

**Drug Eluting Stent Implantation for High Risk Patients and  
Novel Technologies in Percutaneous Coronary Intervention**

**Medicijn-gecoate stent implantatie bij hoge risico patiënten en  
nieuwe technieken voor percutane coronaire interventies**

**Shuzou Tanimoto**

## **Cover illustrations:**

**Front Cover:** Color of Thoraxcenter format for presentation slides

**Back Cover:** Picture of “Dejima”

Dejima (出島, literally “protruding island”, Dutch: Desjima or Deshima, sometimes latinised as Decima or Dezima), was a fan-shaped artificial island in the bay of Nagasaki that was a Dutch trading post during Japan’s self-imposed isolation (‘sakoku’) of the Edo period, from 1639 until 1859. Only the Netherlands was allowed trading partner during that period, although their trading or traveling activity was restricted in the small island. Truly, Dejima was the only window or literally the contact to the West for the government and people of Japan. Through this island, an unmeasurable amount of foreign culture, technology, science and every kind of Western knowledge was introduced to Japan from Dutch. Dutch, the Dutch language, was also the only Western foreign language the Japanese could study for many years, which stimulated a wider interest in Dutch studies (called ‘Rangaku’ in Japan). Accordingly, the Dutch had been the great source of most Japan’s break of day knowledge on Western medicine and it had contributed enormously to the advance in Japanese medicine itself.

# **Drug Eluting Stent Implantation for High Risk Patients and Novel Technologies in Percutaneous Coronary Intervention**

**Medicijn-gecoate stent implantatie bij hoge risico patiënten en nieuwe  
technieken voor percutane coronaire interventies**

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Erasmus University Rotterdam  
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**Prof. dr. H.G. Schmidt**

**and in accordance with the decision of the Doctorate Board**

**The public defence shall be held on  
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**by**

***Shuzou Tanimoto***  
***born in Hiroshima, Japan***



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*For Tomoko, Yui and Junya*



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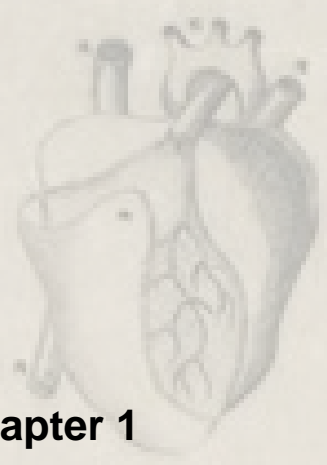
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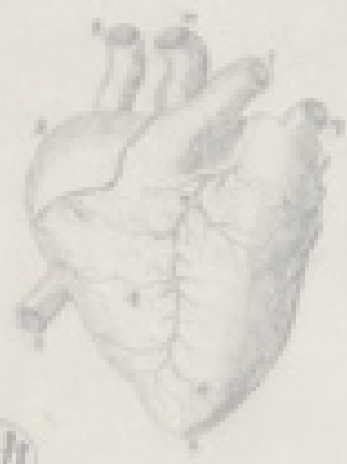
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四脈管及心囊



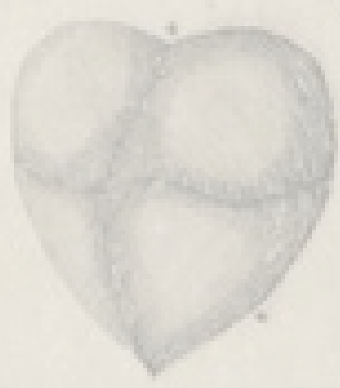
剖心囊視冠脈



Chapter 1

Introduction and overview

全形



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豎剖心視兩室



心障膜





## INTRODUCTION AND OVERVIEW OF THE THESIS

Percutaneous coronary intervention is a major treatment strategy for patients with coronary artery disease, and currently coronary stents are widely used in the world.<sup>1</sup> Although stent implantation itself has shown to reduce restenosis by preventing both early elastic recoil and late vascular remodeling compared to balloon angioplasty, in-stent restenosis (ISR) still occurs in 10-40% of patients and has been the 'Achilles' heel' of coronary interventions, frequently resulting in repeated revascularization.<sup>2,3</sup> Restenosis after coronary stenting occurs secondary to the accumulation of smooth muscle cells and extracellular matrix proteoglycans.<sup>4</sup> Despite the sophistication of the new techniques and enormous advance in devices, ISR requiring repeat procedure has been considered as a main limitation of coronary stenting.

The advent of drug eluting stents (DES), which consist of a drug (immunosuppressive or antiproliferative drug), a polymer and a metallic platform, has revolutionized the practice of interventional cardiology by significantly reducing the rates of restenosis and repeat revascularization as compared to bare metal stents.<sup>5</sup> After the first approval of DES, a large number of patients with coronary artery disease have undergone percutaneous revascularization with DES. However, many trials conducted in the 'real world' showed that the problem of restenosis was not completely resolved and still persists. Effect of DES for patients at high risk for ISR, such as acute myocardial infarction, small coronary vessels, aorto-ostial lesions, or lesions of chronic total occlusion (**Part 1 of this thesis**), have not been fully investigated. In addition, certain potential safety concerns regarding the widespread use of DES have arisen. The most notable drawback of DES is that they could increase the risk of thrombotic complication, especially late stent thrombosis<sup>6</sup>, although its incidence is low.<sup>7</sup> The increased risk of thrombosis with DES utilization may be associated with altered endothelial function<sup>8</sup> and/or delayed vascular healing<sup>9</sup> induced by cytotoxic and cytostatic drug use. Localized hypersensitivity reactions to the polymer coating of DES and drug itself may also contribute to stent thrombosis.<sup>10</sup> To retain the positive clinical aspects of DES and overcome their drawbacks, new concept stents have been developed (**Part 2 of this thesis**).

### Part 1: Efficacy of drug eluting stent for complex patients and lesions

Many randomized clinical trials showed that sirolimus and paclitaxel eluting stents are remarkably reduced ISR and target lesion revascularization, compared to bare metal stents. However, these trials had many exclusion criteria. The efficacy of DES for patients and lesions at high risk for restenosis has not been evaluated in detail. To assess the safety and efficacy of unrestricted utilization of sirolimus and paclitaxel eluting stents in a patient population representing the "real world", several registries were conducted at the Thoraxcenter, Erasmus University (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-analysis for "complex patients and lesions" such as patients with acute myocardial infarction (**Chapter 2 and 3**), small vessel disease (**Chapter 4 and 5**), aorto-ostial lesions (**Chapter 6**) or lesions of chronic total occlusion (**Chapter 7 and 8**) were analyzed.

## **Part 2: New concept stents for percutaneous coronary intervention**

Stent thrombosis is the most considerable drawback of DES. To overcome this undesirable complication, new concept stents have been developed. One of these stents is the MAHOROBA tacrolimus eluting stent and this device may have the potential to reduce both ISR and stent thrombosis (**Chapter 9**). In **Chapter 10**, the MAHOROBA trial, which is the first clinical investigation using the MAHOROBA tacrolimus eluting stents in de novo coronary artery stenoses, was reported. Fully absorbable polymer stent is also one of the new concept stents. This may diminish chronic inflammation between foreign body (stents) and surrounding tissue, accelerate healthy endothelialization of treated vessels and prevent stent thrombosis. The bioabsorbable everolimus eluting stent (BVS), which is composed of poly-L-lactic acid backbone, coated with bioabsorbable polymer containing the antiproliferative drug everolimus, has been developed and its safety and feasibility in diseased coronary artery were assessed in the ABSORB trial. In **Chapter 11 and 12**, mechanical properties of the BVS were reported. Potential advantages for the assessment of in-stent lumen of the BVS over metallic stents were also evaluated (**Chapter 13 and 14**).

## **Part 3: New imaging modality for coronary intervention**

Optical coherence tomography is a new intravascular imaging modality using infrared light. Because this modality has 10 times higher image resolution compared to intravascular ultrasound, detailed information of coronary structures were obtained (**Chapter 15**). In **Chapter 16 and 17**, ex vivo and in vivo quantitative analysis of optical coherence tomography was performed and its measurement accuracy was investigated.

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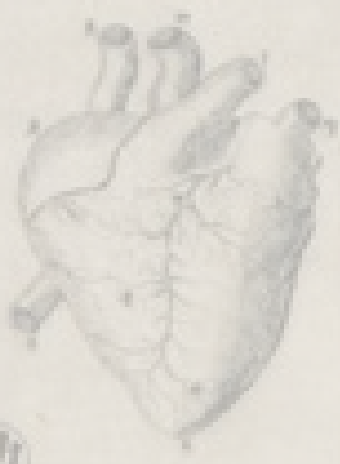


心管圖

四脈管及心囊



剖心囊視冠脈



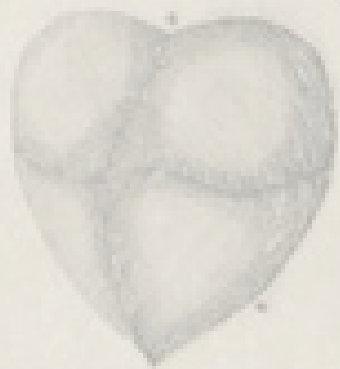
Part 1

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Efficacy of drug eluting stent for complex patients and lesions

全形



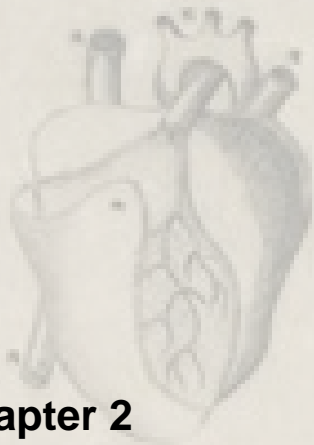
心障膜



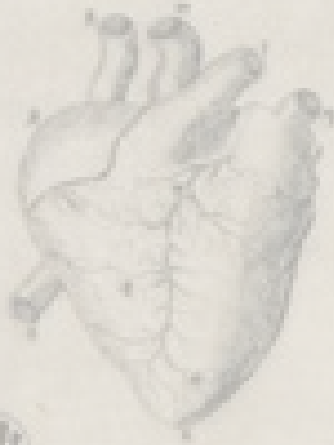


心篇圖

四脈管及心囊



剖心囊視冠脈



Chapter 2

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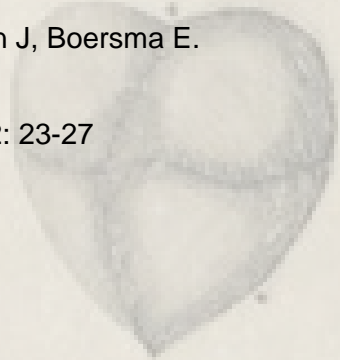
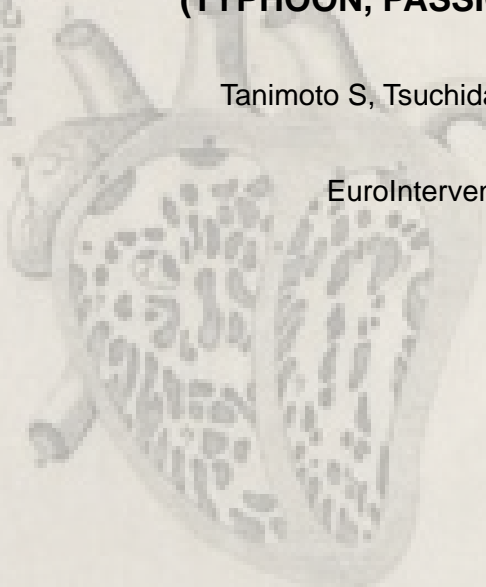
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**Drug-eluting stent implantation in acute myocardial infarction.  
Do we need another randomized trial?  
(TYPHOON, PASSION and HORIZONS trials)**

全形

Tanimoto S, Tsuchida K, Daemen J, Boersma E.

EuroIntervention. 2006;2: 23-27



心障膜





## Drug-eluting stent implantation in acute myocardial infarction. Do we need another randomised trial? (TYPHOON, PASSION and HORIZONS trials)

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*All authors declare no conflict of interests.*

The goal of treatment of patients with acute myocardial infarction (AMI) is to achieve optimal and rapid restoration of coronary blood flow in the infarct-related vessel and to maintain the initial result at follow-up. There are two main treatment methods of re-opening an occluded artery: administering a thrombolytic agent and primary percutaneous coronary intervention (PCI) with or without stenting. In the 1990s and the beginning of the 2000s, many randomized studies comparing these two reperfusion procedures have shown that primary PCI with routine stent implantation for AMI has a better outcome than thrombolytic therapy<sup>1,2</sup> or balloon angioplasty<sup>3-5</sup>. A recent meta-analysis also indicated that primary PCI was more effective than thrombolytic therapy for the treatment of ST-segment elevation myocardial infarction (STEMI)<sup>6</sup>.

In the last 3 to 4 years, drug-eluting stents (DES), either sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES), have been used in various clinical settings and have revolutionized the interventional cardiology practice by reducing restenosis and revascularization rates in comparison to bare metal stents (BMS). Two pivotal trials using DES in relative high risk patients with complex lesions reported single-digit restenosis rates and a lower incidence of revascularization than BMS<sup>7,8</sup>. These trials, however, only included elective procedures. Despite the lack of sufficient evidence, the

experience in stable patients was extrapolated to patients with unstable angina pectoris, non ST-segment elevation acute coronary syndrome (NSTEMI-ACS) and ST-segment elevation acute coronary syndrome (STEMI-ACS); thereby the large number of DES currently used in urgent procedures.

Previous studies suggested that sirolimus could alter and decrease endothelial function *in vitro*<sup>9</sup> and in humans<sup>10</sup>, enhance agonist-induced platelet aggregation<sup>11</sup> and tissue factor expression<sup>12</sup>, and delay vascular healing<sup>13-15</sup>. Moreover, a hypersensitivity reaction to the polymer coating of SES was observed<sup>16-18</sup>. As for paclitaxel, a recent study suggested PES also induced a hypersensitivity reaction<sup>18</sup>. These features of DES can increase the risk of thrombotic complications and have led to prolonged antiplatelet treatment and cautious use of DES in the acute phase of unstable angina and myocardial infarction. Indeed, discontinuation of antiplatelet drugs was a strong independent factor of DES thrombosis<sup>19-21</sup> and a recent publication reported on patients treated with PES for AMI who presented with late stent thrombosis after cessation of antiplatelet drugs<sup>22</sup>.

So far, only 7 reports about DES implantation in AMI patients were published (see Table). One study evaluated clinical and angiographic outcomes of SES implantation in a consecutive series of

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**Table 1. Published and non-published trials on drug-eluting stent implantation in patients with acute myocardial infarction**

Study	Year	Trial design	No. of patients			Follow-up time	Follow-up methods
			BMS	SES	PES		
Published							
RESEARCH <sup>26</sup>	2004	Non-randomized	183	186	•••	10 months	Clinical
Weber <i>et al.</i> <sup>27</sup>	2004	Non-randomized	50	50	•••	6 months	Clinical & angiographic
STRATEGY <sup>28</sup>	2005	Randomized	88	87	•••	8 months	Clinical & angiographic
Cheneau <i>et al.</i> <sup>29</sup>	2005	Non-randomized	504	103	•••	6 months	Clinical
Saia <i>et al.</i> <sup>23</sup>	2003	Single arm registry	•••	89	•••	6 months	Clinical & angiographic
Margheri <i>et al.</i> <sup>24</sup>	2004	Single arm registry	•••	•••	43	4 months	Clinical
T-SEARCH <sup>25</sup>	2005	Non-randomized	•••	186	136	12 months	Clinical
Non-published							
TYPHOON <sup>39</sup>	2006	Randomized	357	355	•••	12 months	Clinical & angiographic
PASSION <sup>40</sup>	2006	Randomized	310	•••	309	12 months	Clinical

RESEARCH: Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital, STRATEGY: Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent vs Abciximab and Bare Metal Stent in Myocardial Infarction, T-SEARCH: Taxus-Stent Evaluated At Rotterdam Cardiology Hospital, TYPHOON: Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty, PASSION: Paclitaxel-Eluting Stent versus Conventional Stent in ST-segment Elevation Myocardial Infarction, BMS: bare metal stent, SES: sirolimus-eluting stents, PES: paclitaxel-eluting stents.

89 patients<sup>23</sup>. Another study analysed short-term clinical outcomes of consecutive 43 patients treated with PES implantation<sup>24</sup>. The latest report made a comparison of the efficacy between PES and SES<sup>25</sup>. The other 4 studies<sup>26-29</sup> assessed the advantage of SES over BMS. We compiled the results of these 4 studies and performed a meta-analysis, as there were no published trial comparing PES with BMS in the clinical setting of AMI. The range of clinical follow-up time varied between 6 and 10 months.

It should be mentioned that the study design and methodology of the four studies included in the present meta-analysis were variable, and all of them were conducted in one single centre. The STRATEGY (Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent vs Abciximab and Bare Metal Stent in Myocardial Infarction) trial<sup>28</sup>, was the only prospective, single blind, randomized controlled study presenting 8 months of follow-up. The Rotterdam study<sup>26</sup>, as a part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry, and the German study<sup>27</sup> adopted a similar methodology. Patients treated with SES were prospectively enrolled and compared to control patients treated with BMS in the immediate preceding period before the introduction of SES. Enrolled patients were followed for 10 and 6 months, respectively. The last study was a retrospective analysis<sup>29</sup>. SES implanted patients were compared to patients treated with BMS in the preceding 5-year period before the approval of SES, and followed up to 6 months. The robustness of each study is variable, so that some limitations may be created in the result of our tentative meta-analysis, which –as we should point out– does not collect individual data of enrolled patients in the 4 studies.

The result of the meta-analysis is shown in the accompanying figure 1. Overall, SES is associated with a 28% relative reduction in all-cause deaths, an 80% relative reduction in target vessel revascularization (TVR), and a 53% relative reduction in major adverse cardiac events (MACE), which include all-cause mortality, non-fatal myocardial infarction, and TVR (we could not analyse the non-fatal myocardial infarction rates because one study<sup>26</sup> did not state the incidence

of this complication separately). These results provide for a better outcome after SES utilization in patients with AMI. Noteworthy, the rate of TVR is similar to values reported in randomized trials of elective SES use.

At follow-up, the incidence of death in patients treated with SES was comparable in 3 studies with the exception of the German study; it was approximately 7% to 8%, which seemed similar to the one observed in the control arms (approximately 8% to 10%). As the German study included patients with not only STE-ACS but also NSTEMI-ACS and excluded patients presenting cardiogenic shock, this might be the explanation that its mortality rate is lower than in the other studies. In the pooled data, short-term (30 days) mortality rate was 3.8% in the SES arm and 3.4% in the BMS arm. Moreover, no angiographic stent thrombosis, including acute, subacute and late thrombosis, was seen in patients treated with SES. In the BMS arm, the subacute thrombosis rate was 1.1%, which is comparable with the incidence of BMS thrombosis in the treatment of patients for stable coronary lesions<sup>30</sup>. No late stent thrombosis was observed in the BMS arm. The fact that patients with DES tended to take antiplatelet therapy during longer period than control patients might affect these results. However, SES is likely to be as safe as BMS and does not seem to increase the thrombotic complications in the clinical setting of AMI at least in both short- and medium-term.

In each study, the medium-term TVR rate in the SES arm was remarkably lower than in the BMS arm. The TVR rate of the pooled data in patients treated with SES was only 2.3%, whereas 11.3% of patients treated with BMS underwent revascularization and this rate was close to the result of previous studies<sup>1-3</sup>. In the STRATEGY trial, the TVR rates in both stent arms were higher than those observed in the other 3 non-randomized trials. The reason for this discrepancy is not readily apparent. The lesions of patients who were enrolled in the STRATEGY trial might have been more complex than those in the other trials. It might also reflect the fact that different glycoprotein IIb/IIIa inhibitors were used in each arm; abciximab

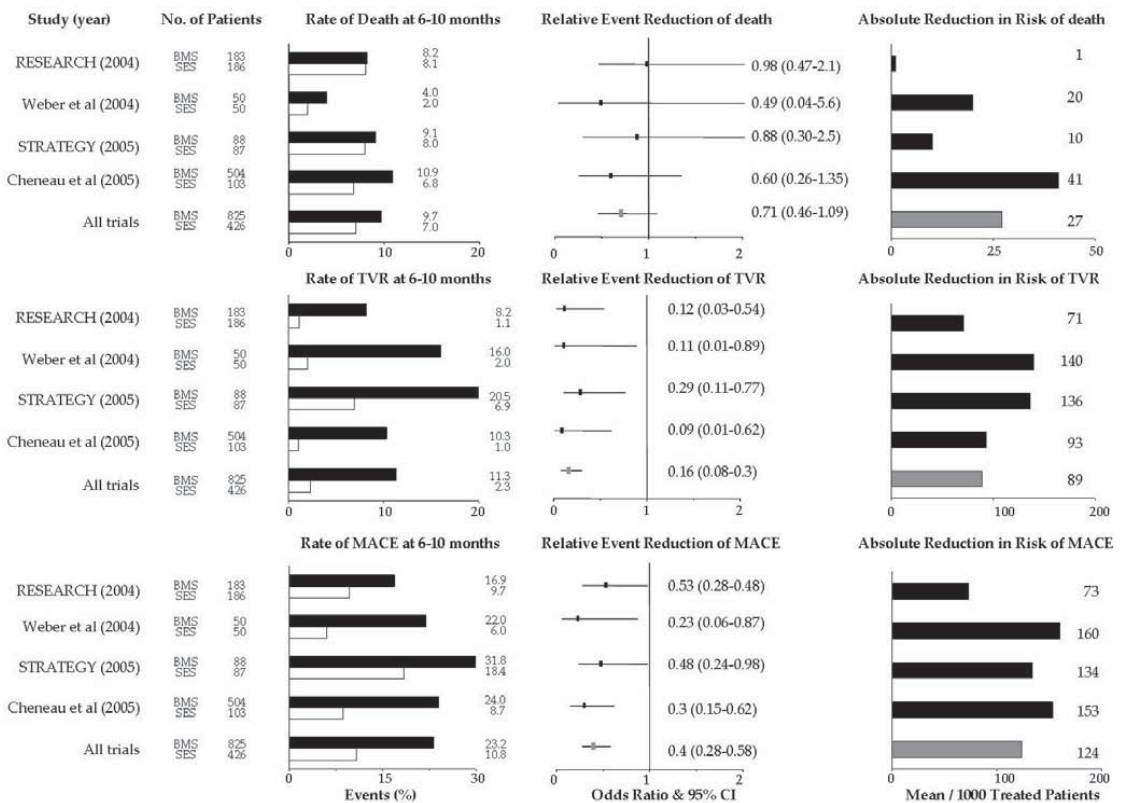


Figure 1. Rates and the relative and absolute reduction in the risk of death, TVR and MACE among patients treated with SES, as compared with those treated with BMS, at six to ten months. Open boxes represent patients treated with SES. Shaded boxes represent patients treated with BMS. Off-white boxes represent overall results. BMS: bare metal stents, SES: sirolimus-eluting stents, RESEARCH: Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital, STRATEGY: Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent vs Abciximab and Bare Metal Stent in Myocardial Infarction, TVR: target vessel revascularization, MACE: major adverse cardiac events, CI: confidential intervals.

was administered in the BMS arm and single high dose bolus tirofiban (25 µg/kg) in the SES arm.

Among the 4 studies, angiographic assessment was systematically performed for enrolled patients in the STRATEGY trial and the German study. Only the first 89 consecutive patients in the RESEARCH registry also underwent angiographic analysis<sup>23</sup>. The late lumen loss in SES arms ranged from -0.22 mm to 0.12 mm and the binary restenosis rate varied from 0% to 11%. Negligible, or very small late lumen loss is associated with a lower incidence of angiographic restenosis as well as a reduced need for TVR, which was well described in many previous trials investigating patients with stable coronary disease<sup>31-34</sup>. Such an angiographic analysis indicated that SES retained its ability of inhibiting neointimal formation even in the clinical setting of AMI. Consequently, the medium-term MACE rate in the SES arm was significantly lower in comparison with the BMS arm (10.8 % vs 23.2%, respectively;  $p < 0.001$ ). Low TVR rates accounted for lower MACE rates in patients treated with SES.

Recent head-to-head (SES vs PES) trials indicated that SES was significantly better at reducing neointimal hyperplasia and had a slight-

ly advantage over PES in clinical outcomes, such as target lesion revascularization (TLR) and TVR<sup>35-37</sup>. Similarly, the study of Hofma *et al.*<sup>25</sup>, which was the only study comparing the efficacy of SES and PES in the clinical setting of AMI and published as a subanalysis of the Taxis-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry<sup>38</sup>, showed a higher rate of TLR, TVR and MACE in the PES arm than in the SES arm. In the PES arm, 2.9% of all patients experienced stent thrombosis, whereas in the present meta-analysis we did not find any stent thrombosis in the pooled SES arms as mentioned previously. Different drug-release kinetics and mechanism of neointimal inhibition between SES and PES might have contributed to the observed difference in their performance. At the present time, we cannot conclude that PES is inferior to SES in patients with AMI. Further investigations are needed to identify which DES is more effective in this clinical setting.

In conclusion, our analysis suggests that SES is a safe and effective device for the prevention of restenosis in the clinical setting of AMI. As a result, the use of SES leads to low TVR and MACE rates, and seems to be superior to BMS even in this subset of patients. SES appears to

be an attractive therapeutic approach for patients admitted with AMI. However, the number of enrolled patients in each study was too small so that they are underpowered to assess definitely the effect of SES on the rate of TVR or MACE. As for PES utilization in AMI, only a few trials were published. Much more information are needed to confirm whether PES implantation in patients with AMI is safe and feasible compared to BMS or SES. To establish the safety and advantage of both DES in AMI, larger randomized trials are imperative.

At the American College of Cardiology 2006 Scientific Sessions, two multi-centre and randomized trials about DES implantation in the clinical setting of AMI were presented: the TYPHOON<sup>39</sup> (Trial to Assess the Use of Cypher stent in Acute Myocardial Infarction treated with Angioplasty) trial and the PASSION<sup>40</sup> (Paclitaxel-Eluting Stent versus Conventional Stent for ST-segment Elevation Myocardial Infarction) trial. The TYPHOON trial included 712 patients and assessed the effectiveness and safety of SES as compared to BMS at 1 year. The TVR rate in patients treated with SES was significantly lower than those who received BMS (5.6% vs 13.4%,  $p < 0.001$ ). The MACE rate was also lower in the SES group (5.9% vs 14.6% in the BMS group,  $p < 0.001$ ). These clinical outcomes confirm the result of our meta-analysis, if not quantitatively at least qualitatively. The PASSION trial, which enrolled 619 patients, was the first trial comparing PES with BMS in the clinical setting of AMI. This trial failed to find an advantage of PES over BMS in terms of MACE (8.7% and 12.6%,  $p = 0.12$ ) and TLR (6.2% and 7.4%,  $p = 0.23$ ) at 1 year. These findings are at variance with the results of the TYPHOON trial. We will have to wait for the results of the HORIZONS trial, in which 3400 patients will be randomized and the superiority of PES over BMS will be investigated.

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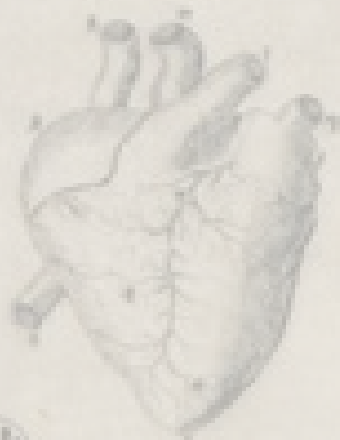
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Chapter 3

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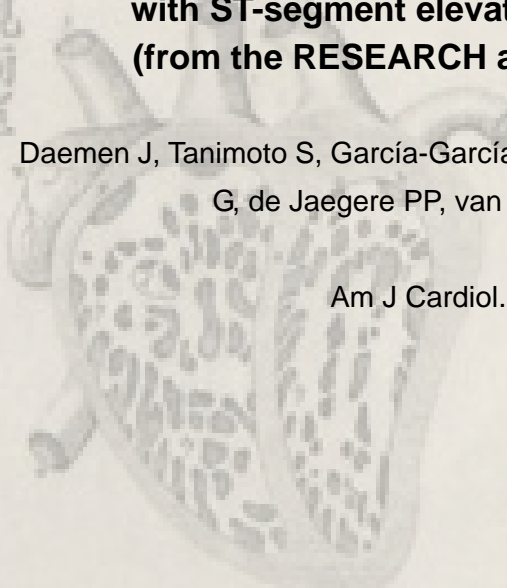
**Comparison of three-year clinical outcome of sirolimus- and paclitaxel-eluting stents versus bare metal stents in patients with ST-segment elevation myocardial infarction. (from the RESEARCH and T-SEARCH Registries)**

全形

Daemen J, Tanimoto S, García-García HM, Kukreja N, van de Sande M, Sianos G, de Jaegere PP, van Domburg RT, Serruys PW.

Am J Cardiol. 2007;99:1027-32

心障膜





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

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

Primary percutaneous coronary intervention, with or without stenting, has been shown to result in superior long-term outcome compared with thrombolytic therapy in patients with acute myocardial infarction (MI).<sup>1</sup> Recently, several studies have reported that sirolimus-eluting stents (SESs) and paclitaxel-eluting stents (PESs) are more effective in decreasing restenosis and the frequency of repeat interventions than are bare metal stents (BMSs), which rapidly resulted in an unrestricted use of drug-eluting stents also in patients with ST-segment elevation MI (STEMI).<sup>2–4</sup> Shortly after the introduction of SESs in 2002 the first studies appeared, hypothesizing that the therapeutic range of SESs could be extended to use in patients presenting with MI. Compared with BMSs, SESs were associated with less restenosis and target vessel revascularization (TVR) up until 1 year of follow-up.<sup>3,5</sup> Currently it is unclear whether this also holds for PESs.<sup>4,6</sup> To date, there are no data on the long-term outcome of the use of SESs and PESs in patients

with STEMI, a growing high-risk subgroup that is becoming a substantial recipient of the total number of percutaneous coronary interventions in many centers all over the world. For that reason, we evaluated the 3-year clinical outcomes of a series of consecutive patients with STEMI treated with BMSs, SESs, or PESs as part of a primary percutaneous coronary intervention strategy.

## Methods

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

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## Chapter 3

Table 1

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

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

Values are percentages of patients or means ± SDs.

\* Defined as a fasting total serum cholesterol level >5.5 mmol/L (210 mg/dl) or use of lipid-lowering therapy.

TIMI = Thrombolysis In Myocardial Infarction.

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

All procedures were performed according to current standard procedural guidelines and their details have been reported previously.<sup>8,9</sup> Baseline and postprocedural flows were evaluated offline according to the Thrombolysis In Myocardial Infarction criteria by cardiologists blinded to

stent group and clinical outcomes. All patients were advised to maintain lifelong aspirin. At least 1 month of clopidogrel treatment (75 mg/day) was recommended for patients treated in the BMS group. In the 2 drug-eluting stents groups, clopidogrel was prescribed for ≥3 months unless multiple SES implantation (>3 stents), total stented length >36 mm, persistent total occlusion, or bifurcations was present. In these cases clopidogrel was prescribed for ≥6 months.

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

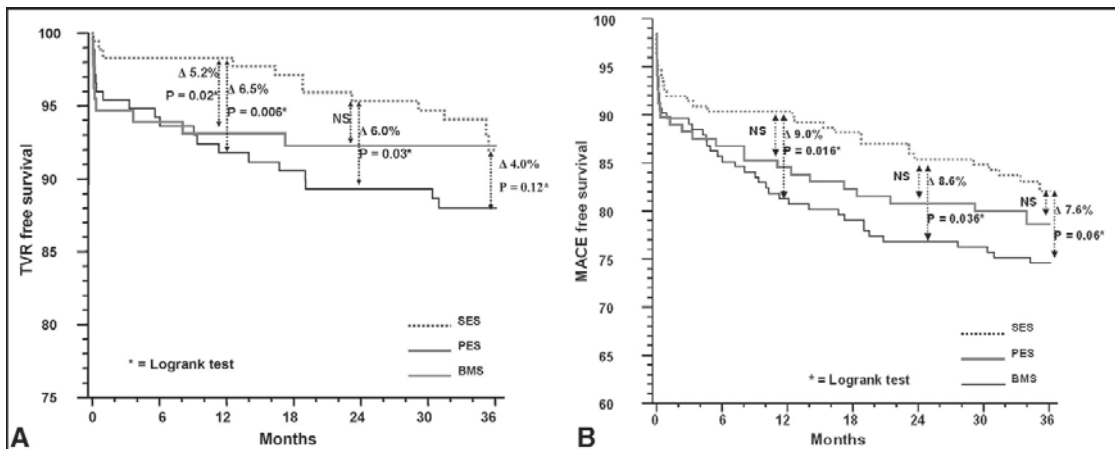


Figure 1. Kaplan-Meier survival curves of (A) TVR and (B) combined cumulative incidence of major adverse cardiac events (MACE; death, MI, and TVR).  $\Delta$  = change.

Table 2

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

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

MACEs = major adverse cardiac events.

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

Three-year survival status was obtained through municipal civil registries. Health questionnaires were subsequently sent to all living patients and inquired about post-

discharge repeat coronary interventions (surgical or percutaneous) and MI. If a patient had an MI or a reintervention at another center, medical records or discharge letters were requested and systematically reviewed. Local cardiologists or general practitioners were contacted if necessary. Follow-up was available for 98% of patients with BMSs, 98% of patients with SESs, and 97% of patients with PESs.

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

Table 3  
Major adverse cardiac events up to three years

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

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

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

## Results

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

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

group and 20.6% in the PES group (Figure 1). Events occurring in the second and third years of follow-up are presented in Table 2.

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

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

## Discussion

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



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

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

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

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

The total incidence of stent thrombosis in this high-risk patient population was 2.4% and was, although mostly due to the longer follow-up, higher than that in previous reports in which stent thrombosis rates were 1.0% to 1.7%.<sup>12,20,21</sup>

The incidence of stent thrombosis in the BMS group in the present study was 1.6% and is in agreement with that in previous reports.<sup>22</sup> Stent thrombosis occurred in 2.9% of patients in the PES group, all within the first week after the index percutaneous coronary intervention. No late stent thrombosis was observed from 1 year to 3 years. This latter observation does not concur with a previous study, which reported late stent thrombosis rates of ~0.8% in patients treated with PESs.<sup>23</sup> However, the occurrence and rate of early stent thrombosis in the PES group was comparable to that in the BMS group, occurring mainly within the first 2 weeks after stent implantation.<sup>24</sup> It is unknown whether the late deaths of unknown cause were due to stent thrombosis.

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

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

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

## Appendix

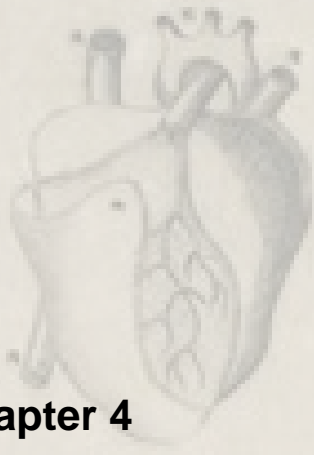
The following operators were involved in the procedures of the discussed patient population: Chourmouziou A. Arampatzis, MD, Eugene McFadden, MD, PhD, Pim J. de Feyter, MD, PhD, Willem J. van der Giessen, MD, PhD, Sjoerd H. Hofma, MD, PhD, Angela Hoye, MBChB, MRCP, Peter P.T. de Jaegere, MD, PhD, Patrick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

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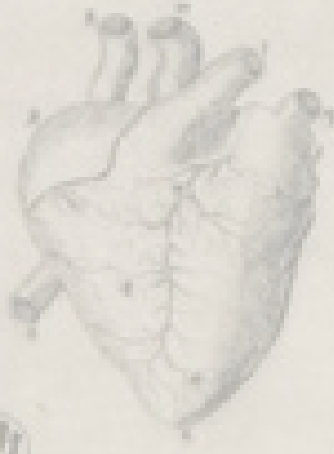
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心篇圖

四脈管及心囊



剖心囊視冠脈



Chapter 4

**Two-year clinical outcome after coronary stenting of small vessels using 2.25mm sirolimus- and paclitaxel-eluting stents: Insight into the RESEARCH and T-SEARCH registries.**

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Cathet Cardiovasc Intervent. 2007;69: 94-103

心障膜



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豎剖心視冠室



# Two-Year Clinical Outcome After Coronary Stenting of Small Vessels Using 2.25-mm Sirolimus- and Paclitaxel-Eluting Stents: Insight Into the RESEARCH and T-SEARCH Registries

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**Objectives:** To evaluate long-term outcomes after drug-eluting stents (DES) implantation in small coronary vessels. **Background:** Sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) have been reported to improve both the angiographic and clinical outcomes compared with bare metal stents even in 'real world' settings. Currently, no data is available on long-term outcomes after DES implantation in small vessels. **Methods:** Since April 2002, our institution has implanted DES, either SES or PES, as a default strategy in all patients irrespective of their clinical presentation. Between October 2002 and September 2003, 197 consecutive patients were enrolled: 107 consecutive patients received at least one 2.25-mm SES (SES group) and 90 consecutive patients received at least one 2.25-mm PES (PES group). **Results:** The two cohorts presented with high-risk characteristics. At 2 years, the cumulative incidence of major adverse cardiac events (MACE) in the SES group was significantly lower than that in the PES group (10.3% vs. 23.3%,  $P = 0.02$ ). There were two subacute angiographic stent thromboses in the PES group and none in the SES group. By multivariate analysis, PES utilization (HR 2.37, 95% CI 1.07–5.26), presentation with acute coronary syndromes (ACS) (HR 3.34, 95% CI 1.44–7.70) and multi-vessel disease (MVD) (HR 3.91, 95% CI 1.27–12.0) were identified as independent predictors of MACE. **Conclusions:** In an unselected population treated for small vessel disease, SES were associated with significantly better 2-year clinical outcomes than PES. The use of PES and the presentation with ACS and MVD were identified as independent predictors of MACE. © 2006 Wiley-Liss, Inc.

**Key words:** coronary artery disease; drug-eluting stents; sirolimus; paclitaxel

## INTRODUCTION

Percutaneous coronary intervention (PCI) is a major treatment strategy for patients with ischemic heart disease, and currently coronary stents are widely used [1]. Bare metal stents (BMS) reduce coronary restenosis and significantly improve the angiographic and clinical outcomes in vessels with a reference diameter (RD) more than 3 mm by their ability to prevent both early elastic recoil and late vascular remodeling, as compared to balloon angioplasty [2–4]. On the other hand, several randomized trials have failed to show an advantage of BMS over balloon angioplasty in vessels with a RD less than 3 mm [5,6]. Therefore, whether stent implantation in small vessels improves outcomes compared to balloon angioplasty alone still remains controversial. At present, however, PCI in small vessels of less than 3 mm accounts for almost 50% of all revascularization procedures and leads to a higher incidence of restenosis and adverse cardiac events [7].

In the last 3–4 years, drug-eluting stents (DES), either sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES), have revolutionized the interventional cardiology practice by reducing restenosis and the need for repeat revascularizations as compared to BMS. Several multicenter randomized trials have evaluated the efficacy of DES for the treatment of vessels with a RD

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less than 3 mm and shown a significant reduction in both restenosis and clinical events [8–11]. More recently, several trials comparing SES with PES were performed [12–17]. The general conclusion from a meta-analysis of these trials is that SES are significantly better at reducing neointimal hyperplasia and confer an advantage over PES in terms of clinical outcomes [18]. However, there is limited information on the relative safety and efficacy of SES compared to PES in patients with small vessel disease [19,20].

Some recent studies have also cautioned that either SES or PES could increase thrombotic complications compared to BMS, especially late stent thrombosis [21,22], due to decreased endothelial function [23], delayed vascular healing [24], and/or hypersensitivity reactions to the polymer coating of the DES and the drug itself [25,26]. Although BMS implantation in small vessels had been previously cited as a risk factor for stent thrombosis [27], improved techniques of optimal stent deployment and dual antiplatelet regimens appear to have largely resolved this problem so that the risk of stent thrombosis in small vessel stenting now seems to be similar to that in larger vessel stenting [28]. But, DES implantation in small vessels may increase the risk of stent thrombosis because of their features as mentioned earlier. Therefore, long-term follow-up as well as short- and medium-term follow-up are needed to determine whether DES implantation is safe in the subset of patients with small vessel disease.

To the best of our knowledge, there is currently no available publication comparing the long-term efficacy of SES and PES for the treatment of small coronary arteries. The present study, which is derived from our previous study population [19], is conducted to compare clinical outcomes in terms of safety and efficacy at 2 years after implantation of 2.25-mm diameter SES and PES.

## MATERIALS AND METHODS

### Study Design and Patient Population

Since April 2002, SES (Cypher<sup>®</sup>; Cordis Corporation, Warren, NJ) have been implanted as the default strategy for every PCI in our institution as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry [29]. This strategy continued until February 2003, when PES (Taxus<sup>™</sup>; Boston Scientific Corporation, Galway, Ireland) implantation became the default strategy for all patients with coronary artery disease as part of the Taxus-Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry [30]. The methods and design of both studies have been described previously [29,30]. Both trials evaluated the safety and efficacy of SES and PES implantation for patients treated in daily

practice. All patients were included irrespective of their clinical presentation and lesion characteristics.

Between October 2002 and September 2003, a total of 197 consecutive patients were enrolled: 107 patients received at least one 2.25-mm diameter SES (SES group) and 90 patients received at least one 2.25-mm diameter PES (PES group). The study protocol was approved by the institutional ethics committee, and all patients provided written informed consent.

### Procedures and Postinterventional Medications

All procedures were performed in accordance with standard techniques. The interventional strategy and use of glycoprotein IIb/IIIa inhibitors were left entirely to the discretion of the operator. All patients were advised to take aspirin lifelong (at least 80 mg/day). A loading dose of 300 mg clopidogrel was given before the intervention. Postprocedural clopidogrel treatment (75 mg/day) differed between the two groups. For patients treated with SES, clopidogrel was prescribed for at least 3 months, unless one of the following was present (in which case clopidogrel was maintained for at least 6 months): multiple SES implantation ( $\geq 3$  stents), total stent length  $\geq 36$  mm, chronic total occlusion, and bifurcations. Patients treated with PES were prescribed at least 6 months of clopidogrel in accordance with the product labeling and instructions for use, based on existing data from randomized, controlled trials [31]. The methodology of quantitative coronary angiography (QCA) evaluation has been described previously [19].

### Definition and Follow-Up

Patients were prospectively followed-up for the incidence of major adverse cardiac events (MACE), which included all-cause mortality, nonfatal myocardial infarction, and target lesion revascularization (TLR) or target vascular revascularization (TVR). Myocardial infarction (MI) was diagnosed by a rise in the creatine kinase-MB fraction (CK-MB) of more than three times the upper limit of normal, according to the American Heart Association/American College of Cardiology guidelines [32]. TLR was defined as a repeat intervention (surgical or percutaneous) to treat a luminal stenosis within the stent or in the 5-mm distal or proximal segments adjacent to the stent. TVR was defined as a reintervention driven by any lesions located in the same treated epicardial vessel. Stent thrombosis was defined as angiographically documented complete occlusion (TIMI flow grade 0 or 1) or flow-limiting thrombus (TIMI flow grade 1 or 2) in previously successfully treated artery. Information about the in-hospital outcomes was derived from our institutional electronic clinical database and by review of the hospital



**TABLE I. Baseline Characteristics**

	SES (n = 107)	PES (n = 90)	P value
Age (years $\pm$ SD)	61.3 $\pm$ 11.1	62.9 $\pm$ 12.4	0.34
Male, n (%)	75 (70.1)	59 (65.6)	0.54
Diabetes mellitus, n (%)	20 (18.7)	20 (22.2)	0.6
Type I, n (%)	6 (5.6)	6 (6.7)	0.77
Type II, n (%)	14 (13.1)	14 (15.6)	0.68
Hypertension, n (%)	47 (43.9)	44 (48.9)	0.57
Hypercholesterolemia, n (%)	72 (67.3)	55 (61.1)	0.38
Family history, n (%)	35 (32.7)	48 (53.3)	0.004
Current smoking, n (%)	20 (18.7)	28 (31.3)	0.047
Previous myocardial infarction, n (%)	35 (32.7)	40 (44.4)	0.11
Previous angioplasty, n (%)	28 (26.2)	25 (27.8)	0.87
Previous coronary bypass surgery, n (%)	9 (8.4)	6 (6.7)	0.79
Vessel disease			0.91 <sup>a</sup>
1-vessel disease, n (%)	33 (30.8)	24 (26.7)	
2-vessel disease, n (%)	42 (39.3)	44 (48.9)	
3-vessel disease, n (%)	32 (29.9)	22 (24.4)	
Multivessel disease, n (%)	74 (69.2)	66 (73.3)	0.53
Clinical presentation			0.86 <sup>a</sup>
Stable angina, n (%)	61 (57.0)	52 (57.8)	
Unstable angina, n (%)	33 (30.8)	28 (31.1)	
Acute myocardial infarction, n (%)	13 (12.1)	10 (11.1)	
Acute coronary syndrome, n (%)	46 (43.0)	38 (42.2)	1.00
Left ventricular ejection fraction (%)	50.4 $\pm$ 9.70	51.2 $\pm$ 9.50	0.61
Number of implanted stents/patients $\pm$ SD	1.40 $\pm$ 0.69	1.31 $\pm$ 0.57	0.32
Total stent length/patient (mm $\pm$ SD)	23.4 $\pm$ 14.5	21.6 $\pm$ 11.1	0.35
Number of lesions/patient $\pm$ SD	1.50 $\pm$ 0.71	1.63 $\pm$ 0.77	0.19
Glycoprotein IIb/IIIa use, n (%)	33 (30.8)	30 (33.3)	0.76

<sup>a</sup>Across all groups.

records of those discharged to referring hospitals. Postdischarge survival status was obtained from the municipal civil registries. Health questionnaires were subsequently sent to all living patients, inquiring about postdischarge repeat coronary interventions (either surgical or percutaneous) and the occurrence of MI. All repeat interventions and rehospitalizations were prospectively collected during follow-up. Referring physicians and institutions were contacted for additional information if required.

### Statistical Analysis

Continuous variables were presented as mean  $\pm$  SD and were compared by means of the Student's unpaired *t* test. Categorical variables were presented as counts and percentages and compared by means of the  $\chi^2$  test or Fisher's exact test. The cumulative incidence of adverse events was estimated according to the Kaplan–Meier method and compared by the log rank test. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. Multivariate analyses were performed to identify independent predictors of adverse events, using all clinical, angiographic, and procedural variables included in Tables I and II. Cox proportional hazards survival models were used to assess risk reduction of adverse events. The hazard ratio (HR) and its 95%

confidence intervals (CI) were computed for outcome measures. A *P* value of <0.05 was considered statistically significant.

## RESULTS

### Patient Characteristics

Table I shows baseline characteristics of the study population. No significant differences were observed between both groups apart from a higher prevalence of smoking and family history of coronary artery disease in the PES group. A large number of patients with previous history of MI (38.1%), multi-vessel disease (MVD) (71.1%), and acute coronary syndromes (ACS) (42.6%) were enrolled. The number of implanted stents and total stent length per patient were similar in both groups.

