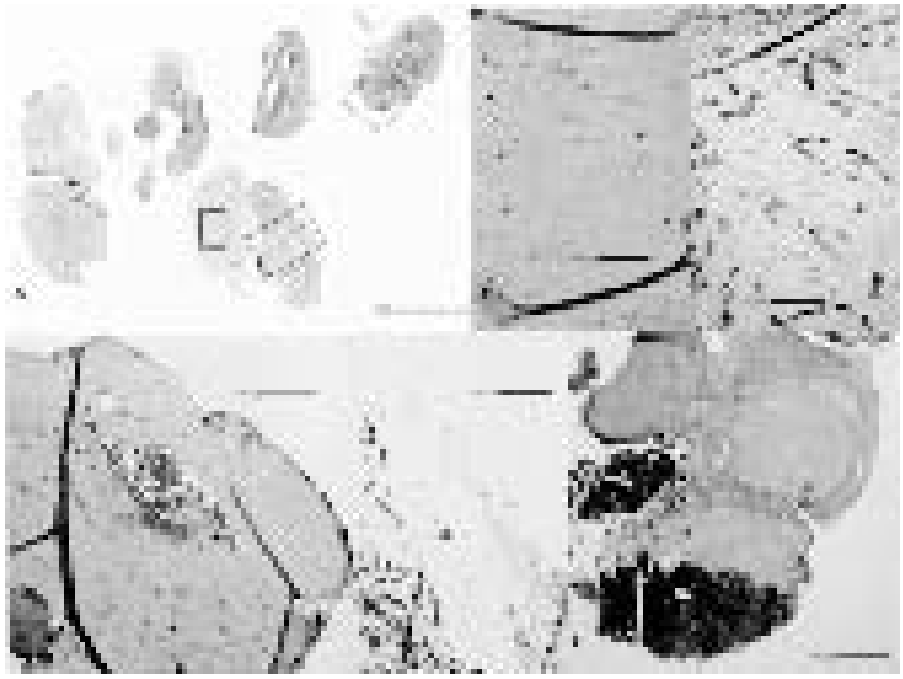

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Figure 2. Overview **(A)** and details (left: **B, C**; mid: **D, E**; right: **F**) of the atherectomy specimen obtained six months following stent placement. Histology shows a mixture of myxoid **(B, C)** and fibrous material **(F)** consisting of smooth muscle cells **(C, E)** within variable amounts of extracellular matrix. Some fragments contained thrombus remnants (Th) (**D, E**) and calcifications (Ca) (**F**). **A** = elastin stain; **B, D, F**= hematoxylin eosin; **C, E** = immunocytochemistry for smooth muscle cell-specific alpha actin.

early functional endothelial lining can be expected in the interstrut space, although the interstrut area in the animal model (healthy coronary artery undergoing direct stenting) was covered with functional endothelium within 48 h; this situation differs substantially from a human pathologic atherosclerosis vessel after balloon injury. In addition, the bioactivity of these prototype EPC capture stents used in HEALING-FIM registry was unstable and was easily reduced by sterilization with gamma irradiation. It was subsequently discovered through the use of a bioassay that gamma irradiation lessened the immunoaffinity of EPC capture prototype stents used in this trial. Therefore, it is likely that the reduced bioactivity of EPC capture stents in the HEALING-FIM registry may not have been enough to inhibit neointimal hyperplasia after stent implantation.

The technology behind the creation of an EPC affinity surface is achieved by attaching murine monoclonal antihuman CD 34 antibodies to the stent. An immunoreaction against the murine monoclonal antibody may occur in patients who have human ant-murine antibody (HAMA). In addition, production of HAMA may result in the neutralization of the EPC capture surface. In this registry, increased HAMA levels were not observed in the four patients who underwent serial HAMA testing, and no patients exhibited systemic symptoms of immunoreaction. This safety issue was in agreement with other trials, evaluating immunologic treatment using murine antibody for ovarian cancer (10).

Because of the small sample size and single-center en-

Table 4. Evolution of Endothelial Progenitor Cell Capture Stent: Improvement From HEALING-FIM (H1) to HEALING II (H2)

Device
H1 - Wet, hand-crimped
H2 - Dry, premounted
Stability
H1 - Wet; supplied in sodium azide preservative; required rinsing before use
H2 - Dry, formulated to preserve antibody structure & activity
Sterilization
H1 - Gamma irradiation; 15 to 25 kGy
H2 - Gamma irradiation; <15 kGy
Bioactivity
H1 - Significant reduction in activity with sterilization
H2 - Stable with sterilization

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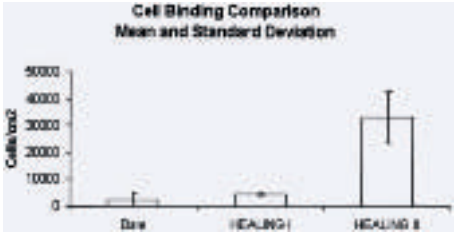

Figure 3. Endothelial progenitor cell capture stent bioactivity (in vitro). The cell-binding activity of the HEALING-FIM and HEALING-II stents was compared with negative controls (bare stents). In the bioassay, stents were exposed to a suspension of human CD34+ cells (kg-1a cells, American Type Culture Collection) for 1 h with agitation. Excess cells are removed and bound cells are tagged with a fluorescent nuclear stain (DAPI, 4′6-diamidino-2-phenylindole). After rinsing, the stents were placed in a microplate for analysis in a fluorescent plate reader. The number of cells bound was calculated by interpolation from standard curve on the same plate.

rollment, the present study did not fully evaluate the efficacy of this device. However, further developments in this technology, such a providing a dry stent premounted on a delivery system and maintaining good activity post-sterilization, are currently being evaluated in the HEALING-II registry (Table 4). The technology for preserving antibody structure and bioactivity has advanced, resulting in a higher capture of EPCs (Fig. 3). As a result of these improvements, further clinical investigation of this technology is warranted to evaluate the efficacy of this device for the treatment of coronary artery disease.

Conclusions. The present study demonstrates that the EPC capture stent is safe and feasible. Further study and development of this promising technology are needed to confirm the clinical efficacy of this bio-engineered stent.

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Part 4

Future direction to the interventional cardiology

Chapter 19

Emergent strategies in the interventional cardiology

Aoki J, Rodriguez-Granillo GA, Serruys PW. Revista Espanola de Cardiologia.

2005;58:962-973

UPDATE

Myocardial Revascularization (VII)

Emergent Strategies in Interventional Cardiology

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Despite the advances in the treatment of patients with coronary artery disease, sudden cardiac death is still unacceptably prevalent. Patients with ischemic heart disease usually require a combination of therapies (drugs and coronary intervention) and may continue to experience symptoms.

Recently, numerous percutaneous interventional treatments and diagnostic tools have been developed to diagnose the vulnerable plaque and to treat the large number of patients with myocardial ischemia. Ongoing research on the use of drug eluting stents, catheter based bypass graft (percutaneous approaches that use the adjacent venous circulation to bypass an obstructed artery and stent-based approach for ventricle to coronary artery bypass), therapeutic angiogenesis and myogenesis, and the catheter based devices to detect the plaque vulnerability and composition (lipid-rich atheromatous core, thin fibrous cap, and expansive vessel remodeling) may result in additional diagnostic and therapeutic options for patients with coronary artery disease.

Key words: *Percutaneous coronary bypass. Angiogenesis. Myogenesis. Vulnerable plaque.*

Estrategias emergentes en cardiología intervencionista

A pesar de los avances que se han efectuado en el tratamiento de los pacientes con enfermedad coronaria, los cuadros de muerte súbita por causa cardíaca tienen todavía una prevalencia inaceptable. Los pacientes con cardiopatía isquémica requieren habitualmente la combinación de distintas formas de tratamiento (fármacos e intervención coronaria), a pesar de lo cual pueden seguir presentando sintomatología.

Recientemente, se han desarrollado numerosas formas de tratamiento mediante intervención percutánea y distintas herramientas diagnósticas que permiten la detección de las placas vulnerables y el tratamiento del elevado número de pacientes que presentan isquemia miocárdica. La investigación actual respecto al uso de endoprótesis con capacidad de liberación de fármacos, *bypass* coronario efectuado con catéteres (abordajes percutáneos en los que se utiliza la circulación venosa adyacente para revascularizar la arteria obstruida, así como el abordaje mediante endoprótesis para la conexión entre el ventrículo y la arteria coronaria), los abordajes terapéuticos de angiogénesis y miogénesis, y las técnicas intracoronarias para la detección de la vulnerabilidad y la composición de las placas (placas ateromatosas con abundante core lipídico, cubierta fibrosa fina y remodelado positivo), puede facilitar opciones diagnósticas y terapéuticas adicionales en los pacientes con enfermedad coronaria.

Palabras clave: *Bypass coronario percutáneo. Angiogénesis. Miogénesis. Placas vulnerables.*

INTRODUCTION

In-stent restenosis has long been considered the main limitation hampering the long-term efficacy of coronary stenting. However, use of drug eluting stents, such as sirolimus eluting stents (Cypher) and paclitaxel eluting stents (TAXUS), are associated with markedly reduced restenosis rates in several randomized trials and registries.[1-4] Drug eluting stents are now used in a majority of intracoronary stenting procedures. Nevertheless, in-stent restenosis still occurrs in some patients and some specific problems, such as late thrombosis after discontinuation of antiplatelet therapy has been reported.[5]

Recently, other approaches to treat the coronary artery disease have been introduced. Percutaneous ap-

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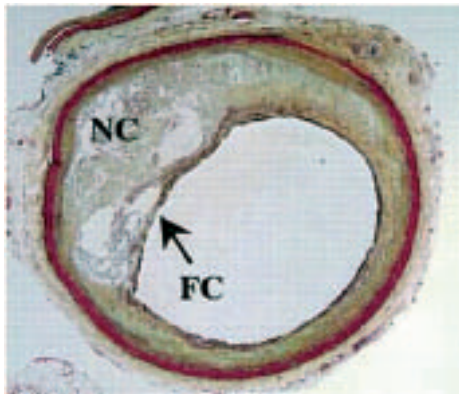

Figure 1. Thin-cap fibro atheroma (TCFA). TC indicates thin fibrous cap; NC, Large necrotic lipid core.[6]
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proaches that use the adjacent venous circulation to bypass an obstructed artery and stent-based approach for ventricle to coronary artery bypass are being tested. Therapeutic angiogenesis and myogenesis are also being tested. Ongoing research on angiogenetic gene therapies and stem-cell transfer may result in additional therapeutic options benefiting patients with myocardial ischemia.