### Baseline Angiographic and Procedural Characteristics

Baseline angiographic and procedural data are displayed in Table II. There were 127 lesions in the SES group and 97 lesions in the PES group. A larger stent, in addition to 2.25-mm stent, was deployed in 76.6 and 85.6% of SES and PES patients (*P* = 0.11). The reasons for stenting with a 2.25-mm device were reported in detail in a previous paper [19]. A high

**TABLE II. Angiographic and Procedural Characteristics**

	SES ( <i>n</i> = 127)	PES ( <i>n</i> = 97)	<i>P</i> value
Treated vessel			
Right coronary artery, <i>n</i> (%)	20 (15.7)	9 (9.3)	0.17
Left anterior descending, <i>n</i> (%)	29 (22.8)	25 (25.8)	0.64
Diagonal, <i>n</i> (%)	31 (24.4)	18 (18.6)	0.33
Left circumflex, <i>n</i> (%)	35 (27.6)	25 (25.8)	0.88
Obtuse or intermediate marginal, <i>n</i> (%)	12 (9.4)	18 (18.6)	0.07
Bypass graft, <i>n</i> (%)	0 (0)	2 (2.1)	0.19
ACC/AHA modified lesion classification			
Type A or B1, <i>n</i> (%)	58 (45.7)	38 (39.2)	0.34
Type B2 or C, <i>n</i> (%)	69 (54.3)	59 (60.8)	0.34
Calcification (moderate/severe), <i>n</i> (%)			
	15 (11.8)	7 (7.2)	0.37
Thrombus, <i>n</i> (%)			
	10 (7.9)	8 (8.2)	1.00
Ostial, <i>n</i> (%)			
	36 (28.3)	15 (15.5)	0.025
Bifurcation, <i>n</i> (%)			
	32 (25.2)	24 (25.3)	1.00
Total occlusion, <i>n</i> (%)			
	33 (26.0)	22 (22.7)	0.64
TIMI grade 3 flow post procedure, <i>n</i> (%)			
	122 (96.0)	95 (97.9)	0.70
Number of stent/lesion $\pm$ SD			
	1.17 $\pm$ 0.42	1.21 $\pm$ 0.48	0.58
Total stent length/lesion (mm $\pm$ SD)			
	19.8 $\pm$ 10.9	19.8 $\pm$ 9.5	0.99
Direct stenting, <i>n</i> (%) $\pm$ SD			
	65 (51.2)	58 (60.4)	0.22
Postdilatation, <i>n</i> (%) $\pm$ SD			
	30 (23.6)	18 (18.6)	0.41
Max. pressure (atm $\pm$ SD)			
	16.0 $\pm$ 3.3	14.9 $\pm$ 3.0	0.046
Quantitative coronary angiography analysis			
Pre			
Reference diameter (mm $\pm$ SD)	1.86 $\pm$ 0.37	1.95 $\pm$ 0.38	0.15
Minimal lesion diameter (mm $\pm$ SD)	0.47 $\pm$ 0.38	0.57 $\pm$ 0.38	0.06
Diameter stenosis (% $\pm$ SD)	74.8 $\pm$ 20.1	70.3 $\pm$ 19.3	0.10
Lesion length (mm $\pm$ SD)	13.0 $\pm$ 8.5	16.4 $\pm$ 10.4	0.02
Post			
Minimal lesion diameter (mm $\pm$ SD)	1.73 $\pm$ 0.31	1.82 $\pm$ 0.36	0.06
Diameter stenosis (% $\pm$ SD)	12.3 $\pm$ 10.0	14.0 $\pm$ 9.80	0.19

ACC, American College of Cardiology; AHD, American Heart Association; TIMI, Thrombolysis In Myocardial Infarction.

prevalence of bifurcation lesions was observed in the entire cohort (25.0%). The prevalence of target lesions located at an ostium was significantly higher in the SES group than in the PES group (28.3% vs. 15.5%,  $P = 0.025$ ). The mean maximal pressure at stent deployment was significantly higher in the SES group (16.0  $\pm$  3.3 atm vs. 14.9  $\pm$  3.0 atm in the PES group,  $P = 0.046$ ). The number of implanted stents and total stent length per lesion were comparable between the two groups. By QCA analysis, the minimal lesion diameter both pre- and post-PCI was smaller in the SES group (0.47  $\pm$  0.38 mm and 1.73  $\pm$  0.31 mm vs. 0.57  $\pm$  0.38 mm and 1.82  $\pm$  0.36 mm in the PES group;  $P = 0.06$  and 0.06, respectively), whereas lesion length was significantly longer in the PES group than in the SES group (16.4  $\pm$  10.4 mm vs. 13.0  $\pm$  8.5 mm;  $P = 0.02$ ).

### Clinical Outcome

Two-year follow-up data were obtained for 105 patients (98.1%) in the SES group and 89 patients (98.9%) in the PES group. MACE was analyzed at 1

month (30 days), 1 year (365 days), and 2 years (730 days) (Table III).

### One-Month (30 Days) and One-Year (365 Days) Follow-Up

The 1-month and 1-year clinical outcomes have been previously reported [19]. Briefly, three patients died in the first month (2 PES and 1 SES); all these patients presented with MVD and ACS on their admission and died of cardiac cause. There were two episodes of angiographically documented subacute thrombosis in the PES group (2.2%) and none in the SES group ( $P = 0.21$ ). These two patients who presented with stent thrombosis were alive at 2-year follow-up.

At 1 year, one patient (0.9%) died in the SES group, and four patients (4.3%) died in the PES group ( $P = 0.18$ ): their causes of death were cardiac. The incidence of TLR, TVR, and TVR-MACE was more frequent in the PES group, but it did not reach statistical significance (11.1, 12.2, and 18.9% vs. 6.5, 7.5, and 9.3% in the SES group;  $P = 0.31$ , 0.33, and 0.06, respectively). TLR-MACE rate was significantly lower



**TABLE III. Major Adverse Cardiac Events**

Events		SES (n = 107)	PES (n = 92)	P value <sup>a</sup>	
30 days	Death, n (%)	1 (0.9)	2 (2.2)	0.59	
	MI, n (%)	3 (2.8)	6 (6.7)	0.31	
	TLR, n (%)	3 (2.8)	5 (5.6)	0.47	
	TVR, n (%)	3 (2.8)	5 (5.6)	0.47	
	Death or MI, n (%)	4 (3.7)	7 (7.8)	0.35	
	TLR MACE, n (%)	5 (4.7)	11 (12.2)	0.07	
	TVR MACE, n (%)	5 (4.7)	11 (12.2)	0.07	
	Stent thrombosis <sup>b</sup>	0 (0)	2 (2.2)	0.21	
	365 days	Death, n (%)	1 (0.9)	4 (4.3)	0.18
		MI, n (%)	3 (2.8)	7 (7.8)	0.19
TLR, n (%)		7 (6.5)	10 (11.1)	0.31	
TVR, n (%)		8 (7.5)	11 (12.2)	0.33	
Death or MI, n (%)		4 (3.7)	9 (10.0)	0.09	
TLR MACE, n (%)		9 (8.4)	17 (18.9)	0.04	
TVR MACE, n (%)		10 (9.3)	17 (18.9)	0.06	
Stent thrombosis <sup>b</sup>		0 (0)	2 (2.2)	0.21	
730 days		Death, n (%)	2 (1.9)	7 (7.6)	0.08
		MI, n (%)	3 (2.8)	7 (7.6)	0.19
	TLR, n (%)	7 (6.5)	11 (12.2)	0.22	
	TVR, n (%)	8 (7.5)	12 (13.3)	0.24	
	Death or MI, n (%)	5 (4.7)	12 (13.3)	0.04	
	TLR MACE, n (%)	10 (9.3)	21 (23.3)	0.01	
	TVR MACE, n (%)	11 (10.3)	21 (23.3)	0.02	
	Stent thrombosis <sup>b</sup>	0 (0)	2 (2.2)	0.21	
	366–730 days	Death, n (%)	1 (0.9)	3 (3.3)	0.33
		MI, n (%)	0 (0)	0 (0)	
TLR, n (%)		0 (0)	1 (1.1)	0.46	
TVR, n (%)		0 (0)	1 (1.1)	0.46	
Death or MI, n (%)		1 (0.9)	3 (3.3)	0.33	
TLR MACE, n (%)		1 (0.9)	4 (4.3)	0.18	
TVR MACE, n (%)		1 (0.9)	4 (4.3)	0.18	
Stent thrombosis <sup>b</sup>	0 (0)	0 (0)			

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

<sup>a</sup>By Fisher's exact test or the  $\chi^2$ -test.

<sup>b</sup>Angiographically documented stent thrombosis.

in the SES group (8.4% vs. 18.9% in the PES group;  $P = 0.04$ ). Angiographic late stent thrombosis, which was defined as occurring 30 days after stent implantation, was not seen during the first year.

### Two-Year (730 Days) Follow-Up

At 2 years, there were two deaths (1.9%) in the SES group and seven deaths (7.6%) in the PES group ( $P = 0.08$ ). The combined endpoint of death and MI was significantly different between the two groups (4.7% in the SES group and 13.3% in the PES group;  $P = 0.04$ ). An event-free survival rate of this composite endpoint is shown in Fig. 1 (log rank  $P = 0.031$ , by Kaplan–Meier estimate). The prevalence of TLR and TVR was lower in the SES group compared to the PES group, but did not achieve statistical significance ( $P = 0.22$  and  $0.24$ , respectively). The 2-year incidence of TVR-MACE was significantly higher in the PES group (23.3% vs. 10.3%

in the SES group;  $P = 0.02$ ), with a MACE-free survival rate of 76.6 and 89.7% in patients treated with PES and SES, respectively (log rank  $P = 0.012$ , by Kaplan–Meier estimate) (Fig. 2).

### Events From One (365 Days) to Two Years (730 Days)

Between 1 and 2 years, five events occurred. There was one death in the SES group and three deaths in the PES group ( $P = 0.33$ ); noncardiac death was observed in one patient in the SES group, the causes of death in the PES group were one cardiac and two unknown. No patient in either group experienced MI or late angiographic stent thrombosis during this period. Including TLR, there was only one additional TVR in the PES group and none in the SES group ( $P = 0.46$ ).

### Multivariate Predictors of Outcomes

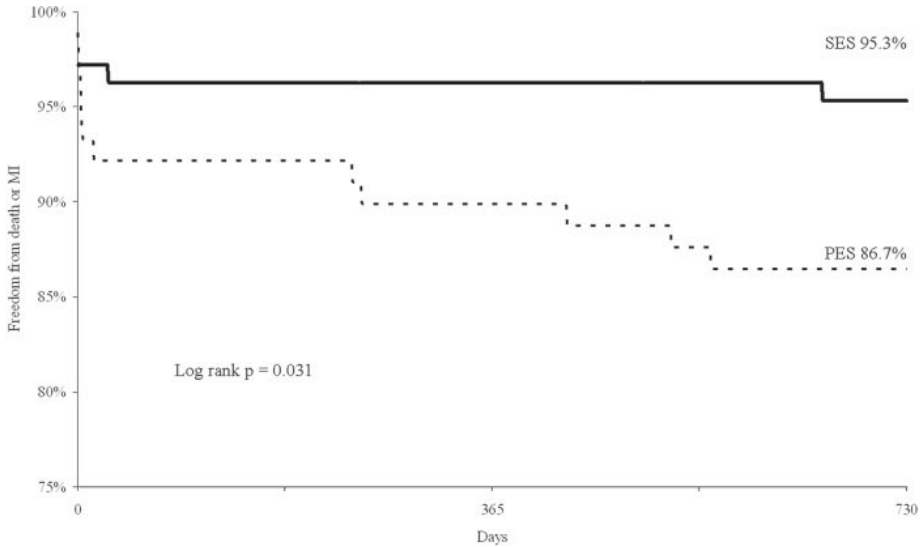
Cox regression analysis was performed to identify independent predictors of MACE and the composite endpoint of death and MI at 2 years (Table IV). PES utilization (HR 2.37, 95% CI 1.07–5.26;  $P = 0.03$ ), the presentation with ACS (HR 3.34, 95% CI 1.44–7.70;  $P = 0.005$ ) and MVD (HR 3.91, 95% CI 1.27–12.0;  $P = 0.017$ ) were found to be significant independent predictors of the 2-year MACE rate. Significant predictors of the 2-year composite endpoint of death or MI included PES utilization (HR 4.48, 95% CI 1.19–16.79;  $P = 0.03$ ), the presentation with ACS (HR 4.46, 95% CI 1.14–17.46;  $P = 0.03$ ) and diabetes mellitus (HR 5.54, 95% CI 1.65–18.62;  $P = 0.006$ ). Hypercholesterolemia was found to be a protective factor for the 2-year composite endpoint of death or MI (HR 0.16, 95% CI 0.04–0.59;  $P = 0.006$ ).

### DISCUSSION

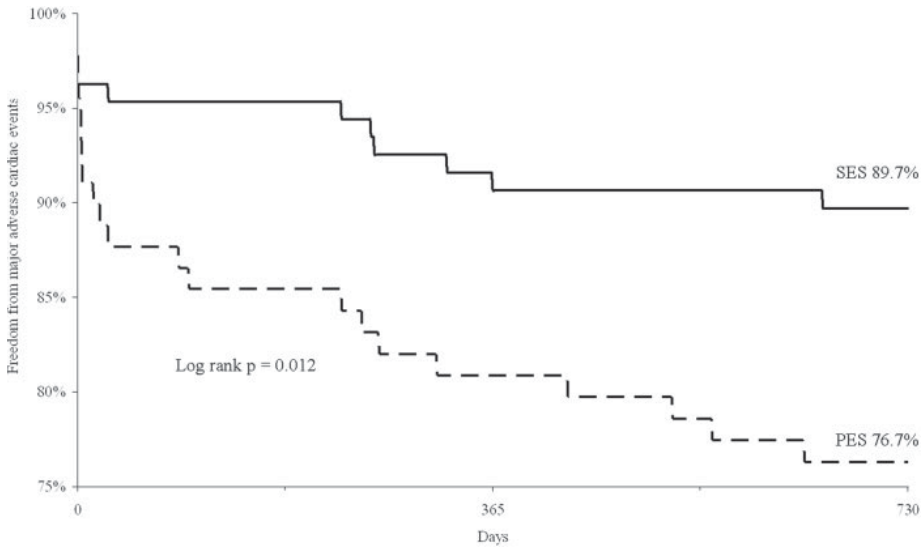
The main findings of this study were (1) SES implantation significantly reduced the incidence of MACE at 2 years as compared to PES implantation, (2) the use of PES and the presence of ACS and MVD were independent factors of 2-year MACE, and (3) the efficacy of the SES was maintained up to 2 years in a very challenging real world population.

### Study Population

It is noteworthy that the overall population included in this study had a markedly increased risk of adverse outcomes. We included clinical and procedural subsets commonly excluded from most studies such as patients with acute MI, totally occluded vessels, left ventricular



**Fig. 1.** Survival free of the composite of death or myocardial infarction of patients treated with sirolimus-eluting stents (SES) versus paclitaxel-eluting stents (PES) by Kaplan-Meier estimate up to 2 years.



**Fig. 2.** Survival free of major adverse cardiac events (MACE) of patients treated with sirolimus-eluting stents (SES) versus paclitaxel-eluting stents (PES) by Kaplan-Meier estimate up to 2 years.

dysfunction, and thrombotic and calcified lesions. Indeed, there was a marked high prevalence of patients with MVD (71.1%), ACS (42.6%), and chronic total

occlusion (24.4%) in the present study. In addition, mean RD of the target vessels was particularly small ( $1.90 \pm 3.8$  mm).

**TABLE IV. Independent Predictors of MACE and the Composite Endpoint of Death or MI at 2-Year Follow-Up**

	MACE at 2 years		Death or MI at 2 years	
	HR	<i>P</i> value	HR	<i>P</i> value
PES utilization	2.37 (1.07–5.26) <sup>a</sup>	0.03	4.48 (1.19–16.79)	0.03
Acute coronary syndrome	3.34 (1.44–7.70)	0.005	4.46 (1.14–17.46)	0.03
Multivessel disease	3.91 (1.27–12.0)	0.02	2.32 (0.46–11.74)	0.31
Diabetes mellitus	1.56 (0.66–3.68)	0.31	5.54 (1.65–18.62)	0.006
Hypercholesterolemia	0.55 (0.25–1.19)	0.13	0.16 (0.04–0.590)	0.006

MACE, major adverse cardiac events; MI, myocardial infarction; PES, paclitaxel-eluting stents; HR, hazard ratio; CI, confidence intervals.

<sup>a</sup>Values in parentheses are 95% CI.

**TABLE V. Published Papers on Drug-Eluting Stent Implantation in Patients With Very Small Vessels**

	Study											
	SES-SMART [35]			TAXUS V subanalysis [36]			ISAR-SMART 3 [20]			The present study		
Trial design	Randomized trial			Randomized trial			Randomized trial			Nonrandomized		
Clinical follow-up (month)	8			9			12			24		
Angiographic follow-up	8			9			6–8			NA		
Stent	SES	BMS	<i>P</i> value	PES	BMS	<i>P</i> value	SES	PES	<i>P</i> value	SES	PES	<i>P</i> value
No. of patients, <i>n</i>	129	128		108	95		198	204		107	92	
Reference diameter (mm)	2.22	2.17	0.15	2.07	2.10	0.46	2.44	2.40	0.34	1.86	1.95	0.15
Lesion length (mm)	13.0	10.7	<0.01	16.6	16.4	0.91	12.9	11.7	0.12	13.0	16.4	0.02
In-stent restenosis (%)	4.9	49.1	<0.01	24.7	44.7	<0.01	8.0	14.9	0.04	NA	NA	NA
TLR (%)	7.0	21.1	<0.01	10.4	21.5	0.03	6.6	14.7	0.008	6.5	12.2	0.22
MACE (%)	9.3	31.3	<0.01	18.9	26.9	0.23	NA	NA	NA	10.3	23.3	0.02
Stent thrombosis (%)	0.8	3.1	0.21	1.0	1.1	>0.99	NA	NA	NA	0.0	2.2	0.21

TLR, target lesion revascularization; MACE, major adverse cardiac events; SES, sirolimus-eluting stents; PES, paclitaxel-eluting stents; BMS, bare metal stents; NA, not available.

## Clinical Results

Small vessel size is known to be an independent predictive factor of restenosis after PCI [33]. It remains controversial whether BMS placement in small vessels less than 3 mm in diameter is actually superior to balloon angioplasty. The latest meta-analysis on small vessel stenting reported that rates of restenosis and MACE in patients treated with BMS were 27.8 and 17.6%, respectively [34]. This high restenosis rate is due to the fact that absolute late lumen loss after stenting in small vessels is similar to that in large vessels so that even a small volume of neointimal hyperplasia induce a diameter stenosis more than 50% in small vessels more easily than in large vessels [28]. The high incidence of angiographic restenosis could lead to high MACE rates in this clinical setting.

The advent of DES, which markedly inhibited neointimal hyperplasia and reduced restenosis, created the expectation of reducing restenosis substantially in patients with small vessels. Indeed, several randomized studies have demonstrated that both DES resulted in remarkably low angiographic restenosis rates (~0–6%) and revascularization rates (~3–4%) as compared to BMS for the treatment of vessels with a RD of less

than 3 mm [8–11]. But in some trials, which focused on DES implantation in small vessels (mean RD less than 2.5 mm), the incidence of cardiac events was relatively high and differed between SES and PES utilization (Table V). The SES-SMART trial [35], which enrolled patients with small vessels (mean RD was 2.2 mm), showed that the incidence of TLR and MACE in the SES arm was 7.0 and 9.3%, respectively. The subanalysis of TAXUS V trial [36], in which patients treated with 2.25-mm diameter PES were included and mean RD was 2.08 mm, indicated that the TLR and MACE rates were 10.4 and 18.9%, respectively. The most important conclusion of the subanalysis of TAXUS V was that there was no significant difference between the MACE rates in the PES and BMS arms despite considerably lower rates of angiographic restenosis and TLR in the PES arm when compared with the BMS arm. The ISAR-SMART 3 study [20] was a head-to-head comparative trial (SES vs. PES) for patients with small vessel disease (mean RD was about 2.4 mm), and reported that SES was more effective in reducing restenosis and TLR when compared with PES (8.0 and 6.6% in the SES group vs. 14.9 and 14.7% in the PES group; *P* = 0.04 and 0.008, respectively). Interestingly, our clinical results

in the two arms at 1 year were comparable to these three trials, though the mean RD of the entire cohort was smaller (mean RD 1.90 mm) and the present populations were at higher risk of clinical events as mentioned above. In addition, our results, like those in the ISAR-SMART 3 trial, also indicated that the SES tended to have a lower 1-year TLR rate as compared to the PES (6.5% vs. 11.1%;  $P = 0.31$ ). Moreover, by multivariate analysis, the use of SES rather than PES was found to be an independent protective factor for the prevention of MACE at 2 years in the present study.

Considering these results, it can be said that the SES is likely to be more effective than the PES in this clinical setting. This propensity was verified by the results of recent large head-to-head, randomized controlled trials [13–15,17,18], which indicated that SES was significantly better at reducing neointimal hyperplasia and had a slight advantage in clinical outcomes when compared with PES. Different drug-release kinetics and mechanisms of inhibiting neointimal hyperplasia between SES and PES presumably accounts for the observed difference in their performance. However, it is difficult to directly compare previous trials with the present study because the inclusion criteria and endpoints of each study were different. In addition, the number of enrolled patients in each study was too small and underpowered to definitely assess the effect of DES on the rate of TVR or MACE in this patient population. Moreover, it is worth emphasizing that to date the ISAR-SMART 3 trial is the only randomized controlled prospective study comparing the efficacy of SES with that of PES in patients with small vessels. Further investigations are needed to identify which DES is more effective than the other in this particular clinical setting.

### **Safety Concerns of DES Implantation in Small Vessels**

After DES were approved, these devices were implanted in a large number of patients with coronary artery disease and many trials indicated the use of them to be feasible and safe. Recently, however, certain potential issues with their use have been raised. One of the problems was delayed restenosis, which was usually called a “late catch-up phenomenon” and noticed as a complication following brachytherapy. This concern has been fueled by findings in the porcine model [37,38]. In humans, continued hyperplastic growth of neointima during the follow-up period was noted in some trials in which serial intravascular ultrasound analyses were performed [39–41]. The precise reason for this observation is still unclear. Delayed neointimal hyperplasia could cause a high incidence of

TLR and MACE with long-term follow-up. The present study showed only one patient treated with PES presented with TLR in the second year of follow-up. This result might suggest an absence of the late catch-up phenomenon within these small vessels. All we can mention with certainty in the present study is that the efficacy of DES, especially SES, was maintained up to 2 years.

Late stent thrombosis is another topical issue following DES deployment. Our result demonstrated that in the entire cohort the overall angiographic stent thrombosis rate was 1.0% and no late stent thromboses were seen. This incidence rate seems acceptable. However, it should be mentioned that not all patients suffering from stent thrombosis underwent coronary angiography. Indeed, as indicated in the results section, three patients in our study who died suddenly during the first month after stent implantation were suspected of having subacute stent thrombosis but they could not be confirmed as having stent thrombosis in the absence of coronary angiography. To assess this rare and unexpected late complication precisely, a much larger sample size and long-term follow-up are needed. Nevertheless, this study provides some reassurance about this safety concern for both DES in the small vessel subsets.

### **Independent Factors of Late Cardiac Events**

Besides the use of PES, the presence of ACS and MVD were also independent predictive factors of 2-year TVR-MACE. These factors are well known to be predictors of restenosis and late cardiac adverse events. The patients receiving small vessel stenting, who presented with ACS and MVD on admission, should be attended and followed-up carefully. ACS as well as diabetes mellitus, in addition to the use of PES, were also significant predictive factors for the composite endpoint of death or MI. To prevent the onset of ACS, detecting vulnerable patients early is very important. It is imperative that intensive glucose control physically and pharmaceutically is implemented to reduce late cardiac events. Curiously, in our multivariate analysis, the presence of hypercholesterolemia was a protective factor for the composite endpoint of death or MI. This result is not easy to explain.

### **Study Limitation**

This study presents several limitations related to its small sample size, nonrandomized nature, and lack of a true control group. The fact that a large percentage of the population enrolled in the present study were simultaneously treated with larger stent size DES (more than 2.25 mm) might have influenced the accuracy of our result. Another potential limitation is that

each group was treated in different time periods. This might lead to some bias in terms of patient selection and affect procedural characteristics, as treatment strategy has evolved over time. However, it should be noted that this study enrolled consecutive patients treated in daily practice: we enrolled all comers and had no exclusion criteria. To definitively address the efficacy and safety of each DES in patients with small coronary arteries, larger head-to-head randomized trials are needed.

## CONCLUSIONS

In an unselected population treated for small vessel disease, SES was associated with significantly better 2-years clinical outcomes, especially MACE, when compared with PES. The use of PES and the presence of MVD and ACS were independent predictors of 2-year MACE. The efficacy and safety of SES utilization was maintained up to 2 years.

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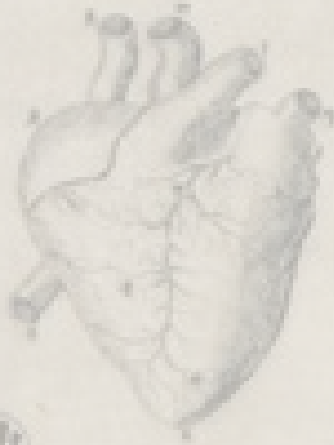
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心篇圖

四脈管及心囊



剖心囊視冠脈



Chapter 5

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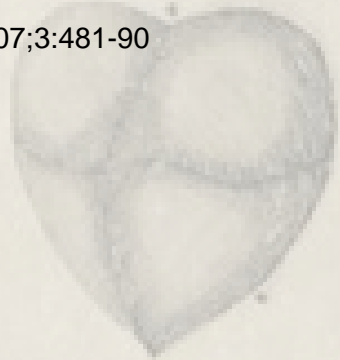
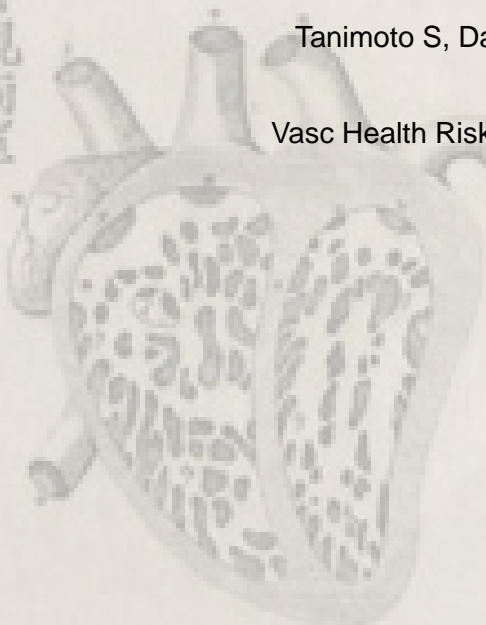
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Recent studies on the TAXUS stent system in small vessels.

Tanimoto S, Daemen J, Serruys PW.

Vasc Health Risk Manag. 2007;3:481-90

全形



心障膜







# Update on stents: Recent studies on the TAXUS<sup>®</sup> stent system in small vessels

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**Abstract:** Small vessel size (<3 mm) has been identified as an independent predictive factor of restenosis after percutaneous coronary intervention when using bare metal stents (BMS). It remains controversial whether BMS placement in small vessels has an advantage over balloon angioplasty in terms of angiographic and clinical outcomes. The advent of drug eluting stents (DES), either paclitaxel-eluting stents (PES) or sirolimus-eluting stents (SES), has strongly impacted interventional cardiology by significantly reducing restenosis and the need for repeat revascularization. Therefore, it was also expected that DES could substantially reduce restenosis in smaller vessels. However, even in the DES era, small vessel size remains an independent predictor of angiographic and clinical restenosis. To date, only a few studies systematically investigate the clinical effect of DES placement in small vessels. In addition, some potential issues with the use of DES have been raised, such as late stent thrombosis and late restenosis. In order to (i) establish the superiority of DES over BMS; (ii) verify the efficacy and safety of DES; and (iii) critically assess the superiority of one DES over the other in patients with small coronary arteries, further multicenter, randomized clinical trials with larger sample size are warranted.

**Keywords:** paclitaxel, stent, coronary artery disease, restenosis

## Introduction

Percutaneous coronary intervention (PCI) is a major treatment strategy for patients with coronary artery disease (CAD), and currently coronary stents are widely used in the world (Brophy et al 2003). As compared to balloon angioplasty, bare metal stents (BMS) prevent both early elastic recoil and late vascular remodeling. These abilities of BMS reduce coronary restenosis and significantly improve the angiographic and clinical outcomes in vessels with a reference vessel diameter (RVD) typically more than 3 mm as assessed by quantitative coronary angiography (QCA) (Serruys et al 1994; Fischman et al 1994; Macaya et al 1996; Betriu 1999; Kiemeneij 2001). On the contrary, in terms of stent implantation in vessels with a RVD = 3 mm, several randomized trials have failed to show an advantage of BMS over balloon angioplasty (Kastrati et al 2000; Park et al 2000; Koning et al 2001; Moer et al 2001). A recent meta-analysis of small vessel BMS stenting reported that rates of restenosis, repeat revascularization and major adverse cardiovascular events (MACE; defined as death, myocardial infarction (MI), and repeat revascularization) were 27.8 %, 14.9% and 17.6%, respectively (Agostini et al 2005). The high observed restenosis rate (27.8%) may be attributed to a comparable absolute late lumen loss after stenting in both small and large vessels: a similar small volume of neointimal hyperplasia would induce a diameter stenosis = 50% in small vessels more easily compared to large vessels by virtue of their smaller RVD (Akiyama et al 1998). The higher angiographic restenosis rate may translate into high repeat revascularization and MACE rates in the

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clinical setting. In addition, small vessel size is known to be an independent predictive factor of restenosis after PCI (Bauters et al 1998; Serruys et al 1999). Therefore, it remains controversial whether BMS implantation in small vessels improves outcomes compared to balloon angioplasty alone. At present, however, PCI in small vessels with a RVD <3 mm accounts for almost 50% of all revascularization procedures and leads to a higher incidence of restenosis and adverse cardiac events (Wong et al 2000).

In the last 3 to 4 years, drug-eluting stents (DES), either sirolimus-eluting stents (SES: Cypher®; Cordis Corporation, Warren, NJ) or paclitaxel-eluting stents (PES: TAXUS™; Boston Scientific Corporation, Natick, MA), have revolutionized the interventional cardiology practice by dramatically reducing restenosis and the need for repeated revascularization as compared to BMS (Moses et al 2003; Schofer et al 2003; Schampaert et al 2004; Stone et al 2004a). The superiority of DES over BMS has been observed not only in simple lesions but also in complex lesions, such as chronic total occlusions, diffused long lesions, saphenous vein graft lesions, restenotic lesions, and acute coronary syndromes. Consequently, the advent of DES creates the expectation of reducing restenosis substantially in patients with small vessels.

Many clinical trials indicated DES implantation to be feasible and safe. However, certain potential safety issues of DES usage have arisen with its widespread use. Some recent studies have cautioned that either SES or PES could increase thrombotic complications compared to BMS, especially late stent thrombosis (occurring >30 days after stent placement) (McFadden et al 2004; Iakovou et al 2005; Ong et al 2005; Moreno et al 2005). As another problem, delayed restenosis (occurring beyond the first 6 to 9 months after stent placement), usually referred to as the “late catch-up phenomenon”, has been discussed emphasizing the need for long-term follow-up data. This complication was especially noted after brachytherapy, a procedure whose use has been discontinued. Since PCI in small vessels constitutes a more complicated treatment strategy than simple lesions, which leads to a higher incidence of adverse cardiac events after procedure, physicians should carefully follow patients treated with small vessel DES stenting.

In this review, we describe efficacy and safety results from clinical trials of the TAXUS® stent system placement in small vessels and compare the angiographic and clinical outcomes of 3 direct comparison (PES vs SES) trials.

## **Paclitaxel and TAXUS® stent system**

Paclitaxel is an anti-tumor agent used to treat several kinds of solid tumors, most commonly tumors of the breast and ovary. This drug interferes with microtubule organization by interrupting mitosis (M phase) and extracellular secretion. Microtubular dynamics regulate many of the inflammatory and profibrotic steps of the restenotic cascade. Paclitaxel interrupts this cascade at multiple levels and inhibits cell proliferation and migration (Axel et al 1997; Hui et al 1998; Giannakakou et al 2001).

Use of the TAXUS® stent system in patients with CAD has been fully investigated in the TAXUS trials (see Table 1). Results from a total of 6 TAXUS trials have been reported to date (Grube et al 2003; Colombo et al 2003; Tanabe et al 2003; Stone et al 2004a; Stone et al 2005; Dawkins et al 2005). Follow-up of patients in 4 TAXUS trials (TAXUS II, IV, V, and VI) are still ongoing as of the date of this review. Several versions of the TAXUS stent technology using different platform types (NIRx, EXPRESS, EXPRESS<sup>2</sup>) and drug release kinetics (slow-release and moderate-release) but similar polymers, stent materials and drug concentrations (1.0 µg/mm<sup>2</sup> of paclitaxel), were used among these 6 trials (see also Table 1).

The TAXUS NIRx stent was a slotted-tube stainless steel stent coated with paclitaxel incorporated into a slow-release (SR) or a moderate-release (MR) copolymer carrier system with biphasic drug release. The initial release is over the first 48 hours followed by SR over the next 10 days. Release kinetics of the TAXUS NIRx MR stent in vivo has been shown to be faster than that of the TAXUS NIRx SR stent, resulting in a 3-fold higher in vivo drug release at 10 days. The TAXUS EXPRESS stent consists of a balloon-expandable EXPRESS stent with TRANSLUTE™ polymer-coating containing paclitaxel. The TAXUS EXPRESS<sup>2</sup> stent is composed of a balloon-expandable EXPRESS<sup>2</sup> stent with a triblock copolymer coating with paclitaxel. This coating serves as a carrier to provide uniform and controlled biphasic release of the drug into the vessel wall. SR and MR formulations of the polymer are available in the TAXUS EXPRESS<sup>2</sup> stent. The MR formulation also results in approximately 3-fold higher drug release than the SR polymer. The SR polymer formulation of the TAXUS EXPRESS<sup>2</sup> stent is commercially available now.

## **PES versus BMS in small vessels**

So far, no dedicated, prospective multicenter, randomized clinical study comparing the PES to BMS in patients with small vessel disease has been conducted. However, the

**Table 1** An overview of the TAXUS trials

	<b>TAXUS I</b> (Grube et al 2003)	<b>TAXUS II</b> (Colombo et al 2003)	<b>TAXUS III</b> (Tanabe et al 2003)
<b>Published year</b>	2003	2003	2003
<b>Trial design</b>	Randomized	Randomized	Single arm
<b>Used device</b>	TAXUS NIRx	TAXUS NIRx	TAXUS NIRx
<b>Release kinetics</b>	SR	SR and MR	SR
<b>Patient number</b>	TAXUS 31 Control 30	TAXUS SR 131, SR control 136 TAXUS MR 135, MR control 134	TAXUS 28
<b>Lesion morphology</b>	Single de novo or restenotic lesion in a native coronary artery	Single de novo lesion in a native coronary artery	In-stent restenosis in a native coronary artery with evidence of ischemia
<b>Lesion length</b>	= 12 mm	= 12 mm	= 30 mm
<b>Vessel diameter</b>	3.0 to 3.5 mm	3.0 to 3.5 mm	3.0 to 3.5 mm
<b>Primary endpoint</b>	MACE at 30 days	Mean % stent volume obstructed by neointimal proliferation measured by IVUS at 6 months	N/A
	<b>TAXUS IV</b> (Stone et al 2004a)	<b>TAXUS V</b> (Stone et al 2005)	<b>TAXUS VI</b> (Dawkins et al 2005)
<b>Published year</b>	2004	2005	2005
<b>Trial design</b>	Randomized	Randomized	Randomized
<b>Used device</b>	TAXUS EXPRESS	TAXUS EXPRESS <sup>2</sup>	TAXUS EXPRESS <sup>2</sup>
<b>Release kinetics</b>	SR	SR	MR
<b>Patient number</b>	TAXUS 662 Control 652	TAXUS 577 Control 579	TAXUS 219 Control 227
<b>Lesion morphology</b>	Single de novo lesion in a native coronary artery	Single de novo lesion in a native coronary artery	De novo lesion within a single native coronary artery
<b>Lesion length</b>	10 to 28 mm	10 to 46 mm	18 to 40 mm
<b>Vessel diameter</b>	2.5 to 3.75 mm	2.25 to 4.0 mm	2.5 to 3.75 mm
<b>Primary endpoint</b>	Ischemia driven TVR at 9 months	Ischemia driven TVR at 9 months	TVR at 9 months

IVUS, intravascular ultrasound; MACE, major adverse cardiac events; N/A, not available; MR, moderate release; SR, slow release; TVR, target vessel revascularization.

existing PES versus BMS clinical studies have reported substudy results in small vessels as a subgroup analysis, thus restricting the interpretation of the results (see Table 2). Small vessel subgroup analyses from 3 of the 4 larger controlled, multicenter TAXUS trials are briefly described below.

### TAXUS IV trial

In the TAXUS IV trial (Stone et al 2004a, 2004b), various types of subgroup analyses were performed. With regard to vessel size, enrolled patients were divided into the following 3 groups per RVD; = 2.5 mm, >2.5 mm to <3.0 mm and = 3.0 mm. In the smallest RVD group (= 2.5 mm, n = 176), the 9-month angiographic restenosis rate in the PES group was significantly lower than in the BMS group (PES, 10.2% versus BMS, 38.5%;  $p < 0.001$ ). In addition, 12-month target lesion revascularization (TLR) rate was significantly lower in the PES group (5.6%) as compared to the BMS group (20.6%,  $p < 0.0001$ ). Moreover, in multivariate analysis, the RVD was not related with 12-month TLR rate in the PES group, while it was an independent predictor of 12-month TLR rate

in the BMS group. No other angiographic parameters and clinical outcomes in this subgroup analysis were reported in this trial.

### TAXUS V trial

In the TAXUS V trial (Stone 2005), subgroups of patients with complex lesions, requiring 2.25 mm or 4.0 mm long stents and multiple stents (>1 stent), were investigated. In the patient group treated with the 2.25 mm stent, which consisted of 17.6% of total enrolled population, the mean RVD was 2.08 mm. Both treatment groups (PES and BMS) had similar acute clinical outcomes. At the 9-month follow-up, the restenosis rate as well as repeat revascularization rate was significantly lower in the PES group than in the BMS group (31.2% and 10.4% [PES] versus 49.4% and 21.5% [BMS];  $p = 0.01$  and  $0.03$ , respectively), although both parameters in the PES group were still high. In this underpowered posthoc analysis, numerical differences in the 9-month MACE rate between both treatment groups did not reach statistical significance (18.9% [PES] versus 26.9% [BMS];  $p = 0.23$ ).

**Table 2** Clinical and angiographic results in patients with small vessel disease in the TAXUS trials

	TAXUS IV subanalysis RVD <2.5 mm (Stone et al 2004a, 2004b)			TAXUS V subanalysis 2.25 mm stent implantation (Stone et al 2005)			TAXUS VI subanalysis RVD <2.5 mm (Dawkins et al 2005)		
	PES	BMS	p value	PES	BMS	p value	PES	BMS	p value
<b>Clinical outcomes</b>									
<b>Acute phase</b>									
30 days									
Death				0	0				
MI				5.6%	1.1%	0.12			
TLR				0.9%	1.1%	1.00			
TVR				1.9%	2.1%	1.00			
MACE				5.6%	2.1%	0.29			
Stent thrombosis				0.9%	1.1%	1.00			
<b>Follow up</b>									
12 months									
9 months									
9 months									
Death				1.9%	1.1%	1.00			
MI				5.7%	2.2%	0.29			
TLR	5.6%	20.6%	<0.0001	10.4%	21.5%	0.03	5.0%	29.7%	0.0003
TVR				16.0%	24.7%	0.16			
MACE				18.9%	26.9%	0.23			
Stent thrombosis				1.0%	1.1%	1.00			
<b>Baseline QCA</b>									
RVD				2.07 ± 0.31	2.10 ± 0.33	0.46			
Lesion length				16.6 ± 9.7	16.4 ± 9.2	0.91			
<b>Follow-up QCA</b>									
9 months									
9 months									
Late Loss (in-stent)				0.49 ± 0.61	0.90 ± 0.63	<0.001	0.23 ± 0.45	0.95 ± 0.52	<0.0001
Late Loss (segment)				0.36 ± 0.53	0.61 ± 0.59	0.004			
Restenosis (in-stent)				24.7%	44.7%	0.007	7.3%	40.4%	<0.0001
Restenosis (segment)	10.2%	38.5%	<0.001	31.2%	49.4%	0.01			

BMS, bare metal stent; MACE, major adverse cardiac events; MI, myocardial infarction; PES, paclitaxel-eluting stent; QCA, quantitative coronary angiography; RVD, reference vessel diameter; TLR, target lesion revascularization; TVR, target vessel revascularization.

Of note, the rate of periprocedural MIs in the PES arm was numerically higher than in the BMS arm without any statistical significance (5.7% versus 2.2%,  $p = 0.27$ ). Designed as a trial assessing outcomes in more complex lesions, most of the affected patients were characterized by an overlap of multiple complexities such as treatment of longer lesions in smaller vessels often with multiple overlapping stents.

### TAXUS VI trial

In the TAXUS VI trial (Dawkins 2005), angiographic and clinical outcomes were followed up to 9 months. Some subgroup analyses were performed per classic risk factors for restenosis, including clinical outcomes in patients with small vessels (RVD <2.5 mm). In this subgroup, in-stent late lumen loss was considerably smaller in the PES group than in the BMS group (PES,  $0.23 \pm 0.45$  mm versus BMS,  $0.95 \pm 0.52$  mm;  $p < 0.0001$ ), explaining the significantly lower angiographic restenosis observed in the PES group (7.3% [PES] versus 40.4% [BMS];  $p < 0.0001$ ). The incidence of TLR was also significantly lower in the PES group (5.0% [PES] versus 29.7% [BMS];  $p = 0.0003$ ).

Taking these results into the consideration, PES seems to confer clinical benefit in patients with small vessels compared to BMS. As shown in angiographic assessments, PES markedly inhibit in-stent and in-segment (including implanted stent and 5 mm distal and proximal to the stent) neointimal hyperplasia, contributing to the significantly lower TLR rate observed in these patients (see Table 2). To date, however, PES implantation in small vessels has not been studied prospectively in a dedicated study. Only subgroup analysis data exist and the number of study patients is very small. Future multicenter randomized trials with large sample size, which focus on patients treated with PES for small vessel CAD, are required to better understand whether PES is more effective in patients with small vessels than BMS.

### SES versus BMS in small vessels

SES is another commercially available DES promising improved clinical and angiographic results in patients with small vessel disease as compared to BMS. In contrast to paclitaxel, only a single stent type coated with one specific dose formulation for controlled release of sirolimus has been

investigated over the last several years: the SES consists of the Bx Velocity stent loaded with 1.4 ug/mm<sup>2</sup> sirolimus. Sirolimus is a macrolide with immunosuppressive, antiproliferative and antifungal properties. Different from the mechanism of paclitaxel, sirolimus prevents progression from the G1 phase (cell growth) to the S phase (DNA replication), resulting in inhibition of the growth of vascular smooth muscle cells, which is a major process of in-stent restenosis.

The SIRIUS trial showed that SES had a significant lower 1-year TLR rate than BMS in patients with RVD  $\leq$  2.75 mm (6.6% [SES] versus 22.3% [BMS];  $p < 0.0001$ ) (Holmes et al 2004). In an angiographic substudy of the SIRIUS trial (Popma et al), patients were categorized into tertiles according to RVD and angiographic outcomes between SES and BMS were assessed. The smallest tertile had mean RVD of 2.32 mm in the SES group and 2.31 mm in the BMS group ( $p = 0.683$ ). Angiographic restenosis rate in the SES group was significantly lower than in the BMS group (17.6% vs 42.7%,  $p < 0.001$ ). The SES-SMART trial (Ardisso et al 2004), which enrolled patients with small vessels (mean RVD 2.2mm), indicated that the incidence of TLR and MACE in the SES arm was 7.0% and 9.3% versus 21.1% and 31.3% in the BMS arm ( $p = 0.002$  and  $p < 0.001$ , respectively). In addition, angiographic restenosis rate in the SES arm was also significantly lower compared to the BMS arm (9.8% vs 53.1 %,  $p < 0.001$ ).

These results indicated that SES is no less effective than PES in patients with small vessel CAD. However, which

DES is superior to the other in small vessel stenting still remains controversial.

### PES versus SES in small vessels

Several recent trials (de Lezo et al 2005; Kastrati et al 2005a; Dibra et al 2005; Windecker et al 2005; Goy et al 2005; Morice et al 2006) and a meta-analysis (Kastrati et al 2005b) have compared PES with SES. While suggesting advantages of SES in reducing neointimal hyperplasia, many of the comparative trials have been limited by inadequate sample size, execution in single center, and use of institutional rather than independent core labs and event committees limiting the acceptability of these datasets for establishment of formal treatment guidelines. Indeed, when these comparative trials are scored by Silver score (Silber 2005) (see Table 3), which rate the level of evidence provided by the various DES trials (range from 0 to 10) and intend to help physicians evaluate the strength of evidence, calculated scores are relatively low (high scores can be considered strong evidence): CORPAL study (de Lezo et al 2005) is 1, ISAR-DESIRE (Kastrati et al 2005a) 4, ISAR-DIABETES (Dibra et al 2005) 4, SIR-TAX (Windecker et al 2005) 6, TAXi (Goy et al 2005) 5 and REALITY (Morice et al 2006) 4. In addition, there is limited information on the relative efficacy and safety of PES compared to SES in patients with small vessel disease. Only 3 trials were reported: 1 randomized trial and 2 non-randomized trials (see Table 4). We describe these 3 trials in the section below.

**Table 3** Silver score system

Evaluation Parameter	Possible points
Clinical Primary Endpoint (TLR, TVR, TVF, MACE)	Yes = 3 No = 0
Double-Blind (including physicians)	Yes = 1 No = 0
Evaluation Interval of Primary Endpoint $\geq$ 6 Months	Yes = 1 No = 0
Multi-Center (at least 3 centers)	Yes = 1 No = 0
Clinical Events Committee/Data Safety Monitoring Board Independent and External from Steering Committee	Yes = 1 No = 0
Primary Endpoint Reached	Yes = 1 No = 0
Power of $\geq$ 80% for Primary Endpoint Achieved	Yes = 1 No = 0
Follow-up Percentage $\geq$ 80% for Angiographic Primary Endpoint or Follow-up Percentage of $\geq$ 95% for Clinical Primary Endpoint	Yes = 1 No = 0
Maximum Silber Score	10
Minimum Silber Score	0

TLR, target lesion revascularization; TVF, target vessel failure; TVR, target vessel revascularization; MACE, major adverse cardiac events.

**Table 4** Clinical and angiographic results of the studies comparing PES to SES implantation in patients with small vessel disease

	ISAR-SMART 3 (Mehilli et al 2006)			Park et al (Park et al 2006)			RESEARCH and T-SEARCH subanalysis (Rodriguez-Granillo et al 2005; Tanimoto et al 2006)		
	SES	PES	p value	SES	PES	p value	SES	PES	p value
Patient number	n = 180	n = 180		n = 121	n = 76		n = 107	n = 92	
Trial design	Randomized trial			Non-randomized trial			Non-randomized trial		
<b>Clinical outcomes</b>									
<b>Acute phase</b>	30 days			In hospital			30 days		
Death				0%	0%	1	0.9%	2.2%	0.59
MI	3.9%	3.3%	0.78	12.4%	13.2%	0.54	2.8%	6.7%	0.31
TLR	0%	0.6%	0.32	0%	0%	1	2.8%	5.6%	0.47
TVR							2.8%	5.6%	0.47
MACE				12.4%	13.2%	0.54	4.7%	12.2%	0.07
Stent thrombosis	0%	0%	>0.99	0%	0%	1	0%	2.2%	0.21
<b>Follow up</b>	12 months			9 months			12 months		
Death	1.7%	2.2%	>0.99	0%	0%	1	0.9%	4.3%	0.18
MI	3.9%	3.3%	0.78	12.4%	13.2%	0.54	2.8%	7.8%	0.19
TLR	6.6%	14.7%	0.008	3.3%	14.4%	<0.01	6.5%	11.1%	0.31
TVR							7.5%	12.2%	0.33
MACE				15.7%	27.6%	<0.01	9.3%	18.9%	0.06
Stent thrombosis							0%	2.2%	0.21
<b>Baseline QCA</b>									
RVD	2.44 ± 0.34	2.40 ± 0.38	0.34	2.47 ± 0.21	2.44 ± 0.25	0.19	1.86 ± 0.37	1.95 ± 0.38	0.15
MLD	0.99 ± 0.40	1.03 ± 0.39	0.33	0.86 ± 0.33	0.81 ± 0.42	0.31	0.47 ± 0.38	0.57 ± 0.38	0.06
DS	59.4 ± 15.3	57.2 ± 14.4	0.15	65.4 ± 13.0	67.5 ± 16.0	0.22	74.8 ± 20.1	70.3 ± 19.3	0.10
Lesion length	12.9 ± 8.0	11.7 ± 6.7	0.12	25.2 ± 14.7	27.1 ± 12.7	0.34	13.0 ± 8.5	16.4 ± 10.4	0.02
<b>Post-PCI QCA</b>									
MLD (in-stent)	2.44 ± 0.36	2.44 ± 0.37	0.8				1.73 ± 0.31	1.82 ± 0.36	0.06
MLD (segment)	2.04 ± 0.47	2.00 ± 0.47	0.41	2.52 ± 0.33	2.42 ± 0.35	0.45	12.3 ± 10.0	14.0 ± 9.8	0.19
DS (in-stent)	5.6 ± 7.5	6.3 ± 7.7	0.36						
DS (segment)	16.7 ± 7.7	18.5 ± 7.2	0.05	3.7 ± 7.1	5.8 ± 8.3	0.06			
<b>Follow-up QCA</b>									
	6 months			6 months					
MLD (in-stent)	2.21 ± 0.66	1.88 ± 0.67	<0.001						
MLD (segment)	1.91 ± 0.61	1.67 ± 0.63	<0.001	2.32 ± 0.56	1.77 ± 0.77	<0.01			
DS (in-stent)	17.2 ± 21.5	26.7 ± 21.8	<0.001						
DS (segment)	28.4 ± 19.7	35.0 ± 20.6	<0.002	5.38 ± 22.5	31.7 ± 34.9	<0.01			
Late loss (in-stent)	0.25 ± 0.55	0.56 ± 0.59	<0.001						
Late loss (segment)	0.13 ± 0.56	0.34 ± 0.57	<0.001	0.29 ± 0.42	0.69 ± 0.62	<0.01			
Restenosis (in-stent)	8.0%	14.9%	0.04						
Restenosis (segment)	11.4%	19.0%	0.047	6.7%	27.7%	<0.01			

DS, diameter stenosis; MACE, major adverse cardiac events; MI, myocardial infarction; MLD, minimal lumen diameter; PES, paclitaxel-eluting stent; QCA, quantitative coronary angiography; RVD, reference vessel diameter; SES, sirolimus-eluting stent; TLR, target lesion revascularization; TVR, target vessel revascularization.

The ISAR-SMART 3 trial was a first head-to-head comparative (PES vs SES) randomized trial for patients with small vessel disease (mean RVD was about 2.4 mm) (Mehilli et al 2006). Angiographic and clinical outcomes were followed up to 8 months. SES was more effective in reducing restenosis and TLR than PES (11.4 and 6.6% in the SES group vs 19.0 and 14.7% in the PES group,  $p = 0.047$  and 0.008, respectively). These results indicated that PES induced a greater late lumen loss and were less effective in reducing restenosis in small coronary vessels as compared to SES. Consequently, SES was associated with a lower

incidence of angiographic restenosis as well as a reduced need of repeat revascularization.

There were 2 additional non-randomized trials comparing the efficacy between PES and SES in patients with small vessel disease. One was a study of Park et al, which was a retrospective study including 197 patients with a mean RVD of nearly 2.45 mm (Park et al 2006). Angiographic restenosis rate at 6 months and TLR rate at 9 months were 6.7 and 3.3% in the SES group, while 27.7 and 14.4% in the PES group ( $p < 0.01$  and  $< 0.01$ , respectively).

Another was a substudy of the RESEARCH and T-SEARCH registries, which adopted a non-randomized design (Rodriguez-Granillo et al 2005, Tanimoto et al 2006). This substudy was the only 1 investigating long-term follow-up (up to 2 years) of patients treated with PES or SES in small coronary vessels. Patients treated with 2.25 mm diameter PES or SES were evaluated in terms of clinical outcomes without systematic angiographic follow-up and therefore evaluated only clinical benefit. The incidence of 1 year TLR and MACE was numerically more frequent in the PES group, but they did not reach statistical difference (11.1 and 18.9% vs 6.5 and 9.3% in the SES group;  $p = 0.31$  and  $0.06$ , respectively). TLR at 2 years was observed more frequently in the PES group (12.2% vs 6.5% in the SES group,  $p = 0.22$ ); only 1 patient in the PES arm underwent repeat revascularization in the second year. The 2-year MACE rate was significantly higher in the PES group than in the SES group (23.3% vs 10.3%,  $p = 0.02$ ).

Considering these results, SES has been implied to offer slight advantages over PES in small vessel stenting regarding angiographic and sometimes even clinical outcomes. Nevertheless, the root cause for such differences between PES and SES remains unclear. The mechanical differences of both DES may affect angiographic restenosis as a study of Briguori et al which showed that strut thickness was an independent predictor of angiographic restenosis in small coronary arteries (RVD of 2.75 to 2.99 mm); thinner-strutted stents were associated with lower incidence of restenosis than thicker-strutted stents (Briguori et al 2002). But the strut thicknesses of PES and SES are very similar (0.132 mm and 0.140 mm, respectively) so that such a mechanical property does not influence the result of angiographic outcomes obtained by both DES implantations. Different mechanisms of inhibiting neointimal hyperplasia and drug-release kinetics between PES and SES presumably accounts for the observed difference in their performance.

At the moment, however, it is difficult to conclude that SES is superior to PES in small vessel stenting. It is underscored that to date only one randomized controlled trial (ISAR-SMART 3) was performed to compare differences between PES and SES in small vessel stenting. This randomized study was open-labeled trial and was conducted at only 2 investigative sites, therefore the Silver score is 3 out of 10. In addition, this study excluded patients with diabetes mellitus, which was a famous independent predictor leading to worse angiographic and clinical outcomes. Moreover, the number of enrolled patients in each study was too small and underpowered to definitely assess the effectiveness of both

DES for small coronary artery lesions regarding with TLR, TVR or MACE. The other 2 trials comparing the efficacy of PES and SES in small vessels were non-randomized studies so that their strength of evidence were low. Inclusion and exclusion criteria of each study varied. It must be noted that larger, multicenter (at least  $\geq 3$ ), randomized, blinded trials, with a defined clinical endpoint in patients with small vessels are required to firmly determine a clinical advantage of one DES over the other. As of present, limited results from these 3 trials do not confirm a significant advantage of SES over PES in this patient population.

## Safety concern of small vessel DES stenting

After DES were approved, these devices have been implanted in a large number of patients with CAD including several kinds of clinical and anatomic situations such as acute MI, bifurcation lesions and overlapping stent deployment. Their use seems to be feasible and safe. Recently, however, certain potential issues have been raised.

One of the issues is stent thrombosis. Although rare, some studies have cautioned that as compared to BMS, either PES or SES could increase the incidence of this complication, especially that of late stent thrombosis (occurring  $>30$  days after stent placement) (McFadden et al 2004; Iakovou et al 2005; Ong et al 2005; Moreno et al 2005). Increased risk for thrombosis may be associated with the decreased endothelial function (Hofma et al 2006), and/or delayed vascular healing (Degertekin et al 2002; Guagliumi et al 2003; Joner et al 2006) induced with DES. In addition, hypersensitivity reactions to the polymer coating of the DES and the drug itself may also contribute to stent thrombosis (Virmani et al 2004; Nebeker et al 2006). Although BMS implantation in small vessels had been previously cited as a risk factor for stent thrombosis (Karrillon et al 1996; Mak et al 1996; Moussa 1997), improved techniques of optimal stent deployment and dual antiplatelet regimens appear to have largely resolved this problem so that the risk of stent thrombosis of BMS in small vessel stenting now seems to be similar to that in larger vessel stenting (Akiyama 1998; Lau et al 2000). But, DES implantation in small vessels may increase the risk of stent thrombosis because of their features as mentioned above. The incidence of stent thrombosis in small vessel DES stenting has not been shown to differ between PES and BMS or SES. In a subanalysis conducted in the TAXUS V clinical trial, both acute and late stent thrombosis rate were similar between PES and BMS (0.9% versus 1.1% and 1.0% versus 1.1%,  $p = 1.00$  and  $1.00$ , respectively) (Table 2). In



the ISAR-SMART 3 trial and a study of Park et al, no acute stent thrombosis was reported in both the SES and PES arms, while there was no information about late stent thrombosis in either trial (see Table 4). In a subanalysis of the RESEARCH and T-SEARCH registries, 2.2% of patients had acute stent thromboses in the PES arm; no thrombosis was observed in the SES arm (see also Table 4). This observation was not significant ( $p = 0.21$ ). No late stent thrombosis occurred in either arm. It should be mentioned that the definition of stent thrombosis varied (clinical or angiographic) and treated lesion type differed among clinical trials. In addition, though most trials reported their outcomes within 1 year, late stent thrombosis often occurred more than 1 year after DES placement. To better understand this adverse event, a much larger sample size and longer-term follow-up are warranted.

Delayed restenosis, which is also called a “late catch-up phenomenon”, is another issue after DES deployment. This event was first observed in the porcine model (Farb et al 2001; Carter et al 2004). Also in humans, continued neointimal growth of during the follow-up period was noted in some trials in which serial intravascular ultrasound (IVUS) analyses

were performed (Aoki et al 2005a; Aoki et al 2005b; Aoki et al 2005c). The precise reason for this phenomenon is still unclear. Delayed neointimal hyperplasia could lead to higher incidence rates of TLR and MACE observed during long-term follow-up. This is especially relevant with small vessel DES stenting, since even a small volume of neointimal tissue can affect the incidence of angiographic restenosis by virtue of the smaller RVD. With respect to small vessel stenting, few long-term follow-up data exist (Table 5). In a subanalysis of the SIRIUS 2-year outcomes (Weisz et al 2006), TLR rate in the second year was 1.7% in the SES group and 0.8% in the BMS group ( $p = 0.17$ ). In a substudy of the RESEARCH and T-SEARCH registries, only 1 patient (1.1%) treated with PES presented with TLR in the second year (0% in the SES arm,  $p = 0.46$ ). In these 2 studies, angiographic parameters were not reported, thus the increase of neointima was unknown during the second year. However, according to these results, it may be inferred that if late catch-up phenomenon occurred after small vessel DES stenting, its effect might be restrictive in this clinical setting. The efficacy of DES was ascertained up to 2-years even in treatment of small vessel CAD.

**Table 5** Long-term clinical follow-up trials in small vessel DES stenting

	SIRIUS subanalysis RVD < 2.75 mm (Weisz et al 2006)		p value	RESEARCH and T-SEARCH subanalysis (Tanimoto et al 2006)		p value
	SES	BMS		SES	PES	
Patient number	n = 533	n = 525		n = 107	n = 92	
Trial design	Randomized trial			Non-randomized trial		
<b>1-year follow up</b>						
death				0.9%	4.3%	0.18
MI				2.8%	7.8%	0.19
TLR	6.6%	22.3%	<0.0001	6.5%	11.1%	0.31
TVR				7.5%	12.2%	0.33
MACE				9.3%	18.9%	0.06
Stent thrombosis				0%	2.2%	0.21
<b>2-year follow up</b>						
death				1.9%	7.6%	0.08
MI				2.8%	7.6%	0.19
TLR	8.3%	23.0%	<0.0001	6.5%	12.2%	0.22
TVR				7.5%	13.3%	0.24
MACE				10.3%	23.3%	0.02
Stent thrombosis				0%	2.2%	0.21
<b>1-year to 2-year</b>						
death				0.9%	3.3%	0.33
MI				0%	0%	
TLR	1.7%	0.8%	0.17	0%	1.1%	0.46
TVR				0%	1.1%	0.46
MACE				0.9%	4.3%	0.18
Stent thrombosis				0%	0%	

BMS, bare metal stent; MI, myocardial infarction; MACE, major adverse cardiac events; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; TLR, target lesion revascularization; TVR, target vessel revascularization.



At present, small vessel stenting by using either PES or SES seems to be safe and does not increase adverse cardiac events in short- and medium-term follow-up. However, long-term follow-up and larger sample multicenter studies are needed to determine whether DES implantation is safe in patients with small vessel CAD.

## Conclusion

In this manuscript, we reviewed the placement of BMS, PES, and SES in small vessels with respect to efficacy and safety. At present, the following general conclusions about small vessel stenting can be made: (1) PES considerably reduce the incidence of angiographic restenosis and TLR as compared to BMS; (2) a trend is observed with regard to better angiographic and clinical outcomes of SES over PES, but there is little and weak information to support this result; and (3) Both PES and SES seem to be safe and don't increase severe cardiac complication, such as acute and late stent thrombosis.

Even in the DES era, small RVD is still an independent predictor of angiographic and clinical restenosis (Kastrati 2006). However, there are a very limited number of studies focusing on small vessel DES stenting. Therefore, large-sample size, double-blinded, randomized-controlled multicenter trials with long-term follow-up and a clinical primary endpoint are needed to establish the fact that both PES and SES are effective and safe in small vessel coronary disease.

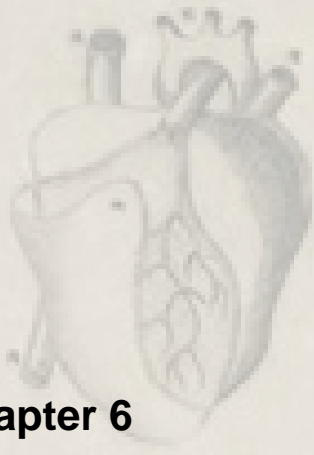
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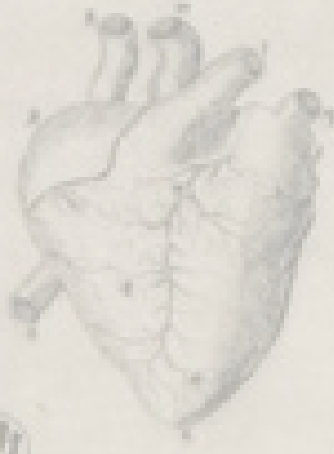
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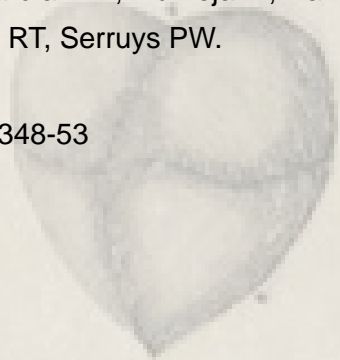
Chapter 6

Two-year outcome of the use of paclitaxel-eluting stents in aorto-ostial lesions.

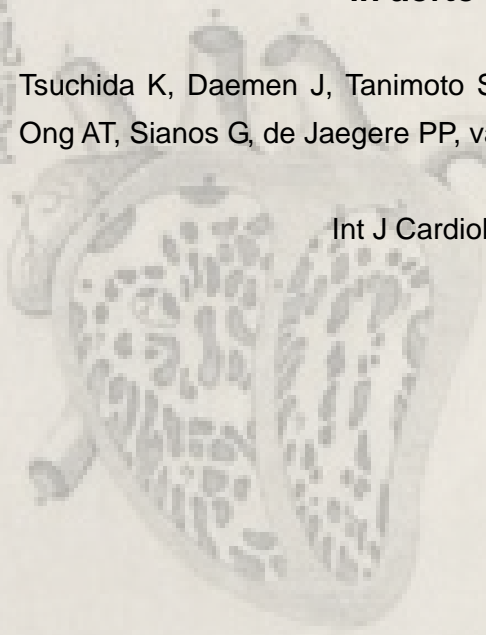
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## Two-year outcome of the use of paclitaxel-eluting stents in aorto-ostial lesions

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### Abstract

**Background:** Percutaneous treatment of stenoses involving aorto-ostial lesions is technically demanding and has been associated with lower procedural success and poorer clinical and angiographic outcomes when compared with non-ostial lesions. This study evaluated the immediate and long-term (2-year) outcome of aorto-ostial stenoses treated with paclitaxel-eluting stents (PES).

**Methods:** From February 2003 to December 2004, a total of 76 consecutive patients with 76 lesions underwent percutaneous intervention with PES for aorto-ostial lesions (right coronary artery, 37; left main, 26; saphenous vein graft, 13). All patients were clinically followed for the occurrence of major adverse cardiac events (MACE), defined as cardiac death, non-fatal myocardial infarction (MI), target lesion revascularization (TLR) or target vessel revascularization (TVR).

**Results:** All stents (1.7/lesion) were successfully deployed. Three lesions (3.9%) were pre-treated with debulking devices. Thirty-seven lesions (48.7%) were post-dilated with non-compliant balloons (balloon/artery ratio, 1.2). Stents were positioned protruding into the aortic lumen in 29 lesions (38.2%). Cumulative 2-year event-free survival was 68.4%. There was one angiographically-proven stent thrombosis occurring 427 days after TLR for restenosis after the index procedure. The restenosis rate at 7 months (median) was 20.0% and in-stent late lumen loss was 0.48 mm in 40 patients with angiographic follow-up.

**Conclusions:** Utilization of PES in this complex lesion subset is feasible and associated with favorable angiographic results at 7 months. However, the gradual increase in later events up to 2 years suggests that aorto-ostial disease remains problematic even in the era of drug-eluting stents.

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**Keywords:** Aorto-ostial lesion; Paclitaxel-eluting stent; Percutaneous coronary intervention; Aorto-ostial lesion; Paclitaxel-eluting stent

### 1. Introduction

Percutaneous treatment of stenoses involving aorto-ostial lesion is a technically demanding procedure for interventionalists and has been associated with lower procedural success, and poorer clinical and angiographic outcomes

when compared with treatment of non-ostial lesion [1,2]. The extremely sclerotic and calcified nature of this lesion site [3–5] has contributed to suboptimal immediate and long-term results after balloon angioplasty as a stand-alone strategy [6]. Debulking strategies with directional coronary atherectomy (DCA) or rotational atherectomy (rotablator) were assumed to alter outcomes for this particular lesion subset, but their efficacies have not been determined. To counter the ostial elasticity resulting in high restenosis rates (enhanced recoil), stent implantation is a reasonable strategy for lesion scaffolding, and bare metal stents have resulted

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in better outcomes than conventional balloon angioplasty [7–9]. However, in addition to acute and chronic stent recoil, excessive neointimal growth after stenting in this location has been documented [10]. Although drug-eluting stents (DES) have shown even better clinical and angiographic results than bare metal stents, data on the efficacy of DES for ostial lesions are still limited, mostly due to the exclusion of these high risk lesions in the majority of the published randomized trials [11–14]. Percutaneous treatment with sirolimus-eluting stent (SES) for aorto-ostial lesions has already been reported to improve short-term clinical and angiographic outcomes [15]. Polymer-based paclitaxel-eluting stent (PES, TAXUS™ Express2™, Boston Scientific Corp., Natick, MA) is another FDA-approved drug-eluting stent that has been shown to reduce clinical events in simpler lesions [13]. To date, few reports are available on the treatment of ostial stenoses using PES. In addition, little is known about the long-term results of percutaneous treatment of aorto-ostial lesions using DES. This study was made to evaluate both the 7-month angiographic and 2-year clinical outcomes of the use of PES for aorto-ostial narrowings.

## 2. Methods

From February 2003 to December 2004, a total of 93 consecutive patients underwent percutaneous intervention for 93 aorto-ostial lesions in our institution. All the eligible lesions were primary culprit lesions for each patient and therefore stenting due to dissection, extended stenting from non-ostial lesions, or spasm induced by catheter tip were excluded. Seventeen patients were excluded from this study because of deployment of SES (Cypher™, Cordis/Johnson & Johnson, Warren, NJ) in 7, bare metal stents in 5, angioplasty without stenting in 2, unsuccessful guidewire crossing in 2 (chronic total occlusions), and PES with a different type of platform (Infinium™, Sahajanand Medical Technologies Pvt. Ltd., Gujarat, India) in 1. Thus, the study population consisted of 76 consecutive patients treated with TAXUS™ Express2™ stents. The study population is a constitutive part of Taxus-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry of which the design and goals have been described previously [16]. An aorto-ostial lesions were defined as being located less than 3 mm (as measured by quantitative angiographic analysis) of the orifice of the right coronary artery, left main coronary artery, or saphenous venous graft when visualized in an angiographic projection without foreshortening [6]. The study protocol was approved by the local ethics committee and is in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

### 2.1. Medications and interventional procedures

Elective patients were all pre-treated with aspirin and clopidogrel. A loading dose of 300 mg of clopidogrel was adopted in emergency cases. Post-interventional prescription

of antiplatelet was life-long aspirin and 6-month clopidogrel with daily dose of 75 mg. PESs were available in diameters of 2.25, 2.5, 2.75, 3.0 and 3.5 mm. Usage of debulking devices (DCA or rotablator), distal protection devices and administration of glycoprotein IIb/IIIa inhibitors was left to the discretion of each physician. Slight stent protrusion into the aortic lumen was determined in the least foreshortened angiographic projection. Angiographic success was defined as residual diameter stenosis <30% in the presence of Thrombolysis in Myocardial Infarction (TIMI) flow grade 3.

### 2.2. Clinical follow-up and definitions

Adverse events were assessed at 30 days, 1 and 2 years. The primary endpoint was the occurrence of major adverse cardiac events (MACE), defined as a composite of cardiac death, non-fatal myocardial infarction (MI), target lesion revascularization (TLR), and target vessel revascularization (TVR). All deaths were regarded as those of cardiac origin unless a noncardiac origin was proven either clinically or by autopsy. Non-fatal MI was defined as the occurrence of an elevated creatine kinase-MB fraction (CK-MB) >3 times the upper limit of normal [16]. TLR was defined as either surgical or percutaneous reintervention driven by significant ( $\geq 50\%$ ) luminal narrowing either within the stent or the borders 5 mm proximal and distal to the stent that was undertaken in the presence of either anginal symptoms or objective evidence of ischemia. TVR was defined as reintervention in the treated vessel outside the target lesion. Stent thrombosis was defined as angiographically-documented complete occlusion (TIMI flow grade 0 or 1) or flow-limiting thrombus (TIMI flow grade 1 or 2) in a previously treated artery. Stent thrombosis was categorized according to its timing relative to the index procedure as early (within 30 days) or late (>30 days) thrombosis.

All patients were clinically followed for the occurrence of MACE. Information about in-hospital outcomes was obtained from an electronic clinical database maintained at our institution and by review of patients' records. Post-discharge survival status was examined from the Municipal Civil Registries. Occurrence of MI or revascularization at follow-up was collected by consulting our institutional electronic patient database and by contacting referring physicians and institutions.

### 2.3. Quantitative angiographic analysis

Quantitative angiographic analysis was performed using the computer-based validated QCA system (CAAS II, Pie Medical Imaging, Maastricht, the Netherlands). Quantitative measurements included the diameter of the reference vessel, the minimal luminal diameter, percentage (%) diameter stenosis, and late luminal loss (the difference between the minimal luminal diameter after the procedure and the minimal luminal diameter at follow-up). Binary restenosis was defined as a stenosis of at least 50% of the minimal

Table 1  
Baseline clinical and angiographic characteristics ( $n=76$ )

Age, years	66.0±10.9
Male gender, $n$ (%)	51 (67.1)
Smoking:	
current, $n$ (%)	15 (19.7)
Former, $n$ (%)	14 (18.4)
Diabetes:	
type I, $n$ (%)	13 (17.1)
Type II, $n$ (%)	4 (5.3)
Hypertension, $n$ (%)	31 (40.8)
Hypercholesterolemia, $n$ (%)	44 (57.9)
Renal insufficiency, $n$ (%)	9 (11.9)
Family history, $n$ (%)	28 (36.8)
Prior myocardial infarction, $n$ (%)	26 (34.2)
Previous intervention, $n$ (%)	18 (23.7)
Previous bypass surgery, $n$ (%)	17 (22.4)
Multivessel disease, $n$ (%)	55 (72.4)
Stable angina pectoris, $n$ (%)	31 (42.1)
Unstable angina pectoris, $n$ (%)	32 (42.1)
Acute myocardial infarction, $n$ (%)	13 (15.8)
Cardiogenic shock, $n$ (%)	4 (5.3)

luminal diameter in the target lesion at angiographic follow-up. In most cases, reference vessel diameter was obtained only from a point distal to the lesion. Angiographic patterns of restenosis were also determined [17].

#### 2.4. Statistical analysis

Values in the text and tables are presented as mean±SD, or frequency (percentage) for descriptive purposes. The cumulative incidence of adverse events was estimated according to the Kaplan–Meier analysis. Statistical analyses were performed with SPSS 12.0.1 for Windows (SPSS Inc., Chicago, IL). A  $p$  value <0.05 was considered statistically significant.

### 3. Results

#### 3.1. Baseline characteristics

Baseline patient, lesion, and procedural characteristics are shown in Tables 1 and 2. Multivessel disease was observed in 72.4% of the patients. More than half of the cases underwent index PCI for an acute coronary syndrome (unstable angina, 42.1%; acute myocardial infarction, 15.8%). There was no documentation of non-atherosclerotic etiologies associated with aorto-ostial disease such as syphilitic cardiovascular disease, Takayasu's arteritis, etc. [18].

The seventy-six target vessels in the present study consisted of 37 right coronary arteries, 26 left main coronary arteries, and 13 venous grafts. These lesions included seven restenotic lesions following bare metal stent implantation (9.2%). Moderate to severe calcification was documented in 19 lesions, presence of thrombus in 13, restenosis of bare

metal stent in 7, chronic total occlusion (an occlusion period more than 3 months) in 1.

#### 3.2. Procedural results

Target lesions were treated using  $1.69\pm 0.97$  stents (total stent length per lesion,  $32.11\pm 26.58$  mm) that were post-dilated using balloons  $3.6\pm 0.44$  mm diameter (mean balloon–artery ratio, 1.24). Lesion modification by debulking devices or cutting balloon was made in 7 patients. Stent placement with slight protrusion of the proximal edge into the ascending aorta was performed in 38.2% of the cases. Two patients were complicated by aorto-coronary dissection involving in the sinus of Valsalva, which regressed conservatively over a short period. Thirty-five patients (46.1%) underwent concomitant treatment of non-ostial lesions either in the same or different vessels.

#### 3.3. Clinical outcome up to 2 years

Thirty-day, one-year as well as 2-year outcomes in terms of clinical events are reported in Table 3.

Table 2  
Baseline lesion and procedural characteristics ( $n=76$ )

Lesion characteristics	
Lesion location	
Right coronary artery, $n$ (%)	37 (48.7)
Left main coronary artery, $n$ (%)	26 (34.2)
Venous graft, $n$ (%)	13 (17.1)
In-stent restenosis of bare metal stent, $n$ (%)	7 (9.2)
Chronic total occlusion, $n$ (%)	1 (1.3)
Thrombus-containing lesion, $n$ (%)	13 (17.1)
Moderate to severe calcification, $n$ (%)	19 (25.0)
Eccentric lesion, $n$ (%)	24 (31.6)
TIMI flow grade $\leq 2$ :	
Baseline, $n$ (%)	18 (23.7)
After procedure, $n$ (%)	3 (3.9)
Procedural characteristics	
Number of stents/lesion, $n$	1.69±0.97
Total stent length/lesion, mm	32.11±26.58
Maximal balloon size, mm	3.64±0.44
Balloon/artery ratio	1.24±0.23
Maximal inflation pressure, atm	20.18±2.65
Debulking, $n$ (%)	
Cutting balloon, $n$ (%)	4 (5.3)
Direct stenting, $n$ (%)	33 (43.4)
Post-dilatation, $n$ (%)	37 (48.7)
Use of glycoprotein IIb/IIIa inhibitors, $n$ (%)	10 (13.2)
Distal protection device, $n$ (%)	12 (15.8)
Intra-aortic balloon pump, $n$ (%)	4 (5.3)
Left ventricular assist device (LVAD), $n$ (%) <sup>a</sup>	1 (1.3)
Periprocedural stent thrombosis, $n$ (%)	0 (0.0)
Stent protrusion, $n$ (%)	29 (38.2)
Aorto-coronary dissection after procedure, $n$ (%)	2 (2.6)
Concomitantly treated lesion, $n$ (%)	35 (46.1)
Angiographic success, $n$ (%)	73 (96.1)

<sup>a</sup> The Impella LVAD Recover LP 2.5 (Impella Cardiotechnik, Aachen, Germany).



Table 3

Major adverse cardiac events	
30-day outcome	
Death	6 (7.9)
Non-fatal myocardial infarction	4 (5.3)
Target vessel revascularization	0
Target lesion revascularization	0
MACE	10 (13.2)
Stent thrombosis*	1 (1.3)
1-year outcome	
Death	6 (7.9)
Non-fatal myocardial infarction	4 (5.3)
Target vessel revascularization	8 (10.5)
Target lesion revascularization	3 (3.9)
MACE	18 (23.7)
Stent thrombosis*	1 (1.3)
2-year outcome	
Death	9 (11.8)
Non-fatal myocardial infarction	6 (7.9)
Target vessel revascularization	11 (14.5)
Target lesion revascularization	3 (3.9)
MACE	24 (31.6)
Stent thrombosis <sup>†</sup>	3 (3.9)

\*Subacute stent thrombosis in a concomitantly-treated non-ostial target vessel (left anterior descending) 21 days after the index PCI; <sup>†</sup>One is subacute thrombosis in a non-ostial target vessel (left anterior descending) 2 days after stenting and the other is late thrombosis in the right coronary ostial lesion 427 days after TLR. MACE = major adverse cardiac events.

3.3.1. 30-day outcome

In the first month, 6 patients died, four of whom exhibited fatal MI resulting in refractory cardiogenic shock as a baseline clinical presentation, although stents were successfully deployed in each of the target lesions (1 right and 3 left main coronary arteries). One patient with stable angina underwent elective stenting for ostial left main disease, but died due to a rapid hemodynamic collapse resulting from compromised blood flow to the jailed left circumflex artery. One patient died 21 days after concomitant stenting in 2 target lesions (ostial right coronary artery and left anterior descending artery). This case was strongly suspected of having early stent thrombosis either in the territory of the right coronary artery or left anterior descending artery as the cause of sudden death, which was not angiographically-documented.

Out of the 4 MIs, 3 were MIs during the index procedures and the other was a subacute stent thrombosis in a concomitantly-treated different vessel (left anterior descending artery) 21 days after the index procedure. There were no cases of TLR or TVR in the first 30 days.

3.3.2. 1-year outcome

Neither further death nor MI was documented after 30 days up to 1 year. TVR was required in 8 patients (TLR, 3/8), all of which were treated percutaneously.

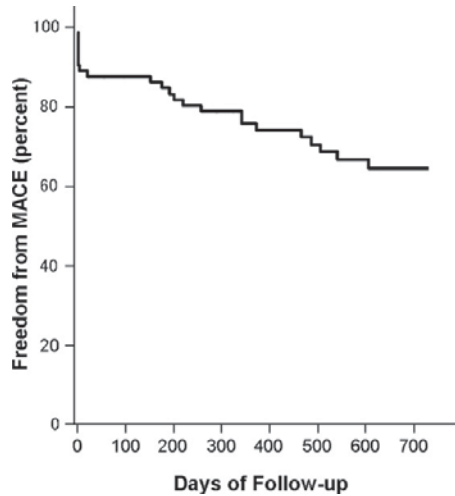


Fig. 1. Kaplan–Meier event-free survival at 2 years for major adverse cardiac events (MACE).

3.3.3. 2-year outcome

There was a gradual increase in MACE throughout 2 years (Fig. 1). There were 3 more deaths identified between 1 and 2 years. One patient who died 465 days after stenting was strongly suspected of having late stent thrombosis in the territory of the right coronary artery as the cause of sudden

Table 4

Quantitative coronary angiography (n=76)

Baseline	
Reference vessel diameter, mm	3.04±0.56
Minimum luminal diameter, mm	0.92±0.51
Diameter stenosis, %	69±16
Lesion length, mm	14.24±15.06
Post procedure	
Reference vessel diameter, mm	3.30±0.51
Minimum luminal diameter, mm	2.73±0.52
Diameter stenosis, %	17±9
Follow-up (n=40) at 7 months <sup>a</sup>	
Reference vessel diameter, mm	3.26±0.54
Minimum luminal diameter, mm	2.23±0.94
Diameter stenosis, %	34±26
In-stent late lumen loss, mm	0.48±0.88
Restenosis, n (%) <sup>b</sup>	8 (20%)
Focal — articulation	1
Focal — margin	1
Focal — body	2
Diffuse — intrastent	1
Diffuse — proliferative	1
Diffuse — total occlusion	2

<sup>a</sup>Median of follow-up period.

<sup>b</sup>Restenosis patterns were adopted from the classification by Mehran et al. (Ref. [17]).



death, though this was not angiographically confirmed. Additional 3 clinically-driven TVRs were performed. The 2-year cumulative incidence of MACE was 31.6%. There were two additional stent thromboses (early and late) identified. One occurred 2 days after stenting a non-ostial lesion (left anterior descending) and the other was a late thrombosis 427 days after the index PCI for the right coronary ostial lesion.

### 3.4. Angiographic results

Quantitative coronary angiographic analysis is summarized in Table 4. The mean reference vessel diameter was 3.04 mm. Angiographic follow-up data were obtained in 40 patients (52.6%) at the median timing of 7 months after the index stenting. Binary in-stent restenosis rate was 20.0% (8/40). Focal patterns of restenosis were found in 50% (4/8). In-stent late lumen loss of PES in this lesion subset was 0.48 mm.

## 4. Discussion

The present study provides the 7-month angiographic and 2 year clinical outcomes of PES in aorto-ostial lesions in a larger consecutive population than that of earlier studies [1,9,15,19]. The results of the present study suggest the following two main findings: 1) PES utilization is a feasible treatment option in this complex lesion setting by keeping the restenosis rate to 20.0% and thereby TLR rate to 5.3%; 2) The long-term efficacy of PES, however, in overall clinical outcome still remains to be determined due to the subsequent increase in later events.

Aorto-ostial disease can be a critical cause of fatal myocardial infarction or sudden cardiac death due to the relatively large myocardial territory exposed to risk [3]. Lesions in this location are distinctive from branch ostial lesions because of their specific histopathological characteristics such as highly increased fibrous cellularity, calcification and sclerosis [3–5]. Reflecting this lesion background, Tsunoda et al. reported that excessive neointimal growth and chronic stent recoil might be two important etiologic factors for stent restenosis at this particular location [10]. With regards to the former factor, stents coated with antiproliferative agents are reasonable devices of choice and PES demonstrated successful reduction of neointimal growth after stenting (late loss, 0.48 mm). To overcome another potential factor for restenosis, the combination of debulking and DES may be a particularly optimal approach. Plaque modification prior to stent implantation has been initially embraced as a preferred treatment strategy for this lesion subset [4]. However, since the role of debulking in the era of DES has not been clarified, we performed adjunctive debulking in only 3 patients. Instead of using atherectomy devices, we aggressively post-dilated by adopting a relatively large-sized non-compliant balloon (balloon–artery ratio, 1.24) in order to achieve a satisfactory angiographic

result. Because of the delayed healing response of injured vessel wall after implantation of DES [20], it might be speculated that the relatively high mechanical injury resulting from atherectomy further delayed healing process following DES placement. Furthermore, atherectomy of aorto-ostial lesions is technically demanding because of the need to pull the guiding catheter from the coronary ostium while leaving the atherectomy catheter in position for debulking. Additionally, when performing DCA or rotablation for aorto-ostial lesions, great care should be taken to avoid excision of guiding catheter material [21,22].

Slight stent protrusion into the aorta is usually associated with a benign clinical course. However, unapposed protruding stent struts may theoretically promote platelet activation, thrombosis, and/or distal embolization. In addition, protruding stent struts may not only pose an inability to easily re-engage the ostium with either diagnostic or guiding catheters, but also can complicate future interventional as well as surgical procedures [23–26]. We encountered only one angiographically-documented stent thrombosis related to the target vessel and stent protrusion was not implicated in this case. Of the 2 possible stent thrombosis cases, stent placement with slight protrusion was performed in one (465 days after stenting) and not in the other (21 days after stenting). The 2 cases with very late stent thrombosis occurring beyond 1 year suggest that current US Food and Drug Administration-approved indications for 6-month clopidogrel use following TAXUS implantation may not be sufficient to prevent late stent thrombosis. Eisenstein et al. showed that longer-term clopidogrel use may be associated with more favorable clinical outcome for patients receiving DES [27]. However, the small number of patients evaluated in this analysis do not allow for any definitive statement with respect to the safety profile of this stenting technique. So far, it appears that positioning of PES with protrusion of only a short segment of stent into the aorta might instead contribute to lower restenosis by adequately covering the lesion.

Despite the low incidence of TLR at 2 years, the limited role of PES on overall long-term outcome was also indicated because of the gradual increase in TVR rate. Obstruction at the origin of a coronary artery is most often associated with more generalized coronary atherosclerosis and the presence of multivessel coronary artery disease (72.4%). It may be helpful for long-term favorable outcome to prevent and adequately detect the progression of other non-ostial lesions that are not significant at time of treatment of ostial lesions in the same vessel. Long-term evaluation of non-ostial lesions in the target vessels should be considered.

### 4.1. Study limitations

There were several limitations in this study. First, this was a single-center's experience with implantation of PES in aorto-ostial stenoses. Second, no control group was used to compare the long-term efficacy of PES with other devices. In this regard, direct comparison between PES and bare stent/

SES would have been interesting to address whether a different drug and different stent platform might influence the incidence of restenosis. Third, the rate of follow-up angiography was limited to 52.6% of 76 patients. Finally, since each treatment strategy was not prespecified, the results may reflect our bias toward our treatment technique. However, this study more likely represents “real-life” practice of PES utilization.

## 5. Conclusions

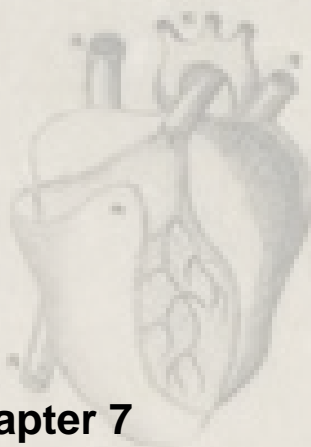
In conclusion, our findings suggest that PES in aorto-ostial lesions is safe and feasible in light of the low incidence of restenosis at 7 months. However, the increase in later events, especially the TVR rate, may attrite the long-term benefit of PES in patients with this complex lesion subset.

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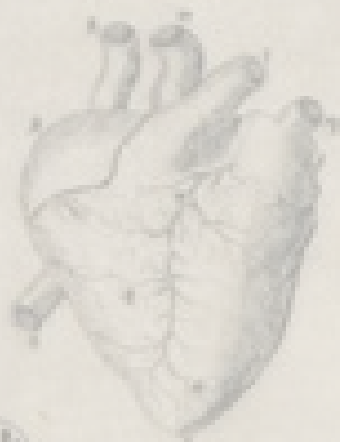
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心篇圖

四脈管及心囊



剖心囊視冠脈



Chapter 7

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豎剖心視兩室

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

全形

García-García HM, Daemen J, Kukreja N, Tanimoto S, van Mieghem CA, van der Ent M, van Domburg RT, Serruys PW.

Catheter Cardiovasc Interv. 2007;70:635-9

心障膜





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

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**Background:** We previously reported that the 1-year survival-free from target lesion revascularization was 97.4% in patients with chronic total occlusion (CTO) treated with sirolimus-eluting stents (SES). There are currently no long-term results of the efficacy of SES in this subset of lesions. We assessed the 3-year clinical outcomes of 147 patients with CTO treated with either SES or bare metal stents (BMS). **Methods and Results:** A total of 147 (BMS = 71, SES = 76) patients were included. Four patients died in the BMS group while five patients died in the SES group,  $P = 0.8$ ; two myocardial infarctions occurred in both groups,  $P = 0.9$ ; and target vessel revascularization was performed in nine patients in the BMS and seven in the SES group,  $P = 0.5$ . The cumulative event-free survival of MACE was 81.7% in BMS group and 84.2% in SES group,  $P = 0.7$ . Two patients of the SES group had a coronary aneurism at 3-year angiographic follow-up. **Conclusions:** The use of SES was no longer associated with significantly lower rates of target vessel revascularization and major adverse cardiac events in patients with CTOs after 3 years of follow-up compared with BMSs. © 2007 Wiley-Liss, Inc.

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

## INTRODUCTION

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

tionalists, the clinical and angiographic long-term follow-up of the DES is still a major concern, especially in high-risk populations. We therefore investigated the 3-year clinical and angiographic follow-up of patients with CTO in a consecutive series of 147 patients, with comparison between the bare metal stents and SESs.

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## MATERIALS AND METHODS

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

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

### CTO Definition

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

### Angiographic Analysis

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

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

Our primary endpoints were the 3-year incidence of MACE, a compound endpoint of all-cause mortality, nonfatal myocardial infarction and target-vessel revas-

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

### Three-Year Follow-Up Data

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

### Statistical Analysis

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

**TABLE I. Baseline Patient Characteristics**

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

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

## RESULTS

### Baseline and Procedural Characteristics

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

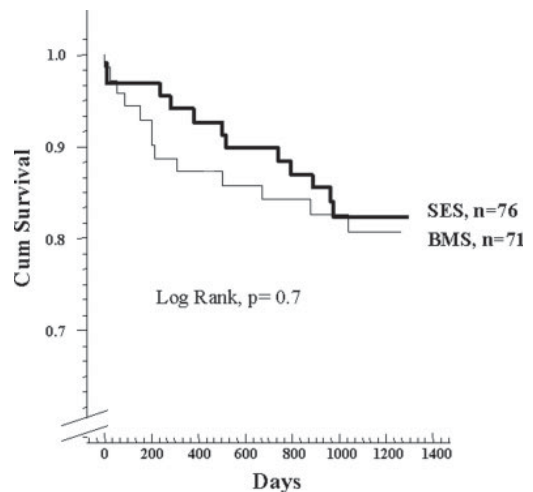
### Three-Year Clinical Follow-Up

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

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

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

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



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

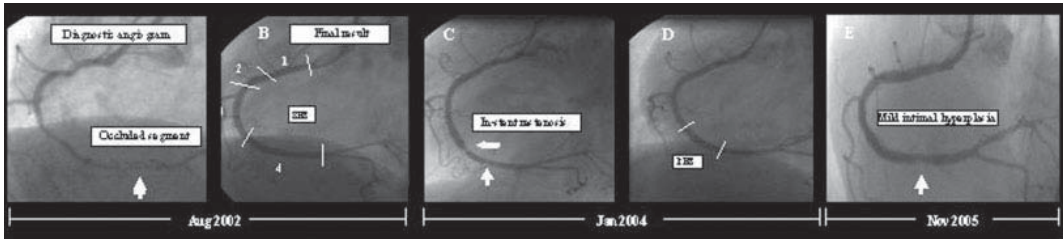
Two MI's occurred in both groups,  $P = 0.9$ ; and TVR was performed in nine patients in the BMS and seven in the SES group,  $P = 0.5$ . The cumulative survival-free of MACE was 81.7% in BMS group and 84.2% in SES group,  $P = 0.7$  (Table II and Fig. 1). No cases of late stent thrombosis were identified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

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

### Three-Year Angiographic Follow-Up

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





**Fig. 2.** A patient with a chronic total occlusion in the distal right coronary artery (panel A) was treated with four sirolimus stent (SES), in panel B the final result. Seventeen months later the patient underwent coronary angiogram due to stable angina and focal stent restenosis was seen in the gap between

SES 3 and 4 (panel C). In addition, mild intimal hyperplasia was observed in the body of the SES number 4. Patient was treated with a PES (panel D). In the three-year angiographic follow-up an increase was seen in the intimal hyperplasia (panel E).

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

## DISCUSSION

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

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

Although due to the study design some baseline characteristics are different between the two groups such the presence of diabetes, treatment of the LAD (no statistically significant), and diameter of the stent, in the 6-month [9] and 1-year [14] reports in patients treated with SES a marked reduction in restenosis rate and MACE was observed compared with BMS. In turn, this 3-year follow-up report showed no difference whatsoever in any of the MACE components. This is in agreement with other two long-term follow-up sub-studies of the RESEARCH registry, patients with diabetes mellitus and acute MI [16]. The former report compared the 2-year clinical outcome of 708 consecu-

tive diabetic patients treated with either a BMS ( $n = 252$ ), a SES ( $n = 206$ ), or a PES ( $n = 250$ ). TVR rates were 19.5% in the BMS group, vs. 15.3% in the SES group and 9.7% in the PES group. PES (21.2%) but not SES (28.9%), were superior to BMS (29.7%) in reducing MACEs. However, after propensity analyses, none of the differences remained significant. The second report where primary angioplasty was performed in a consecutive group of 505 patients (BMS,  $n = 183$ ; SES,  $n = 186$ ; PES,  $n = 136$ ), showed that the cumulative incidence of death or MI was comparable in the three groups: 16.6% in the BMS group, 14.6% in the SES group, and 16.9% in the PES group. At 3 years, TVR was 12.0% in the BMS group, compared with 8.0 and 7.7% in the SES and PES groups, respectively. The cumulative incidence of death, MI or TVR was 25.5% in the BMS group compared with 17.9 and 21.4% in the SES and PES groups, respectively. In light of these results, it seems that a late clinical restenotic phenomenon is observed in specific subsets of patients, and that the beneficial effects in restenosis rates of DES observed in the first year might drop over the time.

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

## CONCLUSIONS

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



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

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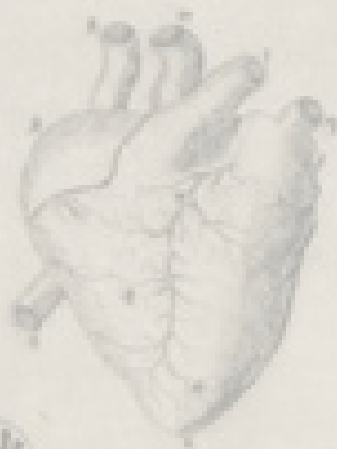


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Chapter 8

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

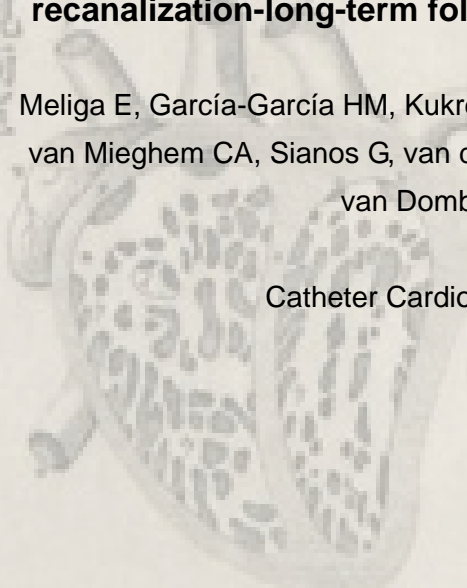
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van Domburg R, Serruys PW.