Despite the advances in the treatment of patients with coronary artery disease, sudden cardiac death is still prevalent. Sudden cardiac death occurs in half of all cardiac deaths and plaque rupture is the cause in more than 70% of such deaths.[6,7] In addition, silent plaque rupture and its consequent wound healing accelerate plaque growth and is a more frequent feature in arteries with less severe luminal narrowing.[8]

It has been established that atherosclerotic plaque composition is a key determinant of the fate of such lesions.[9] Lipid-rich necrotic cores occupying a large percentage of the plaque are considered highly thrombogenic and prone to rupture.[9,10] In addition, high levels of free-cholesterol and cholesterol clefts are common features of ruptured plaques and its most prevalent predecessor, the thin-cap fibro atheroma (TCFA) (Figure 1).[6,11]

A previous study of a large series of sudden death patients showed the presence of ruptured TCFA as the underlying cause of 60% of acute thrombi. Furthermore, 70% of those patients presented additional TCFAs without overlying rupture.[12] Several novel invasive imaging techniques have been developed with the intention to identify one of more features of TCFA.[13] Such techniques target the main characteristics of TCFA lesions: large lipid core, thin cap (≤65 μm) and positive remodeling. Detection of these non-obstructive, lipid rich, high-risk plaques may potentially have an important impact in the prevention of acute myocardial infarction and sudden death.

CATHETER-BASED CORONARY BYPASS

Percutaneous in Situ Coronary Venous Arterialization

Catheter based coronary bypass has evolved since 1995.[14,15] Percutaneous approaches that use the adjacent venous circulation to bypass an obstructed artery are being tested**.** In percutaneous *in situ* coronary venous arterialization (PICVA), a coronary artery is connected to the adjacent vein at one site upstream from the lesion, directing oxygenated blood flow into the vein (Figure 2). The oxygenated blood then travels through the venous system in the reverse direction to perfuse the myocardium. In a percutaneous *in situ* coronary artery bypass (PICAB), 2 channels are created between the coronary artery and the adjacent vein, one upstream and the other downstream from the lesion (Figure 3). The blood enters the upstream channel, flows through the isolated vein to bypass the lesion, and re-enters the healthy segments of the artery through the downstream channel. Oesterle et al reported the initial clinical experience with PICVA.[15] PICVA was attempted in eleven patients with severe angina and no reasonable option for either angioplasty or surgical revascularization. In 6 patients, the adjacent vein could not be adequately targeted for successful needle and wire delivery. PICVA was successfully completed in 5 patients. Two of the 5 cases had catastrophic complications and died within 48 hr of the procedure. Of the remaining 3 cases, all patients experienced an improvement in their anginal symptoms. However, 3-month follow-up angiography revealed a closed PICVA channel in 2 patients. After this initial clinical experience, the system of devices is currently undergoing significant modification (the new imaging strategy and modified connecting and blocking devices), and a further clinical study is underway.

Stent-Based Approach for Ventricle to Coronary Artery Bypass

Alternative approach, also performed via sternotomy, is a ventricle to coronary artery bypass (VCAB). In this procedure, a stent-based device (VSTENT) is used to create a conduit between the left ventricle and the left coronary artery, thereby increasing flow in the coronary artery. The advantage of this approach is that no grafting is necessary and it can be performed rapid-

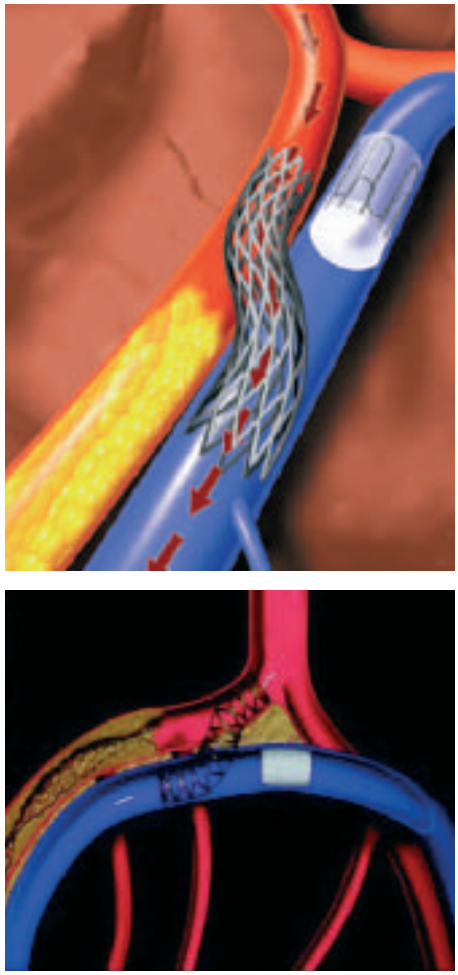

Figure 2. Percutaneous in situ coronary venous arterialization (PICVA).[15]
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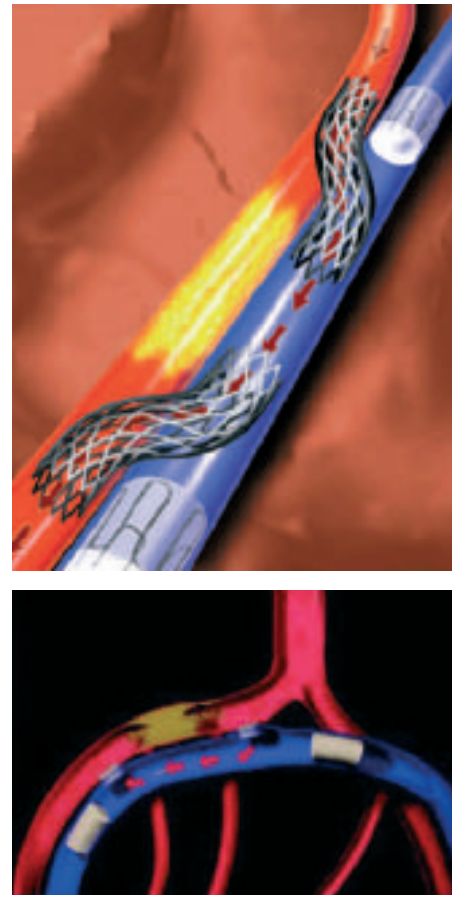

Figure 3. Percutaneous in situ coronary artery bypass (PICAB).[15]
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ly. Only one experimental revascularization procedure has been reported.[16]

RETROGRADE PERFUSION

Synchronized retroinfusion with arterial blood to coronary veins was able to partially reduce myocardial ischemia in patients undergoing percutaneous coronary angioplasty (PTCA).[17] In general, patients with left main stenosis or left main-equivalent stenosis are considered to be at high risk for PTCA. Pohl et al reported on the 1-year results of a prospective randomized single center study (Myoprotect I) in 44 patients with symptomatic left main or left main-equivalent lesions, who were randomly assigned to the stent group (n=23) or the bypass group (n=21).[18] In all patients randomized to percutaneous treatment, selective pressure-regulated retroperfusion of arterial blood into the anterior cardiac vein was applied during ischemia. Twenty-eight-day mortality and 1-year mortality rate as well as quality of life scores were

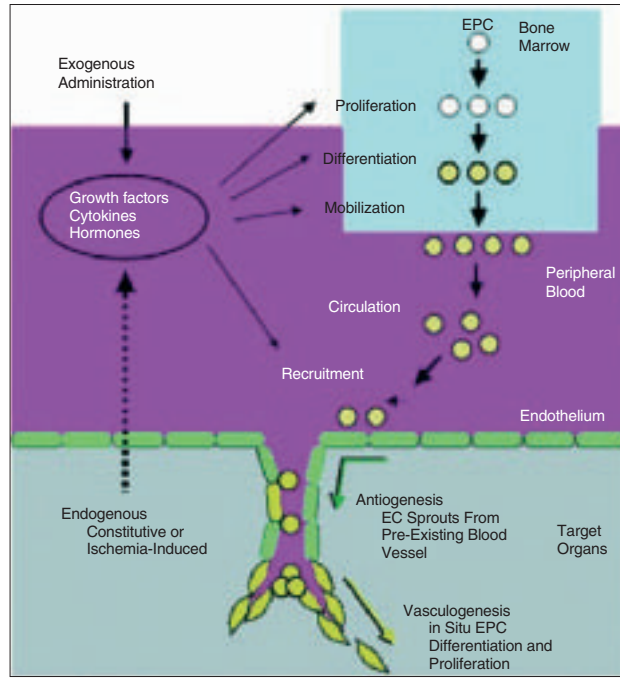

Figure 4. Growth factors, cytokines, or hormones released endogeneously in response to tissue ischemia, or administered exogenously for therapeutic neovascularization, act to promote endothelia progenitor cell (EPC) proliferation, differentiation, and mobilization from bone marrow (via the peripheral circulation) to neovascular foci.[19]
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similar in both groups. Though event free survival was lower and target lesion revascularization rate was higher in the stent group, retroperfusion-supported stent implantation was associated with substantially lower costs and might be considered as an alternative treatment option in the selected group of high-risk patients.