Catheter Cardiovasc Interv. 2007;70:21-5

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

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**Objective:** To compare the postprocedural and long-term clinical outcomes of two groups of patients, all presenting with chronic saphenous vein graft (SVG) occlusion, who underwent either SVG or native vessel reopening. **Background:** Chronic total occlusions (CTO) treatment in patients who underwent previous surgical revascularization is a dilemma and the choice of performing native vessel or SVG recanalization is not always easy. **Methods:** Between July 2002 and October 2004, a total of 260 patients were successfully treated for a CTO. Of them, we selected all patients ( $n = 24$ ) who had previous bypass surgery with graft occlusion. Of this final group, 13 patients underwent a percutaneous graft recanalization while 11 underwent native vessel reopening. **Results:** Primary end points were in-hospital and 3-year rates of death, myocardial infarction, target lesion revascularization, and target vessel revascularization. No events occurred in either group during the in-hospital period. Cumulative 3-year event-free survival in the native vessel and SVG group was 81.8% and 83.9% respectively ( $P = \text{NS}$ ). One death and one TVR occurred in each group. **Conclusion:** In selected cases, SVG reopening instead of the native vessel is feasible. In such a high-risk population, drug-eluting stent implantation in both SVG and native CTO lesions is associated with good long-term outcomes. © 2007 Wiley-Liss, Inc.

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

## INTRODUCTION

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

always attempt to treat the native bypassed coronary arteries?

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

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

## METHODS

### Population

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

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

### End Points

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

### Definitions

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

### Interventional Technique

The operators performed the procedure according to standard techniques of the time via the femoral or brachial approach. All procedural and technical details and the choice of devices were left to the operator's judgment. In the cardiac catheterization laboratory,

**TABLE I. Baseline Clinical Characteristics**

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

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

patients received a bolus of 10,000 units of heparin followed by repeated boluses per a weight-based protocol to achieve an activated clotting time  $>250$  sec. All the lesions were treated with DES implantation. Periprocedural abciximab was administered at the operator's discretion. After the procedure, clopidogrel (75 mg daily) was prescribed to all patients for 6 months after stent implantation; aspirin was given indefinitely.

### Follow-up

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

### Statistical Analysis

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

**TABLE II. Angiographic and Procedural Characteristics**

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

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

## RESULTS

### Baseline and Procedural Variables

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

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

### Procedural and In-Hospital Outcomes

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

Both technical and procedural success rates were 100%. No death, postprocedural infarction, or urgent re-PCI occurred in either group. Two patients experi-

**TABLE III. Procedural and In-Hospital Outcomes**

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

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

enced hemodynamic instability, both in the SVG group. One patient needed an intra-aortic balloon pump (none in native vessel group) and one patient needed temporary pacing (none in native vessel group).

### Follow-up Clinical Outcomes

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

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

## DISCUSSION

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

**TABLE IV. Three-Year Follow-up Clinical Outcomes**

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

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

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

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

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

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

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

In this study, the use of DES for CTO recanalization, associated with the use of antiplatelet drugs led to excellent postprocedural and in-hospital outcomes. No death, MI, urgent TVR, or distal embolization

occurred in either group. Additionally, only two patients with PCI for SVG occlusion had in-hospital hemodynamic instability (15.3%), one requiring an IABP and one requiring temporary pacing.

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

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

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

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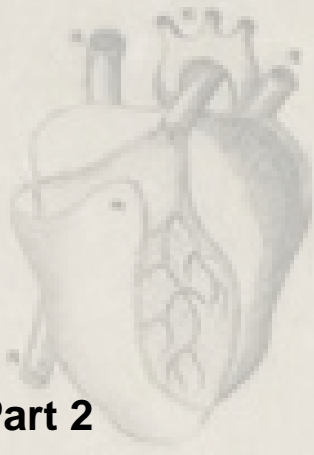


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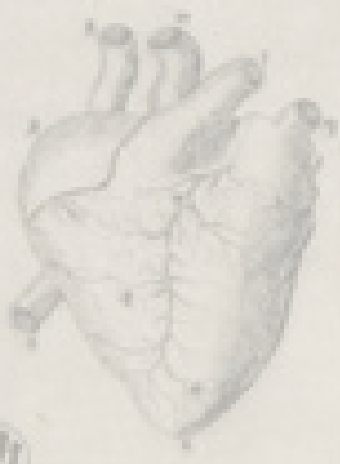


心篇圖

四脈管及心囊



剖心囊視冠脈

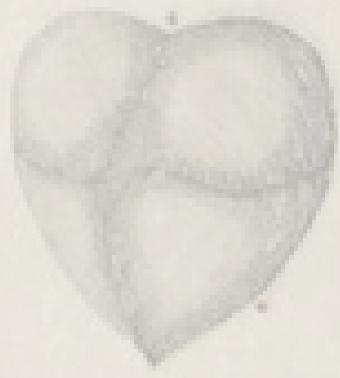


Part 2

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New concept stents for percutaneous coronary intervention

全形



心障膜



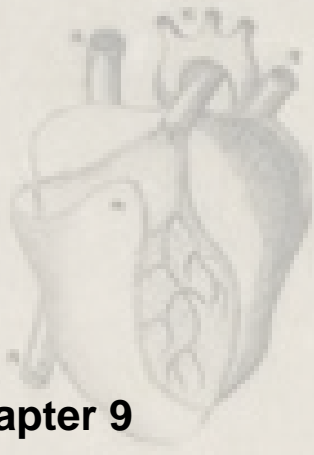
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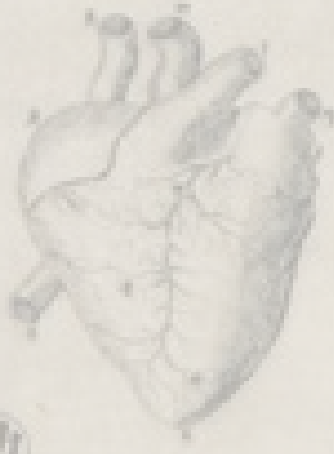


心篇圖

四脈管及心囊



斜心囊視冠脈



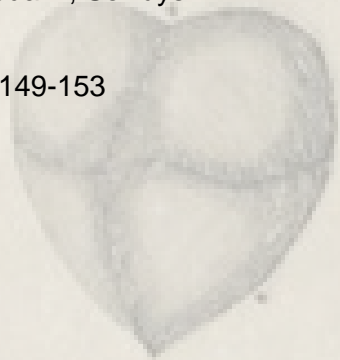
Chapter 9

**MAHOROBA: Tacrolimus eluting coronary stent.**

Tanimoto S, van der Giessen W, van Beusekom, M, Sorop O, Kukreja N, Fukaya K, Nishide T, Nakano R, Maeda H, Serruys PW.

EuroIntervention. 2007;3:149-153

全形

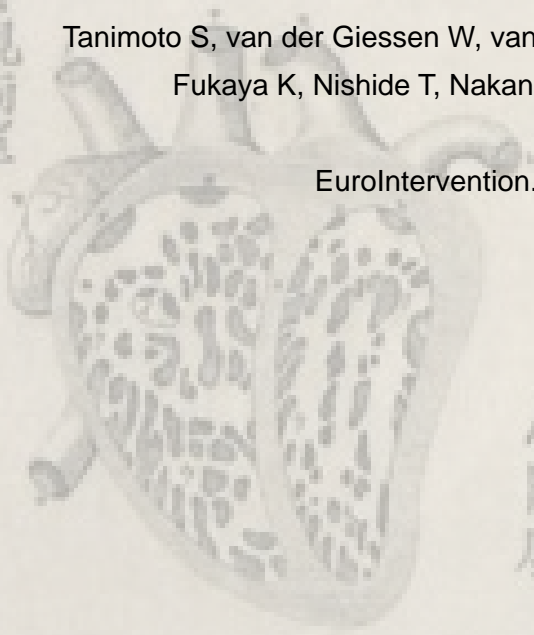


心障膜



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## MAHOROBA™: Tacrolimus eluting coronary stent

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All other authors have no conflict of interest to declare.

### Description

Kaneka's coronary stent, MAHOROBA™, is a new drug eluting stent (DES), which combines a thin, flexible cobalt-chromium (CoCr) metal stent platform coated with a biodegradable polymer including the pharmaceutical agent tacrolimus. The device has been designed and developed to inhibit the growth of neointimal hyperplasia and avoid interference with the vascular healing response.

### History

The advent of DES has revolutionised the practice of interventional cardiology by inhibiting the development of neointimal hyperplasia and thereby reducing the rates of restenosis and repeat revascularisation as compared to bare metal stents (BMS)<sup>1-4</sup>. After the first approval of DES in 2002, a large number of patients with coronary artery disease have undergone percutaneous revascularisation with DES. Recently, however, certain potential safety concerns regarding their widespread use have arisen. The most notable drawback of DES is that they could increase the risk of thrombotic complications, especially late stent thrombosis. In order to discuss this serious problem, the US Food and Drug Administration held a medical device advisory panel meeting on December 7-8, 2006<sup>5</sup>. They concluded that DES are associated with a numerical excess of late stent thrombosis (after 1-year post implantation), although the magnitude of this excess is uncertain. The increased risk of thrombosis with the use of DES may be associated with altered endothelial function<sup>6</sup> and/or delayed vascular healing<sup>7</sup> induced by cytotoxic and cytostatic drug use. In addition, localised hypersensitivity reactions to the polymer coating of the DES and drug

itself may also contribute to stent thrombosis<sup>8,9</sup>. To retain the positive clinical aspects of DES and overcome their drawbacks, Kaneka Corporation has developed a new DES, MAHOROBA™, which aims to inhibit excessive neointimal growth whilst avoiding the interruption of the vascular healing process, including re-endothelialisation.

### Stent characteristics

#### 1. PLATFORM

Material: cobalt chromium (CoCr) alloy  
 Deployment: balloon expandable  
 Strut thickness: 75 µm (0.0030 inches)  
 Size available: 3.0 x 18 mm and 3.5 x 18 mm  
 Number of cells: both 8 cells and 10 cells are combined  
 Number of joints: 2  
 Radial force: 0.17 N/mm (for the 3.0 mm diameter stent)  
 Recoil/shortening: 3%/3%  
 Nominal/rated burst pressure: 9 atm/16 atm

#### 2. DRUG

Used drug: tacrolimus

#### 3. COATING

Characteristics: biodegradable polymer  
 Composition: poly DL-lactide-co-glycolide (PLGA: 3.58 µg/mm<sup>2</sup>) + tacrolimus (0.94 µg/mm<sup>2</sup>)  
 Coating methods: whole abluminal surface coating of the stent platform  
 Drug release kinetics: controlled with half the drug released over more than 84 days

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## 4. DELIVERY SYSTEM

Guide compatibility: 6 Fr

Outer diameter: 2.7/2.1 Fr (in the distal/proximal shaft)

### Technical specifications

#### 1. PLATFORM

The material of the stent platform is CoCr. The stent has an open-cellular balloon-expandable design and consists of two helical coils inter-crossed with two phase-different links on each turn, in which each link deviates diagonally along the longitudinal axis (Figure 1). This novel link configuration allows for low elastic recoil, sufficient radial force and good scaffolding while featuring excellent flexibility both mounted on the delivery balloon as well as after expansion. In addition, the stent strut thickness (75  $\mu\text{m}$ , 0.0030 inch) of the MAHOROBA™ stent is thinner than most other DES (Table 1). Randomised clinical trials have revealed that thin-strut BMS have significantly reduced restenosis rates as compared to thick-strut BMS<sup>10</sup>, probably because thin-strut stents cause less arterial injury at deployment. Therefore, the MAHOROBA™ stent may reduce the growth of neointimal hyperplasia more than the other DES.

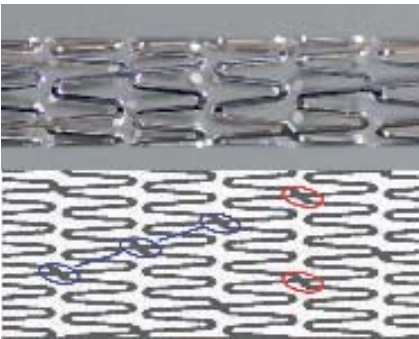


Figure 1. MAHOROBA™ Tacrolimus eluting coronary stent. The upper part of this figure is a magnified image of the MAHOROBA™ tacrolimus eluting coronary stent. The lower is a schematic of the stent structure itself. Two helical coils inter-cross with two phase-different links (red circle). Blue circles and arrows indicate that each link deviates diagonally along the longitudinal axis. These novel configurations of links achieve high flexibility and vessel scaffolding.

#### 2. DRUG

Tacrolimus (FK 506; Astellas Pharma Inc., Tokyo, Japan) is a water-insoluble macrolide immunosuppressant indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver or kidney transplantation. Tacrolimus binds to FK-binding protein12 (FKBP12), forming a compound (Tacrolimus-FKBP12 complex), which inhibits the production of pro-inflammatory cytokines such as interleukin 2 by preventing the activation of calcineurin and suppresses T-cell proliferation (immunosuppressive effect)<sup>11</sup>. This complex also inhibits several steps of the cascade of events leading to neointimal formation<sup>12</sup> and reduces the proliferation of smooth muscle cells (SMC)<sup>13</sup>, which play an important role in the mechanism of restenosis (antiproliferative effect). These two effects of tacrolimus contribute to the inhibition of neointimal growth.

Unlike drugs used in other DES, tacrolimus has a different mode of action for the cell cycle (Table 1). By reducing the expression of cell cycle proteins, tacrolimus holds cells in the G0 phase, in which cells are able to function, but unable to replicate. Sirolimus, zotarolimus and everolimus arrest cell replication in the G1 phase (cytostatic effect), whilst paclitaxel prevents mitosis and then halts the metaphase (cytotoxic effect). Therefore, tacrolimus is a non-cytotoxic and non-cytostatic agent, which may be beneficial in preventing excessive vessel injury.

Additionally, tacrolimus is also expected to demonstrate less inhibition of endothelial cell (EC) proliferation, which is an important process for vascular healing. Matter et al reported in an *in vitro* study that the inhibitory concentration<sub>50</sub> (IC<sub>50</sub>) value of tacrolimus for EC is markedly higher than that for SMC, while the IC<sub>50</sub> value of sirolimus for EC is remarkably lower than that for SMC<sup>14</sup> (Figure 2). This result implies that if equipotent concentrations for suppressing SMC proliferation are used, tacrolimus may allow better re-endothelialisation than sirolimus. Moreover, unlike sirolimus and paclitaxel, tacrolimus does not affect tissue factor expression, which can lead to the initiation of coagulation causing thrombus formation<sup>15,16</sup>. Tacrolimus may therefore reduce the incidence rates of stent thrombosis as compared to the other drugs. Considering these characteristics, if effective local drug concentrations are achieved, tacrolimus can exert its antiproliferative and anti-inflammatory effects while being vascular protective with less prothrombotic effects. Therefore, tacrolimus is a promising compound for the next generation of DES.

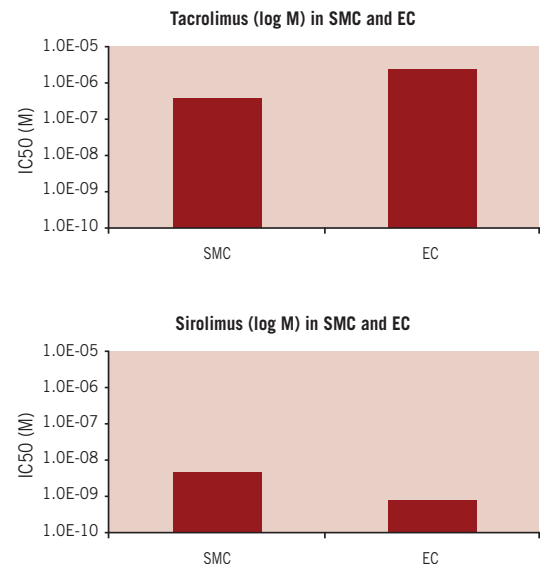


Figure 2. Inhibitory concentration<sub>50</sub> (IC<sub>50</sub>) values of tacrolimus and sirolimus for smooth muscle cells and endothelial cells. The upper panel shows the inhibitory concentration<sub>50</sub> (IC<sub>50</sub>) values of tacrolimus for smooth muscle cells (SMC) and endothelial cells (EC). The bottom panel shows the IC<sub>50</sub> values of sirolimus for SMC and EC. The IC<sub>50</sub> value of tacrolimus for EC is markedly higher than that for SMC, while the IC<sub>50</sub> value of sirolimus for EC is remarkably lower than that for SMC. Data are extracted from Matter et al<sup>14</sup>.



**Table 1. Different characteristics of DES.**

	MAHOROBA™	Cypher®	Taxus®	Endeavor™	Xience™
Company name	Kaneka	Cordis	Boston Scientific	Medtronic	Abbott vascular
Platform					
Material	CoCr	Stainless steel	Stainless steel	CoCr	CoCr
Strut thickness, µm	75	140	132	91	81
Strut thickness, inch	0.0030	0.0055	0.0052	0.0036	0.0032
Number of cells	8 and 10	6	6 and 9	10	6
Number of joints	2	6	3	2	3
Coating Drug					
Drug	Tacrolimus	Sirolimus	Paclitaxel	Zotarolimus	Everolimus
Action point	G0	G1	M	G1	G1
Coating					
Composition	PLGA	PEVA/PBMA	SIBS	PC	
Characteristics	Bioabsorbable	Durable	Durable	Durable	Durable

CoCr = cobalt chromium; PLGA = poly DL-lactide-co-glycolide; PEVA = polyethylene-co-vinyl acetate; PBMA = poly n-butyl methacrylate; SIBS = polystyrene-block-polyisobutylenebutadiene-block-polystyrene; PC = phosphorylcholine

### 3. COATING POLYMER AND DRUG RELEASE KINETICS

The whole abluminal surface of the stent platform is coated with a matrix containing bioabsorbable polymer and tacrolimus. The surface of the coating layer is generally smooth and no cracks or peeling are observed even when the stent expands (Figure 3). Most other DES are coated with a durable polymer as a drug carrier (Table 1). A durable polymer may lead to hypersensitivity with eosinophilic infiltration in surrounding tissues at the stent deployment site<sup>17</sup> since the polymer exists permanently. This hypersensitivity reaction could be associated with stent thrombosis<sup>8</sup>. To minimise this undesirable reaction, biodegradable materials can be an alternative vehicle for drug delivery because they are fully metabolised into carbon dioxide and water<sup>18</sup>, and thus no chemical substances remain permanently. Kaneka Corporation has developed a specially designed fully biodegradable polymer composed of PLGA to achieve a long degradation time. In a porcine model, the PLGA completely disappears from the coronary artery in approximately 6 months (Figure 4). As the drug is uniformly distributed in the polymer layer, tacrolimus will be released continually for several months and completely disappear concomitantly with PLGA degradation. Indeed, in an *in vivo* porcine coronary model, the tacrolimus release kinetics of the MAHOROBA™ stent are controlled with 26% and 45% of the drug released in 28 days and 84 days, respectively, while the sirolimus-eluting stents (Cypher®: Cordis Corporation, Warren, NJ, USA) are designed such that 79% of the sirolimus has been released by 28 days<sup>19</sup>. This sustained drug release property results in subsequent retention of a sufficient concentration of tacrolimus in target coronary arterial tissues for several months (Figure 5).

The coating method of the MAHOROBA™ is completely different from a previously investigated tacrolimus-eluting stent (Janus™, Sorin Biomedica Cardio s.r.l., Saluggia, Italy)<sup>20</sup>. The Janus™ stent does not have any polymer vehicle, but has deep reservoirs containing tacrolimus on the external abluminal stent surface, in which controlled drug release is difficult. Consequently, the vessel wall may acutely be exposed to extremely high concentration of the drug, leading to excessive inflammation in vascular walls. An animal study showed that the tacrolimus concentration in the arterial wall peaked a few days after the Janus™ stent implantation and then



Figure 3. Surface of MAHOROBA™ stent.

Scanning electron microscopy images show that the surface of the expanded stent is smooth (left panel). Even in the magnified images (right panel), no cracks or peeling are observed.

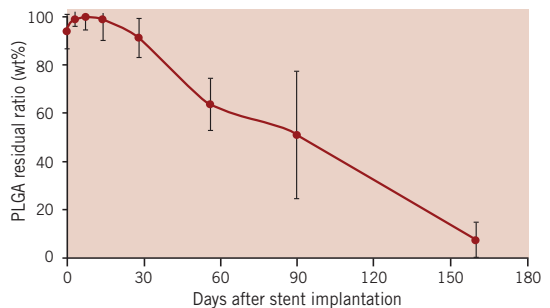


Figure 4. Residual ratio of PLGA after stent implantation in a porcine coronary artery.

The PLGA degrades gradually and completely disappears in approximately 6 months.

steeply fell to steady values<sup>12</sup>. These release kinetics may be a part of the reason why the Janus™ stent had a neutral effect on restenosis (in-stent late luminal loss of 0.65 mm) as shown in the Jupiter II trial<sup>20</sup>. Although the same drug is used, the MAHOROBA™ stent may prevent more neointimal hyperplasia than the Janus™ stent, because the MAHOROBA™ stent features controlled drug release.

### 4. DELIVERY SYSTEM

The delivery system is based on the rapid exchange type PTCA balloon catheter (Fortis™, developed by Kaneka Corporation) with a semi-low-compliant balloon. This device is approved and has been sold in Japan.

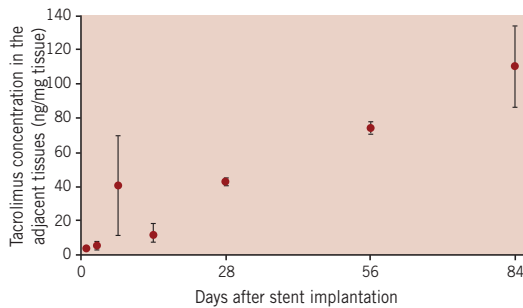


Figure 5. Tacrolimus concentration in the adjacent arterial tissues. Drug concentration in the surrounding tissues gradually increases, resulting in the retention of a sufficient concentration of tacrolimus in target coronary vessels for several months.

### Preclinical experience

Preclinical testing started in 2005 and is ongoing into the second quarter of 2007. The initial animal results were presented during EuroPCR 2006<sup>21</sup>. It showed that the MAHOROBA™ reduced neointimal thickening and neointimal area at 1 and 3 months following stent deployment as compared to BMS, while it allowed for vascular healing and endothelialisation. Kaneka in-house porcine data also showed that well endothelialised neointima was visible as early as 14 days (Figure 6) after stenting without visible qualitative differences between MAHOROBA™ and BMS. The biodegradable PLGA polymer did not cause obvious luminal inflammation.

### Future directions

In summary, the principal characteristics of MAHOROBA™ are the following. First, the coating drug, tacrolimus, is a non-cytotoxic and non-cytostatic drug. Tacrolimus prevents the growth of neointimal hyperplasia and allows for better re-endothelialisation. Second, the coating polymer is fully absorbable and minimises adverse effects caused by the permanent presence of polymer. Third, the specially designed biodegradable polymer can sustain longer drug release, which allows a sufficient concentration of tacrolimus in coronary arterial tissues for several months. Lastly, the stent strut thickness is small, which may also contribute to reducing neointimal growth. The primary goal of the next generation of DES is no longer the complete inhibition of neointimal hyperplasia but the restitution of a healthy, functionally active endothelial lining capable of modulating the healing process, in order to prevent potential drawbacks of DES, such as stent thrombosis. The MAHOROBA™ is a second generation of DES, which aims to address these issues. To evaluate the safety and efficacy of the MAHOROBA™ stent in humans, the first-in-man study, which is a prospective, single-armed, multicentre, core lab analysis study, will be launched in May 2007.

Study name: MAHOROBA I

Study P.I.: Patrick W. Serruys

Enrolment: 45 patients

Primary endpoint: In-stent late luminal loss at 4 and 12 months

Clinical site: 3 clinical sites in The Netherlands

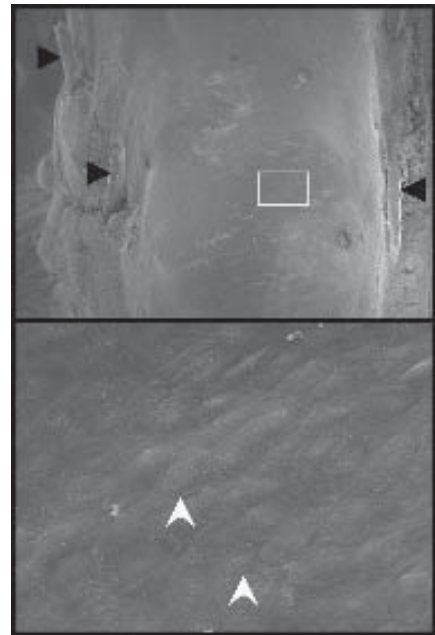


Figure 6. Representative scanning electron microscopy images from MAHOROBA™ at low and high power magnification. MAHOROBA™ shows almost complete re-endothelialisation 14 days after deployment (upper panel: low magnification). Stent struts are almost completely covered by the endothelial cells and embedded in the arterial wall. Black arrowheads indicate stent struts. Bottom panel is a magnified image of the white box in the upper panel. Endothelial junctions (white arrow head) are clearly visible.

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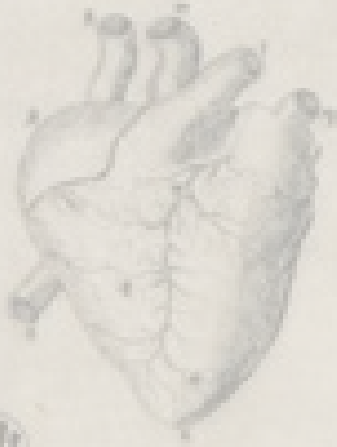


心篇圖

四脈管及心囊



剖心囊視冠脈



Chapter 10

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豎剖心視兩室

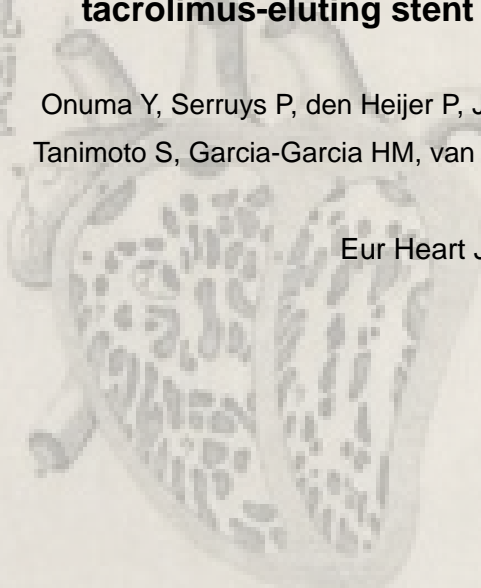
MAHOROBA, first-in-man study:

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心障膜







# MAHOROBA, first-in-man study: 6-month results of a biodegradable polymer sustained release tacrolimus-eluting stent in *de novo* coronary stenoses<sup>†</sup>

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## Aims

To report the 4-month angiographic and 6-month clinical follow-up in first-in-man study using the tacrolimus-eluting bioabsorbable polymer-coated cobalt–chromium MAHOROBA<sup>™</sup> stent.

## Methods and results

A total of 47 patients with either stable angina or unstable angina, or silent myocardial ischaemia, based on a *de novo* coronary stenosis that could be covered by a single 18 mm stent in a native coronary artery with a diameter between 3.0 and 3.5 mm were enrolled at three sites. The primary endpoint was in-stent late loss at 4 months. The secondary endpoints include %volume obstruction of the stents assessed by intravascular ultrasound (IVUS) at 4 months and major adverse cardiac events (MACE) at 6 months. Forty-seven patients were enrolled. Procedural success was achieved in 97.9%. At 4-month follow-up, in-stent late loss was  $0.99 \pm 0.46$  mm, whereas in-stent %volume obstruction in IVUS was  $34.8 \pm 15.8\%$ . At 6 months, there were no deaths, but 2 patients suffered from a myocardial infarction and 11 patients required ischaemia-driven repeat revascularization. The composite MACE rate was 23.4%.

## Conclusion

This tacrolimus-eluting stent failed to prevent neointimal hyperplasia, despite the theoretical advantages of the tacrolimus, which has less inhibitory effects on endothelial cells than smooth muscle cells.

## Keywords

Tacrolimus-eluting stent • First-in-man study • Drug-eluting stent • Coronary artery disease

## Introduction

Sirolimus-eluting stents (SESts) and paclitaxel-eluting stents (PESts) have markedly reduced the rate of in-stent restenosis and late lumen loss compared with bare-metal stents (BMSs),<sup>1</sup> resulting in a significant reduction in repeat revascularizations. Accordingly, percutaneous coronary intervention (PCI) using drug-eluting stents (DESts) has been accepted as the most effective treatment option for *de novo* coronary artery disease.

However, enthusiasm for this technology has recently been dampened by concerns about late stent thrombosis, an event often associated with lethal consequences. Delayed re-endothelialization after DES has been suggested as one of the plausible causes of late stent thrombosis.<sup>2–4</sup> Pathological autopsy studies also support the hypothesis of delayed endothelialization, showing an association between lack of neointimal strut coverage after DES implantation and stent thrombosis. Localized hypersensitivity reactions to the durable polymer coating and/or to the drug

<sup>†</sup>This article has not been published and is not under consideration elsewhere.

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itself may also theoretically add to stent thrombosis.<sup>5</sup> Furthermore, endothelial dysfunction after DES has lately attracted considerable attention. Recent reports suggest that DES may impair endothelial responses to acetylcholine or exercise-mediated vasodilation in humans.<sup>6,7</sup>

Tacrolimus is a macrolide immunosuppressant drug licensed for prophylaxis of rejection in recipients of organ transplantation.<sup>8</sup> The intracellular receptors are the FK binding proteins (FKBP, including FKBP12); the tacrolimus–FKBP complex binds to inhibit the calcineurin–calmodulin complex,<sup>8</sup> which suppresses proliferation of T-cells, smooth muscle cells (SMCs), and endothelial cells (ECs). Tacrolimus has a much less inhibitory effect on SMC and EC than sirolimus, but tacrolimus depresses EC less than SMC.<sup>9–11</sup> These results suggest that tacrolimus may allow better re-endothelialization than sirolimus if proper concentrations for suppressing SMC proliferation are used. Furthermore, unlike sirolimus or paclitaxel, tacrolimus does not affect the tissue factor and e-NOS expression, which might attenuate the risk of stent thrombosis.<sup>12,13</sup>

A poly D, L-lactide-co-glycolide (PLGA) polymer with sustained drug release for several months was employed to maintain high tissue concentration of tacrolimus. This polymer coating is fully absorbable and theoretically minimizes adverse effect, such as possible hypersensitivity reactions, caused by the permanent presence of a durable polymer. In a porcine model, the MAHOROBA stent (Kaneka, Osaka, Japan) demonstrated early re-endothelialization and reduction of neointimal thickening up to 90 days after the implantation.<sup>14</sup> Conversely, it has yet to be demonstrated that the biodegradation of the polymer in human atherosclerotic vessels does not in itself induce an inflammatory and proliferative response.

The objective of the MAHOROBA I, first-in-man (FIM) study was to test the safety and feasibility of the MAHOROBA™ stent to treat *de novo* coronary lesions.

## Methods

### Study design and patient selection

The study enrolled 47 patients at three participating sites in The Netherlands. The local Ethics Committee approved the protocol for each study site, and all patients gave written informed consent before the procedure. Patients over 18 years of age were eligible, provided they had stable angina, unstable angina, or silent myocardial ischaemia with a *de novo* coronary artery lesion with >50 and 100% stenosis of a length that could be covered by a single 18 mm stent with a diameter between 3.0 and 3.5 mm in one or two major epicardial arteries. The second lesion should fit with inclusion/exclusion criteria and be treated with the same study stent. Patients were not eligible for enrolments if they had an evolving acute myocardial infarction (MI) within 72 h, renal dysfunction (serum creatinine >2.0 mg/dL), a total occlusion with a TIMI flow of 0 or 1, low left ventricular ejection fraction (<30%), a platelet count of <100 000 cells/mm<sup>3</sup> or >700 000 cells/mm<sup>3</sup>, a white blood cell count of <3000 cells/mm<sup>3</sup>, previous drug-eluting or BMS implantation in the target vessel, a target lesion supplied by an arterial or venous bypass graft, a heavily calcified lesion, a bifurcation lesion involving a side branch >2.0 mm in diameter with an ostial disease, unprotected left-main disease, planned PCI within 60 days after trial stent implantation, planned surgery within 6 months after

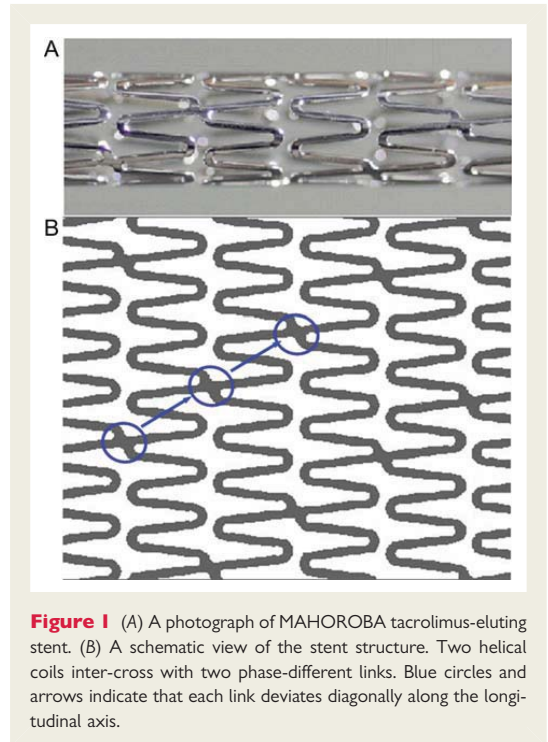
stent implantation, stroke or transient ischaemic attack within the prior 6 months, a known allergy to aspirin, clopidogrel, cobalt–chromium alloy, heparin, tacrolimus (or similar drugs), or contrast agents that cannot be adequately premedicated.

### The MAHOROBA stent

The MAHOROBA tacrolimus-eluting stent (TES) comprises a drug-eluting PLGA coating and a cobalt–chromium (CoCr) stent with a strut thickness of 75 µm, as previously described.<sup>15</sup> The stent has an open-cellular balloon-expandable design and consists of two helical coils inter-crossed with two phase-different links on each turn, in which each link deviates diagonally along the longitudinal axis (Figure 1). The entire abluminal surface of the stent is coated with a fully biodegradable PLGA polymer matrix. The molecular weight of the PLGA polymer was 84 000 Da. The mass ratio of the drug and polymer was 20.6 and 79.4 wt%, respectively. The dose density of tacrolimus and the polymer was 0.94 and 3.58 µg/mm<sup>2</sup>, respectively. The purity of the polymer was over 99.9%. The PLGA polymer was proven by compliance with the ISO 10093s. In the porcine artery model, the PLGA degrades and disappears completely in 6 months.<sup>16</sup> Tacrolimus is released continually for several months and completely resolves with PLGA degradation.

### Study procedure

Lesions were treated using standard interventional techniques with mandatory pre-dilatation prior to stent implantation. The following sizes of MAHOROBA stent were used in the study: 18 mm length and either 3.0 or 3.5 mm diameter. Intravascular ultrasound (IVUS) was performed after angiographically optimal stent placement and was repeated if additional post-dilatation was required. Treatment



**Figure 1** (A) A photograph of MAHOROBA tacrolimus-eluting stent. (B) A schematic view of the stent structure. Two helical coils inter-cross with two phase-different links. Blue circles and arrows indicate that each link deviates diagonally along the longitudinal axis.



with aspirin, at a minimal dose of 100 mg per day, was started prior to procedure and continued indefinitely. A loading dose of 300 mg of clopidogrel was administered at least 6 h before the procedure, followed by 75 mg daily for at least 13 months.

## Follow-up

Patients were evaluated clinically at 30 days and 4 months with further evaluation scheduled at 9 and 12 months followed by annual evaluation out to 5 years: patients were asked specific questions about major cardiac adverse events and the interim development of angina according to the Canadian Cardiovascular Society classification of stable angina. Angiographic and IVUS evaluations were performed at 4 months.

## Quantitative coronary angiography

Quantitative coronary angiography (QCA) analyses were performed by a corelab (Cardialysis B.V., Rotterdam, The Netherlands) with the CAAS II analysis software (Pie Medical B.V., Maastricht, The Netherlands). In each patient, the stented segment and the peri-stent segments defined by a length of 5 mm proximal and distal to the stent edge were analysed. The following QCA parameters were computed: minimal luminal diameter (MLD), reference diameter obtained by an interpolated method, and percentage diameter stenosis. Binary restenosis was defined in every segment (proximal, distal, and stent) as diameter stenosis  $\geq 50\%$  at follow-up. Stent-to-artery ratio was calculated as a mean diameter of the last balloon at the highest pressure divided by the baseline reference vessel diameter. Late loss was defined as the difference between MLD post-procedure and MLD at follow-up. Results are presented as means using matched pair of angiographic views using multiple X-ray views.

For the assessment of acute stent recoil, two sequential angiographic images were analysed: first an image of the complete expansion of the largest balloon at the highest pressure, whereas the second was an image immediately after the final balloon deflation. These two images were analysed in the same angiographic projection. When the stent delivery balloon was used for stent expansion, QCA measurements were performed between the markers of the stent delivery balloon and within the deployed stent markers. Acute stent recoil was calculated as previously described.<sup>17–19</sup>

## Intravascular ultrasound

All cases were imaged with a 2.5 F Atlantis SR pro imaging 40 MHz catheter (Boston Scientific, Santa Clara, CA, USA). Post-procedure and at follow-up, stented culprit vessel segments were examined with mechanical IVUS using automated pullback at 0.5 mm per second. The coronary segment was examined by IVUS beginning 5 mm distal to and extending 5 mm proximal to the stented segment. A validated offline quantitative computer-based IVUS software was used for semi-automated three-dimensional reconstruction and analysis (CURAD Vessel analysis, Wijk bij Duurstede, The Netherlands).<sup>20</sup> The lumen, stent boundaries, and the external elastic membrane were detected in longitudinal reconstructed views. In order to obtain a smooth appearance of the vessel wall structures in the longitudinal views, a retrospective image-based gating method was applied (e.g. Intelligate™).<sup>21</sup>

The volumetric parameters of the stent, lumen, and obstruction [e.g. neointima hyperplasia (NIH)] volume and percentages were calculated as:

$$\text{Stent\_Volume} = \sum_{i=1}^n (\text{Stent\_Area}(i)) \times H,$$

where Stent\_Area(*i*) is the stent area in one of the cross-sections of the stent, *n* the number of cross-sections, and *H* the distance between two consecutive cross-sections.

$$\text{Lumen\_Volume} = \sum_{i=1}^n (\text{Lumen\_Area}(i)) \times H,$$

where Lumen\_Area(*i*) is the lumen area in one of the cross-sections of the stent. The other parameters are similar as described in the above formula.

$$\text{NIH\_Volume} = \sum_{i=1}^n (\text{Stent\_Area}(i) - \text{Lumen\_Area}(i)) \times H,$$

where Stent\_Area(*i*) is the stent area in one of the cross-sections of the stent, Lumen\_Area(*i*) the lumen area in the same, and the other parameters are similar as described in the above formula.

$$\% \text{NIH\_Obstruction} = \frac{\text{NIH\_Volume}}{\text{Stent\_Volume}} \times 100\%.$$

Incomplete apposition was defined as one or more stent struts separated from the vessel wall with evidence of blood speckles behind the strut by ultrasound, whereas late acquired incomplete apposition was defined as incomplete apposition of the stent at 4-month follow-up which was not present at post-procedure.

## Clinical endpoint definitions

Target vessel (or lesion) revascularization was considered to be ischaemia-driven if the target vessel (or lesion) diameter stenosis  $\geq 50\%$  by core laboratory quantitative analysis with ischaemic symptoms or with objective signs of ischaemia at rest or during exercise test, or a target vessel (or lesion) diameter stenosis  $\geq 70\%$  with or without documented ischaemia. Major adverse cardiac events (MACE) was defined as the composite of cardiac death, any MI, or ischaemia-driven target lesion revascularization (TLR). Spontaneous MI was defined as either a typical rise and gradual fall (Troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with ischaemic symptoms, development of new pathological Q-waves on the ECG or ECG changes indicative of ischaemia, or pathological findings of an acute MI, or development of new pathological Q-waves on follow-up ECG in the absence of cardiac biomarker assessment during the acute event.<sup>22</sup> Stent thrombosis was prospectively adjudicated using the Academic Research Consortium definitions.<sup>23</sup> Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation of thrombosis.

## Study endpoints

The primary study endpoint was in-stent late loss at 4 months as measured by QCA. Angiographic secondary endpoints include in-segment late loss, binary restenosis rate, percentage diameter stenosis, and proximal and distal late loss at 4 months. Secondary IVUS endpoints at 4 months include minimal lumen area, stent volume, luminal volume, intrastent neointimal volume, %volume obstruction, incomplete stent apposition, and plaque volume behind the stent struts. Secondary clinical endpoints at 6 months included all-cause death, MI, coronary artery bypass surgery, TLR, definite stent thrombosis, and MACE.<sup>23</sup>

## Statistical analysis

Continuous variables are presented as means  $\pm$  standard deviation, and categorical variables are presented as counts and percentages. Paired comparisons between post-procedure and 4-month follow-up

were done by a Wilcoxon's signed rank test. All statistical tests were two-tailed and a  $P$ -value of  $<0.05$  was considered as statistically significant. The current study is a FIM and single-arm study, and was designed to provide preliminary hypothesis-generating observations for further studies. The sample size was not defined on the basis of an endpoint hypothesis but rather to provide some information about the device efficacy and safety. The sample size requirement was established by the assessment of the minimum number of patients needed to provide reliable and non-trivial results, but is in range of the test group of the FIM trials of the SES ( $n = 45$ ).<sup>24,25</sup> Statistical analysis was performed with SAS 8.2 (SAS Institute Inc., NC, USA).

## The role of funding source

The study was sponsored by Kaneka (Osaka, Japan). In collaboration with the investigators, the sponsor designed the study. Data collection and data analysis were done by an independent clinical research organization (Cardialysis B.V.). The sponsor had no role in data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

### Patient characteristics

Forty-seven patients were included between May 2007 and November 2007. The baseline clinical characteristics are presented in Table 1. The average age of the patients was  $61.1 \pm 9.4$  years, whereas 19.1% were diabetic and 66.0% were male. Procedure success was 97.9% since, in one patient, the MAHOROBA stent did not cross the lesion due to severe calcification. Since the follow-up is planned up to 5 years, the follow-up will be accomplished in November 2012.

### Quantitative coronary angiography analysis

Angiographic follow-up at 4 months was achieved in 41 patients (Figure 2). The angiographic parameters with matched pair analysis for phase and projection at baseline, post-procedural, and follow-up angiography ( $n = 37$ ) are presented in Table 2. Table 3 presents the results of QCA parameters related to acute stent recoil assessment. Acute absolute recoil was  $0.22 \pm 0.20$  mm. At 4 months, the mean in-stent late loss, in-stent percentage diameter stenosis, and the rate of binary angiographic restenosis were  $0.99 \pm 0.46$  mm,  $38.66 \pm 20.79\%$ , and  $26.7\%$ , respectively. Figure 3 demonstrates the cumulative frequency of in-stent MLD immediately after the index procedure and after 4 months.

### Intravascular ultrasound evaluation

At 4 months, IVUS evaluation was performed in 40 patients. The results are tabulated in Table 4. A significant reduction of luminal volume was observed ( $187.4 \pm 93.4$  mm<sup>3</sup> at post-procedure vs.  $123.5 \pm 67.2$  mm<sup>3</sup> at follow-up,  $P < 0.0001$ ) with %volumetric obstruction of  $34.78 \pm 15.76\%$ .

Incomplete stent strut apposition at baseline was reported in 16 of 46 (34.8%) patients, and this was resolved in 10 and persisted in 7 patients at 4-month. There were three cases of late acquired incomplete apposition based on the IVUS definition of

**Table 1** Baseline clinical, lesion, and procedural characteristics

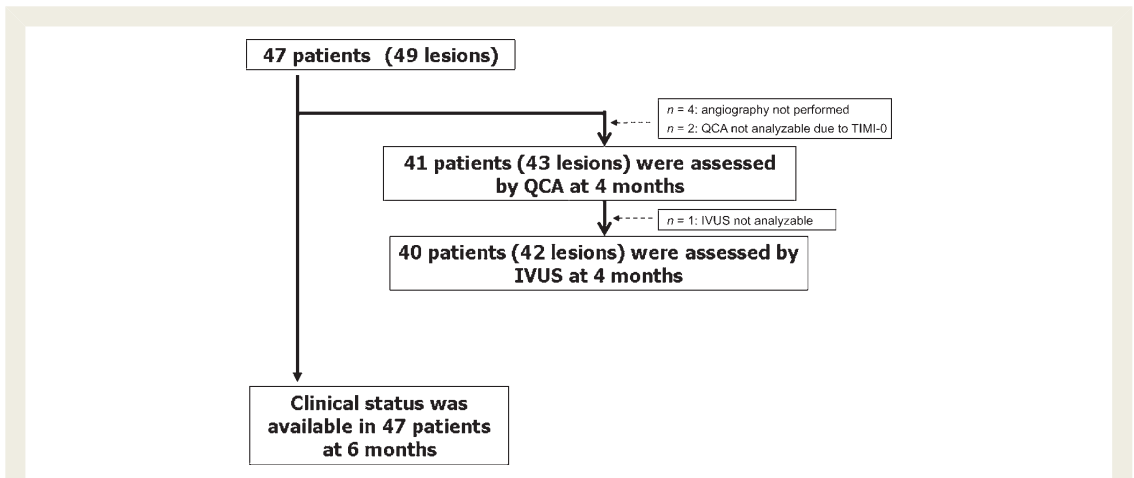
Patient (n)	47
Male [n (%)]	31 (66)
Age (years $\pm$ SD)	$61.1 \pm 9.4$
BMI (kg/m <sup>2</sup> $\pm$ SD)	$28.2 \pm 3.5$
Cardiovascular risk	
Diabetes mellitus [n (%)]	9 (19.1)
Current smoker [n (%)]	14 (29.8)
Hypercholesterolaemia [n (%)]	34 (72.3)
Family history of CAD [n (%)]	27 (57.4)
Hypertensive [n (%)]	24 (51.1)
Previous MI [n (%)]	12 (25.5)
Previous CABG [n (%)]	2 (4.3)
Prior PCI [n (%)]	5 (10.6)
Anginal status [n (%)]	
Silent ischaemia	3 (6.4)
Stable angina	38 (80.9)
Unstable angina	6 (12.8)
Target vessel [n (%)]	
Left anterior descending artery	20 (40.8)
Left circumflex artery	12 (24.5)
Right coronary artery	16 (32.7)
AHA/ACC lesion classification [n (%)]	
A	1 (2.1)
B1	23 (48.9)
B2	22 (46.8)
C	1 (2.1)
Reference vessel diameter (mm $\pm$ SD)	$2.76 \pm 0.46$
Lesion length (mm $\pm$ SD)	$11.69 \pm 5.36$
Minimal lumen diameter (mm $\pm$ SD)	$1.09 \pm 0.36$
Stent/artery ratio (mean $\pm$ SD)	$1.17 \pm 0.15$
Maximal inflation pressure (atm $\pm$ SD)	$16.3 \pm 3.00$

SD, standard deviation; BMI, body mass index; CAD, coronary artery disease; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

malapposition of at least one stent strut separated from the vessel wall. According to a methodology, previously reported by our group, the malapposed volume at follow-up was  $3.99$  mm<sup>3</sup> in median (inter-quartile range  $1.88$ – $7.39$ ).<sup>26</sup>

### Major adverse cardiac events

Major adverse cardiac events are listed in Table 5. There were two cases of MI: one patient suffered a non-Q-wave MI at 64 days after the implantation of one MAHOROBA stent in the proximal left anterior descending artery, whereas the other experienced a non-Q-wave MI at 4 days after the procedure with angiographically proven definite stent thrombosis in the proximal left circumflex. Both patients were taking dual antiplatelet therapy at the time of MI. The latter patient experienced second TLR at 124 days due to restenosis of the MAHOROBA stent. There were other nine



**Figure 2** Study profile.

**Table 2** Results of quantitative coronary angiographic analysis in matched pairs (n = 37)

Variables	In-stent	In-segment
Reference vessel diameter (mm)		
After procedure	2.94 ± 0.41	2.90 ± 0.43
At 4 months	2.57 ± 0.48	2.57 ± 0.48
Minimal luminal diameter (mm)		
After procedure	2.57 ± 0.36	2.27 ± 0.46
At 4 months	1.58 ± 0.63	1.55 ± 0.62
P-value	<0.0001	<0.0001
Late loss (mm)	0.99 ± 0.46	0.72 ± 0.51
Diameter stenosis (%)		
After procedure	12.50 ± 5.73	21.54 ± 8.75
At 4 months	38.66 ± 20.79	40.00 ± 20.29
P-value	<0.0001	<0.0001
Binary restenosis rate at 4 months <sup>a</sup> (%)	26.7	26.7

<sup>a</sup>Binary restenosis was calculated based on the unmatched data.