THERAPEUTIC ANGIOGENESIS AND VASCULOGENESIS

Chronic imbalances of myocardial oxygen supply and demand produced by a coronary artery stenosis or occlusion have been shown to increase growth of the coronary collateral circulation. Angiogenesis and vasculogenesis are adaptive responses of the coronary collateral circulation to myocardial ischemia.

Therapeutic angiogenesis and vasculogenesis, which involves the administration of angiogenic growth factors, cytokines or stem cells to stimulate collateral formation and improve myocardial perfusion, is being tested as an alternative strategy for patients with medically intractable angina who are not candidates for mechanical revascularization therapies (Figure 4).

Angiogenic Cytokines

Preclinical studies have established a foundation for rational development of therapeutic angiogenesis.[20-23] A variety of growth factors and chemokines convincingly increase the formation of small blood vessels in experimental models. Most clinical trials to date involve transfer of vascular endothelial growth factor (VEGF) or fibroblast growth factor (FGF) by several delivery strategies (Figure 5).[24]

Protein Transfer

With the advent of recombinant DNA technology, large quantities of purified proteins can be produced for therapeutic use (Table 1).[25] Advantages of locally administering purified angiogenic factors include easy dose titration, repeat administration if necessary, and rapid metabolism to prevent toxicity.[25] The primary disadvantages have been either a lack of efficacy in placebo-controlled studies or a need for administration during coronary artery bypass graft (CABG). Methods combining angiogenic proteins with slow-release systems are in development.

Gene Therapy

Gene therapy is an approach in which the genetic material directing production of a protein is transferred in place of the protein itself. A number of vehicles are used for transferring DNA to heart tissue, including purified DNA, DNA/lipid complexes, adeno-associated viruses, or adenovirus.[24,25] An advantage of this approach appears to be localized, sustained but not indefinite production of angiogenic factors.[26] Apparent disadvantages are the possibilities of vector toxicity, an immune response to the gene therapy vector, or inappropriately localized gene transfer resulting in angiogenesis in a tumour or the retina.

The efficacy of gene transfer approaches to therapeutic angiogenesis is now being tested in clinical trials (Table 2).[25,27-33] Early uncontrolled open-label clinical trials generally gave positive results, although the possibility of a placebo effect was not excluded. Controlled Phase II trials are providing positive but not definitive results. This is promising, since the patient population being studied has failed all other therapies and is likely to be refractory to intervention. However, most of the efficacy measures studied to date are surrogate endpoints such as exercise tolerance time (ETT), angina, or perfusion. While these measures are useful in suggesting clinical efficacy, hard clinical endpoints such as mortality, myocardial infarction (MI) and the need for revascularization should be studied. Long-term follow up data are also necessary. An important observation is that the safety results of these trials indicate no major problems. Potential side-effects such as worsening of atherosclerosis, retinopathy or cancer, have not been observed in clinical trials.

Two large Phase III clinical trials (AGENT 3 and 4) were designed to evaluate further the safety and efficacy of Ad5FGF4.[31] Both trials were designed as randomized, double blind and placebo controlled trials. In each trial, a recruitment goal was 450 patients and these patients would be randomized to 3 groups (placebo group, Ad5FGF-4 at a dose of 10^9 vp group, and Ad5FGF-4 at a dose of 10^{10} vp group). In January 2004, enrollment was stopped (416 patients in AGENT 3 and 115 patients in AGENT 4) because interim data analysis of AGENT 3 indicates that the studies will provide insufficient evidence of efficacy. However, enrolled patients' follow-up continues and final data will be presented in the near future.

Cell Based Therapy

Another alternative method for increasing coronary vascularization is the transplantation of stem or progenitor cells.[34,35] These cells not only produce a variety of growth factors and cytokines, but participate structurally in the formation of new vascular tissue and myocyte.

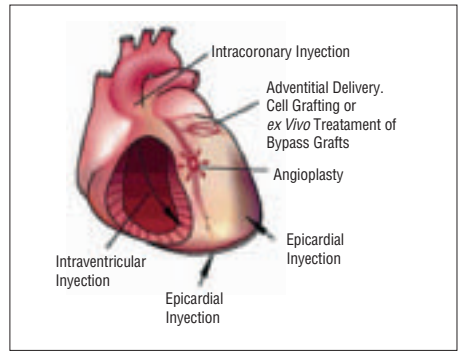

Figure 5. Clinical feasible gene delivery routes.[25]
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The promising results from experimental studies promoted the initiation of clinical trials.[36,38] Stem and progenitor cells are being tested in patients with both acute myocardial infarction and chronic ischemic heart failure (Table 3 and 4).[35,39-46] Improved wall motions or increased perfusion was demonstrated in most of study patients. However, BOOST is the sole randomized controlled clinical trial.[42] Sixty patients with ST-segment elevation myocardial infarction

TABLE 1. **Proteins That Stimulate Angiogenesis in Preclinical Studies***.[25]

Growth factors
VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, PLGF
FGF-1, FGF-2, FGF-4, FGF-5
Angiopoietin-1, Angiopoietin-2
HGF, PDGF-BB
GM-CSF, neurotropin
IGF-1, IGF-2
Chemokines
MCP-1
Transcription factors
HIF-1, Egr-1, Prox-1
Others
Del-1,Cyr 61, PR39
Tissue kallikrein, Secreted frizzled-related protein
eNOS, iNOS

*VEGF indicates vascular endothelial growth factors. PLGF, placental growth factors; FGF, fibroblast growth factors; HGF, hepatocyte growth factors; PDGF, platelet derived growth factors; GM-CSF, granulocyte macrophage colony stimulating factors; IGF, insulin like growth factors; MCP, monocyte chemotactic protein; HIF, hypoxia inducible transcription factors; Egr-1, early growth response factor-1; Prox-1, prospero-related homeobox-1; Del-1, developmentally regulated endothelial cell locus-1; Cyr 61, cysteine-rich angiogenic inducer 61; PR 39, praline and arginine-rich peptide; eNOS, endothelial nitric oxide synthetase; iNOS, inducible nitric oxide synthetase.

TABLE 2. **The Result of Controlled Phase II Clinical Trials Testing Angiogenic Factors to Treat Coronary Heart Disease***,[25]

Trial	Therapeutic Agent	No.	End Point	Results
VIVA[27]	Recombinant VEGF protein	178	ETT (60 days)	Negative
FIRST[28]	Recombinant FGF-2 protein	337	ETT (90 days)	Negative
GM-CSF[29]	Recombinant GM-CSF protein	21	Invasive collateral flow index (2 weeks)	Positive
AGENT[30]	Adenovirus-FGF-4	79	ETT (4 weeks)	Positive
AGENT II [31]	Adenovirus-FGF-4	52	MPI (8 weeks)	Positive
KAT [32]	Adenovirus-VEGF 165 Plasmid/liposome VEGF165 (Adeno only)	103	MPI (6 months)	Positive
Euroinject One [33]	Plasmid VEGF165	74	MPI (3 months)	Negative

*VEGF indicates vascular endothelial growth factors; FGF, fibroblast growth factors; ETT, exercise tolerance time; MPI, myocardial perfusion improvement.

were randomly assigned to either a control group that received optimum post infarction medical treatment, or a bone-marrow-cell group that received optimum medical treatment and intracoronary transfer of autologous bone marrow cells 4.8 days after percutaneous coronary intervention (PCI). After 6 months, mean global left ventricular ejection fraction (LVEF) had significantly increased in the bone-marrow-cell group, compared to the control group. However, most studies at present are limited by the small patient enrolment, and recently some papers reported that bone-marrow-derived haematopoietic stem cells do not transdifferentiate into cardiac myocytes in ischemic myocardium.[47,48]

PERCUTANEOUS MYOBLAST TRANSPLANTATION

Most preclinical experience has been reported on transplantation of skeletal myoblasts in infarcted myocardium.[49-52] These studies demonstrated that transplanted skeletal myoblasts in damaged myocardium are capable of cellular engraftment, myotube formation, and long-term graft survival. Several clinical percutaneous myoblast transplantation trials, using both the transendocardial and the transvenous approaches, have been reported.

Transendocardial Approach

A pilot safety and feasibility study on percutaneous transplantation of autologous skeletal myoblasts by transendocardial injection in five patients with ischemic heart failure was reported by the group of Rotterdam.[50] Autologous skeletal myoblasts were obtained from the quadriceps muscle and cultured in vitro for cell expansion. With a NOGA®-guided catheter system, 196±105 million cells were transendocardially injected into the infarcted area. After 3 months, LV ejection fraction increased and regional wall analysis by magnetic resonance image (MRI) showed significant increased wall thickening at the target area. In the light of these preliminary favourable results, a multicenter European uncontrolled investigation has been started. Overall, 15 patients have been enrolled and treated with transendocardial skeletal myoblasts injection.

TABLE 3. **Stem/Progenitor Cell Therapy (Intracoronary Application) in Patients With Acute Myocardial Infarction***,[35]

Reference	Cell Type	Patients	Results
Strauer et al[39]	BMC (40 mL) versus control	n=10	Hypokinetic area (LVA) ↓, contractility infarct region ↑, end-systolic volume ↓, perfusion (tallium scintigraphy) ↑
TOPCARE-AMI[40,41]	BMC (50 mL) versus CPC (250 mL)	n=20	Global and regional EF (LVA, echo, MRI) ↑, end-systolic volume , viability (PET, MRI) ↑, coronary flow reserve ↑
BOOST (prospective and randomised)[42]	BMC (120 mL) versus CONTROL	n=30	EF (MRI) ↑

*BMC indicates bone marrow cell; CPC, circulating progenitor cell; LVA, left ventricular angiogram; EF, ejection fraction; MRI, magnetic resonance image; PET, positron emission tomography.

TABLE 4. **Stem/Progenitor Cell Therapy in Patients With Chronic Heart Failure***.[35]

Reference	Cell Type	Application	Patients	Results
Stamm et al[43]	CD133+BMC (85-195 mL)	Injection during CABG	n=6	EF in 4 patients (LVA) ↑, perfusion in 5 patients (SPECT) ↑
Tse et al[44]	BMC (50 mL)	Intramyocardial/NOGA	n=8	Wall motion and thickening ↑
Fuchs et al[45]	BMC	Intramyocardial/NOGA	n=10	Angina score and stress-induced ischemia improved
Perin et[46]	BMC (50 mL)	Intramyocardial/NOGA	n=14	EF ↑, end-systolic volume ↓

*CD indicates cluster of differentiation; BMC, bone marrow cell; CABG, coronary artery bypass grafting; EF, ejection fraction; LVA, left ventricular angiogram; SPECT, single photon emission computed tomography; EF, ejection fraction.

The results of this study will be presented in the near future.

Transvenous Approach

A novel catheter-based endovascular system for direct myocardial injection using IVUS guide needle punctures via the coronary venous system (the TRANSAccess™) has been developed (Figure 6).[53] In the POZAN trial, 10 patients underwent intramyocardial injection by using the TRANSAccess.[54] The procedure was not successful in one patient but NYHA class improved in all patients and ejection fraction increased 3%-8% in 6 out of 9 cases during 6 month follow-up.

Ventricular Arrythmia

After intramyocardial injection of skeletal myoblasts, ventricular arrhythmia was reported. Menasche et al[52] reported that implantable cardioverter-defibrillator (ICD) implantation for ventricular arrythmias was required in 4 out of 10 patients after open chest autologus myoblast transplantation.[50,52] One of the 5 patients who were enrolled in the study on percutaneous transplantation of autologous skeletal myoblasts by transendocardial approach had also sustained episodes of ventricular tachycardia and required ICD. This is probably related to: *a)* heterogenecity of action potentials between the native and the transplanted stem cells; *b)* intrinsic arrhythmia potential of injected cells; *c)* increased nerve sprouting induced by stem cell injection; and *d)* local injury or edema induced by myocardial puncture and inflammatory response.

FUTURE PERSPECTIVES TOWARDS INVASIVE DETECTION OF VULNERABLE PLAQUE

Lipid-Rich Atheromatous Core

IVUS provides an accurate tomographic view of the coronary arteries and has shown a high correlation with histology samples in in vitro validation studies.[55-57] However, accurate plaque characterization with visual interpretation of gray-scale IVUS, particularly of lipid rich plaques, remains an unresolved issue.[56] On the contrary, spectral analysis of IVUS radiofrequency data (IVUS-Virtual Histology™ [IVUS-VH]) has demonstrated potential to provide detailed quantitative information on plaque composition and has been validated in studies of explanted human coronary segments (Figure 7).[58]

Angioscopic yellow plaques have been related to atheromatous plaques in previous validation studies.[59] However, this technique evaluates only the luminal surface of the intima thus quantifiable values of lipid core size are out of its scope.

Raman spectroscopy is a technique that can characterize the chemical composition of tissues.[60] In vitro studies have demonstrated that diagnostic algorithms allow the discrimination of coronary arterial tissue in 3 categories: non-atherosclerotic, non-calcified and calcified plaques.[61] Nevertheless, this technique also lacks the ability to provide geometrical information of the vessel and has a shallow penetration depth.

Intravascular ultrasound elastography and palpography are techniques that allow the assessment of local mechanical tissue properties (Figure 8).[62,63] At a defined pressure, soft tissue (lipid-rich) components will deform more than hard components (fibrous-calcified).[64] However, they are unable to provide quantifiable measurements of plaque components.

Finally, intravascular magnetic resonance (IVM-RI) has recently emerged as a potential tool to identify TCFA since it can accurately determine the presence of lipid within the arterial wall.[65,66] In vivo feasibility remains to be proven and acquisition time and extent of the scan analysis requires improvement.

Thin-Fibrous Cap

The threshold to define the cap as "thin" has previously been set at <65 μm.[67] However, it is well

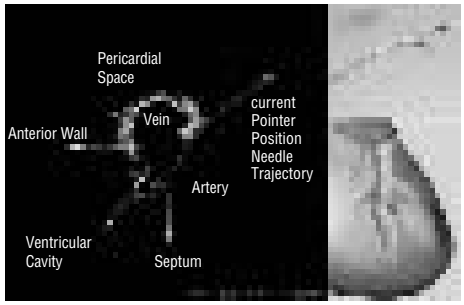

Figure 6. Direct myocardial injection using IVUS guide needle punctures via the coronary venous system.

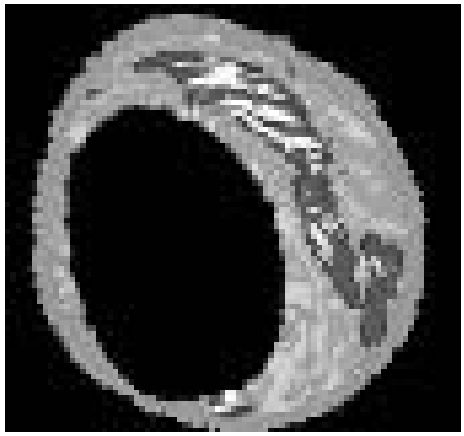

Figure 7. Virtual histology image. Red: lipid core. White: calcium. Yellow: fibrofatty. Green: fibrosis. Gray: media.

established that general tissue shrinkage can not be avoided during dehydration.[68] Shrinkage of up to 60%, 15% and 80% can occur during critical-point-drying, free-drying, and air-drying respectively.[69] Furthermore, post-mortem contraction of arteries further contributes to deteriorate the pathological quantification of atherosclerosis.[70] Accordingly, we believe that the threshold should be higher than 65 µm. Since the axial resolution of IVUS is between 100 and 150 µm, techniques such as IVUS-VH with the capacity to quantify each plaque component and to identify the location of the lipid core in relation to the lumen have the potential to recognize all the 3 features of TCFA lesions.

Optical coherence tomography (OCT) is an imaging technique that allows high-resolution (axial resolution of 15 µm) imaging in biological systems (Figure 9).[71] Accordingly, OCT has the capacity to allow in-vivo, real time visualization of a thin fibrous cap. Recent in vivo data suggest the possibility of detection of macrophages in atherosclerotic plaques.[72]

The sensitivity and specificity of palpography to detect vulnerable plaques has recently been assessed in post-mortem human coronary arteries where vulnerable plaques were detected with a sensitivity of 88% and a specificity of 89%.[63]

Positive Remodeling

The expansive compensatory enlargement of the coronary arteries in response to an increase in plaque area is called positive or expansive remodeling.[73] Several studies showed an increase in inflammatory marker levels, larger lipid cores, and pronounced medial thinning in positive remodeled vessels.[74-76] Recently, the relationship between vascular remodeling and plaque composition was assessed using IVUS.[77-79] In these studies, the remodeling index for soft lesions

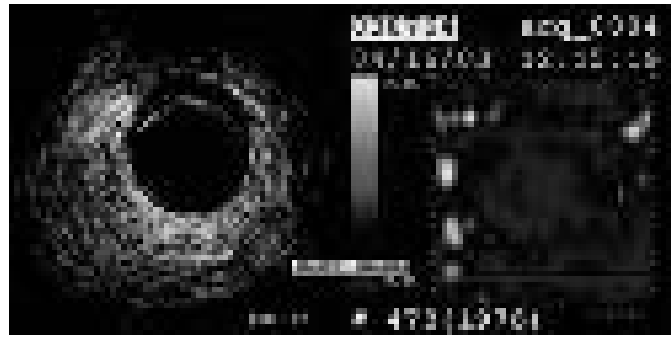

Figure 8. Palpography image. Yellow, high strain spot.

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was significantly higher than those for fibrous/mixed and calcified lesions.[77-79] Aside from gray-scale IVUS, IVUS-VH can also accurately identify, as well as lipid core size and TCFA, the geometry of the vessel.

Pan-Coronary Syndromes

Several studies using angiography, IVUS, angioscopy, and palpography identified a high incidence of high-risk plaques throughout the coronary tree.[80-83] In the study conducted by Rioufol et al,[81] at least one plaque rupture was found away form the culprit lesion in 80% of the patients, away from the culprit artery in 71% and in the 2 non-culprit arteries in 12.5%.[81]

Patients with acute myocardial infarction may present additional complex non-infarct-related coronary plaques. Furthermore, such multiple complex plaques have been found independent predictors of future clinical events.[80]

If the large number of high-risk plaques is detected throughout the coronary tree by means of angiography, angioscopy, IVUS, and palpography potential local preventive strategies could not be cost-effective.[8,80-83] On the contrary, a systemic "plaque stabilization" approach including statins or angiotensin converting enzyme (ACE) inhibitors could be capable of "cooling-down" the inflammatory burden.[84]

CONCLUSIONS

Numerous percutaneous interventional treatments and diagnostic tools have been developed to diagnose the vulnerable plaque and to treat the large and increasing number of patients with myocardial ischemia. The proliferation of these strategies, and the need for multiple approaches in individual patients indicate that the problem of myocardial ischemia is not solved. Ongoing research on the use of drug eluting stents, catheter based bypass graft, therapeutic angiogenesis and myogenesis, and the catheter based devices to detect the plaque vulnerability and composition may result in additional diagnostic and therapeutic options for patients with coronary artery disease.