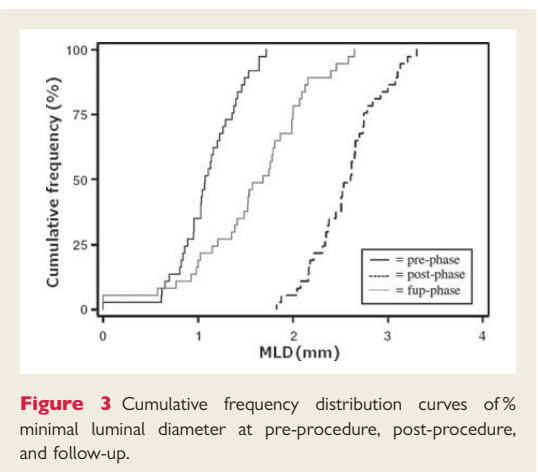
cases of ischaemia-driven TLR (ID-TLR). In total, MACE rate (cardiac death, target-vessel MI, or ID-TLR) at 6 months is 23.4% (11/47).

## Discussion

The efficacy of tacrolimus in inhibiting neointimal proliferation has been demonstrated in preclinical studies. Wieneke *et al.*<sup>27</sup> in an *in vivo* study using rabbit iliac artery model demonstrated that TESs coated with a nanoporous layer of aluminium oxide resulted in a significant reduction of neointimal thickness (NIT) by 50% with

**Table 3** Angiographic parameters related to acute stent recoil assessment (n = 40)

Variables	
Mean diameter of balloon at the highest pressure (mm)	3.17 ± 0.32
Mean diameter of stent immediately after balloon inflation (mm)	2.95 ± 0.37
Acute absolute recoil (mm)	0.22 ± 0.20
Acute per cent recoil (%)	7.11 ± 6.18



**Figure 3** Cumulative frequency distribution curves of % minimal luminal diameter at pre-procedure, post-procedure, and follow-up.

a total dose of 60 µg of tacrolimus and 56% for a dose of 120 µg of tacrolimus, when compared with BMS. In the *in vivo* study by Kollum *et al.*<sup>28</sup> using a swine model of restenosis, TES (JOMED, Rangendingen, Germany) with a nanoporous ceramic aluminium

**Table 4** Intravascular ultrasound measurements in matched pairs at post-procedural and 4 months follow-up (n = 42)

	Post	Follow-up	P-value
Vessel volume (mm <sup>3</sup> ) (mean ± SD)	350.1 ± 170.7	377.2 ± 175.9	0.0002
Stent volume (mm <sup>3</sup> ) (mean ± SD)	188.6 ± 98.7	190.7 ± 100.7	0.316
Luminal volume (mm <sup>3</sup> ) (mean ± SD)	187.4 ± 93.4	123.5 ± 67.2	<0.0001
Plaque volume behind stents (mm <sup>3</sup> ) (mean ± SD)	165.1 ± 75.9	186.48 ± 81.87	<0.0001
Intimal hyperplasia volume (mm <sup>3</sup> ) (mean ± SD)		67.23 ± 48.36	
In-stent volume obstruction (%) (mean ± SD)		34.78 ± 15.76	
Frequency of ISA (%) <sup>a</sup>	34.8	21.4	
Resolved ISA at follow-up [n (%)]		10 (50)	
Persisting ISA at follow-up [n (%)]		7 (35)	
Late acquired ISA at follow-up [n (%)]		3 (15)	
ISA volume (mm <sup>3</sup> ) [median (inter-quartile range)]	2.69 (2.12–7.03)	3.99 (1.88–7.39)	

SD, standard deviation; ISA, incomplete stent apposition.

<sup>a</sup>Frequency of ISA was calculated as number of patients with at least one strut with incomplete stent apposition divided by the total number of patients.

**Table 5** Adverse cardiac events at 6 months (per-patient analysis)

Event	n	%
All-cause death	0	0
Cardiac death	0	0
Stroke	0	0
Myocardial infarction	2	4.3
Target vessel	2	4.3
Non-target vessel	0	0
Cardiac death, stroke, or myocardial infarction	2	4.3
Repeat PCI–ID-TLR <sup>a</sup>	11	23.4
Repeat PCI–non-ID-TLR <sup>b</sup>	1	1
Repeat PCI–TVR	0	0
CABG	0	0
MACE (cardiac death, target-vessel myocardial infarction, or ID-TLR)	11	23.4
Definite stent thrombosis	1	2.1

MACE, major adverse cardiac events; ID-TLR, ischaemia-driven target lesion revascularization; Non-ID-TLR, non-ischaemia-driven target lesion revascularization; TVR, target vessel revascularization; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

<sup>a</sup>One patient experienced ID-TLR twice, but counted as one.

<sup>b</sup>One patient experienced both ID-TLR and non-ID-TLR.

oxide coating at a dose of 180 µg demonstrated a significant inhibitory effect on neointimal proliferation. However, the inhibitory effect on restenosis was counteracted by inflammatory reaction due to major particle debris as a result of cracking of the ceramic coating.

After these preclinical studies, two clinical trials were performed using a TES with a biocompatible and non-thrombogenic carbofilm™ coating (Janus; Sorin Biomedica Cardio, Italy). In the

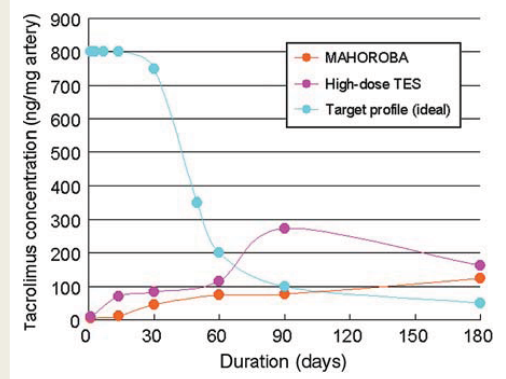
'FIM' study using the Janus stent loaded with a 1.5 µg/mm<sup>2</sup> of tacrolimus, TES was associated with a 3.8% binary restenosis rate at the 6-month follow-up in non-diabetics and 16.9% in diabetics.<sup>29</sup> After increasing the dose of TES from 1.5 to 2.3 µg/mm<sup>2</sup>, the investigators performed a randomized trial including 332 patients to compare the performance of the TES with that of the BMS. The free drug—not incorporated in polymer or excipient—was released from wells carved in the abluminal side of the stent. No differences in angiographic results were observed at 6-month (in-stent late luminal loss; TES 0.65 ± 0.47 vs. BMS 0.66 ± 0.53 mm), and the 12-month MACE rates of TES were not lower than BMS (19.5 vs. 16.1%).<sup>30</sup>

The MAHOROBA strut has its own design with no previous clinical use and its mechanical performances were evaluated in this FIM study. Acute recoil analysis by QCA suggests that the MAHOROBA stent may have a relatively weaker radial strength than contemporary metallic DESs; the absolute recoil of MAHOROBA was 0.22 ± 0.20 mm, whereas % relative recoil was 7.11 ± 6.18%. Different methodologies of recoil assessment render comparison between different stents difficult. However, recent analysis by an independent clinical research organization (Cardialysis B.V.) provides us with comparative recoil analysis of a CoCr everolimus-eluting stent and the MAHOROBA stent employing the same methodology. According to the results, the acute recoil of the MAHOROBA seems to be higher, although stent oversizing can affect the results.<sup>15</sup>

The MAHOROBA stent is characterized by a biodegradable polylactic-co-glycolic acid coating with a bioabsorption time of about 6 months, resulting in a long-term sustained release of the drug. Although the MAHOROBA stent was used in patients with favourable characteristics and simple lesion, angiographic follow-up at 4 months demonstrated a mean in-stent late loss of 0.99 mm, which is equivalent or even slightly higher than the late loss observed in historical series with BMSs.

The reason for the absence of neointimal inhibition in MAHOROBA may be multifactorial: first of all, contrary to the mode of action of sirolimus and its analogues that inhibit mTOR and subsequently up-regulate p27, tacrolimus acts through different

pathways and involves the calcineurin–calmodulin complex. Therefore, its mode of inhibition of SMC proliferation is fundamentally different from sirolimus, and redundancy of signalling pathways for cell growth may supersede the specific inhibitory effect of tacrolimus. Pimecrolimus, a tacrolimus analogue might not only fail to inhibit but might also even promote further neointimal hyperplasia. In the recent prospective, three-arm, GENESIS study randomizing patients with *de novo* coronary artery disease either to paclitaxel-eluting (10  $\mu\text{g}$ ) or pimecrolimus/paclitaxel dual-eluting (162.5/10  $\mu\text{g}$ ) or pimecrolimus-eluting stent (325  $\mu\text{g}$ ), the pimecrolimus-eluting stent demonstrated the highest in-stent late loss (paclitaxel  $0.58 \pm 0.58$  vs. paclitaxel/pimecrolimus  $0.96 \pm 0.73$  vs. pimecrolimus  $1.40 \pm 0.67$  mm) with the highest target vessel revascularization rate (2.0 vs. 14.4 vs. 35.0%) at 6-month.<sup>31</sup> Therefore, the GENESIS study was suspended before complete enrolment was achieved. Taking these results into consideration, tacrolimus and its analogue might not be a suitable drug to prevent the restenosis even though efficacy in neointimal inhibition of neointima had been demonstrated in the animal studies. Secondly, the relatively low intra-arterial concentration during elution may be insufficient to effectively inhibit neointimal hyperplasia. Matter *et al.*<sup>11</sup> demonstrated that in human saphenous vein cells, the IC<sub>50</sub> of sirolimus to inhibit proliferation of vascular SMC was  $4.1 \times 10^{-9}$  mol/L, whereas the IC of tacrolimus was  $0.38 \times 10^{-6}$  mol/L. In the study by Mohacsi *et al.*<sup>10</sup> using human thoracic aorta, IC<sub>50</sub> of sirolimus and tacrolimus was  $1-10 \times 10^{-9}$  and  $1 \times 10^{-6}$ , respectively. These results suggest that a 100- to 1000-fold higher tissue concentration of tacrolimus is necessary to exert the same neointimal inhibition as a SES. The MAHORоба stent has a tissue concentration with a peak value of around 130 ng/mg artery (Figure 4), whereas Cypher is around 6 ng/mg artery<sup>32</sup> in animal models. The concentration of tacrolimus may therefore still be too low to achieve sufficient neointimal inhibition, although it is about 20 times higher than the SES. Recently, in a porcine coronary study, van Beusekom *et al.* assessed neointimal thickening after the implantation of a BMS, polymer-coated stent (Pol) without drug, a slow degrading low dose (1  $\mu\text{g}/\text{mm}^2$ ) TES, and a fast degrading high-dose (2  $\mu\text{g}/\text{mm}^2$ ) TES. The low-dose TES is similar to the MAHORоба stent. Morphometry indicated that NIT in both TES was significantly reduced when compared with BMS and Pol up to 90 days (BMS:  $335 \pm 148$ ; pol:  $381 \pm 186$ ; low-dose TES:  $226 \pm 52$ ; and high-dose TES:  $262 \pm 80$   $\mu\text{m}$ ). However, at 180 days, only the high-dose TES showed significantly lower NIT when compared with BMS or Pol stent because the slow degrading low-dose TES demonstrated catch-up of NIT between 90 and 180 days. Therefore, the inhibitory effect of low-dose TES (equal to MAHORоба stent) on neointimal hyperplasia was somewhat suboptimal in the animal study, and high-dose TES might be optimal for DES. Thirdly, remnant polymer after complete elution of the drug could to some extent continue to stimulate neointimal growth in the stent. In a porcine model, the polymer of the MAHORоба stent continues to be degraded up to 110 days but possibly without sufficient tacrolimus beyond 90 days to dampen the tissue response.<sup>30</sup> Fourthly, the rate of incomplete stent apposition appears high at 35% in this study, although it is still in the range of previous study.<sup>33</sup> The lack of proper elution of the drug at the abluminal



**Figure 4** Comparison of release curves in MAHORоба stent (1  $\mu\text{g}/\text{mm}^2$ , orange), high-dose tacrolimus-eluting stent (2  $\mu\text{g}/\text{mm}^2$ , pink), and ideal curve (light blue).

side might be a potential explanation for the large presence of neointimal hyperplasia observed in this study.

Modification in the dose and release of tacrolimus might be mandatory to create an effective TES. Figure 4 shows the tissue concentration of tacrolimus in TES with different doses. Conversely, the MAHORоба demonstrates the ability to maintain tissue concentrations for longer periods, but in the first 2 weeks is unable to attain sufficient concentration that are considered adequate for neointimal inhibition after stenting. Theoretically, a biphasic-release TES with a burst phase in the first 2 weeks followed by sustained release could have the ability to inhibit neointimal proliferation. A dual polymeric coating with rapid and slow drug-eluting profiles might be necessary to achieve biphasic release. An increased amount of polymer is indispensable to contain higher dose of drug than current, which could result in a thicker profile of the stent struts and a longer duration of absorption. It will be a technological challenge to develop a dual-coated stent with thin struts and an improved polymer degradation profile synchronized with drug release.

Intravascular ultrasound analysis in the current study demonstrated a significant increase in the plaque behind the stent (PBS) 4 months after the procedure. In the PISCES study using PESs with a durable PGLA polymer coating, specially designed for drug delivery with programmable pharmacokinetics, a significant increase in PBS at 4-month was reported in paclitaxel-loaded stents with equal or longer elution than 10 days, but not in-stents with a short elution of 5 days.<sup>34</sup> These results suggest that the long-term presence of either drugs or PGLA polymer might cause extensive remodelling after stent implantation, presumably resulting from vessel inflammation. Also in the study using PESs,<sup>35</sup> a significantly increased peri-stent area was observed at 6 months. However, sirolimus<sup>36</sup> or everolimus-eluting stents<sup>26</sup> with durable polymers, this effect on positive vascular remodelling has not been reported.

The current study has several limitations. The angiographic and IVUS follow-up were only performed at 4 months, which might be

too short to assess the full extent of neointimal hyperplasia after DES implantation. At the time of the study design, further invasive imaging with angiography and IVUS was planned in the protocol at 12 months to assess the full process of neointimal hyperplasia. However, after evidencing high amounts of neointimal hyperplasia with high rates of ischaemic TLR events at 4 months, the protocol was amended by the data safety monitoring board for safety reasons. It was decided to monitor patients more carefully with non-invasive stress ECG testing at 6 months and 9 months. Since the scientific goal had not been achieved, the invasive angiography originally planned at 12 months for scientific purposes was abandoned, and angiographic follow-up after 4 months was only performed for clinical reasons. Frequency of incomplete stent apposition was as high as 34.5%. The rate of malapposition, however, was calculated as the number of patients with at least one strut with incomplete stent apposition divided by the total number of patients and does not reflect the number of malapposed strut or the malapposed volume. This study did not mandate IVUS-guided stenting, so that post-dilation was completely left to the operators' discretion. In addition, given the relatively high stent malapposition rate and % acute recoil, it is difficult to know how much each component of the stent (i.e. polymer, stent platform and drug) could contribute to the failure of this DES.

Despite the conceptual advantages of using tacrolimus with a biodegradable polymer, this FIM study has failed to establish the effectiveness of this stent. Taking the multifactorial reasons of failure into consideration, tacrolimus formulation of the current stent seems unsuitable to prevent restenosis. Technical improvements enable us to construct TES with a higher drug content and improved polymer degradation profile in synchronization with drug release.

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**Conflict of interest:** T.N. is an employee of Kaneka corporation.

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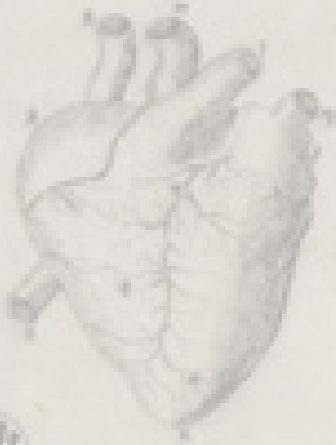




心管圖

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Chapter 11

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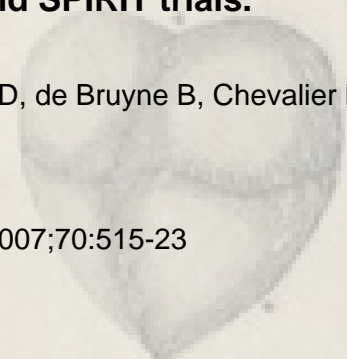
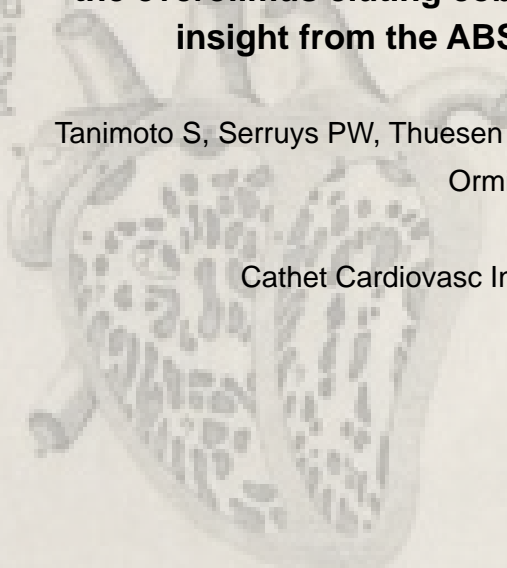
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**Comparison of in vivo acute stent recoil between the bioabsorbable everolimus eluting coronary stent and the everolimus eluting cobalt chromium coronary stent: insight from the ABSORB and SPIRIT trials.**

全形

Tanimoto S, Serruys PW, Thuesen L, Dudek D, de Bruyne B, Chevalier B, Ormiston JA.

Cathet Cardiovasc Intervent. 2007;70:515-23



心障膜





# Comparison of In Vivo Acute Stent Recoil Between the Bioabsorbable Everolimus-Eluting Coronary Stent and the Everolimus-Eluting Cobalt Chromium Coronary Stent: Insights From the ABSORB and SPIRIT Trials

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**Objectives:** This study sought to evaluate and compare in vivo acute stent recoil of a novel bioabsorbable stent and a metallic stent. **Background:** The bioabsorbable everolimus-eluting coronary stent (BVS) is composed of a poly-L-lactic acid backbone, coated with a bioabsorbable polymer containing the antiproliferative drug, everolimus, and expected to be totally metabolized and absorbed in the human body. Because the BVS is made from polymer, it may have more acute recoil than metallic stents in vivo. **Methods:** A total of 54 patients, who underwent elective stent implantation for single de novo native coronary artery lesions, were enrolled: 27 patients treated with the BVS and 27 patients treated with the everolimus-eluting cobalt chromium stent (EES). Acute absolute recoil, assessed by quantitative coronary angiography, was defined as the difference between mean diameter of the last inflated balloon at the highest pressure (X) and mean lumen diameter of the stent immediately after the last balloon deflation (Y). Acute percent recoil was defined as  $(X - Y)/X$  and expressed as a percentage. **Results:** Acute absolute recoil of the BVS and EES was  $0.20 \pm 0.21$  mm and  $0.13 \pm 0.21$  mm, respectively ( $P = 0.32$ ). Acute percent recoil was  $6.9\% \pm 7.0\%$  in the BVS group and  $4.3\% \pm 7.1\%$  in the EES group ( $P = 0.25$ ). **Conclusions:** In vivo acute stent recoil of the BVS is slightly larger but insignificantly different from that of the EES, implying that the BVS may have good radial strength similar to the metallic stent. © 2007 Wiley-Liss, Inc.

**Key words:** bioabsorbable; coronary artery disease; recoil; stents

## INTRODUCTION

Coronary stents have been used as standard mechanical devices for percutaneous coronary intervention (PCI) in the treatment of patients with coronary artery disease (CAD) [1]. They provide vessel wall scaffolding and prevent early elastic recoil and restenosis, which are major limitations of balloon angioplasty. Consequently, the use of coronary stents achieves high success rates of PCI and improves the outcome of CAD patients. However, because of the permanent nature of metallic stents, their presence on the intimal surface of a coronary artery poses risks associated with a continuous interaction between the metal and the surrounding tissue [2]. This can lead to long-term endothelial dysfunction or chronic inflammation, and may result in many potential concerns, such as in-stent neointimal hyperplasia and thrombogenesis. The clinical requirement of stents for vessel scaffolding is tempo-

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rary and limited to the time of the revascularization and, shortly thereafter, until vascular healing and re-endothelialization within the stented coronary segment have taken place. Beyond this period, the advantage of metallic stents diminishes. Indeed, when compared with bare metal stents (BMS), drug-eluting stents (DES) significantly reduce coronary restenosis by applying an antiproliferative drug to inhibit the intimal hyperplastic response [3,4]. However, once the drug is eluted from DES, they behave like metallic stents. In addition, as the drug itself inhibits endothelial function [5] or normal vascular healing [6] or both, prolonged antiplatelet therapy is required to prevent stent thrombosis in patients treated with DES [7,8].

In terms of the short-term need for vessel scaffolding and avoidance of the potential long-term complications of metallic stents, bioabsorbable polymer stents appear to be an ideal alternative candidate material. Further, they can also be used as a vehicle for drug delivery to target lesions. Conceptually, once they are fully absorbed, only the healed vessels are left behind with no residual prosthesis and, therefore, no potential interactions with the coronary artery. Accordingly, long-term antiplatelet therapy may not be warranted. However, in quest for preventing acute vessel recoil, there has been concern that polymer stents may not be efficacious due to their intrinsic characteristics when compared with metallic stents.

The bioabsorbable everolimus-eluting coronary stent (BVS; developed by Bioabsorbable Vascular Solutions, Mountain View, CA) is composed of a poly-L-lactic acid (PLLA) backbone, coated with a bioabsorbable polymer containing the antiproliferative drug everolimus (Certican<sup>®</sup>, Novartis Pharmaceuticals Corporation, Basel, Switzerland). The ongoing first-in-man trial (the ABSORB trial) assesses its safety and feasibility in patients with CAD. In the present study, we evaluated acute stent recoil of the BVS in the ABSORB trial. In addition, using the SPIRIT clinical trials as a control group, we compared the acute stent recoil of the BVS and the XIENCE V everolimus-eluting cobalt chromium stent (EES; manufactured by Advanced Cardiovascular Systems, Santa Clara, CA).

## METHODS

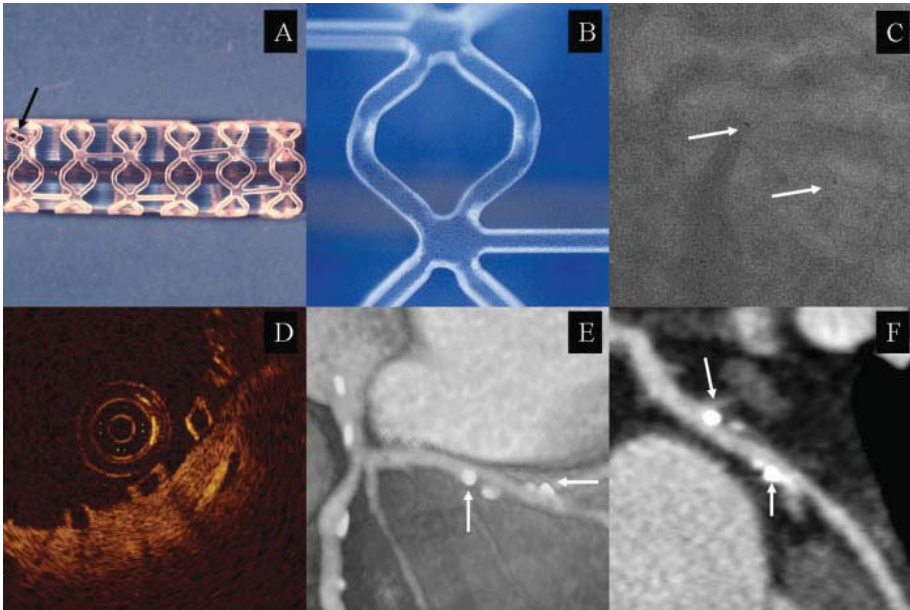
### Study Population

The ABSORB trial is a prospective, open-labeled, multicenter (six clinical sites), first-in-man clinical investigation of the BVS in patients with single de novo native coronary artery lesions. It was approved by the ethics committee at each participating institu-

tion, and all patients gave written informed consent. Patients were eligible for the study if they were aged above 18 years, with a diagnosis of stable or unstable angina, or silent ischemia. Target lesions were selected that could be covered with a single stent of  $3.0 \times 12 \text{ mm}^2$  or  $3.0 \times 18 \text{ mm}$  (i.e. 3.0 mm in diameter by visual estimation, less than 8 mm or 14 mm in length) and a stenosis of between 50% and 99% of luminal diameter with a Thrombolysis in Myocardial Infarction flow grade of 1 or more. Patients were ineligible if they had any of the following: evolving myocardial infarction; left main coronary artery stenosis; an ostial lesion; lesion located within 2 mm of a bifurcation; lesion with moderate-to-heavy calcification by visual assessment; angiographically visible thrombus within the target lesion; a left ventricular ejection fraction of less than 30%; candidate for heart transplant; known hypersensitivity or contraindication to aspirin, heparin, clopidogrel, everolimus, PLLA, or contrast sensitivity that could not be adequately premedicated.

In order to compare the acute stent recoil of BVS and metallic stents, we chose patients enrolled in the recently completed SPIRIT trials as the control group. The SPIRIT trials are planned to assess the safety and efficacy of the EES in patients with CAD. To date, short-term follow-up results of the SPIRIT FIRST trial [9,10] and the SPIRIT II trial [11] have been reported. Both trials were prospective, multicenter, single-blinded, randomized-controlled clinical investigations in patients with the diagnosis of stable or unstable angina, or silent ischemia and compared EES with BMS (SPIRIT FIRST trial) or paclitaxel-eluting stents (SPIRIT II trial). The study protocol of these two trials has been reported previously [9,11]. Briefly, the patients of the SPIRIT FIRST trial had a single de novo native coronary stenosis of less than 12 mm lesion length, covered by a single stent of  $3.0 \times 18 \text{ mm}$ , more than 50% diameter stenosis, and a vessel reference diameter of 3.0 mm, as assessed by online quantitative coronary angiography (QCA). In the SPIRIT II trial, eligibility criteria were the presence of maximum two de novo native coronary lesions, each located in a different major epicardial coronary vessel. Stent sizes available were 2.5, 3.0, 3.5, or 4.0 mm in diameter and 8, 18, or 28 mm in length. Target lesions were less than 28 mm length, covered by a single stent or two overlapping stents, more than 50% diameter stenosis, with the vessel reference diameter ranging from 2.5 to 4.25 mm as assessed by visual estimation. Exclusion criteria of these two SPIRIT trials were similar to those of the ABSORB trial.

Careful considerations were taken to select the control group to adjust for target lesion characteristics, since several differences in inclusion criteria existed and different stent sizes were available among these three trials. Finally, as the control group, we selected consecutive patients who



**Fig. 1.** Bioabsorbable everolimus-eluting coronary stent (BVS). Panel A shows an overview of the stent. The black arrow indicates a radio-opaque platinum marker on the surface of the stent. Panel B is the magnified image of the stent. The stent body is transparent. Two radio-opaque markers (white arrows) on both ends of the stent are easily detected by the fluoroscopy (Panel C), although the stent body is radio-

lucent. Optical coherence tomography can clearly indicate stent struts as a unique box appearance (Panel D). The stent strut thickness is 0.150 mm. In Panel E and F, multislice computed tomography demonstrates that two radio-opaque markers (white arrows) are clearly visible and the stent body is invisible. [Color figure can be viewed in the online issue, which is available at [www.interscience.wiley.com](http://www.interscience.wiley.com).]

received a single  $3.0 \times 18$  mm EES for a single de novo lesion from the SPIRIT FIRST and II trials.

### Description of the Stent

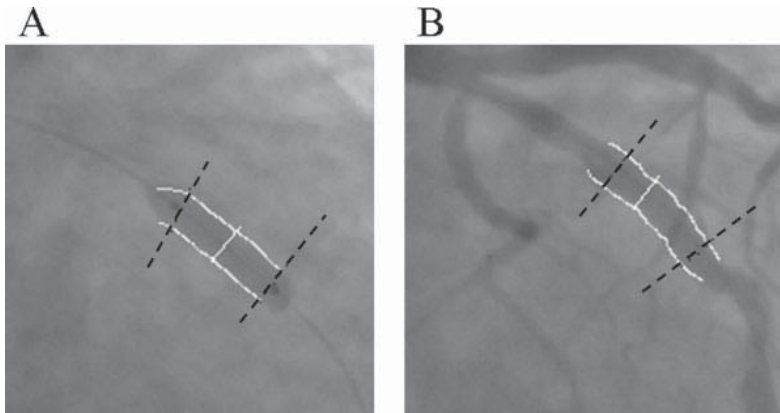
The BVS is comprised of four main components: the polymer stent backbone, the polymer drug reservoir, the antiproliferative drug everolimus, and the delivery system. The polymer stent is balloon-expandable and is composed of a high-molecular-weight PLLA backbone, with serpentine rings connected by links (Fig. 1A and B). The stent body is coated with a matrix of everolimus and poly-D,L-lactic acid (PDLLA) in a 1:1 ratio. PLLA and PDLLA are fully metabolized and totally absorbed in the human body. The BVS is laser-cut from an extruded tube of the PLLA and has two radio-opaque platinum markers on both ends of its surface, to facilitate the identification of the prosthesis (Fig. 1C). Two stent sizes are available:  $3.0 \times 12$  mm or  $3.0 \times 18$  mm. The thickness of the stent struts is 0.150 mm (Fig. 1D). The stent itself is mounted on the VISION RX balloon catheter, which has two radio-opaque balloon markers, reflecting the expanded stent

length. These markers aid in positioning the stent fluoroscopically.

The EES has been described in detail previously [9]. Briefly, the EES is composed of the MULTI-LINK VISION<sup>®</sup> Stent (Abbott Vascular, Santa Clara, CA), which is a balloon-expandable stent with serpentine rings connected by links fabricated from a single piece of medical grade L-605 cobalt chromium alloy, coated with a durable polymer containing everolimus. The morphological design of the EES is similar to that of the BVS. The thickness of the strut is 0.081 mm. The stent is mounted on the MULTILINK VISION<sup>®</sup> balloon catheter, which is identical to the BVS delivery balloon catheter.

### Study Procedure

All procedures were performed electively. Target lesions were treated using standard interventional techniques, with mandatory predilatation and stent deployment at a pressure not exceeding the rated burst pressure (16 atm). Postdilatation with a balloon shorter than the implanted stent was allowed at operator discretion if an optimal angiographic result was not



**Fig. 2. Methodology of acute stent recoil assessment when only the stent delivery balloon was used for stent expansion.** Image A is of complete expansion of the stent delivery balloon. Image B is immediately after balloon deflation. In Image A, analysis is performed between balloon markers (between dotted lines; Segment A). In Image B, analysis is performed within the stent markers (between dotted lines; Segment B).

These two images are analyzed in the same angiographic projection, so that segments A and B are well-matched. In this case, the mean diameter of segments A and B are 3.10 and 2.83 mm, respectively. This corresponds to acute recoil of 0.27 mm or 8.7%. White solid lines indicate the minimum diameter of the balloon or minimum lumen diameter within the analyzed segment.

obtained immediately after stent deployment. Bailout stenting for edge dissection was permitted. During PCI, intravenous boluses of heparin were administered according to local practice. Treatment with aspirin was started at least 24 hr before the procedure, and continued throughout the length of clinical investigation in the ABSORB trial and for at least 1 year in the SPIRIT trials. A loading dose of 300 mg of clopidogrel was administered before the procedure, followed by 75 mg daily for a minimum of 6 months in the ABSORB and SPIRIT II trials and for 3 months in the SPIRIT FIRST trial.

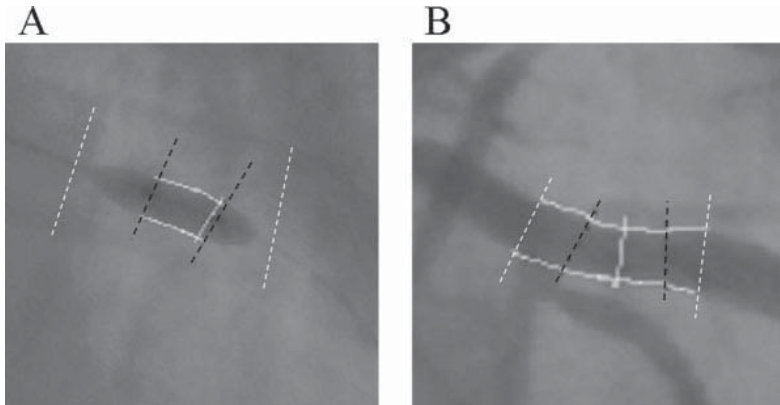
### Quantitative Coronary Angiography Analysis

QCA was performed using the CAAS II analysis system (Pie Medical BV, Maastricht, the Netherlands). For each patient, the stented segment and the peri-stent segment (defined by a length of 5 mm proximal and distal to the stent edge) were analyzed. The following QCA parameters were computed: minimal luminal diameter (MLD), reference vessel diameter, and percent diameter stenosis. In addition to the baseline and post-PCI images, two images were analyzed for acute stent recoil assessment in this study. One was an image of complete expansion of the last balloon (either the stent delivery balloon or the postdilatation balloon) at the highest pressure (Image A, Figs. 2A and 3A). The other was an image immediately after the last balloon deflation (Image B, Figs. 2B and 3B). These two images were analyzed in the same angiographic projec-

tion. The time interval between Images A and B was usually less than 1 min. When the stent delivery balloon was used for stent expansion, QCA measurement was performed between the markers of the stent delivery balloon (Segment A) in Image A and within the deployed stent markers (Segment B) in Image B. In case a postdilatation balloon was used during the procedure, the measurement was performed between markers of the postdilatation balloon in Image A (Segment C) and within the segment area in Image B, where the postdilatation balloon was placed and inflated (Segment D). When bailout stenting was performed and a nonstudy stent overlapped with the study stent, only the study stent segment was analyzed.

### Acute Stent Recoil Assessment

Acute stent recoil was calculated as follows [12,13]: (1) When the stent delivery balloon was used for stent expansion, acute absolute stent recoil was defined as the difference between mean diameter of the stent delivery balloon at the highest pressure in the Segment A ( $X$ ) and mean luminal diameter in the Segment B ( $Y$ ). Acute percent stent recoil was defined as  $(X - Y)/X$  and expressed as a percentage. (2) In case a postdilatation balloon was used in the procedure, acute absolute recoil was defined as the difference between mean diameter of the postdilatation balloon at the highest pressure in Segment C ( $X'$ ) and mean luminal diameter in Segment D ( $Y'$ ). Acute percent recoil was defined as  $(X' - Y')/X'$  and expressed as a percentage.



**Fig. 3.** Methodology of acute stent recoil assessment when a postdilatation balloon was used during the procedure. Image A is of complete expansion of the postdilatation balloon. Image B is immediately after balloon deflation. In the Image A, analysis is performed between balloon markers (between black dotted lines; Segment C). In the Image B, analysis is performed within the stent in the same segment where the postdilatation balloon was placed and inflated (between black

dotted lines; Segment D). These two images are analyzed in the same angiographic projection, so that segments C and D are well-matched. In this case, the mean diameter of segments C and D are 3.33 and 3.15 mm, respectively. This corresponds to acute recoil of 0.18 mm or 5.4%. White solid lines indicate the minimum diameter of the balloon or minimum lumen diameter within the analyzed segment. White dotted lines indicate the stented segment.

### Statistical Analysis

The analysis was performed on patients with analyzable angiographic images. Categorical variables were presented as counts and percentages, and compared by means of the Fisher's exact test. Continuous variables were presented as mean  $\pm$  standard deviation and were compared using the Mann-Whitney *U*-test. A value of  $P < 0.05$  was considered statistically significant. Statistical analysis was performed with SPSS 12.0.1 for Windows (SPSS, Chicago IL).

## RESULTS

### Patient Demographic and Lesion Characteristics

A total of 30 patients were enrolled in the ABSORB trial between March 2006 and July 2006. Three of the 30 were excluded. In one patient, the stent did not pass through the target lesion. This was a clinical device failure. In another patient, angiographic images were not analyzable because there was no matched view for acute stent recoil assessment. In the other patient, catheter calibration was impossible. Hence, the BVS group included 27 patients with 27 lesions. As the  $3.0 \times 18$  mm BVS was launched at the end of enrollment, this stent size was deployed in only one patient, with the other 26 patients receiving the  $3.0 \times 12$  mm BVS.

In the SPIRIT FIRST and II trials, 89 patients (27 from the SPIRIT FIRST trial and 62 from the SPIRIT II

trial) were treated with a single EES of  $3.0 \times 18$  mm for a single de novo lesion. From this population, in order to match the number of the patients in the BVS group with that in the control group, we selected the first 27 consecutive patients with successful EES implantation and analyzable angiography for acute stent recoil assessment. This control group consisted of 19 patients with 19 lesions from the SPIRIT FIRST trial and 8 patients with 8 lesions from the SPIRIT II trial.

Clinical, angiographic, and procedural data are shown in Table I. Both groups shared similar patient demographics. Although neither American College of Cardiology/American Heart Association lesion complexity class type A nor C lesion was observed, lesion complexity was greater in the EES group than in the BVS group, but this difference did not reach the statistical significance ( $P = 0.10$ ). Calcified lesions, identified by core laboratory and classified as moderate or severe grade, tended to be more frequent in the BVS group (30% vs. 15%,  $P = 0.33$ ). Stent-to-artery ratio (defined as mean diameter of the last balloon at the highest pressure divided by baseline reference vessel diameter) and maximum balloon pressure during the entire procedure showed no significant differences between the groups.

### QCA and Acute Stent Recoil Results

QCA assessments of pre- and post-PCI are shown in Table II. Baseline results were similar between the groups, except for the lesion length, which was rela-



**TABLE I. Clinical, Angiographic, and Procedural Characteristics**

	BVS (N = 27)	EES (N = 27)	P value
Age (years)	62.5 ± 9.2	63.7 ± 9.6	0.53
Male, n (%)	15 (56)	16 (59)	1.0
Diabetes, n (%)	1 (4)	2 (7)	1.0
Hypertension, n (%)	19 (70)	20 (74)	1.0
Hypercholesterolemia, n (%)	21 (78)	17 (63)	0.37
Current smoking, n (%)	6 (22)	5 (19)	1.0
Prior myocardial infarction, n (%)	2 (7)	7 (26)	0.14
Lesion location, n (%)			
Right coronary artery	6 (22)	9 (33)	0.54
Left anterior descending	13 (48)	12 (44)	1.0
Left circumflex artery	8 (30)	6 (22)	0.76
ACC/AHA lesion type, n (%)			
Type A	0 (0)	0 (0)	NA
Type B1	17 (63)	10 (37)	0.10
Type B2	10 (37)	17 (63)	0.10
Type C	0 (0)	0 (0)	NA
Lesion calcification, n (%)	4 (15)	8 (30)	0.33
Stent/artery ratio	1.06 ± 0.11	1.11 ± 0.17	0.19
Maximum pressure (atm)	16.3 ± 3.07	15.4 ± 3.00	0.24

ACC/AHA, American College of Cardiology/American Heart Association; NA, not applicable.

**TABLE II. Angiographic Results at Pre- and Post-PCI**

	BVS (N = 27)	EES (N = 27)	P value
Pre-PCI			
Lesion length (mm)	9.1 ± 3.9	10.5 ± 2.7	0.06
Reference vessel diameter (mm)	2.72 ± 0.48	2.67 ± 0.42	0.90
Minimum lumen diameter (mm)	1.08 ± 0.24	0.99 ± 0.27	0.37
Diameter stenosis (%)			
Post-PCI			
Minimum lumen diameter (mm)	2.30 ± 0.32	2.43 ± 0.30	0.03
Diameter stenosis (%)	17.0 ± 7.4	11.3 ± 4.2	0.0003

tively longer in the EES group than in the BVS group (10.5 ± 2.7 mm vs. 9.1 ± 3.9 mm,  $P = 0.06$ ). After PCI, as compared to the EES group, the BVS group had significantly smaller MLD (2.30 ± 0.32 mm vs. 2.43 ± 0.30 mm,  $P = 0.03$ ) and significantly larger diameter stenosis (17.0% ± 7.4% vs. 11.3% ± 4.2%,  $P = 0.0003$ ).

Table III presents the results of QCA parameters related to acute stent recoil assessment. Acute absolute and percent recoil of the BVS were higher than those of the EES, but the differences did not reach statistical significance (0.20 ± 0.21 mm [95% CI: 0.11–0.28] vs. 0.13 ± 0.21 mm [95% CI: 0.05–0.22],  $P = 0.32$ ; 6.9% ± 7.0% [95% CI: 4.1–9.6] vs. 4.3% ± 7.1% [95% CI: 1.5–7.1],  $P = 0.25$ , respectively).

**TABLE III. Angiographic Parameters Related With Acute Stent Recoil Assessment**

	BVS (N = 27)	EES (N = 27)	P value
Mean diameter of balloon at the highest pressure (mm)	2.86 ± 0.34	2.92 ± 0.32	0.55
Mean diameter of stent immediately after balloon inflation (mm)	2.67 ± 0.40	2.78 ± 0.30	0.18
Acute absolute recoil (mm)	0.20 ± 0.21	0.13 ± 0.21	0.32
Acute percent recoil (%)	6.9 ± 7.0	4.3 ± 7.1	0.25

**TABLE IV. Relationship of Angiographic and Procedural Variables With Acute Percent Stent Recoil**

	BVS			EES		
	Number	% Recoil	P value	Number	% Recoil	P value
Reference vessel diameter						
≥3.0 mm	8	3.1 ± 6.4	0.14	6	0.7 ± 9.1	0.18
<3.0 mm	19	8.4 ± 6.7		21	5.3 ± 6.3	
Stent/artery ratio (stent oversizing)						
≥1.1	10	8.4 ± 5.7	0.25	14	8.2 ± 4.1	0.003
<1.1	17	5.9 ± 7.6		13	0.3 ± 7.3	
Maximum balloon pressure						
>16 atm	7	5.9 ± 5.4	0.62	8	2.7 ± 6.1	0.24
≤16 atm	20	7.2 ± 7.5		19	4.9 ± 7.5	
Lesion calcification						
Yes	4	11.8 ± 4.3	0.06	8	5.8 ± 6.2	0.52
No	23	6.0 ± 7.0		19	3.6 ± 7.5	

**Relationship of Angiographic and Procedural Variables With Acute Percent Stent Recoil**

Table IV shows the relationship of angiographic and procedural variables with the acute percent stent recoil. For both groups, smaller reference vessel diameter (<3.0 mm) and lower maximum balloon pressure (≤16 atm) led to higher percent recoil, although no statistical relationship was found. Stent oversizing (stent-to-artery ratio ≥ 1.1) induced significantly higher percent recoil of the EES (8.2% ± 4.1% vs. 0.3% ± 7.3%,  $P = 0.0003$ ), while this factor was not correlated with acute stent recoil of the BVS (8.4% ± 5.7% vs. 5.9 ± 7.6%,  $P = 0.25$ ). There was a trend toward more recoil of the BVS in calcified lesions than in noncalcified lesions (11.8% ± 4.3% vs. 6.0% ± 7.0%,  $P = 0.06$ ). However, this trend was equivocal in the EES group (5.8% ± 7.2% in calcified lesions and 3.6% ± 7.5% in noncalcified lesions,  $P = 0.52$ ).

## DISCUSSION

The principal finding from the present study is that in selected patients, in vivo acute stent recoil of the BVS is slightly larger, but not significantly different from that of the EES.



The main function of metallic stents is to scaffold the vessel wall and prevent early elastic recoil and acute vessel closure. The need for this property is limited to the period ranging from the time of PCI to several months, thereafter, when the stented segment is fully endothelialized and vascular damage has healed. Beyond this period, the scaffolding properties of the stent are probably unnecessary. Their permanent presence induces chronic inflammation between the metal and surrounding tissue [2], which causes in-stent neointimal hyperplasia and thrombogenesis. Further, metallic stents prevent the lumen expansion associated with late favorable remodeling sometimes seen following balloon angioplasty [14,15], impair the vessel geometry, and interfere with surgical reintervention [16] and with recently developed coronary imaging modalities such as multislice computed tomography and magnetic resonance imaging. These imaging modalities may become the default noninvasive diagnostic tool for CAD patients in the near future [17]. To fulfill the short-term need for scaffolding vessel walls and overcome the aforementioned drawbacks of metallic stents, the concept of bioabsorbable polymer stents is attractive. From preclinical studies, the BVS is predicted to be fully metabolized to carbon dioxide and water and to be fully absorbed between 2 and 3 years after implantation. Therefore, the healed natural vessels are left behind, which may no longer require antiplatelet therapy and will no longer restrict potential surgical revascularization of the stented segment. In addition, the absence of metallic stents is amenable to noninvasive imaging modalities (Fig. 1E and F) and may be adaptive to late positive remodeling. However, as polymers are more flexible than metals, there is potential that the radial strength of bioabsorbable polymer stents may be lower than that of metallic stents. Consequently, there has been concern that more acute stent recoil might occur after bioabsorbable polymer stent deployment than after metallic stent deployment. The present study is the first report of a comparison of in vivo acute stent recoil between a bioabsorbable polymer stent and a metallic stent.

In previous human clinical trials, acute stent recoil varied between 3% and 15% following Wiktor or Palmaz-Schatz stent implantation [12,13,18–21]. The wide range of BMS recoil was related in part to differences in stent material and design and in part to the difference in definitions of recoil. Stent recoil was usually defined as the difference between the minimum balloon diameter and the MLD poststent implantation. However, usage of minimum variables, proposed by previous investigators, has the potential for assessing only a part of the stented segment, because the balloon does not expand uniformly, causing asymmetric stent

expansion. To reflect the behavior of the vessel wall of the entire stented segment, we used mean variables and defined acute stent recoil as the difference between the mean diameter of the last inflated balloon and the mean luminal diameter immediately after the last balloon deflation. Our study demonstrated that the acute percent stent recoil of the BVS was 6.9%, which is slightly more than the EES recoil (4.3%), but in line with previously reported in vivo conventional metallic stent recoil [12,13,18–21]. It is noteworthy that, if we adopted the definition using minimum variables to this study, the acute percent stent recoil of the BVS and EES would be calculated as  $8.0\% \pm 10.1\%$  and  $6.8\% \pm 9.7\%$ , respectively ( $P = 0.72$ ), which are also in accordance with previously reported in vivo BMS recoil [20,21]. Taking these results into consideration, the BVS has no less detectable acute stent recoil than the metallic stents in diseased human coronary arteries.