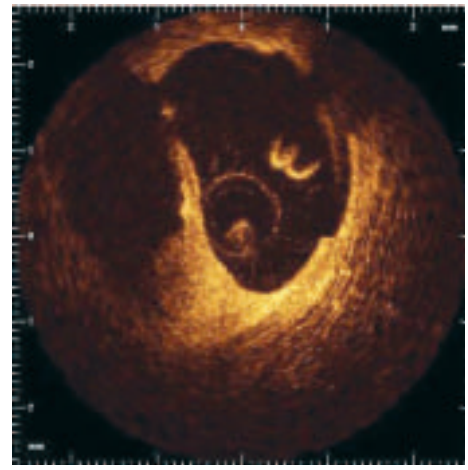

Figure 9. OCT image after plaque rupture.

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Summary and Conclusions

SUMMARY AND CONCLUSIONS

Part 1 Long term tissue growth inside and outside drug-eluting stent in humans

After drug-eluting stents (DES) implantation, vessel reaction inside and outside the stent is not identical. **Chapter 2** presented vessel reaction after sirolimus-eluting stent (SES) implantation. In the first 2 years, the mean plaque volume and plaque compositional change expressed as mean percent (%) hypoechogenic tissue of the plaque behind the stent struts did not significantly change. However, significant plaque shrinking with an increase in plaque echogenicity was observed between 2 years and 4 years. The mean neointimal volume increased over 4 years. However no further statistically significant change occurred between 2 and 4 years. **Chapter 3** showed that vessel reaction after paclitaxel-eluting stent (PES) implantation. Increased plaque outside the stent 6 months after PES implantation regressed completely in the slow release (SR) group and partially in the middle release (MR) group by 2 years. Neointimal suppression with both SR and MR PES is sustained up to 2 years. Whereas neointima decreased in the bare metal stent (BMS) group between 6 months and 2 years, neointima continued to increase in the SR and MR groups without impact on clinical events. **Chapter 4** examined that vessel reaction after various doses and pharmacokinetic release of PES with an erodable polymer. Although type of polymer was different, vessel reaction inside and outside the stent was similar as PES with a durable polymer. **Chapter 5** summarized vessel reaction after DES, including everolimus and ABT 578-eluting stents. Vessel reaction outside the stent was different between limus family (sirolimus, and everolimus) and paclitaxel. Significant expansive remodeling was observed only after paclitaxel release stents, but vessel regressed later time point. Neointima, in other words, vessel reaction inside the stent, regressed after implantation of BMS. However, neointima keeps growing after implantation of all kinds of DES. Although long term follow-up after DES implantation shows a sustained clinical benefit in several randomized trials, delayed neointimal growth beyond the first 6 to 9 months has been reported in serial intravascular ultrasound system (IVUS) analyses in some trials. The issue of a delayed restenosis which was observed after brachytherapy has not been thoroughly evaluated with DES.

Part 2 Efficacy of drug-eluting stent for high risk patients

In the BMS era, long lesion, diabetes mellitus, let main coronary artery disease, chronic total occlusion, and bifurcation lesion are high risk for in-stent restenosis. Clinical effects of SES and PES on patients with these high risk factors were analyzed. **In Chapter 6**,

the medium-term clinical outcome and the potential for adverse effects when very long segments (i.e.≥64mm of stented length) were treated by DES implantation, an approach colloquially referred to as a "full metal jacket" were evaluated. The one-year target vessel revascularization rate was 7.5% and the overall incidence of major adverse cardiac events was 18.0%. These results seemed better than full metal jacket, using BMS (The one-year target vessel revascularization rate was 21.6% and the overall incidence of major adverse cardiac events was 38.0% in the historical control.) Outcomes in SES and PES groups did not differ statistically. **In Chapter 7 and 8,** patients with diabetes mellitus were evaluated. Routine utilization of SES for diabetic patients significantly reduced the rate of adverse cardiac events at 1 year compared to bare metal stents. (17.3% in the SES group versus 30.2% in the pre-SES group (hazard ratio, 0.54 [95% confidence interval, 0.32-0.91]; p=0.02)) PES were associated with a nonsignificantly lower incidence of major adverse cardiac events at 1 year compared with SES (adjusted hazard ratio 0.68, 95% confidence interval 0.37 to 1.24, p = 0.21). **Chapter 9** illustrated a patient with chronic total occlusion of left main coronary artery who was successfully treated with bifurcation stenting with SES. **Chapter 10 and 11** analyzed patients with left main coronary artery disease, the cumulative incidence of major adverse cardiovascular events was lower in the DES cohort than in patients in the pre-DES group (24% versus 45%, respectively; hazard ratio [HR], 0.52 [95% CI, 0.31 to 0.88]; *P*=0.01). Total mortality did not differ between cohorts; however, there were significantly lower rates of both myocardial infarction (4% versus 12%, respectively; HR, 0.22 [95% CI, 0.07 to 0.65]; *P*=0.006) and target vessel revascularization (6% versus 23%, respectively; HR, 0.26 [95% CI, 0.10 to 0.65]; *P*=0.004) in the DES group. PES may perform closely to SES both in terms of angiographic and long-term clinical outcome, the cumulative incidence of major adverse cardiovascular events was comparable (25% in the SES vs. 29%, in the PES group; HR 0.88 [95% CI: 0.43-1.82]; p=0.74), reflecting similarities in both the composite death/MI (16% in the SES and 18% in the PES group) and target vessel revascularization (9% in the SES and 11% in the PES group). Angiographic in-stent late loss (mm) was0.32±74 in the main and 0.36±0.59 in the side-branch the SES vs. 0.46±0.57 and 0.52±0.42 in the PES, respectively (p=0.36 and p=0.41).In **Chapter 12 and 13**, we demonstrated the efficacy of DES implantation for the percutaneous treatment of chronic total occlusions when compared to BMS. Both SES and PES were associated with a low rate of 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). Clinical and angiographic effects for patient with bifurcation lesions were analyzed in **Chapter 14 and 15**. Major adverse cardiac events (MACE) rates for both SES and PES were low compared with historical data of BMS. Our data suggests a higher need for target lesion revascularization 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 (Survival-free of target lesion revascularization was 95.7% for SES versus 86.8% for PES, p=0.01.). Technique of stenting was not a predictor of either MACE or TLR. The most effective techniques for bifurcation stenting remain undefined.

Both SES and PES have almost similar clinical effect to reduce MACE compared to BMS, even if patients have high risk restenosis factors.

Part 3 Endothelial progenitor cell – alternative to drug-eluting stents

DES have dramatically reduced the incidence of in-stent restenosis. However, the incidence of angiographic stent thrombosis in an unselected, complex DES population was 1.0%, within the same range as the corresponding BMS population and concordant with previously published results from the BMS era. (**Chapter 16)** Other technology of reducing the incidence of stent thrombosis is necessary to improve clinical outcome of coronary stenting. The acceleration of the endothelialization of stent is a key factor to reduce stent thrombosis. (**Chapter 17)** Recently, the existence of circulating endothelial progenitor cells (EPC) has been identified as a key factor for re-endothelialization. HEALING-FIM registry is the first clinical experience with implantation of a bio-engineered stent which is anti-CD34 coated stents, designed to capture circulating endothelial progenitor cells. The results of the HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth - First In Man) registry showed that the EPC capture stent is safe and feasible: with no stent thrombosis (30 days or 6 months), MACE occurred in only one patient (6.3%), despite only 30 days of clopidogrel therapy. Further developments in this technology are warranted to evaluate the efficacy of this device for the treatment of coronary artery disease. (**Chapter 18)**

Part 4 Future direction to the interventional cardiology

Chapter 19 summarized that other approach for coronary artery disease, except DES. Ongoing research on catheter based bypass graft, therapeutic angiogenesis and myogenesis, and the catheter based devices to detect the plaque vulnerability and composition may result in additional diagnostic and therapeutic options for patients with coronary artery disease.

In conclusion

Both SES and PES have significant effect to reduce major accident cardiac events, mainly due to reduce target lesion revascularization, even if patients have high risk factors for restenosis. Current issues of DES are long term effects of these devices and stent throm-

bosis. Long-term follow-up after DES implantation shows a sustained clinical benefit in several randomized trials. In the intravascular ultrasound analyses of DES, neointima continued to increase without impact on clinical events. Although plaque outside the stent began to shrink beyond 1 year, longer term follow-up will be required to establish the natural history of local drug delivery by DES. In addition, the EPC capture stent which can rapidly endothelialize stainless steel stents has a possibility to reduce stent thrombosis in the first human study. Further developments in this technology are warranted to evaluate the efficacy of this device and reduce the incidence of stent thrombosis.

Samenvatting en conclusies

SAMENVATTING EN CONCLUSIES

Deel 1 Lange termijn weefselgroei aan binnen-en buitenzijde van drug eluting stents in de mens

Na drug-eluting stent (DES) plaatsing, is de vaatreaktie aan binnen-en buitenzijde van de stent niet identiek. **Hoofstuk 2** toonde de vaatreaktie volgend op sirolimus-eluting stent (SES) implantatie. Gedurende de eerste twee jaar toonde de gemiddelde hoeveelheid plaque en de veranderende plaque samenstelling uitgedrukt als gemiddeld percentage (%) echo-arm weefsel van de plaque achter de stent draden geen verandering van betekenis. Echter, plaque krimp van betekenis met een toename van plaque echo geniciteit werd gezien tussen twee en vier jaar. De gemiddelde neointimale hoeveelheid nam gedurende vier jaar toe. Echter, statistisch gezien werden geen belangrijke veranderingen waargenomen tussen twee en vier jaar. **Hoofdstuk 3** toonde vaatreaktie volgend op paclitaxel-eluting stent (PES) implantatie. Toegenomen plaque, welke zes maanden na PES implantatie aanwezig was aan de buitenzijde van de stent , verminderde volledig in de groep met de langzame afgifte (SR) en gedeeltelijk in de groep met de middelmatige afgifte (MR) gedurende de volgende twee jaar. Neointimale onderdrukking via zowel SR als MR PES duurde tot twee jaar voort. Daar waar neointima in de Bare Metal Stent (BMS) groep afnam tussen 6 maanden en twee jaar, bleef neointima toenemen in de SR en MR groepen zonder van invloed te zijn op klinische gebeurtenissen. **Hoofdstuk 4** onderzocht de vaatreaktie op diverse doses- en farmacokinetische afgifte van PES met een erodeerbaar polymeer. Alhoewel sprake was van verschillende typen polymeer, de vaatreaktie aan binnen-en buitenzijde van de stent was gelijk aan PES met een stabiele polymeer.

Hoofdstuk 5 vatte vaatreaktie na DES samen, inclusief everolimus en ABT 578-eluting stents. De vaatreaktie aan de buitenzijde van de stent was verschillend bij de limus familie (sirolimus en everolimus) en paclitaxel. Belangrijk positieve remodeling werd alleen bij paclitaxel afgevende stents waargenomen maar nam later weer af.

Neointima, met andere woorden, vaatreaktie aan de binnenzijde van de stent, verminderde na BMS implantatie.

Echter, bij alle soorten DES implantatie blijft neointima groeien. Hoewel lange termijn follow-up na DES implantatie een voortdurend klinisch voordeel aantoont in verscheidene gerandomiseerde studies, is vertraagde neointimale groei na de eerste zes tot negen maanden gerapporteerd in opeenvolgende intravasculair utrasound system (IVUS) analyses in enkele onderzoeken. De kwestie van de vertraagde restenosis, welk na brachytherapie werd geobserveerd, is nog niet grondig geëvalueerd met behulp van DES.

Deel 2 Doeltreffendheid van drug-eluting stents for hoog-risico patienten

In het BMS-tijdperk, lange lesie, diabetes mellitus, linker coronair ziekte, chronische totaal occlusie en bifurcatie lesies zijn risicovol voor in-stent restenose. Bij patienten met deze hoog risico factoren werden de klinische effecten van SES en PES geanaliseerd. **Hoofdstuk 6** Klinische resultaten op middellange termijn en het potentieel voor ongunstige resultaten werden geëvalueerd bij patienten waarbij lange segmenten (dat wil zeggen ≥ 64mm aan stent lengte) werden behandeld met DES implantatie (populair "full metal jacket" genoemd). Het éénjarig coronaire revascularisatie percentage was 7,5% en het optreden van belangrijke cardiale eindpunten was 18%. Deze resultaten bleken beter dan "full metal jacket" met BMS (het éénjarig percentage revasculatisatie was 21,6% en het optreden van cardiale gebeurtenissen 38% in de historische controle). Resultaten in SES-en PES groepen toonden statistisch geen verschil. **In hoofdstuk 7 en 8** werden patienten met diabetes mellitus geëvalueerd. In vergelijking met BMS reduceerde routinematig gebruik van SES voor diabetes patienten cardiale gebeurtenissen binnen een jaar aanzienlijk. (17.3% in de SES groep versus 30.2% in de pre-SES groep (risico percentage, 0.54 [95% vertrouwens interval, 0.32-0.91]; p=0.02)). PES werd geassocieerd met een non-significant optreden van cardiale gebeurtenissen binnen een jaar vergeleken met SES adjusted risico percentage 0.68, 95% vertrouwens interval 0.37 to 1.24, p=0.21). **Hoofdstuk 9** illustreerde een patient met een chronische totale occlusie van de linker coronair welke succesvol behandeld werd met bifurcatie stenting met SES. **Hoofdstuk 10 en 11** analyseerde patienten met linker coronair ziekte, het cumulatieve vóórkomen van belangrijke cardiale eindpunten was lager in het DES cohort dan in de pre-DES patienten groep (24% versus 45%, respectievelijk; risico percentage [HR] , 0.52 [95% CI, 0.31 tot 0.88]; *P*=0.01). De totale mortaliteit tussen cohorten verschilde niet, echter, er waren aanzienlijk lagere percentages van zowel myocardinfarct (4% versus 12%, respectievelijk; HR, 0.22 [95% CI, 0.07 tot 0.65]; *P*=0.006) als revascularisatie (6% versus 23%, respectievelijk; HR, 0.26 [95% CI, 0.10 tot 0.65]; *P*=0.004) in de DES groep. PES benadert de werking van SES in termen van angiografische en lange termijn resultaten. Het cumulatieve vóórkomen van cardiale gebeurtenissen was vergelijkbaar (25% in de SES versus 29% in de PES groep; HR 0.88 [95% CI: 0.43 – 1.82]; p=0.74, overeenkomsten weergevend in het samengestelde geheel dood/MI (16% in de SES en 18% in de PES groep). Angiografisch in-stent late-loss (mm) was 0.32 ± 74 in het hoofd vat en 0.36 ± 0.59 in de zijtak de SES vs. 0.46 ± 0.57 en 0.52 ± 0.42 in de PES, respectievelijk (p=0.36 en p=0.41). **In hoofdstuk 12 en 13** demonstreerden we de doeltreffendheid van DES implantatie voor de percutane behandeling van chronische totale occlusie in vergelijking met BMS. Zowel SES als PES werden geassocieerd met een laag percentage revascularisatie. Na één jaar was de overleving zonder noodzaak tot revascularisatie aanzienlijk hoger in de SES en PES groepen dan in de BMS groep (97.4% en 96.4% versus 80.8% respectievelijk, p=0.01). Klinische

en angiografische effecten voor patienten met bifurcatie lesies werden geanalyseerd in **hoofdstuk 14 en 15.** Cardiale eindpunten (MACE) percentages voor zowel SES als PES waren laag in vergelijking met historische BMS data. Onze bevindingen suggereren een grotere noodzaak voor revascularisatie voor de PES vergeleken met de SES, echter meer gerandomiseerd onderzoek is nodig om zowel stenting strategie als mogelijke verschillen tussen de stents (overleving vrij van revascularisatie was 95.7% voor SES versus 86.8% voor PES, p=0.01) te vergelijken. De stenting techniek was geen voorspeller van MACE of TLR. De meest effectieve technieken voor bifurcatie stenting blijven ongedefinieerd. Zowel SES als PES hebben bijna gelijke klinische effecten om MACE te reduceren in vergelijking met BMS, zelfs als patienten beschikken over hoog-risico factoren.

Deel 3 Endotheliale voorlopercellen – alternatief voor drug-eluting stents

DES heeft het optreden van in-stent restenose spectaculair verminderd. Echter, het optreden van angiografische stent thrombose in een ongeselekteerde, complexe DES populatie was 1% en overeenstemmend met eerder gepubliceerde resultaten van het BMS tijdperk. **Hoofdstuk 16** Andere technieken om het optreden van stent thrombose te verminderen zijn nodig om de klinische resultaten van coronair stenten te verbeteren. De versnelling van stent endothelialisatie is een belangrijke factor om stent thrombose te verminderen. **Hoofdstuk 17** Recentelijk, het bestaan van circulerende endotheliale voorloper cellen (EPC) is ontdekt als een belangrijke factor voor re-endothelialisatie. De HEALING-FIM registratie is de eerste klinische ervaring met implantatie van een bio-engineering stent (anti CD-34 gecoate stent) welke ontworpen is om circulerende endotheliale voorloper cellen te vangen. De resultaten van de HEALING-FIM (Healthy Endothelial Accelerated Linning Inhibits Neointimal Growth – First in Man) studie toonden aan dat de EPC stent veilig en bruikbaar is: geen stent thrombose deed zich voor (30 dagen of 6 maanden), MACE trad enkel bij één patient op (6.3%), ondanks clopidogrel-therapie van slechts 30 dagen. Verdere ontwikkelingen in deze technologie zijn gewenst om de doelmatigheid van deze stent te vergroten voor de behandeling van coronair lijden. **Hoofdstuk 18.**

Deel 4 Toekomstige richting van de Interventie Cardiologie Hoofdstuk 19 geeft een samenvatting van alternatieve behandelingen van coronair lijden, behalve DES. Nader onderzoek naar met catheters te plaatsen bypass grafts, therapeutische angio-en myogenese, en de catheter gebaseerde instrumenten om hoge risico-plaque gevoeligheid en opbouw aan te tonen kunnen resulteren in aanvullende diagnostische en therapeutische opties voor patienten met coronair lijden.

In conclusie: Zowel SES als DES hebben grote invloed op de reductie van Cardiale eindpunten (MACE), voornamelijk toe te schrijven aan de vermindering van revascularizatie, zelfs als patienten hoge risico factoren voor restenose hebben. Huidige discussiepunten van DES zijn lange termijn effecten van deze devices en stent thrombose. Lange termijn follow-up na stent implantatie toont een aanhoudend klinisch voordeel aan in diverse gerandomiseerde onderzoeken. In de intravasculaire ultrasound analyses van DES, bleef neointima groeien zonder dat het invloed had op klinische gebeurtenissen, hoewel plaque aan de buitenzijde van de stent na één jaar begon af te nemen. Langere termijn follow-up is nodig om het natuurlijke beloop van lokale drug afgifte door DES vast te stellen. Daarbij, de EPC capture stent heeft de mogelijkheid stent thrombose te reduceren in een eerste humane studie. Verdere ontwikkelingen in deze technologie zijn gewenst om de doelmatigheid van dit device te evalueren en het optreden van stent thrombose te reduceren.