The idea of bioabsorbable stents is not new. Since metallic stents were introduced, several types of polymeric stents have been tested in experimental studies. The Igaki-Tamai stent was the first polymeric stent examined in diseased human coronary arteries [22]. This was a self-expanding coil stent, composed of a high-molecular-weight PLLA monofilament (321 kDa) with a zigzag helical design. Its acute stent recoil assessed by QCA was 22%, which is numerically higher than that of the BVS in our study. Again, this is partly because the definition of stent recoil was different. Acute recoil of the Igaki-Tamai stent was defined as the difference between the maximum balloon diameter and the MLD post stent implantation. If this definition was applied to our study, acute stent recoil of the BVS would be 25.5%, which is similar to the recoil after the Igaki-Tamai stent implantation. Although the stent body of the BVS resembles the Igaki-Tamai stent, one difference between both stents is that the BVS is coated with the antiproliferative drug, everolimus. Considering the fact that angiographic and clinical follow-up results of patients treated with the Igaki-Tamai stent were comparable to those of BMS, the BVS may lead to better short- and intermediate-term angiographic and clinical outcomes than does BMS, because of suppression of the intimal hyperplastic response by everolimus.

Since stent recoil is the resultant of the balance between the elastic recoil and radial strength of the stent, along with the elastic properties of the arterial wall, it can be affected by several lesion or procedural characteristics, such as reference vessel diameter, stent oversizing, maximum balloon pressure, and the presence of lesion calcification. In the EES group, only stent oversizing correlated with acute stent recoil in accordance with previous reports [13]. Conversely, no

relationship was found in the BVS group between these lesion or procedural characteristics, although there was a trend toward higher recoil in patients with calcified lesions. This discrepancy between the BVS and EES may be based on the difference in their composition and design. However, these findings were derived from only a small number of patients, and the technical and clinical relevance remains unclear. Larger studies are needed to assess the association between lesion and procedure-related variables and acute stent recoil of the BVS.

### Limitations

Limitations of the present study include the small number of patients. The lack of statistically significant differences in acute percent stent recoil between the BVS and EES may be due to the small sample size. To detect the difference of acute percent stent recoil between both stents at a 5% significance level with 80% power in a prospective analysis according to the result of this study, 117 patients would be needed in each group. Our study population consisted of patients enrolled in three different trials, in which inclusion/exclusion criteria varied. This may have introduced some bias, although we carefully selected the control patients to adjust baseline and lesion characteristics. Target lesions treated with the BVS were relatively simple, and acute stent recoil of the BVS may increase in more complex lesions. In addition, detailed lesion characteristics, such as plaque composition and lesion eccentricity, were unknown, because we evaluated acute stent recoil only by QCA, and not by intravascular ultrasound or optical coherence tomography. Lastly, the present study evaluated BVS recoil immediately after its implantation. Further investigations are warranted to determine the recoil properties of the BVS beyond this period.

### CONCLUSIONS

In vivo acute stent recoil of the BVS is slightly larger but insignificantly different from that of the EES. This implies that the BVS may have good radial strength similar to the metallic stent. The BVS may result in angiographic and clinical outcomes comparable to the drug-eluting metallic stents at short- and intermediate-term follow-up.

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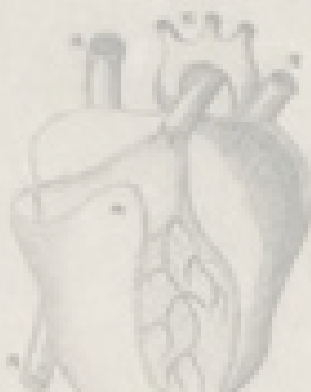
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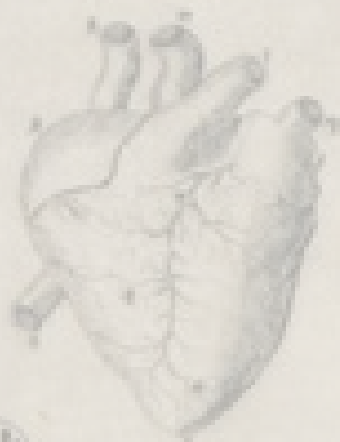


心管圖

四脈管及心囊



剖心囊視冠脈



Chapter 12

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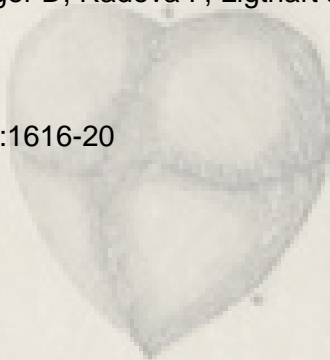
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Late stent recoil of the bioabsorbable everolimus eluting coronary stent and its relationship with plaque morphology.

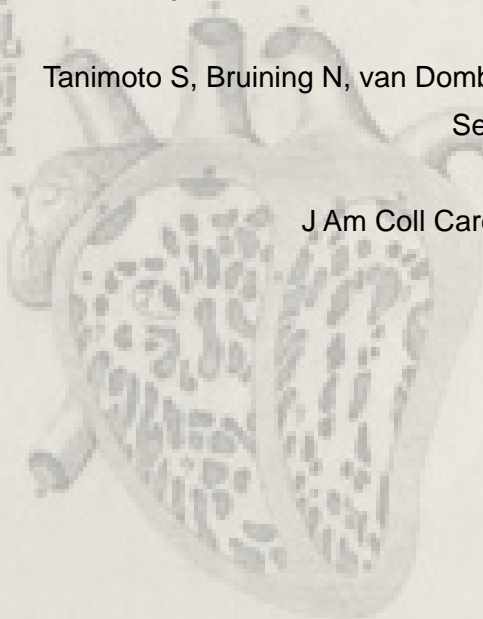
Tanimoto S, Bruining N, van Domburg RT, Rotger D, Radeva P, Ligthart JM, Serruys PW.

J Am Coll Cardiol. 2008;52:1616-20

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心障膜





# Late Stent Recoil of the Bioabsorbable Everolimus-Eluting Coronary Stent and its Relationship With Plaque Morphology

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- Objectives** This study sought to evaluate late recoil of a novel bioabsorbable everolimus-eluting coronary stent (BVS), which is composed of a poly-L-lactic acid backbone, coated with a bioabsorbable polymer containing everolimus.
- Background** Little is known about the mechanical behavior of bioabsorbable polymer stents after deployment in diseased human coronary arteries.
- Methods** The study population consisted of 16 patients, who were treated with elective BVS implantation for single de novo native coronary artery lesions and were followed at 6 months. All patients underwent an intravascular ultrasound examination at post-procedure and follow-up. A total of 484 paired cross-sectional areas (CSAs) were acquired and analyzed. Late absolute stent recoil was defined as stent area at post-procedure (X) – stent area at follow-up (Y). Late percent stent recoil was defined as  $(X - Y)/X \times 100$ . In each CSA, plaque morphology was assessed qualitatively and classified as calcific, fibronectrotic, or fibrocellular plaque.
- Results** Late absolute and percent recoil of the BVS was  $0.65 \pm 1.71 \text{ mm}^2$  (95% confidence interval [CI]: 0.49 to 0.80  $\text{mm}^2$ ) and  $7.60 \pm 23.3\%$  (95% CI: 5.52% to 9.68%). Calcified plaques resulted in significantly less late recoil ( $0.20 \pm 1.54 \text{ mm}^2$  and  $1.97 \pm 22.2\%$ ) than fibronectrotic plaques ( $1.03 \pm 2.12 \text{ mm}^2$  and  $12.4 \pm 28.0\%$ ,  $p = 0.001$  and  $p = 0.001$ , respectively) or fibrocellular plaque ( $0.74 \pm 1.48 \text{ mm}^2$  and  $8.90 \pm 19.8\%$ ,  $p = 0.001$  and  $p = 0.001$ , respectively).
- Conclusions** The BVS shrank in size during the follow-up period. The lesion morphology of stented segments might affect the degree of late recoil of the BVS. (ABSORB Everolimus Eluting Coronary Stent System First in Man Clinical Investigation; NCT00300131) (J Am Coll Cardiol 2008;52:1616–20) © 2008 by the American College of Cardiology Foundation

Compared with metallic stents, bioabsorbable polymer stents could have a lower radial strength, resulting in more stent recoil after implantation, because polymers are more flexible than metals. The bioabsorbable everolimus-eluting coronary stent (BVS) (Abbott Vascular, Santa Clara, California) is composed of a high-molecular-weight poly-L-lactic acid (PLLA) backbone, coated with a matrix of bioabsorbable polymer and everolimus. All components of the BVS, except for 2 radio-opaque platinum markers on both ends of its surface, are expected to be fully metabolized and absorbed in the human body between 2 and 3 years (1,2). Although acute recoil of the BVS as assessed by quantitative coronary angiography (QCA) was slightly but

not significantly higher than that of the everolimus-eluting metallic stent (2), little is known about late mechanical behavior of the BVS. In the present study, we evaluated late recoil of the BVS and assessed its relationship with lesion morphology of the stented segments.

## Methods

**Study population.** Of the 30 patients included in the ABSORB (ABSORB Everolimus Eluting Coronary Stent System First in Man Clinical Investigation) trial, 16 were enrolled at the Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands. The trial has been described in detail previously (1,2). It was approved by the local ethics committee, and all patients gave written informed consent. In brief, patients were eligible for the study if they had single de novo native coronary artery lesions that could be covered with a single BVS. Patients were ineligible if they had evolving myocardial infarction, left main coronary

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artery stenosis, an ostial lesion, a bifurcation lesion, a totally occluded lesion, a lesion with moderate-to-heavy calcification, angiographically visible thrombus within the target lesion, or a left ventricular ejection fraction <30%.

**Study procedure.** Target lesions were electively treated with standard interventional techniques with mandatory pre-dilation and stent deployment at a pressure not exceeding the rated burst pressure (16 atm). Post-dilation with a balloon shorter than the implanted stent was allowed at operator discretion. Bailout stenting for edge dissection was permitted with metallic stents. At the end of the procedure, intravascular ultrasound (IVUS) procedures were performed with a 40-MHz IVUS catheter (Atlantis SR Pro, Boston Scientific Corporation, Natick, Massachusetts) with an automated pullback system at 0.5 mm/s. After IVUS examinations, no other stent-related procedures were added. All patients were planned to undergo both a coronary angiography and an IVUS examination 6 months after the initial procedure.

**QCA and quantitative IVUS analysis.** The QCA was performed with the CAAS II analysis system (Pie Medical BV, Maastricht, the Netherlands) by an independent observer blinded to the clinical and IVUS findings. The following QCA parameters were computed: minimal lumen diameter, reference vessel diameter, percent diameter stenosis, and lesion length. The accuracy of this method has been reported in detail previously (3).

To analyze and compare the IVUS data consistently, all IVUS examinations were retrospectively electrocardiogram (ECG)-gated with the validated Intelligate method, which automatically selects near end-diastolic frames from pre-recorded non-ECG-gated IVUS data (4). The IVUS images of both post-procedure and follow-up studies were analyzed by side-by-side viewing, comparing for matched segments. Only the stented segments were analyzed and were identified by the first and the last cross section containing visible stent struts. The lumen, stent, and external elastic membrane contours were detected with the validated software (CURAD QCU Analysis Software, Curad B.V., Wijk bij Duurstede, the Netherlands), which allows semi-automated detection of the lumen-intima interface and the external elastic membrane in longitudinal reconstructed views of coronary vessels (5,6).

**Late stent recoil assessment.** Stent recoil was computed from measurements of IVUS cross-sectional areas (CSAs), obtained every 0.5 mm. Late absolute stent recoil was defined as stent area at post-procedure ( $X$ ) – stent area at follow-up ( $Y$ ). Late percent stent recoil was defined as  $(X - Y)/X \times 100$ .

**Image-based plaque characterization.** The IVUS appearance of the BVS struts is unique and differs from that of metallic stents. The polymer struts are visible as 2 parallel lines of echoes without acoustic shadowing (AS), due to the fact that the ultrasound is mainly backscattered at the interfaces (blood/polymer interface and polymer/tissue interface) of the struts with the surrounding environment.

Therefore, plaque characterization of BVS implanted segments can be assessed without the image artifacts as seen in IVUS of metallic stents.

To investigate the possible relationship between the degree of late stent recoil and plaque morphology in stented segments, plaque characterization of BVS implanted segments was qualitatively assessed by IVUS appearance. All acquired CSAs were classified into 3 different plaque types: calcific, fibronectrotic, or fibrocellular plaque. Each plaque type was defined as follows (7–11): calcific plaque: highly echogenic areas having a density greater than that of the adventitia and causing AS, possibly combined with reverberations; fibronectrotic plaque: plaque components causing echolucent areas within the plaque combined with AS or plaque having AS without reverberations; and fibrocellular plaque: plaque components other than calcific and fibronectrotic plaques. In case several plaque types were identified in 1 CSA, the predominant plaque type was selected.

**Statistical analysis.** Statistical analysis was performed with SAS software (SAS Institute Inc., Cary, North Carolina). Categorical variables were expressed as counts and percentages. Continuous variables were presented as mean values with SDs. The Student  $t$  test was performed for testing differences of late BVS recoil among 3 different plaque types of stented segments. To adjust for multiple observations/patient, with possible correlations of adjacent cross sections, the  $t$  statistic was divided by  $C = (1 + [m - 1]\rho)$ , where  $m$  is the number of observations/patient and  $\rho$  is the intraclass correlations (12). The intraclass correlation  $\rho$  is defined as: variance (between patients)/(variance [between patients] + variance [within patients]). A value of  $p < 0.05$  was considered statistically significant.

## Results

All patients were successfully treated and underwent follow-up coronary angiography and IVUS procedures at  $6.0 \pm 1.2$  months. Only 1 patient received bailout stenting. A total of 484 paired (post-procedure and follow-up) CSAs were acquired. Baseline and follow-up results are shown in Table 1. According to the protocol, lesion complexity was relatively simple: no type C lesion, short lesion length ( $9.83 \pm 4.02$  mm), large reference vessel diameter ( $2.96 \pm 0.48$  mm), and mild degree of diameter stenosis ( $62 \pm 13\%$ ). Late absolute stent recoil was  $0.65 \pm 1.71$  mm<sup>2</sup> (95% confidence interval [CI]: 0.49 to 0.80 mm<sup>2</sup>), and late percent stent recoil was  $7.60 \pm 23.3\%$  (95% CI: 5.52% to 9.68%). All acquired CSAs were qualitatively assessable in terms of lesion morphology of stented segments. The fibrocellular,

### Abbreviations and Acronyms

<b>AS</b>	= acoustic shadowing
<b>BVS</b>	= bioabsorbable everolimus-eluting coronary stent
<b>CI</b>	= confidence interval
<b>CSA</b>	= cross-sectional area
<b>ECG</b>	= electrocardiogram
<b>IVUS</b>	= intravascular ultrasound
<b>PLLA</b>	= poly-L-lactic acid
<b>QCA</b>	= quantitative coronary angiography



**Table 1** Clinical, Lesion, and Procedural Characteristics

Patient demographic data (n = 16 patients)	
Age, yrs	60.9 ± 8.6
Male	11 (69%)
Hypertension	10 (63%)
Hypercholesterolemia	12 (75%)
Diabetes	1 (6%)
Current smoking	4 (25%)
Prior myocardial infarction	2 (13%)
Lesion characteristics (n = 16 lesions)	
Treated vessel	
Right coronary artery	4 (25%)
Left anterior descending	5 (31%)
Left circumflex artery	7 (44%)
ACC/AHA lesion type	
Type A	0 (0%)
Type B1	8 (50%)
Type B2	8 (50%)
Type C	0 (0%)
Procedural characteristics	
Pre-dilation before stenting	16 (100%)
Post-dilation	12 (75%)
Maximal pressure during entire procedure, atm	16.1 ± 0.89
Stent/artery ratio	0.98 ± 0.16
Clinical success	16 (100%)
QCA results	
Pre-procedure	
Lesion length, mm	9.83 ± 4.02
Reference vessel diameter, mm	2.96 ± 0.48
Minimal lumen diameter, mm	1.09 ± 0.31
Diameter stenosis, %	62 ± 13
Post-procedure	
Minimal lumen diameter, mm	2.45 ± 0.33
Diameter stenosis, %	19 ± 8
Acute gain, mm	1.36 ± 0.46
Follow-up	
Minimal lumen diameter, mm	2.00 ± 0.27
Diameter stenosis, %	29 ± 14
Late loss, mm	0.45 ± 0.39
IVUS results (n = 484 CSAs)	
Post-procedure	
Stent area, mm <sup>2</sup>	6.94 ± 1.47
Follow-up	
Stent area, mm <sup>2</sup>	6.29 ± 1.70
Lumen area, mm <sup>2</sup>	5.83 ± 1.51
Neointimal area, mm <sup>2</sup>	0.47 ± 0.58
Late absolute stent recoil, mm <sup>2</sup>	0.65 ± 1.71
Late percent stent recoil, %	7.60 ± 23.3

Values are mean ± SD or n (%).

ACC/AHA = American College of Cardiology/American Heart Association; CSA = cross-sectional area; IVUS = intravascular ultrasound; QCA = quantitative coronary angiography.

fibronectin, and calcific group consisted of 204, 126, and 154 CSAs, respectively. The relationship between late stent recoil and lesion morphology is shown in Figure 1. Late absolute and percent stent recoil were significantly less in calcified lesions ( $0.20 \pm 1.54 \text{ mm}^2$  and  $1.97 \pm 22.2\%$ , respectively) than in fibrofatty lesions ( $0.74 \pm 1.48 \text{ mm}^2$  and  $8.90 \pm 19.8\%$ ,  $p = 0.001$  and  $p = 0.001$ , respectively)

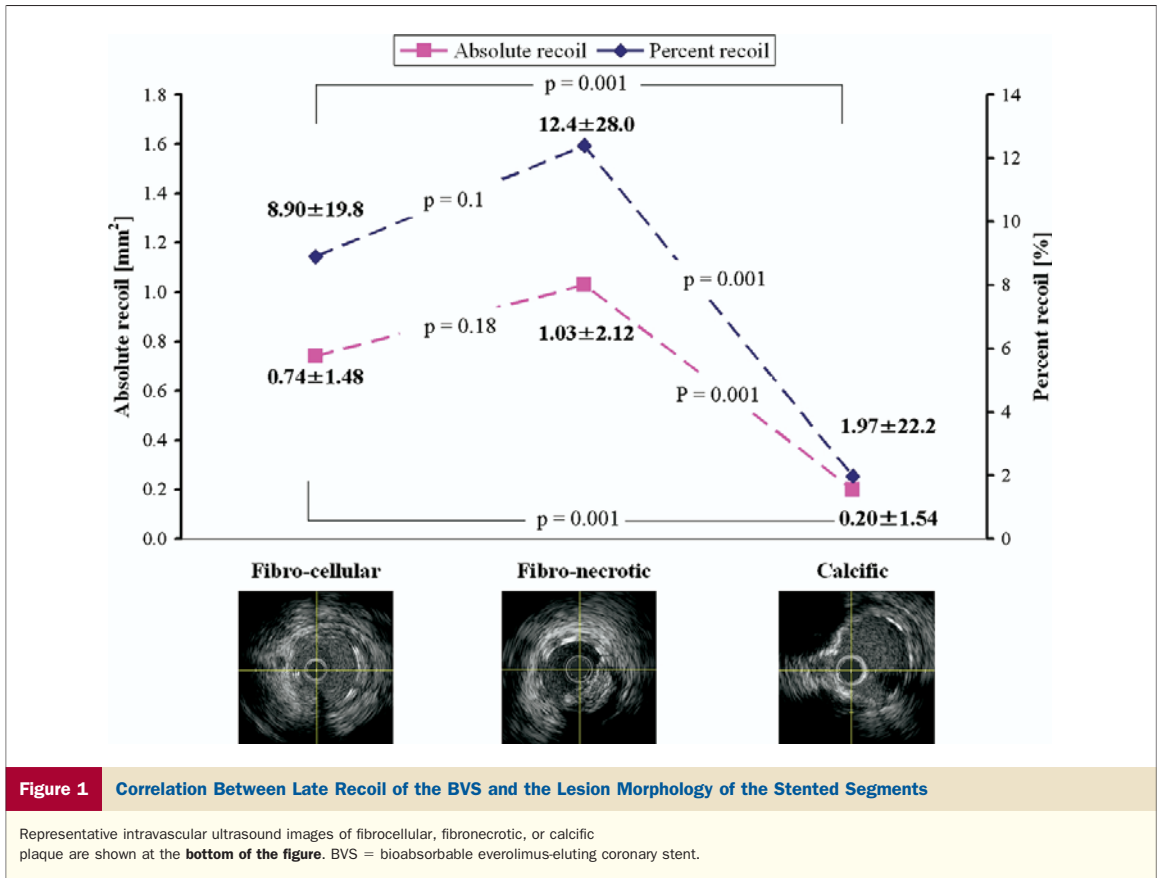
or in fibronectin lesions ( $1.03 \pm 2.12 \text{ mm}^2$  and  $12.4 \pm 28.0\%$ ,  $p = 0.001$  and  $p = 0.001$ , respectively). Although there was a trend toward more recoil in fibronectin lesions than in fibrofatty lesions, no significant differences in late absolute and percent stent recoil were observed between these 2 lesion types ( $p = 0.18$  and  $p = 0.1$ , respectively).

## Discussion

The present study indicated that the BVS shrank in size during the follow-up period. This observation was at variance with the observed 6 months' late recoil of the Igaki-Tamai stent, which was the first polymeric stent examined in diseased human coronary arteries (13). Although the Igaki-Tamai stent was composed of the same material (PLLA) as the BVS, it became larger in size ( $0.71 \text{ mm}^2$  at 6 months according to IVUS analysis). This discrepancy could have been caused by the differences in study protocols and/or baseline characteristics of the target lesions between 2 studies. However, the main reason might be associated with differences in stent design. Because the Igaki-Tamai stent was self-expandable, whereas the BVS was balloon-expandable, the Igaki-Tamai stent tends to expand gradually in time until it reaches fully unconstrained dimensions.

The current results also differed from reported late recoil of metallic stents as assessed by IVUS. The Palmaz-Schatz stent exhibited only a little recoil ( $0.1 \text{ mm}^2$  and  $0.6\%$ ) at 4 months (14). Late recoil of the XIENCE V everolimus-eluting stent (Abbott Vascular), which is a metallic stent coated with the same antiproliferative drug as in the BVS, was computed as  $0.02 \text{ mm}^2$  and  $0.3\%$  at 6 months (1,15). These changes are in the range of reproducibility measurements. However, it is obvious that the vessel scaffolding properties of the BVS have not been maintained for a long period compared with metallic stents, even if the BVS shows a good radial strength, similar to metallic stents, immediately after deployment (2). This might be due to differences in material components between both stent types. Because polymers are more flexible than metals, there is a potential that polymer stents are affected by the elastic properties of the arterial wall more directly and have been compressed steadily. In addition, because the BVS is designed to be gradually metabolized, the polymer backbone will lose its structural integrity over time, which could diminish its radial strength and lead the stent to shrink. However, no clear image of such a degradation process of the BVS was documented, even when using a 40-MHz IVUS catheter, probably due to an insufficient resolution of IVUS to clarify this phenomenon.

Because the extent of stent recoil is the result of the balance between the elastic recoil and radial strength of the stent, along with the elastic properties of the arterial wall, it can be affected by the plaque characteristics of the stented segments. The elastic property of the arterial wall is determined by atherosclerotic plaque constituents. Previous studies revealed the following: 1) calcific plaques had stiffer mechanical properties than other types of plaques and thus



exhibited less elasticity; and 2) fibrofatty or fibronecrotic plaques had more elasticity than calcific plaques, but no significant difference was observed between these 2 plaque types (10,11). In concurrence with these statements, the present study demonstrated that calcified plaques resulted in significantly less late recoil than the other plaque types and that fibrocellular or fibronecrotic plaques induced more late recoil than calcified plaques, although no significant differences in late recoil were observed between these 2 plaque types (Fig. 1). These findings suggest that an IVUS examination of the target lesion before stenting could be useful to predict the extent of stent recoil in case of BVS implantation. **Study limitations.** Limitations are the small number of enrolled patients and that the clinical implication of the BVS shrinkage remains unclear. Target lesions were relatively simple, and late recoil of the BVS might increase in more complex lesions. Further investigations are warranted to determine the recoil properties of the BVS at the time of its complete degradation.

## Conclusions

A certain degree of late stent recoil was observed 6 months after BVS implantation, indicating that the BVS shrank in size

during the follow-up period. The lesion morphology of stented segments might affect the extent of late recoil of the BVS.

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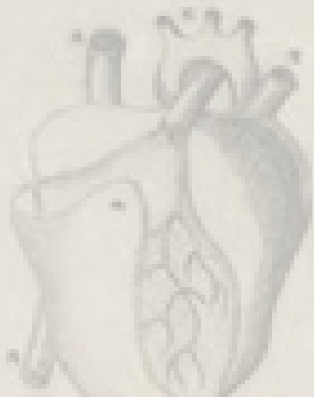
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**Key Words:** bioabsorbable ■ coronary artery disease ■ recoil ■ stents.

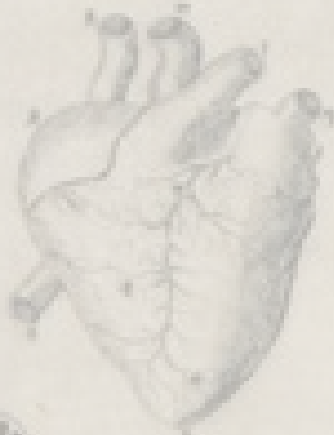


心篇圖

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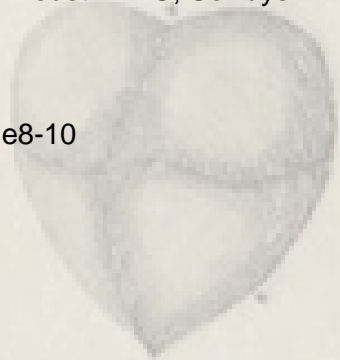
Chapter 13

"Radio-lucent" and "radio-opaque" coronary stents characterized by multislice computed tomography.

Otsuka M, Tanimoto S, Sianos G, Kukreja N, Weustink AC, Serruys PW, de Feyter PJ.

Int J Cardiol. 2009;132:e8-10

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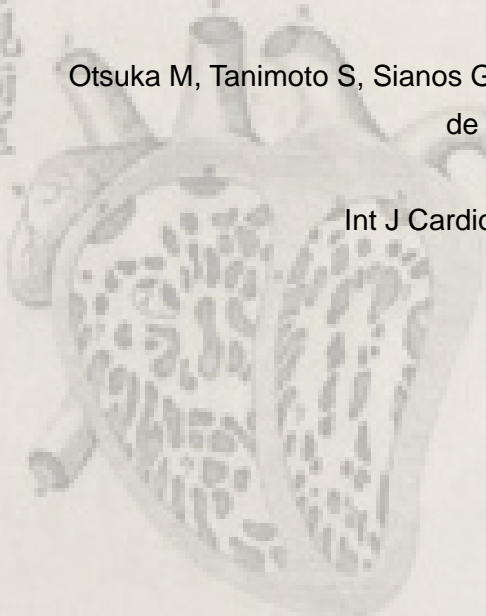


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Letter to the Editor

## “Radio-lucent” and “radio-opaque” coronary stents characterized by multislice computed tomography

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### Abstract

A 71-year-old man was admitted with stable angina pectoris. The coronary lesion in the obtuse marginal branch was successfully treated with a BVS bioabsorbable poly-L-lactic acid everolimus-eluting coronary stent and a Cypher stent. On multislice computed tomography (MSCT) coronary angiography performed after stenting, the in-stent lumen within radio-lucent polymer struts of the BVS stent was clearly depicted. In contrast, the metallic struts of the Cypher stent hampered precise in-stent luminal evaluation due to blooming artifact.

Non-metallic coronary stents composed of radio-lucent polymers might have potential advantages compared to metallic stents with respect to non-invasive MSCT imaging.

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**Keywords:** Multislice computed tomography; Stents; Imaging; Angiography; Coronary disease

### 1. Case report

A 71-year-old male ex-smoker with hypercholesterolemia, was admitted with stable angina pectoris. Conventional coronary angiography revealed a high grade stenosis at the proximal segment of the obtuse marginal branch (Fig. 1A). The patient was enrolled in the ABSORB trial, a first-in-man clinical investigation of the bioabsorbable poly-L-lactic acid everolimus-eluting coronary stent (BVS: Bioabsorbable Vascular Solutions, Inc., Abbott Laboratories, Mountain View, CA) in patients with single *de novo* native coronary artery lesions [1,2]. After predilation, a 3.0×12 mm BVS stent was implanted at the target lesion. Due to distal stent-

edge dissection, and according to the study protocol, a 3.0×13 mm bailout Cypher stent (Cordis, Miami Lakes, FL) was successfully implanted with minimal overlap with the BVS stent (Fig. 1B).

Multislice computed tomography (MSCT) coronary angiography performed 4 days later with a dual-source 64-slice CT scanner (Somatom Definition, Siemens, Forthheim, Germany) demonstrated these two stents with contrasting characteristics (Fig. 2). The radio-lucent polymer struts of the BVS stent were invisible, therefore the in-stent lumen was clearly depicted on MSCT. The 2 radio-opaque platinum markers indicated both ends of BVS stent. In contrast, the metallic struts of the Cypher stent hampered clear depiction of the in-stent lumen due to the “blooming” effect.

### 2. Discussion

MSCT coronary angiography has emerged as a non-invasive diagnostic modality to evaluate coronary artery disease. Rapid progress of MSCT technology with the

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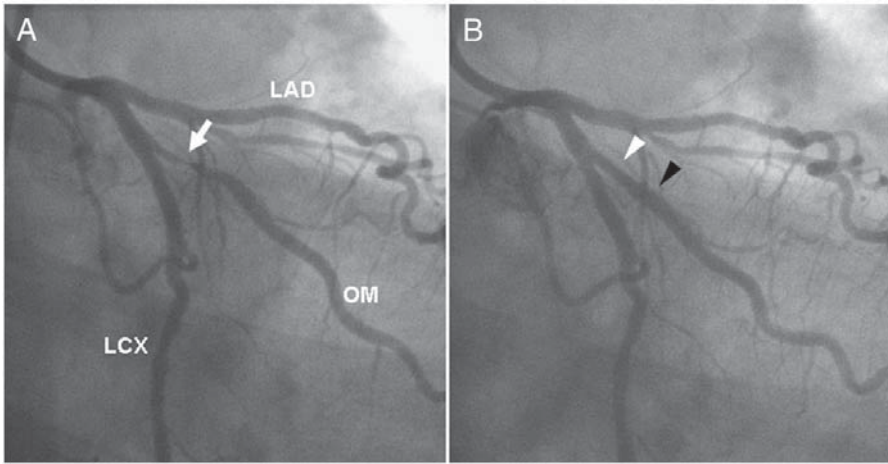


Fig. 1. Conventional coronary angiograms of the left coronary artery before (A) and after (B) percutaneous coronary intervention. The lesion in the proximal obtuse marginal branch (OM) (arrow) was successfully treated with a BVS bioabsorbable poly-L-lactic acid everolimus-eluting coronary stent (white arrow head) and a Cypher stent (black arrow head). LAD, left anterior descending coronary artery. LCX, left circumflex coronary artery.

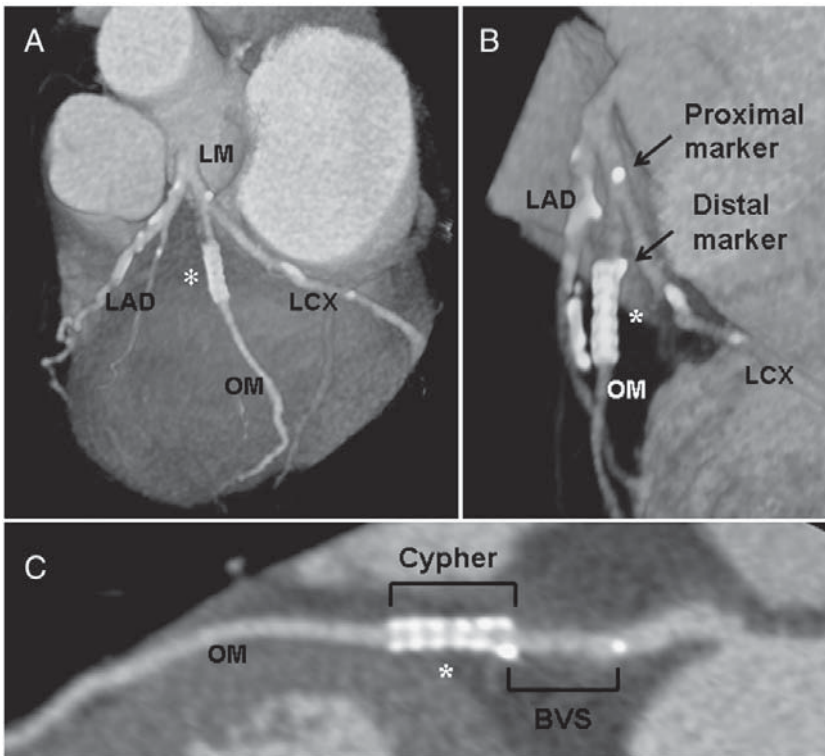


Fig. 2. Three-dimensional volume-rendered images (A, B) and curved multiplanar reconstructions of the obtuse marginal branch (C) by multislice computed tomography coronary angiography after stenting. The polymer struts of the BVS stent are invisible, and only 2 radio-opaque platinum markers at either end of the stent can be seen (arrows). In contrast, the metallic struts of Cypher stent (\*) are brightly visible with blooming, hampering precise in-stent luminal evaluation. LM, left main coronary artery.



number of detectors increased to 16–64 and faster speed of gantry rotation promises more accurate coronary images with improved spatial and temporal resolution and has resulted in progressively its high ability for detection of coronary stenoses, as compared to catheter-based conventional angiography [3]. However, visualization or evaluation of the in-stent lumen by MSCT is still challenging owing to blooming artifact caused by metallic stent struts. Some reports have shown the limited assessability or the impact of blooming artifact on the in-stent evaluation [4,5]. In terms of evaluating the stented segment noninvasively and visualizing these segments accurately using MSCT, the polymer stents might have potential advantages when compared to metallic stents [2,6].

The MSCT images of the present case contrastively demonstrate both the “radio-lucent” non-metallic BVS stent composed of bioabsorbable polymers and the “radio-opaque” metallic stent implanted in the same coronary vessel. Although the nominal diameters of both stents were same, the in-stent lumen of the BVS stent was clearly depicted on MSCT compared to the metallic stent.

The BVS stent is expected to be fully absorbed in a few years after implantation. Therefore, the stent may not require long lasting antiplatelet therapy and the stented segment may allow for future surgical revascularization [1,2]. In addition,

the polymer stent could be amenable to MSCT that will play an increased role in the future for evaluating of neointimal growth and arterial remodeling of the stented segment.

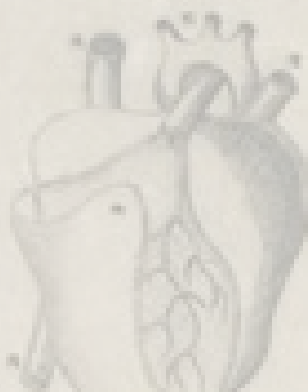
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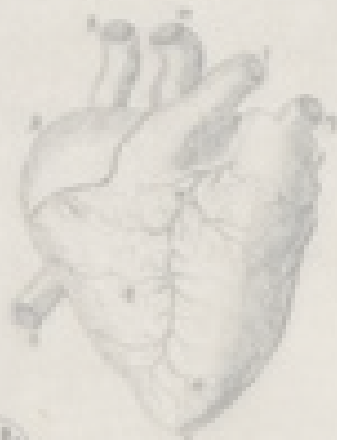


心管圖

四脈管及心囊



剖心囊視冠脈



Chapter 14

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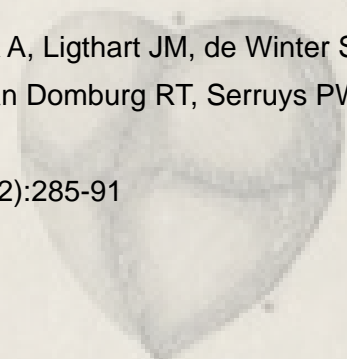
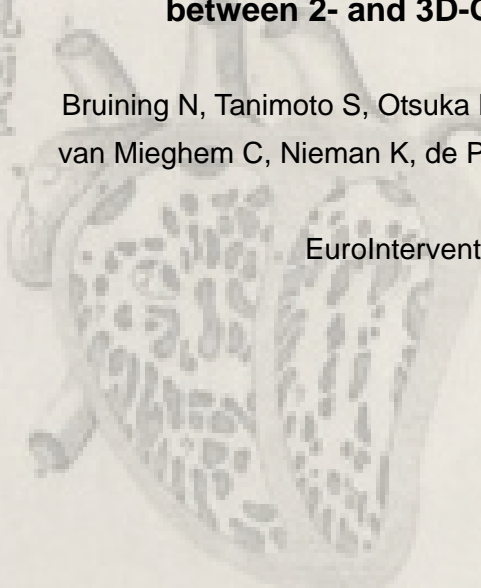
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Quantitative multi-modality imaging analysis of a bioabsorbable poly-L-lactic acid stent design in the acute phase: a comparison between 2- and 3D-QCA, QCU and QMSCT-CA.

Bruining N, Tanimoto S, Otsuka M, Weustink A, Ligthart JM, de Winter S, van Mieghem C, Nieman K, de Peyter PJ, van Domburg RT, Serruys PW.

EuroIntervention. 2008;4(2):285-91

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## Quantitative multi-modality imaging analysis of a bioabsorbable poly-L-lactic acid stent design in the acute phase: a comparison between 2- and 3D-QCA, QCU and QMSCT-CA

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

### KEYWORDS

Intravascular  
ultrasound,  
image processing,  
coronary artery disease

### Abstract

**Aims:** To investigate if three-dimensional (3D) based quantitative techniques are comparable to each other and to explore possible differences with respect to the reference method of 2D-QCA in the acute phase and to study whether non-invasive MSCT could potentially be applied to quantify luminal dimensions of a stented coronary segment with a novel bioabsorbable drug-eluting stent made of poly-L-lactic-acid (PLLA).

**Methods and results:** Quantitative imaging data derived from 16 patients enrolled at our institution in a first-in-man trial (ABSORB) receiving a biodegradable stent and who were imaged with standard coronary angiography and intravascular ultrasound were compared. Shortly, after stenting the patients also underwent a MSCT procedure. Standard 2D-QCA showed significant smaller stent lengths ( $p < 0.01$ ). Although, the absolute measured stent diameters and areas by 2D-QCA tend to be smaller, the differences failed to be statistically different when compared to the 3D based quantitative modalities. Measurements made by non-invasive QMSCT-CA of implanted PLLA stents appeared to be comparable to the other 3D modalities without significant differences.

**Conclusions:** Three-dimensional based quantitative analyses showed similar results quantifying luminal dimensions as compared to 2D-QCA during an evaluation of a new bioabsorbable coronary stent design in the acute phase. Furthermore, in biodegradable stents made of PLLA, non-invasive QMSCT-CA can be used to quantify luminal dimensions.

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## Introduction

Coronary stenting has resolved the problem of acute recoil and late remodelling after a coronary balloon dilatation procedure<sup>1</sup>. The introduction of drug-eluting stents (DES), not so long ago, solved partially the problem of in-stent restenosis occurring in patients treated with bare metal stents<sup>1</sup>. However, the combination of an implanted metallic device into the coronary vessel wall and the elution of antiproliferative drugs from durable polymer coated stent struts for long-lasting inhibition of neointima hyperplasia (NIH) proliferation<sup>2</sup>, potentially delayed the healing process<sup>2,3</sup>. The non-endothelialised polymer coated stent struts may stay in direct contact with the bloodstream, even after a period of two years, which may possibly lead to late stent thrombosis after discontinuation of the antiplatelet therapy<sup>4,5</sup>. A possible solution to overcome this problem could be a fully bioabsorbable DES stent which will maintain the benefits of a mechanical scaffold post-balloon procedure while eluting temporarily the local pharmaceutical treatment<sup>6,7</sup>.

To investigate the effectiveness of a bioabsorbable stent made from poly-L-lactic acid (PLLA)<sup>8</sup>, coated with the proven effective NIH inhibiting drug everolimus<sup>9</sup>, a multi-modality quantitative imaging study was implemented as a sub-study of the ABSORB trial<sup>10</sup>. The ABSORB trial is the first-in-man study of the implantation of the Abbott Vascular BVS bioabsorbable stent (Bioabsorbable Vascular Solutions, Santa Clara, CA, USA).

Besides the usually applied imaging techniques to evaluate the results of new stent designs in these kind of studies (e.g., two-dimensional (2D) quantitative coronary angiography (QCA)<sup>11</sup> and quantitative intravascular ultrasound (QCU)<sup>12</sup>, also the newly available imaging techniques of three-dimensional (3D) QCA<sup>13</sup> and quantitative non-invasive imaging by multi-slice computed tomography coronary angiography (MSCT-CA)<sup>14</sup> were applied during the acute phase to evaluate their respective imaging values and future application. Metallic stents, with their inherent radiopacity hampers the luminal assessment of these devices with MSCT-CA<sup>15</sup>. PLLA does not cause MSCT-CA related image artefacts and thus could provide an improved visualisation of the lumen in BVS stented coronary segments. MSCT-CA was applied for evaluation since most patients might prefer its friendly non-invasive nature in case they participate in a longitudinal study evaluating these new stent modalities.

This study compared these imaging methodologies for the quantitative assessment of BVS stented coronary arteries.

## Methods

### Patients and study design

Sixteen patients (11 men and five woman, 60.9±8.6 years) were included in this sub-analysis, which was part of the multicentre ABSORB trial<sup>10</sup>. The study design has been described in detail elsewhere<sup>10</sup>, however in brief: It is a first-in-man prospective, open-labelled multicentre trial of patients with a single *de novo* coronary artery lesion treated with the BVS stent. The local ethical committee approved the study and each patient gave a written informed consent. Target lesions that could be covered by a 3.0 mm±12 mm

or a 3.0 mm±18 mm (diameter, length) stent were selected. Locations of the BVS stent in the 16 patients were: five left anterior descending (LAD), four right coronary arteries (RCA) and seven left circumflex arteries (LCX).

### BVS stent design

The laser-cut PLLA stent design consists of four major components: a high crystalline polymer backbone, a low crystalline polymer coating impregnated with everolimus and a delivery system<sup>6,10</sup> (Figure 1). The stent struts are 150 µm thick and at the distal and proximal edges of the stent two platinum radiopaque markers, each 135 µm, are embedded into the stent struts to facilitate accurate fluoroscopic positioning of the stent.

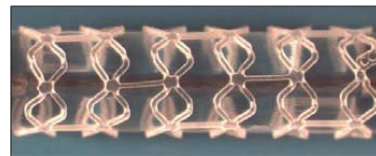


Figure 1. This figure presents the BVS stent design. At the proximal and distal side the two golden coloured platinum markers can be appreciated.

### Coronary Arteriography including Two- and Three-dimensional (2D and 3D) QCA

Coronary arteriography was performed according to standard procedures<sup>16</sup>. Each angiogram was preceded by the injection of 1-3 mg isosorbide dinitrate. Two-dimensional QCA was performed with the CAAS II system<sup>11</sup> (Pie Medical BV, Maastricht, The Netherlands). Three-dimensional QCA was performed with CAAS QCA-3D (CAAS 5.0, Pie Medical BV, Maastricht, The Netherlands). This latter system uses the detected contours in the frontal and lateral images in combination with the projection data available in the DICOM format to make a reconstruction of the coronary artery segment in 3D. In this study two simultaneously acquired orthogonal views by a bi-plane system were used. The QCA measurements were performed off-line.

### Intravascular ultrasound (IVUS) procedure and Quantitative IVUS (QCU)

IVUS was performed after successful implantation and additional balloon dilatation if necessary. The IVUS catheter used was a 40 MHz Atlantis™ catheter (Boston Scientific, Santa Clara, CA, USA) connected to a Galaxy™ ultrasound console (Boston Scientific, Santa Clara, CA, USA). The catheter was pulled back by a continuous speed mechanical device at 0.5 mm/s<sup>17</sup>. IVUS data were acquired after intracoronary injection of isosorbide dinitrate. All image data were digitally stored on CD-ROM and transferred later to an IVUS Picture Archiving and Communications System (IVUS-PACS).

Quantitative IVUS analysis was performed using validated QCU software (CURAD BV, Wijk bij Duurstede, The Netherlands),

allowing semi-automatic detection of the intima- or stent-boundaries in longitudinal reconstructed views of the stented segment<sup>18</sup>. To overcome possible inaccuracies in quantitative analysis and problems using automatic contour detectors, which are common in non-ECG-gated acquired IVUS studies due to longitudinal catheter motion and rotation of the coronary artery around the IVUS catheter during the cardiac cycle<sup>19,20</sup>, the validated retrospective image-based pre-processing gating algorithm Intelligate<sup>®</sup> was applied<sup>21</sup>. This algorithm filters near-end-diastolic frames from a non-gated IVUS study and creates a new retrospective gated IVUS study resulting in smooth longitudinal views in which automatic contour detectors can be applied (Figure 2).

### MSCT-CA procedure and Quantitative MSCT-CA (QMSCT-CA)

The MSCT-CA procedure, in a 64-slice spiral CT scanner (Sensation 64<sup>®</sup>, Siemens, Forchheim, Germany), was performed within three days after implantation of the BVS stent according to a standardised protocol<sup>22</sup>. The x-ray tube rotation time was 330 ms, resulting in a temporal resolution of 165 ms. Detector collimation was 32 x 0.6 mm with a pitch of 0.2 (table advancement was 3.8 mm per rotation). By rapid alternation of the longitudinal position of the focal spot (Z-Sharp<sup>®</sup> Technology, Siemens, Forchheim, Germany), 64 slices could be acquired simultaneously. A tube voltage of 120 kV with tube currents between 800 and 900 mAs were applied.