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Beginning

June 2002, Prof Serruys and Dr Kengo Tanabe (my Japanese predecessor) came to Japan to attend the congress. One night during the congress, I had a dinner with Prof Serruys, Prof Yamaguchi (boss of our group), previous Japanese fellows at the Thoraxcenter (Dr Yukio Ozaki, Dr Ken Kozuma) and Dr Kengo Tanabe. At that dinner, I realized that I was a next candidate for Japanese fellow at the Thoraxcenter. That was a great chance for me, since Prof Serruys is a something god and ex-fellows are very famous in the field of interventional cardiology in Japan. After that dinner, Dr Kazuhiro Hara (my boss) and Prof Yuji Ikari (member of my committee) gave me a financial supports. Owing to all their warm supports, I was able to get an opportunity to learn at the Thoraxcenter, one of the famous institutions all over the world. I would like to express my gratitude for them.

May 2003, SIRS was widely distributed in Asia. I came to Rotterdam with bad flu at the end of May. I thought that everybody would avoid me, since a strange Asian guy with runny nose spoke extremely terrible English. Five days after my arrival at Rotterdam, I had a chance to meet Professor Serruys. Dr Tanabe who was very busy in his last minutes at the Thoraxcenter, took me to Professor Serruys's house (At this moment, I could not imagine that I would go to his house more than hundred times.). Professor Serruys told me that you should know my PC and prepare the presentation on angiogenesis for ESC. Although I did not know anything about angiogenesis, this job was the first work for me at the Thoraxcenter. My room at the Thoraxcenter was Kamer 120 in the Z building. It took 10 minutes to go to Cathlab. My room-mates, Dirk and Evelyn were not in the room. Evelyn worked in CCU and Dirk was in the long vacation. I studied and worked at Z120 alone more than one month. Senior fellows, Francesco, Pedro, Angela, Akis were very kind but they were very busy due to their own works and their rooms were far from Z120. In addition, I was so called "a typical Japanese" taciturn person. It was very difficult for me to take part in the Thoraxcenter. I lost 7kg during first month (from 62 kg to 55kg). However, I realized that the Thoraxcenter was a wonderful place for fellows after a while. I have many forgettable friends from all over the world.

Colleagues at Thoraxcenter

In July 2003, new fellow came to the Thoraxcenter. Andrew Ong, brilliant native English speaker, father of T-SEARCH. I greatly appreciate his wonderful supports. He has checked my English and gave advices for almost all of my manuscripts. We spent one year in the same room. May and their pretty daughter, Natasha invited me to their house several times. I have never forgotten their smiles.

After a while, Carlos van Mieghem, a big clinical fellow and mediator between MSCT and interventional cardiology came. I realized that he is a true European gentleman. His Dutch translation helped me many times.

In August 2003, Gaston Rodriguez, a cheerful young guy, Got of IVUS-VH and my best friend, came from Argentina. He was the first room-mate and spent 2 years in the same room at the Thoraxcenter. We went to drink many times and discussed our own manuscripts, Japanese and Argentinean cultures, private problems, and dreams etc. His beautiful wife, Ines is always smiling and I learned Argentinean custom and spirit from her. "Mate and Bombilla" are one of my treasures.

Shortly, Maniyal Vijayakumar, new room Z 120 resident, came from India. I have never met such a delightful person. One day, Gaston, Vijay and I talked about music. Vijay knows Spice girls, but he did not know Michael Jackson and the Beatles. We laughed so much. I want to go to Cochin to hear "Vijay's tac-tac-tac".

Marco Valgimigli, a genius manuscript writer, Karate master. I understood why Japanese girls like Italian men and brands. Italian man is so gentle especially for ladies. I am very proud that I hold thesis defense on the same day with you. Some day, I will go to Sardinia to meet you and Patrizia.

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Hector Garcia-Garcia, a crazy Mexican, master of statistics. When we talked with Gaston, you kindly spoke in English, not Spanish every times. I know that he is tender-hearted. Please calculate your body mass index and eat non fat Japanese food.

Shuzo Tanimoto, my successor. Thank you very much for your assistance in proceeding in my thesis. I hope that you have unforgettable experiences with your wife and daughter in Rotterdam.

I met many other international fellows. (Sophia from Greece, Pierfrancesco from Italy, Jose and Raquel from Spain, Adrian from Peru, many Dutch clinical fellows and students, Joost and Karel etc)

Instructors at the Thoraxcenter

First of all, I would like to express my deepest gratitude for Professor Serruys and his family. Although professor was always very busy, he checked my manuscripts late evening and weekend. His wonderful family (Dannielle, Michael, Gregory, and Olivia) were always kind for me. At the end of 2003, I and Asato, my wife were invited to Professr's house to celebrate the new-year eve. We enjoyed fireworks. This is a popular custom in Western countries, but not popular in Japan. Some of the fireworks went up to sky. However, some fireworks hit the tree and returned to the ground and some unstable fireworks accidentally fired to professor's car and face. I have to apologize for this accident. Dear Professor, please take care fire works at the new-year eve.

I would like to thank Professor Pim de Feyter, member of my committee, for teaching me the insightful MSCT.

Professor Willem J. van der Giessen, co-promoter of my thesis, is a great investigator in the not only clinical but also experimental field. Many Japanese companies came to learn how to proceed in animal experiments. I hope that I can work with you to test new medical devices made in Japan near future.

I also wish to acknowledge other instructors, Prof Anton van der Steen, Professor P.M.T. Pattynama, Dr Peter de Jaegere, Dr Eugene McFadden, Dr Georgios Sianos, Dr Heleen van Beusekom, Dr Eric Boersma, Dr Sjoerd Hofma, Dr Ron van Domburg, Dr HJ Duckers, and Dr Jan Willem de Jong for their supports.

My topics are related to IVUS. In the Thoraxcenter, there are many IVUS masters. Jurgen Ligthart, God of IVUS, one of my paranymphs. When I had trouble with IVUS, I always asked him. I want to drive his classic car near future.

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I would like to thank all staffs at the Thoraxcenter.
Excellent study coordinators, Paul Cummins, a great Irish man. Please do not speak English too fast. According to your suggestions, I watched the bloody movies, Kill Bill and Zatoichi. Arno Ruiter, a marathon runner, fun of Feyenoord. We watched the foot ball game in Feburary. Score was 7 vs 0. Of course, Feyenoord was won!
Kind secretaries, Anja, I understood some European jokes due to your lessons. Elles, thank you very much for translating the conclusions in this thesis from English into Dutch. Titia, Edith, Sara and Annet always help me.
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Jan and Paula, master of pictures and movies. Before congresses, I always asked them something difficult jobs related to movies for professor Serruys. They always made the complete movies and pictures. I was extremely indebted to them.

Cardialysis

Many big projects were born in Cardialysis. I think that Cardialysis is the best place to learn how to create the trials, how to analyze QCA and QCU, and how to interpret data. It was very interesting and useful for me to join some meetings at the Cardialysis. I greatly thank to all staffs at Cardialysis, Marco, (great statistician and SAS master, I asked many statistic problems to you), Janetta, (very kind lady, I usually heard your laughing voice at the corridor and the entrance of Cardialysis. I miss your vigor.), Ellen (study coordinator of HEALING trial), Ron, Marie-Angela, Mr Van Es, Bianca, Yvonne, Peter, Connie, Alli and others.

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Curriculum Vitae

CURRICULUM VITAE

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List of Publications

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Color figures

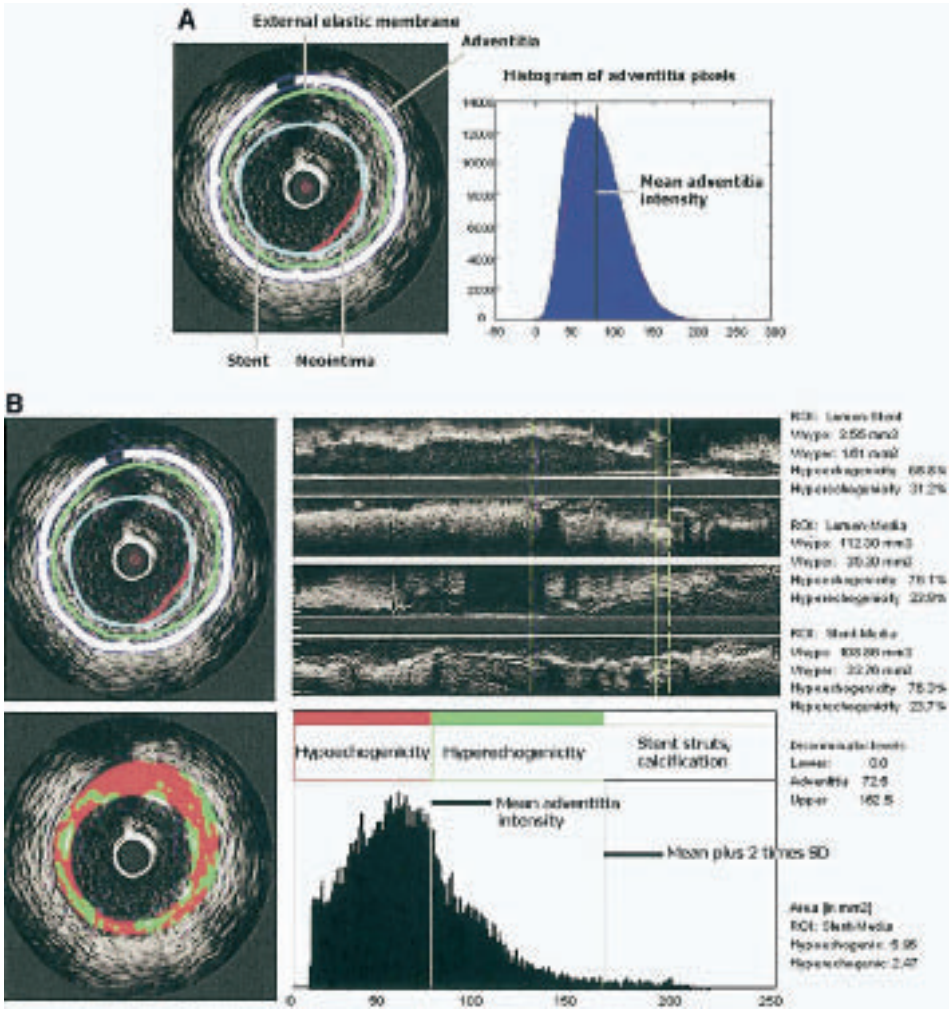

Figure 1. **(A)** The adventitia is defined as tissue outside the external elastic membrane contour. For all non-shadowed adventitia pixels, the mean value and standard deviation are calculated. To observe the suitability, a normal distribution curve based on the same mean and standard deviation histogram is created. **(B)** Cross-sectional image of echogenicity and distribution graph of plaque echogenicity behind the stent struts. Hyperechogenic areas are colored **green**. Hypoechogenic areas are colored **red**. ROI = region of interest.

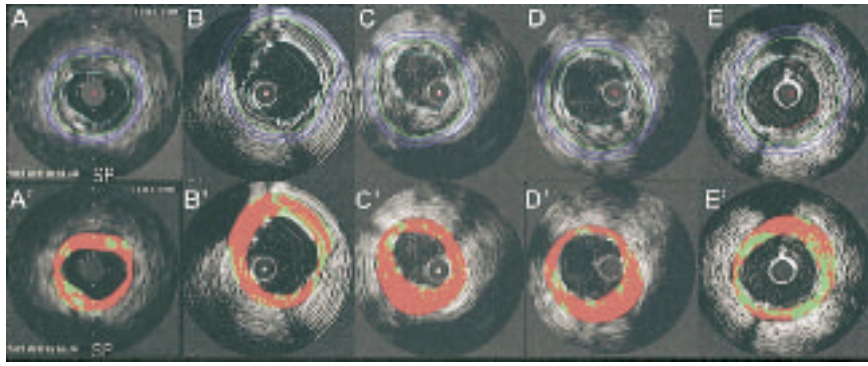

Figure 3. A representative example of a patient with plaque compositional changes between two-year and four-year follow-up. **Top row** shows cross-sectional vessel image at **(A)** post-procedure, **(B)** four months, **(C)** one year, **(D)** two years, and **(E)** four years. **Red line** indicates lumen. **Light blue line** indicates stent. **Green line** indicates media. **Dense blue line** indicates adventitia. **Bottom row** shows cross-sectional echogenicity images. Hyperechogenic areas are colored **green**. Hypoechogenic areas are colored **red**. **(A')** Percent plaque behind stent hypoechogenicity was 84.0% post-procedure, **(B')** 85.3% at four months, **(C')** 88.4% at one year, **(D')** 84.2% at two years, and **(E')** 74.8% at four years.

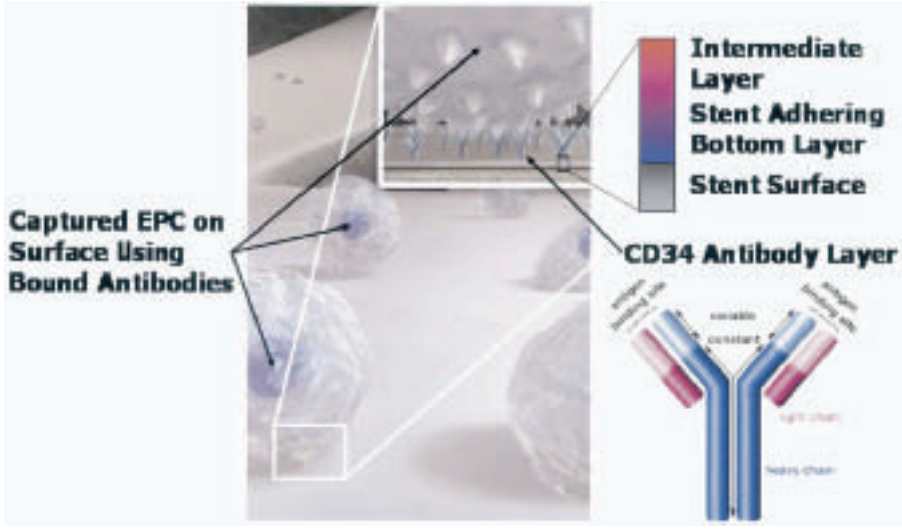

Figure 1. Endothelial progenitor cell (EPC) capture coating technology.

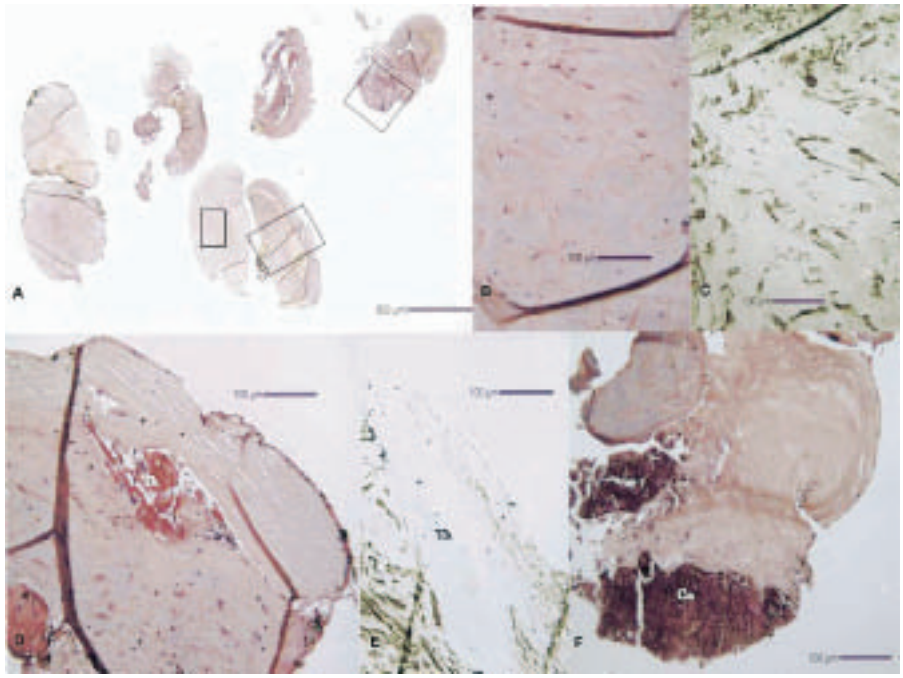

Figure 2. Overview **(A)** and details (left: **B, C**; mid: **D, E**; right: **F**) of the atherectomy specimen obtained six months following stent placement. Histology shows a mixture of myxoid **(B, C)** and fibrous material **(F)** consisting of smooth muscle cells **(C, E)** within variable amounts of extracellular matrix. Some fragments contained thrombus remnants (Th) (**D, E**) and calcifications (Ca) (**F**). **A** = elastin stain; **B, D, F**= hematoxylin eosin; **C, E** = immunocytochemistry for smooth muscle cell-specific alpha actin.

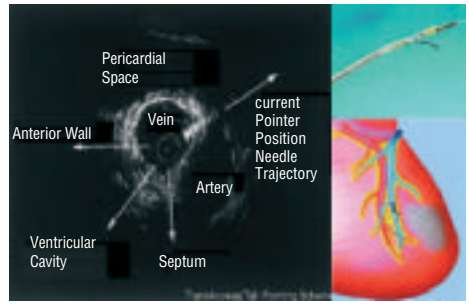

Figure 6. Direct myocardial injection using IVUS guide needle punctures via the coronary venous system.

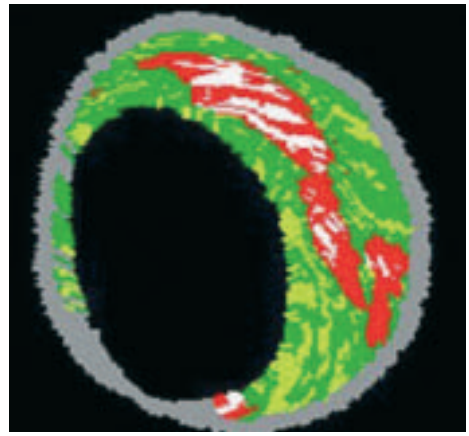

Figure 7. Virtual histology image. Red: lipid core. White: calcium. Yellow: fibrofatty. Green: fibrosis. Gray: media.

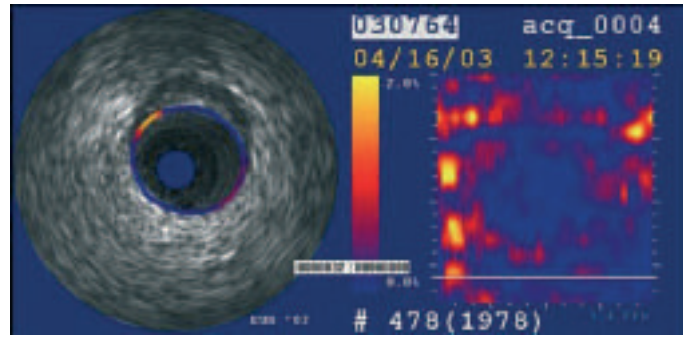

Figure 8. Palpography image. Yellow, high strain spot.