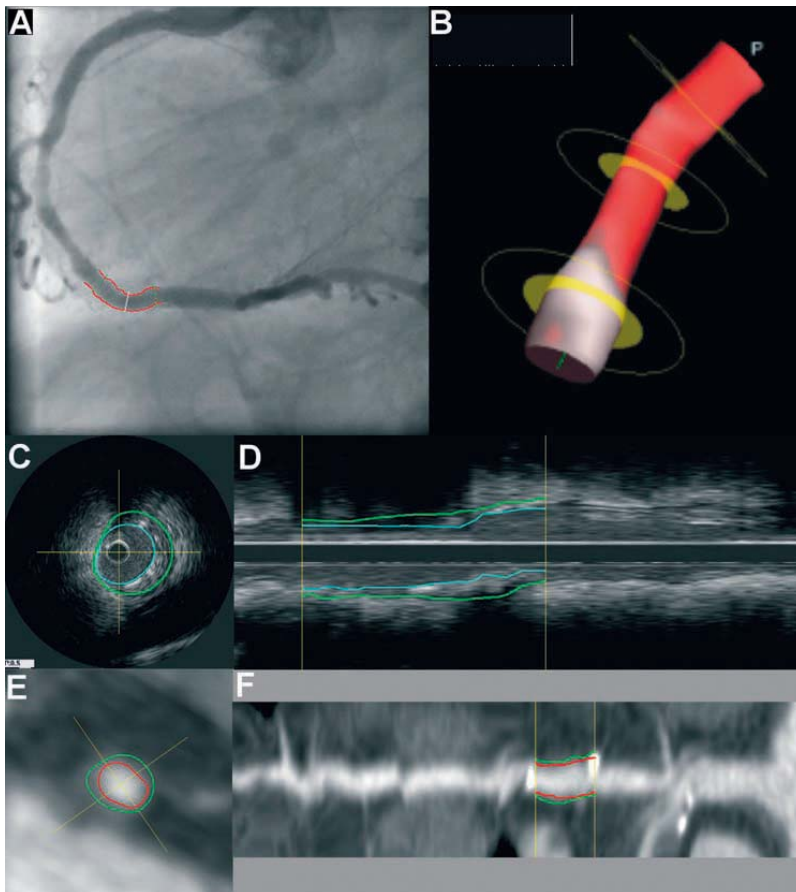


Figure 2. This figure shows examples of all applied quantitative modalities. In panel A, standard 2D quantitative coronary angiography (QCA) and in panel B, a reconstruction made by the new 3D-QCA technique. Panel C shows a cross-sectional measurement of quantitative intravascular ultrasound (QCU) from which a reconstructed longitudinal view (L-views) is presented in panel D. The blue line indicates the stent contour and the green line the external elastic membrane contour. Panel E, shows a cross-sectional measurement of the multi-slice computed tomography coronary angiography imaging (QMSCT-CA). Panel F, the reconstructed L-view, with as red contour the lumen/stent contour and the green contour the outer vessel border. The two bright spots at either side of the contour lines are the metal markers of the stent, which are causing a blooming artefact on the MSCT-CA image.

Patients with a heart rate >60 BPM were given a  $\beta$ -blocker (up to 100 mg of metoprolol) and/or anxiolytic medication (1 mg of lorazepam) 45 min before the procedure. To enhance the coronary arteries a bolus of 100 mL of iomeprol 400 mg/mL (Iomeron®, Bracco, Milan, Italy) was intravenously administered at a rate of 3.5-5 mL/s, depending on the size of the patient.

After the procedure, the image data was retrospective gated and reconstructed using images acquired during the middle- and late phase of diastole by software of the manufacturer (Siemens). The B30f convolution kernel was applied. All image datasets were uploaded to a local MSCT-PACS for later quantitative analysis. The coronary arteries in which the BVS stent was implanted were extracted using dedicated semi-automated MSCT-CA vessel extraction software<sup>14</sup> (CURAD BV). This software allows the creation a new image dataset from the original MSCT-CA image data as if an intravascular imaging procedure like IVUS has been performed. After vessel extraction, quantitative analysis can be performed similar as QCU (Figure 2). Although, the contour detection is of course rather different for QMSCT-CA, the calculated parameters are similar allowing an optimal environment for comparisons between the different imaging modalities. Validation of this software has been described elsewhere<sup>14</sup>.

## Measured parameters

Although the applied quantitative software packages are producing many different parameters of the coronary vessel- and stent dimensions, only a few can be used for comparison. In this study we used the mean values of the measured implanted stent lengths, -diameters and -areas to compare.

To calculate diameters from the original cross-sectional area measurements as being performed by QMSCT-CA and QCU a circular model was assumed and the following formula was applied<sup>23</sup>:

$$\text{Diameter} = 2 \times \sqrt{\frac{\text{Area}}{\pi}}, \text{ Formula 1}$$

To calculate areas from the original diameter measurements by 2D-QCA again a circular model was assumed and the following formula applied:

$$\text{Area} = \pi \times \left(\frac{d}{2}\right)^2, \text{ Formula 2}$$

## Statistical analysis

Quantitative data are presented as mean  $\pm$  standard deviation. Analysis of variance with the Bonferroni post hoc test was used to compare the mean values among groups. In these analyses a p-value of <0.05 was considered to be significant. The results were further analysed by the method proposed by Bland and Altman<sup>24</sup>, and for this study 2D QCA was selected to be the “golden standard”.

## Results

All quantitative measurements for each modality were performed by a different observer, and they were blinded for the other results. In fact the measurements were also performed at different locations to prevent possible crossover bias.

Two-dimensional QCA and QCU were available in all 16 patients. Three-dimensional QCA was not assessable in five patients due to an insufficient reading of the geometry settings of the x-ray equipment. MSCT-CA could not be performed in two patients due to contrast allergies. In two of the remaining 14 patients, quantitative analysis was not possible due to poor image quality (e.g. excess of motion during the scan).

## Stent lengths

Stents were identified by their metal markers on the coronary angiography images for the QCA techniques and on MSCT-CA; and by their first and last visible strut appearance in a given cross-section in the IVUS images (Table 1, Figure 2 and 3). Two patients

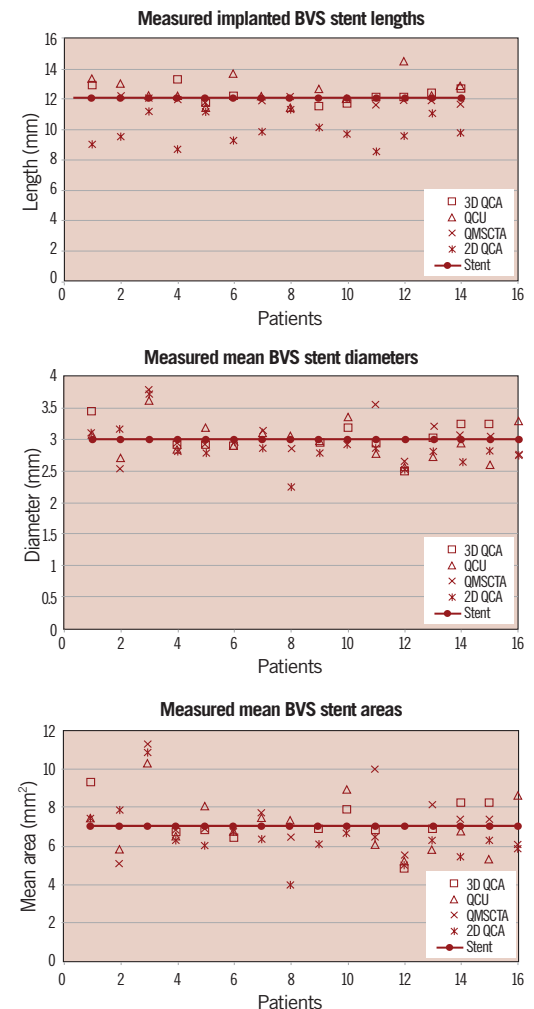


Figure 3. This graph shows all individual implanted measured stent lengths, diameters and areas as measured by the different modalities. It can be clearly appreciated that two-dimensional quantitative angiography (2D-QCA) shows significantly shorter measured lengths.



**Table 1. Measured stent dimensions.**

	2D-QCA	3D-QCA	QCU	QMSCT-CA	Stent
Length [mm]	9.89±0.93	12.24±0.55	12.51±0.85	11.89±0.20	12
Diameter [mm]	2.86±0.31	3.03±0.25	2.98±0.29	3.05±0.36	3
Area [mm <sup>2</sup> ]	6.50±1.47	7.23±1.17	7.10±1.39	7.41±1.78	7.07

Stent dimensional measurements by all applied imaging modalities (presented as mean±SD). The stent column presents the optimal stent implantation dimensions

were not taken into account for comparison of the length measurements, because they received an 18 mm long stent and the 14 others were all 12 mm in length. The metallic markers resulted in a blooming artefact on the MSCT-CA images and therefore the region of interest (ROI) for QMSCT-CA was selected by clipping a small amount off the far ends of these markers (Figure 2H). The length of the stents as determined by two-dimensional QCA was significantly shorter compared to the other modalities ( $p < 0.001$  with all modalities), with an 18% relative difference to the expected nominal stent length (e.g. 12 mm, Table 1). The Bland-Altman analysis shows the differences with the 3D based quantitative methods (Figure 4, Table 2).

**Table 2. 2D-QCA vs. 3D modalities.**

	3D-QCA	QCU	QMSCT-CA
Length [mm]	-2.57±1.23	-2.63±1.51	-1.85±1.00
Diameter [mm]	-0.21±0.20	-0.12±0.32	-0.21±0.34
Area [mm <sup>2</sup> ]	-0.96±0.93	-0.60±1.45	-0.99±1.55

The mean±SD differences of the Bland-Altman analysis for all 3D quantitative analysis vs. the reference method of 2D QCA. In the corresponding Bland-Altman figures (e.g. Fig. 4, 6 and 8) the average of these mean values is presented, this to prevent making the graphs too busy.

## Stent diameters

Comparison of the stent diameter results showed no statistical differences between the quantitative modalities (Table 1). However, 2D-QCA showed smaller absolute diameters (approximately 5%) as compared to the 3D oriented modalities and the nominal stent diameter, respectively. For the stent diameters the Bland-Altman analysis shows that in the majority of cases smaller stent diameters are measured by 2D QCA (Figure 4, Table 2).

## Stent areas

Similar results were also found for the stent area measurements (Table 1). Standard 2D-QCA showed smaller absolute areas as compared to the 3D modalities, although statistically not significant, but with a relative difference of 7% as compared to the nominal stent area. For the stent areas the Bland-Altman analysis showed similar results as for the diameter measurements (Figure 4, Table 2).

## Discussion

This report shows that of the applied 3D oriented quantitative coronary imaging techniques (e.g. 3D-QCA, QCU and QMSCT-CA), luminal measurements in a bioabsorbable stented coronary segment are comparable, but are showing deviation with 2D oriented QCA.

In this study three different imaging modalities were applied with four different quantitative analyses techniques to evaluate the clinical benefits of a new bioabsorbable coronary stent design during the acute phase. In the past two decades only 2D-QCA and QCU were available to study the success or failure of new interventional techniques and new pharmaceutical treatments. Recently, 3D-QCA<sup>13</sup>, an upgrade from 2D-QCA, and non-invasive MSCT-CA<sup>14</sup> imaging became clinically available. Both having their specific advantages and disadvantages. At this point in time the imaging modalities are more complementary to each other, rather than being competitors. However, the question ought to be raised if they are comparable in simple quantitative parametric measurements as stent -length-, -diameters and -areas? This study evaluated the quantitative outcome of these imaging techniques in the acute phase, directly after implantation of a new bioabsorbable stent design and the simple straightforward message is that the 3D based techniques are more in-line with each other and closer to the expected nominal stent dimensions than 2D-QCA measurements.

The measured implanted stent lengths in the 3D based-modalities were comparable but significantly different compared to 2D-QCA. The problem of foreshortening of stenoses and stent lengths by 2D-QCA has been described before<sup>11</sup>. However, 2D-QCA also showed absolute smaller stent diameters and derived areas as compared to the other modalities (Table 1)<sup>25</sup>. Although, it must be underscored that QCA diameters were converted into areas assuming a circular model (Formula 2). In this particular study, e.g. measuring a stent, the assumption of a circular model seems appropriate, although, a non-eccentric appearance after implantation of a PLLA stent is not inconceivable.

The reported smaller stent dimensions as measured by 2D-QCA as compared to QCU, are in-line with previous reports<sup>13,23</sup>. The relative concordance between the measurements obtained by the 3D-QCA, QCU and QMSCT-CA raises the question whether there is a systematic error measurement deviation by 2D-QCA, which should be corrected. A recent study to validate the 3D-QCA software also showed a 10% smaller measured diameter for a phantom introduced into a coronary artery to act as a stenosis with precisely known dimensions<sup>13</sup>.

The three selected parameters for this comparison study may seem basic, however, they are the ones most used in new stent design studies and have acted as endpoints in many multicentre trials. Furthermore, they are the most directly measured being not derived by complicated mathematical computations.

The observation made in this study is that quantitative non-invasive MSCT-CA showed results similar to the currently used reference method, e.g. QCU. Previous reports showed both under- as well as overestimation of coronary lumen dimensions as measured by QMSCT-CA when compared to the *de facto* reference method use of QCU<sup>14,26</sup>. However, it is difficult to compare the results of these studies with the present one, since most of them were not performed in stented segments, which immediately after stenting most likely have a circular shape (which is more easily analysable by most contouring systems). This could have enhanced the concordance between the various quantitative modalities of our study.

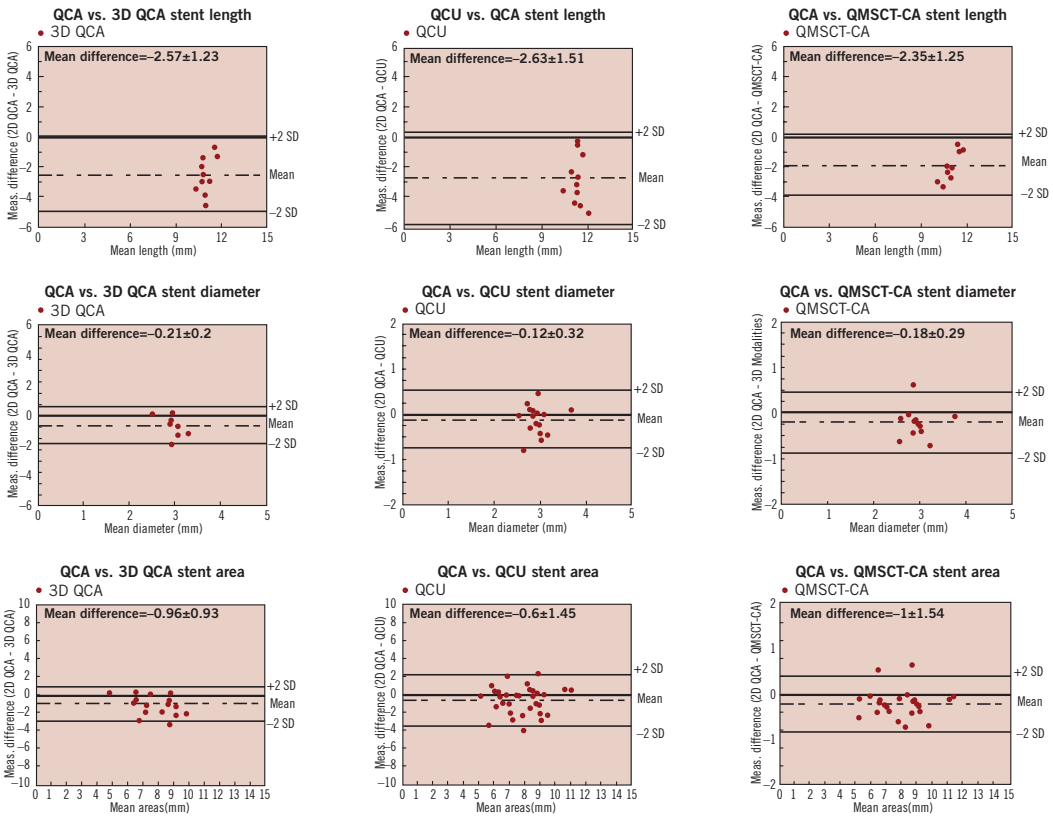


Figure 4. This figure shows all Bland-Altman analyses of the 3D image modalities were 2D QCA was used as golden standard.

The metal markers render the selection of ROI with QCA and QMSCT-CA, although they resulted in a slight underestimation of the implanted stent lengths with MSCT-CA due to the blooming artefact. Leaving the metal markers out seems not to be an option in the research phase, because without them it is impossible to locate the stent using angiography and/or MSCT-CA. Furthermore, the expected bioabsorption of the struts between 2-3 years, may on the other hand make it difficult to retrieve the ROI on IVUS, if the struts are no longer visually detectable. The tiny metal markers (135  $\mu$ m), may by then be embedded into the coronary vessel wall, were already not identifiable at baseline with IVUS.

### Study limitations

Unfortunately, the number of patients of this first-in-man BVS stent study was limited and not every imaging modality could be applied in all patients. While showing a deviation with the 3D techniques, still 2D-QCA was applicable in all patients together with IVUS. Both MSCT-CA and 3D-QCA showed lower success rates, which should be taken into account when planning longitudinal studies. However, this is a unique patient population in which for the first time four different imaging methodologies and one new derived imaging method could be applied and used for quantitative analysis. Of course,

it will be more interesting to see how the applied 3D imaging techniques perform during the long-term follow-up.

### Conclusion

Three-dimensional based quantitative analyses showed similar results quantifying luminal dimensions as compared to 2D-QCA during an evaluation of a new bioabsorbable stent design in the acute phase. Furthermore, in biodegradable stents made of PLLA, non-invasive QMSCT-CA can be used to quantify luminal dimensions.

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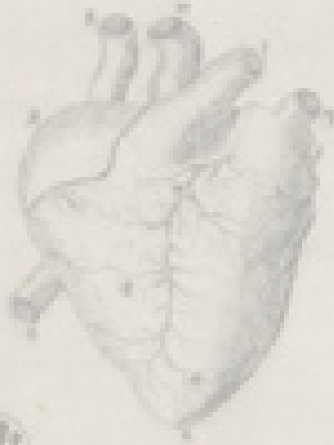


心篇圖

四脈管及心囊



剝心囊視冠脈



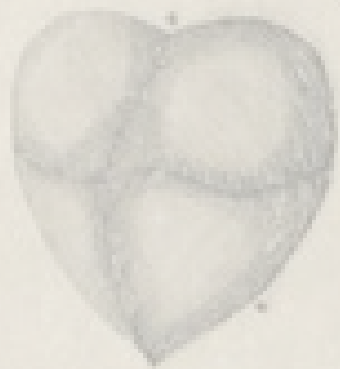
Part 3

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豎剖心視兩室

New imaging modality for percutaneous coronary intervention

全形



心障膜



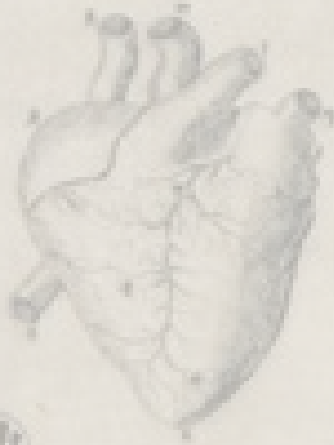


心篇圖

四脈管及心囊



斜心囊視冠脈



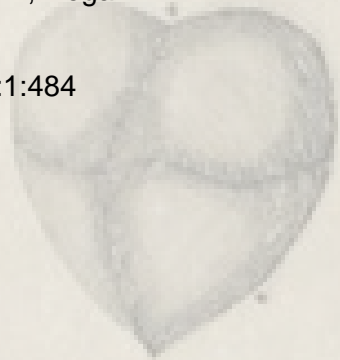
Chapter 15

**Paclitaxel-eluting stent restenosis shows three-layer appearance by optical coherence tomography.**

Tanimoto S, Aoki J, Serruys PW, Regar E.

EuroIntervention. 2006:1:484

全形

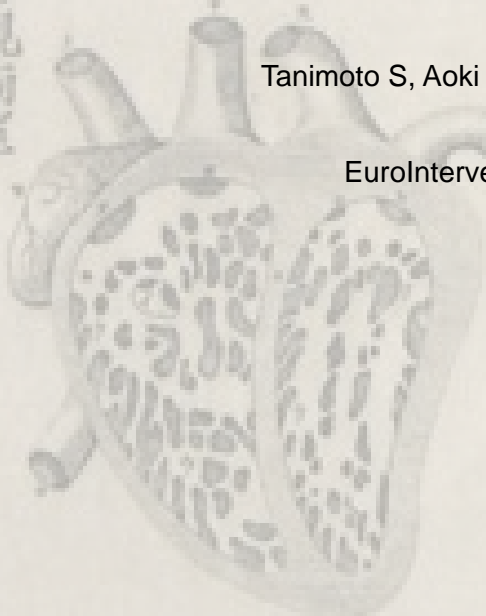


心障膜



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豎剖心視兩室







## Paclitaxel-eluting stent restenosis shows three-layer appearance by optical coherence tomography

Shuzou Tanimoto, MD; Jiro Aoki, MD; Patrick W. Serruys, MD, PhD; Evelyn Regar\*, MD, PhD

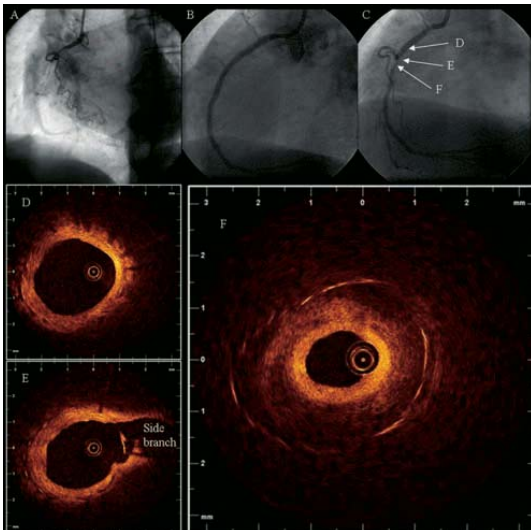
Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands.

All authors contributed to coronary angiography and OCT data acquisition. All authors also contributed to writing and reviewing this manuscript.

All authors have no conflict of interest.

A 73-year-old woman with hypertension, hyperlipidemia and positive familial history of coronary artery disease presented with Canadian Cardiovascular Society class III angina and underwent coronary angiography, which showed a chronic occluded right

coronary artery (Panel A). The vessel was recanalized and treated with three paclitaxel-eluting stents (TAXUS®, Boston Scientific: 3.5 x 32 mm distally, 3.5 x 28 mm in the middle part, 3.5 x 12 mm proximally). Postintervention coronary angiography showed a good result (Panel B). Twelve-month follow-up angiography revealed focal in-stent restenosis (Panel C). Intracoronary optical coherence tomography (OCT: LightLabImaging™, Boston, MA, USA) pullback displayed well-expanded stents covered with a thin, homogenous, highly reflective neointimal layer (Panel D, E). In contrast, the narrowest lesion site (minimal lumen area 1.1 mm<sup>2</sup>; stent area 9.0 mm<sup>2</sup>) showed a three-layer appearance of the neointima (Panel F). The inner luminal layer appeared concentric, homogeneous and signal-rich (maximal thickness 0.27 mm). A second layer consisting of a low-reflective area with poorly delineated borders followed. The third layer was in direct contact with the stent struts and revealed only minimal signal intensity. These signal-poor areas (maximal thickness 1.18 mm) might represent acellular fibrinoid deposition that has been well described in experimental studies. The patient was re-treated with repeat paclitaxel-eluting stent implantation. OCT is an analogue of intravascular ultrasound with an ultra-high resolution (10 μm) superior to any current available imaging modalities. This imaging device may be useful in visualizing neointimal growth in drug-eluting stents and improve our understanding of its underlying pathophysiology in the future.



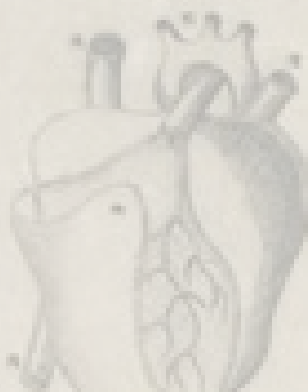
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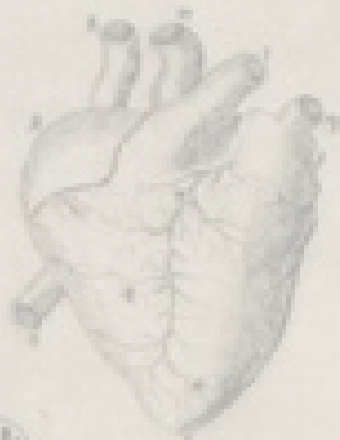


心管圖

四脈管及心囊



剖心囊視冠脈



Chapter 16

勃

豎剖心視冠室

**In vivo validation of a novel three-dimensional quantitative coronary angiography system (Cardiop-B™): comparison with a conventional two-dimensional system (CASS II™) and with special reference to optical coherence tomography.**

Tsuchida K, van der Giessen W, Patterson M, Tanimoto S, Garcia-Garcia H, Regar E, Ligthart JM, Maugeness AM, Maatrijk G, Wentzel JJ, Serruys PW.

EuroIntervention. 2007;3:100-108

心障膜





## ***In vivo* validation of a novel three-dimensional quantitative coronary angiography system (CardiOp-B™): comparison with a conventional two-dimensional system (CAAS II™) and with special reference to optical coherence tomography**

Keiichi Tsuchida, MD, PhD; Willem J. van der Giessen, MD, PhD; Mark Patterson, MRCP; Shuzou Tanimoto, MD; Héctor M. García-García, MD, MSc; Evelyn Regar, MD, PhD; Jurgen M. R. Ligthart, BSc; Anne-Marie Maugeness; Gio Maatrijk; Jolanda J. Wentzel, PhD; Patrick W. Serruys\*, MD, PhD, FACC, FESC

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The authors have no conflicts of interest to declare.

### KEYWORDS

Accuracy, *in vivo* validation, optical coherence tomography, quantitative coronary angiography, three-dimensional reconstruction

### Abstract

**Aims:** To validate a novel 3-D QCA system (CardiOp-B™) and compare the 2-D (CAAS II™) and 3-D systems in *in vivo* experimental settings. The phantom lumen diameters were also assessed *ex vivo* by optical coherence tomography (OCT). The accuracy of the 3-D system has not been appreciated.

**Methods and results:** Precision-drilled plexiglass phantoms with 5 different luminal diameters that ranged from 0.5 to 1.9 mm were percutaneously inserted into the coronary arteries in four Yorkshire pigs. Twenty-two angiographic images of the artificial phantom coronary artery stenoses in the pigs were acquired as an *in vivo* validation test. Quantitative assessments of the minimum and mean lumen diameters were performed using both QCA systems. *Ex vivo* images of the same phantom lumens were also taken and measured using OCT.

Both of the 2-D and 3-D QCA systems significantly underestimated the actual phantom lumen diameters with the exception of measurements taken in the lateral projection at isocenter using the 2-D QCA systems. This underestimation was more significant in the 3-D system (accuracy of 0.19 at isocenter; 0.23 by catheter calibration). There was good agreement between the two QCA systems. OCT measured the *ex vivo* lumen diameter of plexiglass phantoms precisely.

**Conclusions:** The accuracy of the luminal diameter measurements with the current 2-D system was still superior to the 3-D system. Further development and validation studies under various conditions are warranted. The excellent results achieved by OCT with the *ex vivo* images indicate its potential as an intravascular quantitative imaging tool for future clinical practice.

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## Introduction

The field of quantitative coronary angiography (QCA) has undergone substantial improvement since the first automated QCA developments took place 1980's<sup>1</sup>. Two major clinical applications have stimulated this improvement: 1) the on-line use during coronary intervention procedures in catheterisation laboratories; 2) the use as an angiographic endpoint for the assessment of stent or pharmacological treatments in experimental and clinical trials. On the other hand, the use of two-dimensional (2-D) interpretation of lesion or vessel anatomy and the lack of information about the vessel wall (other than for calcification) are well known limitations of current angiography and are situations where intravascular ultrasound (IVUS) can provide supplemental information. Development of online three-dimensional (3-D) vessel reconstruction systems based on angiography may be a solution to the former limitation. The concept of 3-D reconstruction of coronary tree was postulated as early as the 1980's<sup>2</sup>. The routine use of a 3-D quantitative angiography system in the catheterisation laboratory could be a major improvement in interventional cardiology.

Recently, a novel 3-D visualisation and quantitative analysis software system (CardiOp-B™, Paieon Medical Inc., Rosh Ha'ayin, Israel) has been introduced. This newly developed software system uses the detected vessel contours in two projections during coronary angiography to visualise a 3-D reconstruction of an arterial segment. Quantitative results are presented based on the reconstruction. Its utility and potential advantage over 2-D QCA systems has been reported<sup>3,4</sup>. However, to date there have been no studies determining the accuracy of the 3-D quantitative angiographic technique by the *in vivo* measurement of precisely known vessel lumens. Our group has implemented *in vivo* validation techniques using radiolucent cylindrical plexiglass or polyamide stenosis phantoms with precision-drilled eccentric lumens in the field of quantitative angiographic analysis<sup>5-7</sup>. The aim of this study was to validate a novel 3-D QCA system (CardiOp-B™) and compare the 2-D and 3-D systems in *in vivo* experimental settings that simulated a diagnostic coronary angiogram.

Aside from the primary objective, we also tested the accuracy of optical coherence tomography (OCT), a light-based imaging modality with a high resolution (10 µm), in the *ex vivo* measurement of lumen diameter using the same plexiglass phantoms. This additional examination was performed in order to investigate its potential as a quantitative intravascular imaging modality in the future.

## Methods

This study was conducted according to the guidelines of the American Heart Association on animal use in research and was approved by the ethics committee on animal experimentation of the Erasmus Medical Center.

### Plexiglas stenosis phantoms

The stenosis phantoms were manufactured at the workshop of the Erasmus Medical Center. The phantom stenoses that were used consist of radiolucent plexiglass (acrylate) and polyamide cylinders that have had precision-drilled circular lumens of 499 (aimed to be

0.5mm), 707 (0.7 mm), 982 (1.0 mm), 1,367 (1.4 mm) and 1,921 µm (1.9 mm) in diameter (Figure 1). The outer diameters of the cylinders are 3.0 or 3.5 mm; the mean lengths of phantoms are 8.28, 7.96, 7.85, 8.01, and 7.38 mm in 0.5, 0.7, 1.0, 1.4, 1.9 mm diameter phantoms, respectively. Optical calibration of the stenosis channels using 40 fold magnification gives a tolerance of 0.003 mm. A second 1.3 mm diameter lumen, parallel to the stenosis lumen, has been drilled in the cylinders to enable their attachment to the tip of 4 Fr Fogarty catheters (Vermed, Neuilly en Thelle, France). The lumens of the Fogarty catheters contained a removable metallic stylet that aided the intracoronary insertion of the phantoms as well as their positioning in the radiographic isocenter. Details of our experimental approach to QCA validation have been previously described<sup>5-7</sup>.

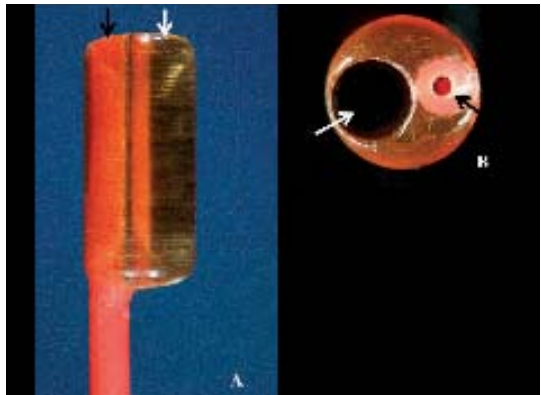


Figure 1. A: The magnified tip of one of the Fogarty catheters used for mounting the phantom. Note the transparent radiolucent cylinder connected to the tip of the catheter with a channel of 1.9 mm diameter (white arrow) and the catheter lumen used for insertion of removable metallic stylet (black arrow). B: The catheter tip photographed perpendicularly to the long axis of the phantom lumen. Note the almost perfect circular aspect of the precision-drilled lumen (diameter 1.9 mm, white arrow). The catheter lumen used for insertion of metallic stylet is indicated with a black arrow.

## Animal preparation

Four Yorkshire pigs (average weight, 40 to 45 kg) were pretreated with intramuscular ketamine (20 mg/kg) and intravenous etomidate (5 mg/kg). The animals were then intubated and ventilated with a mixture of oxygen and isoflurane. Anaesthesia was maintained with a continuous intravenous infusion of pentobarbital (5-20 mg/kg/hour). 12 Fr introducer sheaths were inserted into both carotid arteries to allow the sequential insertion of the guiding catheter and phantoms. Jugular access was used for the administration of medication and fluid. An intravenous bolus (10,000 IU/l) followed by a continuous infusion of heparin was given.

### *In vivo* image acquisition of stenosis phantoms by fluoroscopy

The digital angiograms were obtained with a biplane cine angiographic system (Axiom Artis™, Siemens, Forchheim, Germany) that employs a matrix size of 1,024 x 1,024 pixels. The radiographic sys-

tem settings used were the same (kVp, mA, ms) in all projections. All phantoms were imaged in two projections simultaneously. After engaging the 6 Fr guiding catheter (Mach 1™, Boston Scientific Corp., Natick, MA, USA) in either the left or right coronary artery, intracoronary isosorbide-dinitrate (1 mg) was administered. The first angiogram was then performed for orientation purposes. The phantoms were wedged in the coronary arteries and positioned in the X-ray isocenter using the tip of the metal wire as a marker. The wire was removed prior to angiography. Coronary angiography was performed by manual injection of contrast medium (Visipaque™ 320 mg I/ml, Amersham Health B.V., Eindhoven, The Netherlands). The ventilator was disconnected transiently during contrast injection to minimise the effect of diaphragmatic movement on angiographic images.

## Calibration

Two different calibration methods were used during off-line analysis. 1) Calibration at the isocenter: this method was performed using an automatic isocentric calibration - this is one of the calibration options of the biplane angiographic system. The calculated calibration factor is used for 2-D and 3-D QCA analyses by entering the number in millimetres in the manual calibration mode; 2) Conventional catheter calibration: the non-tapering part of the tip of each 6 Fr guiding catheter filled with contrast was used as a reference.

## Quantitative angiographic analysis of *ex vivo* and *in vivo* phantom images

The off-line measurement of the minimum lumen diameter (MLD) and the mean lumen diameter (mean LD) were performed by 2-D QCA (CAAS II™ version V2.0.1, Pie Medical Imaging, Maastricht, The Netherlands) as well as by 3-D QCA system (CardiOp-B™ version 1671017, Paieon Medical Inc.). For *in vivo* analysis, an end-diastolic cine frame was selected.

Manual edge correction is an option available in both systems, but this was intentionally never allowed in the present analyses. In the 2-D system, a restriction option was applied in order to correct for an unsatisfactorily detected contour in one image. This option is not technically a manual correction, but offers users the possibility of excluding parts of the image of the detection by restricting the area of interest. For the one measurement with the 3-D system, the automatically determined stenotic segment was manually corrected to avoid the measurement of the MLD at the site of a discrete intraluminal filling defect. Minimum values as well as mean values were determined as the diameters of the stenosis phantom lumens. Each angiographic image that was analysed or calibrated (for catheter calibration) was designated specifically by the number of the frame count so that all of the analyses using both QCA systems were performed upon identical images.

## 2-D QCA system

The diameter of the stenosis phantoms was calculated with an automatic contour detection technique. The user is able to define a number of centreline points within the vessel segment. The frontal and the lateral images are analysed separately. The mean LD of the

phantom lumen is obtained with the CAAS II™ system from a user-defined region of interest (ROI) where the two vessel contours are considered to be parallel (Figure 2).

## 3-D QCA system

This system uses the contours detected in the frontal and lateral images in combination with the projection data in the DICOM format into a 3-D reconstruction of an arterial segment. The two acquired images that are used for reconstruction must differ by an angle of at least 30 degrees. In this study, two orthogonal views, simultaneously acquired by the biplane system, were used for reconstructing a 3-D vessel image. If calibration was performed in one view, further calibration was not requested in the second corresponding view. To perform quantitative analysis, the user is requested to mark three points: proximal and distal reference points and point within the

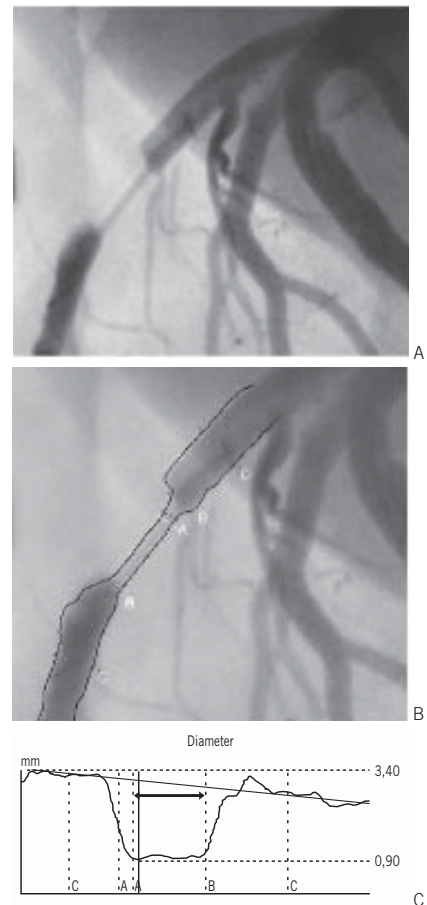


Figure 2. Angiographic visualisation of the artificial coronary obstruction produced by a 1.0 mm stenosis phantom in the left anterior descending artery (A) with subsequent quantitative measurement of luminal diameter by 2-D QCA system (CAAS II™) (B, C). The bidirectional arrow indicates the region of interest for mean luminal diameter (C).

stenosis. The severity of the stenosis is indicated by the colour given by the computer to the reconstructed segment that varies from white (healthy vessel) to dark red (99% cross-sectional area stenosis) (Figure 3). The minimum luminal diameter values are automatically given as one of the default quantitative data. As mean LD within the user-defined ROI is not automatically supplied in this system, we obtained the values using a text import wizard of MS Excel 2003. The current version of 3-D QCA system does not provide quantitative degree of vessel curvature and bifurcation angle between main and side branch.

### Ex vivo image acquisition of stenosis phantoms by OCT

We prepared a fluid mixture containing 90% degassed water and 10% ethanol as an *ex vivo* replacement for blood. The room temperature was kept at 22 °C. These conditions are similar to those required for the preparation for an *ex vivo* validation of intravascular ultrasound<sup>8,9</sup>. The OCT wire was inserted into the five differently sized phantom lumens. Images were obtained with the M2 OCT imaging system (Lightlab Imaging, inc.). The M2 OCT system uses a 1,310-nm broadband light source to produce images with an axial resolution of 15 µm and a lateral resolution of 25 µm by the principle of interferometry. The M2 uses the ImageWire™ imaging probe to deliver light to the tissue and collect the returning signals. The ImageWire™ consists of 0.006-inch (0.15 mm) fiberoptic core, inside a sheath with a maximum o.d. of 0.019 inch (0.48 mm).

### OCT image analysis

The images were stored for off-line analysis in the OCT system computer. The analysis was performed using proprietary software from Lightlab Imaging, Inc. with a mouse based interface. The system was calibrated to the reflection of the OCT imaging wire that is the standard calibration technique for this system. Lumen diameter and lumen area in each of the 5 phantoms were measured.

### Intra- and inter-observer variability assessment

Two independent observers, who were blinded to the real phantom diameters, assessed reproducibility by measuring the minimum and mean luminal diameter using each of the two QCA systems. In the *ex vivo* cases imaged by OCT, only the cross sectional diameter was analysed and used for evaluation of reproducibility. These examinations by two observers were performed on different days. One of the two observers performed second measurements on different days for assessment of individual reproducibility.

### Statistical analysis

The individual values for minimum and mean luminal diameter obtained by both QCA systems were compared with the corresponding values of the phantom by paired t test (two-tailed). Additionally, the data were plotted against the actual phantom diameter values and a linear regression analysis was applied. The mean differences between measured luminal diameters and the corresponding phantom dimensions

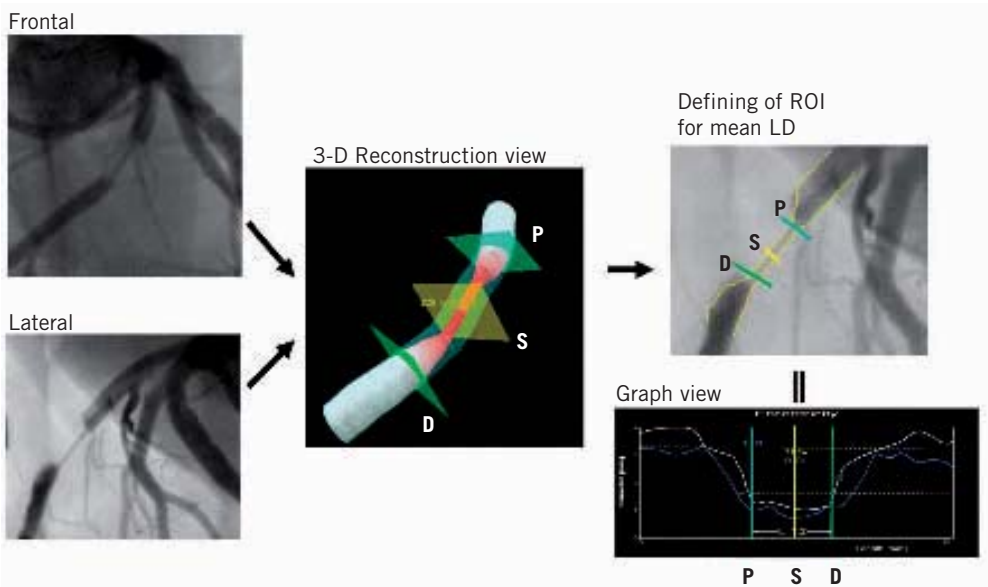


Figure 3. Illustration of the 3-D reconstruction process by CardiOp-BTM. Color-coded 3-D reconstruction of coronary artery with artificial stenotic segment (3-D Reconstruction view) is derived from 2 orthogonal views (Frontal and Lateral). The 3-D colour varies according to the severity of stenosis ranging from white (healthy vessel) to dark red (99% cross-sectional area stenosis). The squares in pale blue, yellow and green denote proximal reference point (P), most stenotic point (S) and distal reference point (D) of the target lesion, respectively. The region of interest (ROI) for calculation of mean luminal diameter can be manually defined by moving the proximal (P) and distal (D) points (Definition of ROI for mean LD; Graph view).



were computed and considered to be an index of the accuracy of the measurements, while the standard deviation of the differences was defined as an index of precision. The relative standard deviation was calculated (precision / mean of measured diameter value x 100) to assess the degree to which the sets of diameter data points varied. In order to determine the agreement between 2-D and 3-D QCA systems, Bland-Altman analysis was performed<sup>10</sup>. Statistical analyses were performed with SPSS 12.0.1 for Windows (SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered statistically significant.

**Results**

Thirty coronary angiographic images were acquired after intracoronary insertion of the stenosis phantoms. Three images were excluded from the QCA analysis because of extreme foreshortening of the stenosis segment in frontal views. Five images that had insufficient arterial filling using the 0.5 or 0.7 mm phantoms were also excluded. The remaining 22 images were used for the diameter measurements using both QCA systems.

In vivo intra- and inter-observer variability of the 2 QCA systems and ex vivo OCT was calculated in all the 22 analysable images (Table 1). Satisfactory reproducibility was noted in all of the two QCA systems and OCT.

**In vivo assessment of luminal diameter by 2-D and 3-D QCA**

The comparative results of the actual phantom lumen diameter and the dimensional values derived from both QCA systems are shown in Table 2 along with Figures 4 and 5. In both systems, accuracy was better with isocentric calibration compared to catheter calibration. Mean luminal diameter measurements yielded better accuracy

than minimum values in any of the dimensional measurements. Among the 8 methods of diameter measurements in the 2-D QCA, mean luminal diameter by isocentric calibration in lateral view proved to have the best accuracy (0.01 mm). Both systems significantly underestimated the actual phantom diameter values, except for minimum and mean diameters in the lateral view with isocentric calibration. There was again good correlation between luminal diameter measurements and phantom actual diameter values with both QCA systems (r=0.961 ~ 0.987). However, the 2-D QCA system demonstrated better values of accuracy than the 3-D system in diameter measurements regardless of the calibration option.

**Agreement between 2-D and 3-D QCA systems**

A direct comparison between the 2-D (frontal views) and the 3-D QCA systems is shown in Figure 6. The two systems demonstrate good correlations in diameter measurements (r=0.947 isocenter, minimum; r=0.982, isocenter, mean; r=0.940, catheter, minimum; r=0.976, catheter, mean). The plot of differences between both systems demonstrates satisfactory agreement over the entire range of phantom sizes. This proved to be true for calibration at the isocenter as well as for catheter calibration (Figure 6).

**Ex vivo assessment of luminal diameter by OCT**

Figure 7A depicts the linear regression analysis of comparison between actual phantom luminal diameter versus ex vivo diameter values derived from OCT. OCT-based dimensional values proved to correlate extremely well with the real luminal diameter (accuracy=-0.03, precision=0.02, relative standard deviation=1.8%, r=1.000, intercept=0.01, slope=1.02). OCT clearly visualised the circular lumen of plexiglass phantom (Figure 7B).

**Table 1. Intra- and inter-observer variability of lumen diameter.**

	Intra-observer				Inter-observer			
	Diff.	r	Intercept	Slope	Diff.	r	Intercept	Slope
<i>Ex vivo analysis</i>								
OCT lumen diameter	0.03±0.02	1.000	-0.01	0.99	0.00±0.05	0.996	0.04	0.97
<i>In vivo analysis</i>								
2-D QCA system								
Isocentric								
Frontal MLD	-0.01±0.03	0.997	-0.01	1.01	0.02±0.11	0.969	-0.02	1.00
Lateral MLD	0.00±0.03	0.998	0.00	1.00	0.06±0.09	0.985	0.03	0.92
Frontal mean LD	-0.01±0.03	0.998	-0.02	1.01	0.02±0.08	0.982	-0.02	1.00
Lateral mean LD	0.01±0.05	0.993	0.02	1.00	0.06±0.08	0.986	0.03	0.93
Catheter								
Frontal MLD	-0.01±0.06	0.991	0.05	0.94	0.00±0.10	0.972	0.01	0.99
Lateral MLD	0.02±0.05	0.993	0.00	1.02	-0.03±0.09	0.983	0.01	1.02
Frontal mean LD	-0.01±0.08	0.981	0.06	0.93	0.00±0.07	0.984	0.00	1.00
Lateral mean LD	0.00±0.05	0.991	0.04	0.97	-0.02±0.07	0.989	0.00	1.02
3-D QCA system								
Isocentric								
MLD	0.01±0.03	0.997	0.01	1.00	0.01±0.09	0.973	0.06	0.95
Mean LD	0.00±0.03	0.997	-0.04	0.97	0.03±0.06	0.988	0.11	0.93
Catheter								
MLD	0.00±0.06	0.986	-0.02	1.03	0.01±0.08	0.973	0.09	0.92
Mean LD	-0.01±0.05	0.994	-0.05	1.04	0.03±0.09	0.972	0.11	0.92

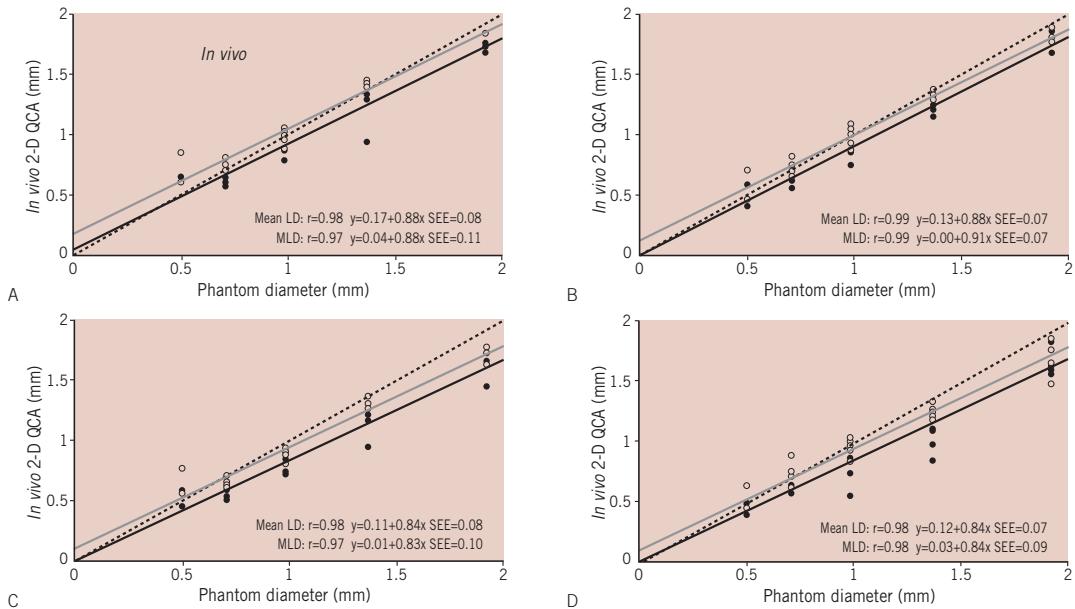
LD = luminal diameter; MLD = minimum luminal diameter; OCT = optical coherence tomography; QCA = quantitative coronary angiography

**Table 2. Summary of *in vivo* validation results of 2-D and 3-D QCA systems (Cardiop-B™) (22 observations)**

	Measured diameter (mm)	Accuracy	Precision	Relative SD* (%)	Correlation	SEE	Intercept	Slope	p-value of paired t test
<b>2-D QCA</b>									
<b>Isocentric</b>									
Frontal MLD	1.07	0.10	0.12	11.1	0.968	0.11	0.04	0.88	0.001
Lateral MLD	1.06	0.10	0.08	7.9	0.985	0.07	0.00	0.91	< 0.0001
Frontal mean LD	1.19	-0.03	0.09	7.9	0.983	0.08	0.17	0.88	0.17
Lateral mean LD	1.15	0.01	0.09	7.6	0.987	0.07	0.13	0.88	0.43
<b>Catheter</b>									
Frontal MLD	0.98	0.18	0.12	12.4	0.971	0.10	0.01	0.83	< 0.0001
Lateral MLD	1.01	0.16	0.11	11.2	0.977	0.09	0.03	0.84	< 0.0001
Frontal mean LD	1.09	0.07	0.11	9.9	0.980	0.08	0.11	0.84	0.005
Lateral mean LD	1.10	0.06	0.10	9.2	0.984	0.07	0.12	0.84	0.009
<b>3-D QCA</b>									
<b>Isocentric</b>									
MLD	0.98	0.19	0.13	13.7	0.966	0.10	0.04	0.80	< 0.0001
Mean LD	1.04	0.13	0.10	9.4	0.985	0.07	0.05	0.85	< 0.0001
<b>Catheter</b>									
MLD	0.93	0.23	0.14	15.2	0.970	0.09	0.05	0.76	< 0.0001
Mean LD	0.99	0.18	0.13	11.4	0.984	0.07	0.05	0.80	< 0.0001

\* (precision/mean of measured diameter value) x 100

LD = luminal diameter; MLD = minimum luminal diameter; OCT, QCA = quantitative coronary angiography; SD = standard deviation



**Figure 4. Two-dimensional QCA assessment of minimum (continuous black lines) and mean luminal diameter (continuous grey lines) with calibration at the isocenter in frontal (A) and lateral views (B) and with catheter calibration in frontal (C) and lateral views (D). The dashed lines indicate the line of identity.**

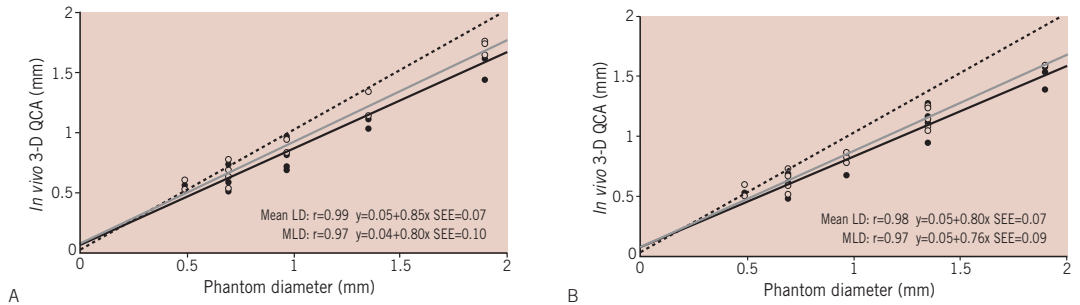


Figure 5. Three-dimensional QCA assessment of minimum (continuous black lines) and mean luminal diameter (continuous grey lines) with calibration at the isocenter (A) and with catheter calibration (B). The dashed lines indicate the line of identity.

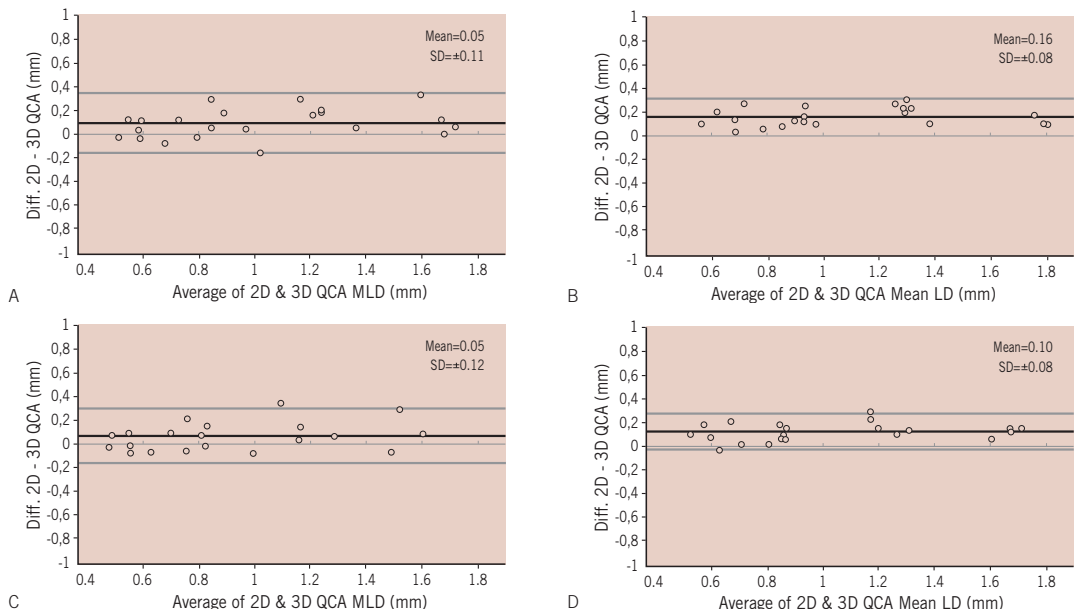


Figure 6. Bland-Altman plots of the differences between the minimum and mean luminal diameter measurements acquired by the 2 systems versus means of the measurements. A: minimum diameter with calibration at the isocenter. B: mean diameter with calibration at the isocenter. C: minimum diameter with catheter calibration. D: mean diameter with catheter calibration. The data from the frontal view are used as 2-D QCA measurements.

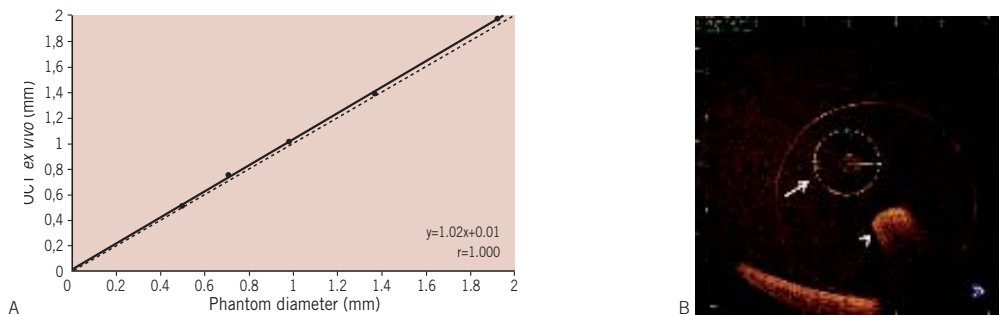


Figure 7. A: Linear regression analysis of the phantom lumen diameter versus the cross-sectional luminal diameter measured with OCT. B: Representative OCT images of the stenosis phantom with 1.4-mm lumen. Arrow: 1.4-mm lumen for measurement; arrow head: lumen for guidewire.

## Discussion

The results of the present study indicate the following three findings: 1) the 3-D QCA system significantly underestimated actual phantom diameter values compared to the 2-D system; 2) the 3-D QCA system showed a good agreement with the 2-D QCA system; 3) the values of the *ex vivo* diameter measurements by OCT were almost identical to the actual phantom diameter values.

As the number of coronary interventions has increased over the years, the complexity of target lesions has increased concomitantly. Development of a 3-D visualisation and quantitative analysis system has been encouraged by the increasing need to better understand the true vessel structure and the spatial orientation of complex features and to quantify vessel morphology more precisely. There is a growing interest in applying this new technology as an additional imaging tool in interventional cardiology. Recently, the feasibility and potential superiority of 3-D QCA system in the measurement of 38 coronary lesions was reported by comparing it with a 2-D QCA system (Medview™, Medcon Telemedicine Technology, Tel Aviv, Israel)<sup>3</sup>. However, this 3-D QCA system should be evaluated in comparison with the largely validated conventional 2-D QCA systems<sup>5,7,11,12</sup>. Moreover, the accuracy or limitations of this system can only be appreciated by measuring *in vivo* vessels of known lumen dimensions. This is especially important since the accuracy of the reconstruction is not only the basis for quantitative results but also for producing a correctly visualised image. In theory the 3-D quantitative analysis should fully correct for foreshortening and out-of-plane magnification differences. Systematic underestimation of luminal diameter measurements was noted for both QCA systems and this was more significant in the 3-D system. The image acquisition was performed by hand injection of contrast and this may result in less radiographic opacity of stenotic segment compared to mechanical injection. Consequently automated detection of vessel boundaries might have been affected leading to smaller diameter values than expected having been derived. However, even with mechanical contrast injection, the angiographic examination of these high-grade stenosis phantoms cannot always be satisfactory because of possible intraluminal thrombus that results from the reduced blood flow or from the presence of intraluminal cellular debris collected during the insertion of the phantoms.

The values of the both QCA systems with catheter calibration were smaller than those obtained with calibration at isocenter. This might be explained by an out-of-plane magnification phenomenon: a greater distance between the image intensifier and the catheter tip than between the image intensifier and the isocenter that would result in a smaller calibration factor<sup>13,14</sup>. In the 2-D QCA system, lateral views showed better accuracy and precision than frontal views. Foreshortened images were more frequently observed in frontal views than in lateral views. Accordingly, suboptimal contour detection of frontal images might have occurred. Although theoretically the 3-D reconstruction should enable the correction of foreshortening and out-of-plane magnification errors, these improvements could not be identified in the present analysis.

OCT is a novel imaging modality that provides intravascular images that have a resolution of approximately 10–20 µm. This 10-fold greater resolution in comparison with IVUS enables visualisation

of microscopic structures within the coronary arteries<sup>15,16</sup>. *In vivo* dimensional and volumetric measurements of implanted coronary stents have shown that OCT can produce accurate results that are comparable to IVUS<sup>17</sup>. Post-mortem analysis suggested that OCT can measure the intima-media thickness more accurately than IVUS<sup>18</sup>. Currently OCT is regarded as a modality that may surpass the performance of angiography or IVUS after stent implantation<sup>19,20</sup>. The present study provided *ex vivo* validation of OCT with respect to diameter measurements. Unfortunately, we could not compare OCT to IVUS because the IVUS catheter could not cross phantom lumens smaller than 1.0 mm. Furthermore *in vivo* examination would most likely prove difficult in these high-grade stenoses as the presence of a wire itself might result in the rapid development of intolerable ischaemic changes for the animals even before the induction of further ischaemia by the OCT occlusion balloon.

## Limitations

This validation test using concentric cylindrical phantoms was originally designed to test 2-D QCA systems<sup>5,7,11,12</sup>. The use of phantoms with a regular circular lumen does not allow the assessment of asymmetry. Here the use of reconstruction from two projections included in one 3-D result supplies information of lesion asymmetry more precisely than that available from 2-D analysis. Since the precise and validated eccentric phantoms were not readily available, we decided to conduct the present study with previously established approach using concentric phantoms<sup>5,7,11,12</sup>. The 3-D reconstruction is based on a two imaged diameters that results in an oval cross section where the 2-D analysis is based on one image results in a single diameter to be used for a circular cross section. However, densitometric analysis available in the 2-D QCA system can provide estimates for cross sectional areas in complex lesions<sup>21,22</sup>. Our results were based on a series of small-size (< 2 mm) lumen phantoms. From a clinical point of view, validation tests using larger-size (> 2.25 ~ 2.5 mm) phantoms might be more relevant to investigate whether this 3D system is useful as a tool to determine the optimal device size, or to confirm the acute post-procedural results during the interventional procedures.

## Conclusions

The minimum and mean luminal diameter measured with the 3-D QCA system underestimated the true phantom lumen diameter more than 2-D QCA. However, since there was a strong correlation with the 2-D QCA system, this system could be a useful alternative in clinical practice. OCT precisely measured the lumen diameter of plexiglass phantoms in this *ex vivo* experimental setting. In addition to its usefulness in the quantitative assessment of coronary plaque, this imaging tool could be developed further as a reliable device for intravascular quantitative assessment with the advancement of less invasive preparation for the image acquisition.

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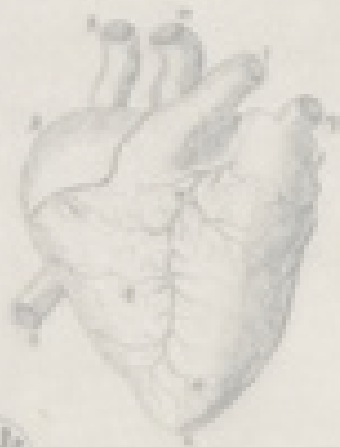


心管圖

四脈管及心囊



剖心囊視冠脈



Chapter 17

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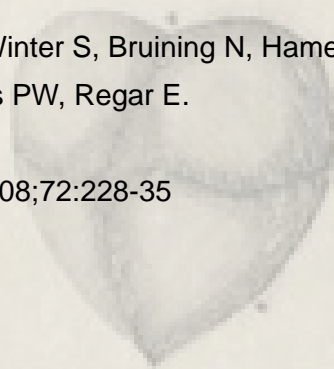
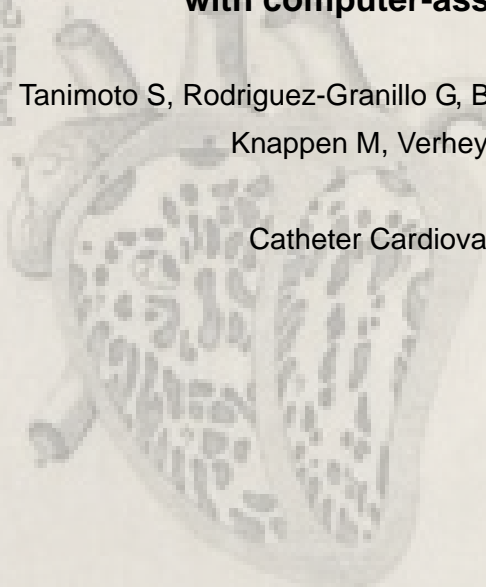
豎剖心視兩室

**A novel approach for quantitative analysis of intracoronary optical coherence tomography: high inter-observer agreement with computer-assisted contour detection.**

Tanimoto S, Rodriguez-Granillo G, Barlis P, de Winter S, Bruining N, Hamers R, Knappen M, Verheye S, Serruys PW, Regar E.

Catheter Cardiovasc Interv. 2008;72:228-35

上形



心障膜







# A Novel Approach for Quantitative Analysis of Intracoronary Optical Coherence Tomography: High Inter-Observer Agreement With Computer-Assisted Contour Detection

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**Objective:** This study aims to examine observer-related variability of quantitative optical coherence tomography (OCT) derived measurements from both in vitro and in vivo pullback data. **Background:** Intravascular OCT is a new imaging modality using infrared light and offering 10 times higher image resolution (15  $\mu\text{m}$ ) compared to intravascular ultrasound. The quantitative analysis of in vivo intracoronary OCT imaging is complicated by the presence of blood, motion artifacts and the large quantity of information that has to be processed. **Methods:** We developed a standardized, automated quantification process for intracoronary OCT pullback data with inter-observer variability assessed both in vitro by using postmortem human coronary arteries and in vivo by studying simple and complex coronary pathology and outcomes following stent implantation. The consensus between measurements by two observers was analyzed using the intraclass and interclass correlation coefficient and the reliability coefficients. Bland-Altman plots were generated to assess the relationship between variability and absolute measurements. **Results:** In vitro OCT assessment was performed in nine postmortem coronary arteries. The time needed for semiautomated contour detection of a 15-mm long coronary segment was  $\sim 40$  min. The absolute and relative difference between lumen area measurements derived from two observers was low [ $0.02 \pm 0.10 \text{ mm}^2$ ; ( $0.3 \pm 0.5\%$ ) respectively] with excellent correlation confirmed by linear regression analysis ( $R^2 = 0.99$ ;  $P < 0.001$ ). Similarly, in vivo measurements demonstrated a high correlation with the main source of inter-observer variation occurring as a result of coronary dissection and motion artifact. The absolute and relative difference between measurements were  $0.11 \pm 0.33 \text{ mm}^2$  ( $1.57 \pm 0.05\%$ ) for lumen area ( $R^2 = 0.98$ ;  $P < 0.001$ ),  $0.17 \pm 0.68 \text{ mm}^2$  ( $1.44 \pm 0.08\%$ ) for stent area ( $R^2 = 0.94$ ;  $P < 0.001$ ), and  $0.26 \pm 0.72 \text{ mm}^2$  ( $14.08 \pm 0.37\%$ ) for neointimal area ( $R^2 = 0.78$ ;  $P < 0.001$ ). **Conclusions:** Highly accurate computer-assisted quantitative analysis of intracoronary OCT pullbacks is feasible with low inter-observer variability. The presented approach allows for observer independent analysis of detailed vessel structures, and may be a valuable tool for future longitudinal studies incorporating OCT. © 2008 Wiley-Liss, Inc.

**Key words:** optical coherence tomography; coronary artery disease; image processing

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Conflicts of interest: Ronald Hamers is an employee of CURAD BV, the Netherlands.

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## INTRODUCTION

Optical coherence tomography (OCT) is a light-based imaging modality that can be used to study biological tissues in vivo [1]. Recently, the concept of catheter-based intracoronary OCT has been introduced [2–4] allowing in vivo imaging of the coronary vessel wall with a lateral resolution of 15  $\mu\text{m}$  and an axial resolution of 25  $\mu\text{m}$  [5]. The currently accepted gold standard, intravascular ultrasound (IVUS), operates at a lateral resolution of  $\sim 120$   $\mu\text{m}$  and axial resolution of 80  $\mu\text{m}$ . The unique high-resolution OCT imaging modality permits the analysis of coronary structures in greater detail. The measurement accuracy of intracoronary OCT has been established in postmortem human coronary arteries and showed good correlation to histomorphometry [6]. However, compared to ex vivo imaging, quantitative analysis of in vivo intracoronary imaging is more complicated due to the presence of blood and motion artifacts during cardiac cycle. Furthermore, the OCT dataset acquired during motorized pullback in vivo is much larger than local imaging of selected cross sections as performed in postmortem studies. A pullback through the region of interest (ROI) is necessary in order to visualize the three-dimensional morphology of the coronary artery. The present research proposes a standardized automated quantification process for intracoronary OCT pullback data. To test its accuracy, inter-observer variability was assessed in vitro and in vivo including both simple and complex vessel anatomy, represented by native coronary arteries before and after stent implantation.

## METHODS

### OCT Imaging System

We used a commercially available system for intravascular OCT imaging (LightLab Imaging, Westford, MA). The light source was a 1310-nm broadband super luminescent diode with an output power in the range of 8.0 mW. The imaging depth was  $\sim 1.5$  mm with an axial and lateral resolution of 15 and 25  $\mu\text{m}$ , respectively. The imaging probe (ImageWire<sup>TM</sup> LightLab Imaging) had a maximum outer diameter of 0.019 in. and contained a single-mode fiber optic core within a translucent sheath. The image wire was connected at its proximal end to the imaging console that permitted real-time data processing and two-dimensional representation of the backscattered light in a cross-sectional plane. Images were acquired at 15 frames/sec. The fiber optic core was withdrawn within the catheter sheath using automated pullback at 1.0 mm/sec.

The accuracy of the OCT system has been recently reported. Diameters of phantoms with precision-drilled

circular holes were measured in vitro using proprietary software from LightLab with excellent accuracy ( $-0.03$ ) and precision (0.02) [7].

### Human Coronary Arteries—Postmortem Study

In all cases ( $n = 9$ ), the left anterior descending artery was studied after pressure fixation using 10% buffered formalin. The take off of the first diagonal branch was used as proximal landmark. Both the proximal and the distal end of the coronary specimen were sutured to a 6F introducer sheath and positioned in a saline bath at 37°C. The OCT imaging wire was introduced via the proximal sheath into the specimen and positioned in such a way that the distal OCT catheter tip was fixed in the distal sheath and an automated OCT pullback was performed.

### Human Coronary Arteries—Clinical Studies

Patients undergoing a stent-implantation procedure ( $n = 10$ ) or a 6-month follow-up angiogram poststent implantation ( $n = 10$ ) were studied. A standard femoral approach with 7F guiding catheters was used. All patients received weight-adjusted intravenous heparin in order to maintain the activated clotting time  $>300$  sec and intravenous analgesics before imaging. First, a dedicated compliant occlusion catheter (Helios, Goodman, Japan) was introduced into the artery and positioned proximally to the ROI. The occlusion catheter allows (a) for limiting the coronary blood flow by very low-pressure (0.3 atm) inflation of a short (6.0 mm length) balloon, (b) for simultaneous clearing of the artery by delivering flush distally to the balloon into the lumen, and (c) for introduction of the OCT imaging wire into the artery. After positioning the occlusion catheter in over the wire technique, the standard 0.014" guide wire was withdrawn, and the OCT imaging wire introduced via the central lumen distal into the target vessel. An automated OCT pullback was then performed. During OCT image acquisition, the artery was cleared with lactated Ringer's solution (flow rate 0.5 ml/sec; temperature 37°C). Sufficient occlusion of the lumen was documented by contrast injection via the guiding catheter and the balloon pressure increased to 0.5 atm if necessary.

### Quantitative OCT

The digitized tomographic OCT image dataset was transformed from digital movie file format (AVI) into the medical DICOM image standard and stored onto a picture archiving system. Quantitative OCT (QOCT) analysis was performed using dedicated software (CURAD vessel analysis, CURAD BV, Wijk bij Duurstede, Netherlands) [8] (Fig. 1). Every third frame of the pullback of long segments was entered. This

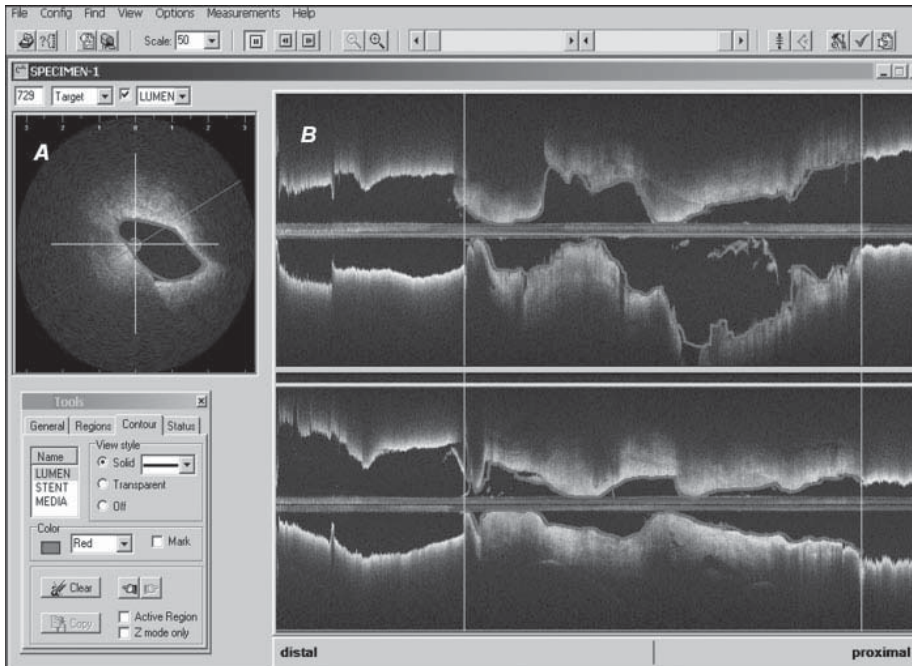


Fig. 1. Example of quantitative OCT analysis in an ex vivo coronary artery. The digitized tomographic OCT image dataset was transformed from digital movie file format (AVI) into the medical DICOM image standard and stored onto a picture archiving system. The dedicated software (CURAD) allows for

simultaneous display of a cross sectional view (A) and two longitudinal cut planes (B). After a selection of a region of interest, the lumen contours are traced using automated contour detection whereby both the cross sectional and the longitudinal image information is exploited.

reduced the number of frames in the Curad software from  $n$  to at most  $(n/2) + 1$  per set. Two blinded observers experienced in the theory and practice of OCT performed the analysis. In nonstented arteries, the lumen area was directly traced and the mean lumen diameter calculated using a circular model. In stented arteries, lumen- and stent-area were both directly traced, the mean lumen- and mean stent-diameter were calculated. Neointimal area was calculated as stent area minus lumen area.

OCT cross sections with a major side branch (diameter  $>2$  mm; or side branch take off occupying more than 60 degrees of the lumen circumference of the parent vessel) were excluded from analysis as well as cross sections, in which the complete lumen circumference of 360 degrees could not be visualized due to motion artifacts during the cardiac cycle.

### Statistical Analysis

Statistical analyses were performed using SPSS 12.0.1 for Windows (SPSS, Chicago, IL). Data are expressed as mean  $\pm$  SD or median and inter-quartile

range, if appropriate. Inter-observer agreement was determined by comparing measurements of each observer (observer 1 vs. observer 2) using the Bland-Altman method [9]. Data are given as plots showing the absolute difference between corresponding measurements of both observers (y-axis) against the average of both observers (x-axis). The relative difference between measurements (absolute difference divided by the average) gives the bias; its standard deviation gives the random variation. The limits of agreement were calculated as mean bias  $\pm$  2 SD. Confidence intervals (95%) were calculated. In addition, absolute data were analyzed for correlation by regression analysis as necessary, but not sufficient, condition for agreement. The regression line was forced through the origin. A  $P$ -value less than 0.05 (two-tailed students  $t$ -test) was considered statistically significant.

## RESULTS

### In Vitro Coronary Arteries

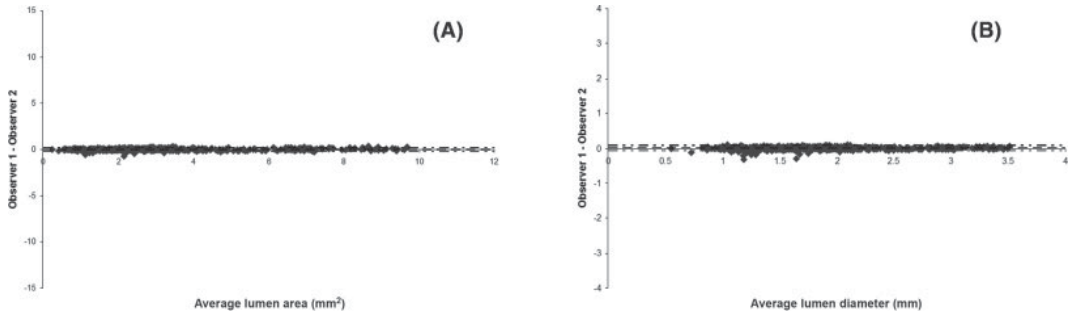
OCT imaging was successfully performed in all specimens ( $n = 9$ ). Computer-assisted contour detection

**TABLE I. Comparison of Lumen Measurements in Ex-Vivo Coronary Arteries,  $n = 772$  Frames**

	Lumen area	Lumen diameter
Observer 1		
Median (IQR)	2.48 (1.81) mm <sup>2</sup>	1.78 (0.64) mm
Mean $\pm$ 1 SD	3.03 $\pm$ 1.95 mm <sup>2</sup>	1.88 $\pm$ 0.58 mm
Observer 2		
Median (IQR)	2.49 (1.75) mm <sup>2</sup>	1.78 (0.62) mm
Mean $\pm$ 1SD	3.02 $\pm$ 1.93 mm <sup>2</sup>	1.87 $\pm$ 0.58 mm
Absolute difference	0.02 $\pm$ 0.10 mm <sup>2</sup>	0.00 $\pm$ 0.04 mm
Relative difference	(0.3 $\pm$ 0.5)%	(0.1 $\pm$ 0.2)%
Linear regression		
Slope	0.9904x	0.9905x
Intercept	0.0125	0.0135
R <sup>2</sup>	0.9974	0.9957
P	<0.001	<0.001

**TABLE II. Comparison of Measurements in In-Vivo Coronary Arteries,  $n = 1,807$  Frames**

	Lumen area	Lumen diameter
Observer 1		
Median (IQR)	4.34 (2.21) mm <sup>2</sup>	2.35 (0.6) mm
Mean $\pm$ 1 SD	4.29 $\pm$ 1.37 mm <sup>2</sup>	2.30 $\pm$ 0.40 mm
Observer 2		
Median (IQR)	4.36 (2.19) mm <sup>2</sup>	2.36 (0.59) mm
Mean $\pm$ 1SD	4.25 $\pm$ 1.34 mm <sup>2</sup>	2.30 $\pm$ 0.39 mm
Absolute difference	0.04 $\pm$ 0.14 mm <sup>2</sup>	0.01 $\pm$ 0.04 mm
Relative difference	(0.6 $\pm$ 0.4)%	(0.3 $\pm$ 0.2)%
Linear regression		
Slope	0.9755	0.9731
Intercept	0.0647	0.0523
R <sup>2</sup>	0.9904	0.9894
P	<0.001	<0.001



**Fig. 2. Bland-Altman plots for measurements in ex vivo coronary arteries. The x-axis shows the mean cross sectional area, and the y-axis shows the difference between the cross sectional measurements by observer 1 and observer 2. The dotted lines indicate the limits of agreement (bias  $\pm$  2 SD). (A) Lumen area (B) Lumen diameter.**

was possible in all pullbacks. In each coronary artery, a ROI of 15 mm in length was selected for analysis. The time needed for computer-assisted contour detection of a 15-mm long coronary segment was  $\sim$ 40 min. Data for lumen dimensions by both observers are given in Table I. The absolute difference in lumen area between the observers was low ( $0.02 \pm 0.10$  mm<sup>2</sup>). Linear regression analysis confirmed these observations and showed excellent correlation between measurements ( $R^2 = 0.99$ ). Bland-Altman plots for lumen area and lumen diameter are shown in Fig. 2.

### In Vivo Native Coronary Arteries

OCT imaging could be successfully performed without complications in all patients. The majority of patients (90%) developed transient ECG changes indicative of ischemia during imaging.

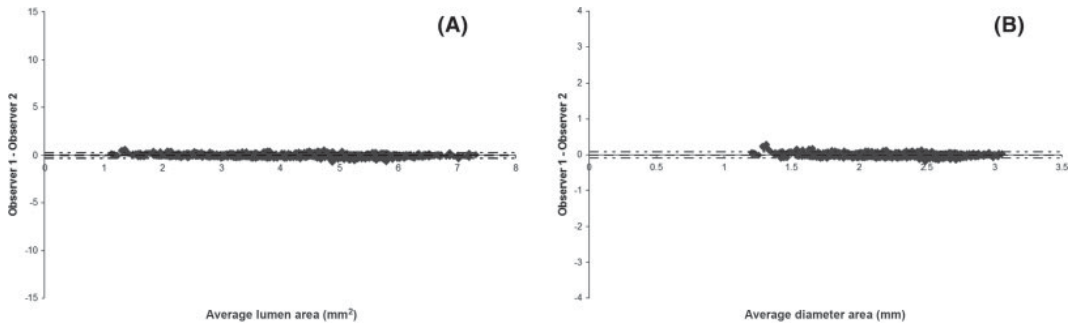
Ten coronary segments of  $28 \pm 9$  mm lengths were studied. A total of 1,807 frames were included in the analysis and 399 frames were excluded due to the presence of a major side branch, or due to incomplete

visualization of the lumen circumference due to motion artifacts.

OCT data are summarized in Table II. The absolute difference between observers was low (lumen area  $0.04 \pm 0.14$  mm<sup>2</sup>) and in the same order of magnitude as for in vitro measurements. Linear regression analysis confirmed these observations and showed high correlation between measurements ( $R^2 = 0.99$ ). Bland-Altman plots for lumen area and lumen diameter are shown in Fig. 3. The bias between the observers was again very low. Main sources of disagreement between observers were situations, in which lumen borders were ambiguous due to anatomical factors (e.g., dissections) or due to motion artifacts during the cardiac cycle.

### In Vivo Stented Coronary Arteries at Follow-Up

Ten coronary segments of  $25 \pm 11$  mm lengths were studied. Stent struts covered by neointimal tissue were clearly visible in all segments and in all cross sections. Inter-observer agreement on the presence of



**Fig. 3. Bland–Altman plots for measurements in in vivo coronary arteries. The x-axis shows the mean cross sectional area, and the y-axis shows the difference between the cross sectional measurements by observer 1 and observer 2. The dotted lines indicate the limits of agreement (bias  $\pm$  2 SD). (A) Lumen area (B) Lumen diameter.**

**TABLE III. Comparison of Measurements in In-Vivo Stented Coronary Arteries,  $n = 2,331$  Frames**

	Lumen area	Lumen diameter	Stent area	Stent diameter	Neointima area
Observer 1					
Median (IQR)	6.1 (3.45) mm <sup>2</sup>	2.79 (0.815) mm	9.28 (4.055) mm <sup>2</sup>	3.44 (0.77) mm	2.96 (2.105) mm <sup>2</sup>
Mean $\pm$ 1 SD	5.97 $\pm$ 2.41 mm <sup>2</sup>	2.69 $\pm$ 0.58 mm	9.02 $\pm$ 2.77 mm <sup>2</sup>	3.34 $\pm$ 0.55 mm	3.05 $\pm$ 1.48 mm <sup>2</sup>
Observer 2					
Median	6.2 (3.63) mm <sup>2</sup>	2.81 (0.85) mm	9.07 (3.915) mm <sup>2</sup>	3.4 (0.75) mm	2.77 (2.14) mm <sup>2</sup>
Mean $\pm$ 1 SD	6.07 $\pm$ 2.46 mm <sup>2</sup>	2.72 $\pm$ 0.59 mm	8.84 $\pm$ 2.63 mm <sup>2</sup>	3.31 $\pm$ 0.52 mm	2.79 $\pm$ 1.53 mm <sup>2</sup>
Absolute difference	0.11 $\pm$ 0.33 mm <sup>2</sup>	0.023 $\pm$ 0.07 mm	0.17 $\pm$ 0.68 mm <sup>2</sup>	0.03 $\pm$ 0.13 mm	0.26 $\pm$ 0.72 mm <sup>2</sup>
Relative difference	(1.57 $\pm$ 0.05)%	(0.79 $\pm$ 0.03)%	(1.44 $\pm$ 0.08)%	(0.72 $\pm$ 0.04)%	(14.08 $\pm$ 0.37)%
Linear regression	0.9699x + 0.0777	0.9763x + 0.0416	0.9191x + 0.5561	0.924x + 0.2255	0.8556x + 0.6645
$R^2$	0.9818	0.9849	0.9407	0.9471	0.7827
$P$	<0.001	<0.001	<0.001	<0.001	<0.001

neointimal tissue was 100%. A total of 2,331 cross sections were included for analysis. In two patients, a total of 80 cross sections were excluded from analysis because of the take-off of a major side branch, and another 73 cross sections because of incomplete visualization of the lumen circumference due to motion artifacts.

OCT data for lumen, stent, and neointimal area are summarized in Table III. Bland–Altman plots for lumen stent and neointimal area, as well as lumen and stent diameter are shown in Fig. 4. As expected, the bias for the calculated variable of neointimal area was somewhat higher than for directly traced stent and lumen area with greater variability observed in assessing stent area. This relates to the operator having to manually trace each individual stent strut compared to a sharply demarcated lumen/vessel border when assessing lumen area.

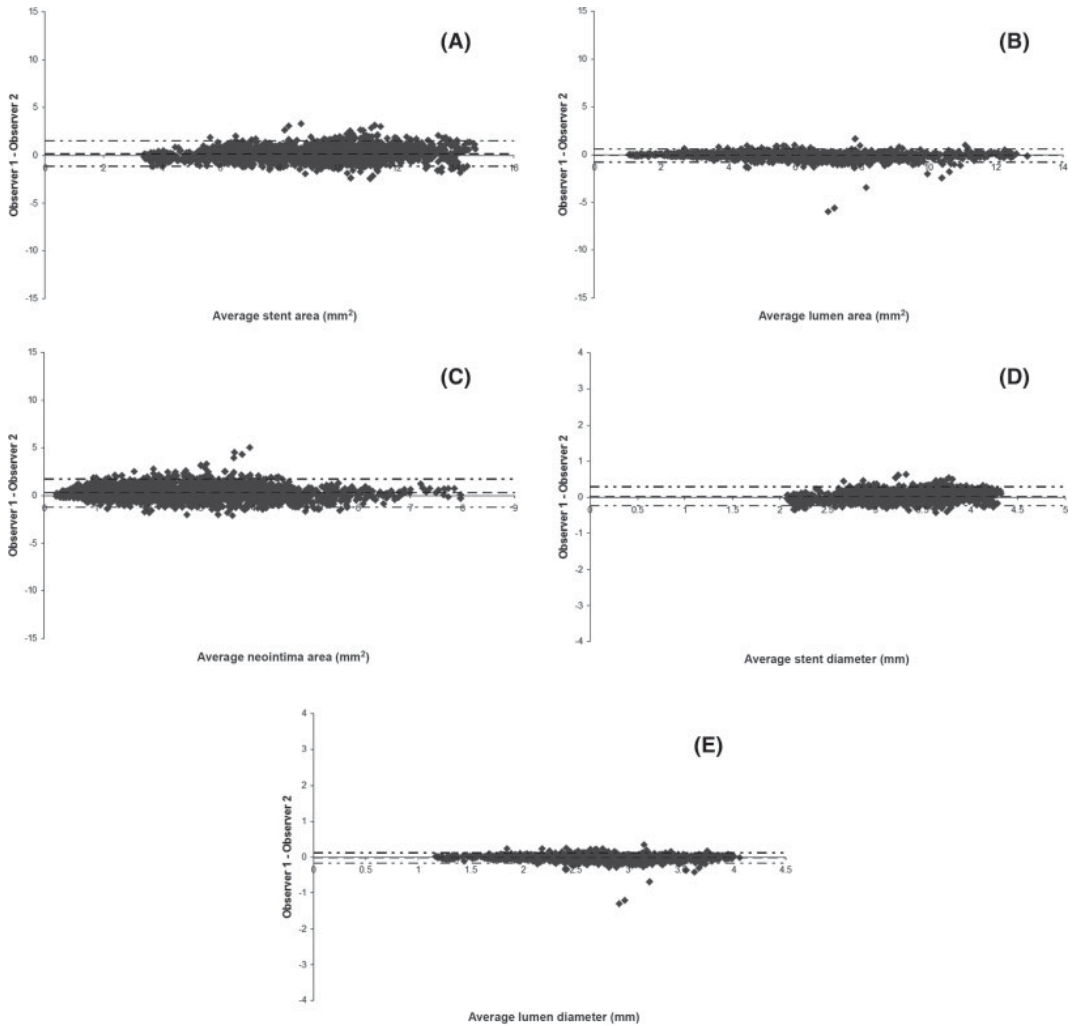
## DISCUSSION

The main findings of this study are: (1) Inter-observer variability for lumen dimensions as measured

by computer-assisted QOCT is extremely low and in a similar range for both in vitro as well as for in vivo studies, despite the occurrence of motion-induced artifacts during the acquisition in vivo. (2) Similarly, inter-observer variability in complex vessel anatomy as represented by chronic coronary stents was very low.

## Optical Coherence Tomography

OCT is a new intravascular imaging technology that permits the visualization of vascular microstructures with high precision. Its unique image resolution, in the range of 15  $\mu$ m, is in the magnitude of 10 times higher than the current golden standard, IVUS. Further, the visualization of plaque morphology in close proximity to the vessel lumen is superior to that obtained with IVUS [10]. To date, findings based on single frame analysis only in distinct areas within the coronary tree have been published. The clinical application of intracoronary OCT has already been demonstrated in both stable and unstable patients [11]. Potential future applications are manifold. They may include in vivo visualization of features associated with vulnerable plaque (e.g., thin fibrous cap) [12], analysis of early athero-



**Fig. 4.** Bland-Altman plots for measurements in in vivo stented coronary arteries. The x-axis shows the mean cross sectional area, and the y-axis shows the difference between the cross sectional measurements by observer 1 and observer 2. The dotted lines indicate the limits of agreement (bias  $\pm$  2 SD). (A) Stent area, (B) Lumen area, (C) Neointimal area, (D) Stent diameter, (E) Lumen diameter.

sclerotic lesions (e.g., local intimal thickening), the assessment of progression mechanisms of coronary artery disease and the analysis of the impact of pharmacological or catheter-based interventions on plaque structures, and vessel architecture. Intracoronary OCT also provides detailed information relating to stent apposition while allowing the accurate quantification of neointimal stent coverage at follow-up. Such analyses, however, require OCT studies over relatively long

epicardial artery segments. We, therefore, used a dedicated OCT system that allows for data acquisition over long coronary segments using an automated motorized pullback.

#### Computer-Assisted Analysis Approach

During a motorized OCT pullback a large quantity of cross-sectional images of the coronary artery are acquired. For example, at a rate of 15 frames/sec and



a pullback speed of 1.0 mm/sec, a ROI of 30 mm will result in 450 individual cross-sections. Separate analysis of all these individual cross-sections is cumbersome and time-consuming. In this study, a method similar to established quantitative IVUS (QCU) was adapted and applied. This resulted in a user-friendly analysis system that allows rapid and observer-independent quantitative analysis. This particular QCU software has been validated in the past [8] and is in use as the golden standard for the analysis of IVUS studies, having been applied in numerous multicenter trials [13–16].

### Comparison to Previous Studies

In a study using IVUS, inter-observer agreement for the presence of neointimal tissue was 62% with discrepancy between observers exclusively in very thin neointimal layers and a neointimal area  $<2 \text{ mm}^2$  [17]. In the present study, the inter-observer agreement on the presence of neointimal tissue was 100% with neointima visible in all cross sections, whereby 23% of cross section had a neointimal area  $<2 \text{ mm}^2$ . The higher resolution of OCT compared to IVUS makes this imaging modality more sensitive at detecting even small quantities of intimal tissue, and this remains one of the major advantages, particularly in the era of drug-eluting stents.

Recent reports using OCT to assess tissue coverage after stent implantation [18,19] have used proprietary off-line software provided by LightLab Imaging. Such an approach involves the operator individually measuring each stent strut at 1-mm intervals (approximately each 15 frames) followed by manually tracing both the stent and lumen area, to derive the neointimal area. We have found this technique to be quite cumbersome and heavily operator dependent with each analysis of a stented segment taking between 120 and 240 min to complete, depending on the stent length. The method presented in this study achieves a more robust and reproducible analysis in a time and cost-effective fashion.

### Clinical Implications

OCT is a unique intravascular imaging modality with the sensitivity to delineate mural and luminal structures. As a result, the scope of OCT, as both a research and clinical tool, remains vast. Such a technology allows the precise assessment of lumen dimensions, plaques, thrombi, and dissections [20], while also being able to assess both immediate and late results of stent implantation. While OCT provides additional morphologic information than IVUS, a considerable quantity of information still needs to be processed. Adopting a semiautomated, computer-assisted approach with contour detection remains pivotal in

making future studies incorporating OCT more reliable and reproducible with less potential sources of operator error.

### LIMITATIONS

This study is obviously limited by the number of observations and the narrow range of arterial dimensions evaluated. However, the target vessel dimensions represent the majority of clinically relevant dimensions in patients. Motion artifacts during the cardiac cycle hampered the visualization of the complete vessel circumference in 9% of the cross sections using the current OCT software. Modifications in software, OCT imaging catheter design and ECG-gated data acquisition [21] or retrospective image-based gating [22] of acquired IVUS data might alleviate such limitations in the future. The high resolution of OCT is at the expense of penetration depth, which is typically limited to  $\sim 1$  to 2 mm into the vessel wall limiting analysis to structures that are relatively close to the inner lumen border.

### CONCLUSIONS

Computer-assisted contour analysis of intracoronary OCT pullback is feasible and enables OCT morphometry with low inter-observer variability. This approach allows independent QOCT analysis for observer, and may be a valuable tool for future longitudinal studies incorporating OCT.

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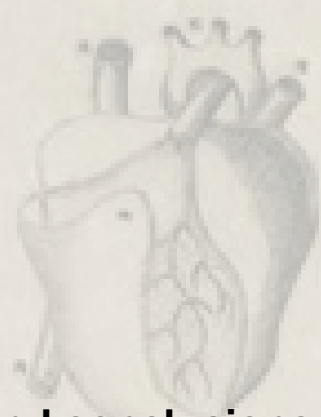
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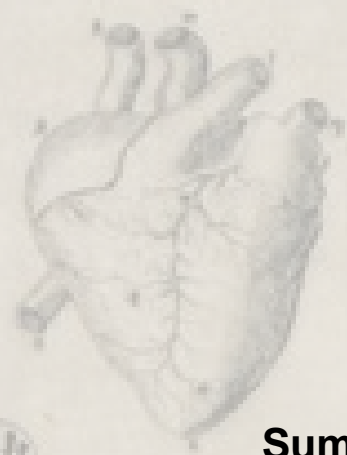


心篇圖

四脈管及心囊

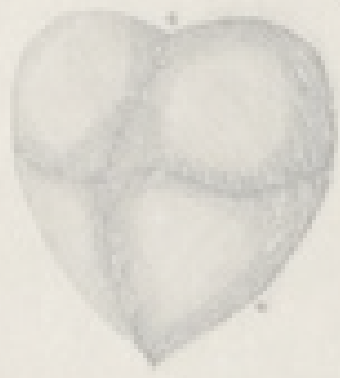


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Summary and conclusions

全形



心障膜



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## SUMMARY AND CONCLUSIONS

### Part 1: Efficacy of drug eluting stent for complex patients and lesions

Since percutaneous coronary intervention was introduced as a treatment option for coronary artery disease, coronary restenosis has been a significant and vexing problem. To prevent restenosis effectively, excessive efforts have been devoted to identifying risk factors and patients group for restenosis. In the era of bare metal stents (BMS), acute myocardial infarction, small coronary vessels, aorto-ostial lesions, and lesions of chronic total occlusion are high risk for in-stent restenosis (ISR). Clinical effects of sirolimus eluting stents (SES) and paclitaxel eluting stents (PES) on patients with these high risk factors were analyzed. In **Chapter 2**, we reviewed the 4 studies, which assessed the medium-term (ranged from 6 to 10 months) clinical advantage of SES over BMS in patients with acute myocardial infarction, and performed a meta-analysis by compiling the results of these studies. In the SES arm, the target vessel revascularization rate was 2.3% (80% relative reduction as compared to the BMS arm) and the overall incidence of major adverse cardiac events (MACE) was 10.8% (50% relative reduction as compared to the BMS arm). No angiographic stent thrombosis was observed in patients treated with SES. These results suggested that SES is a safe and effective device for the prevention of restenosis in this clinical setting. In **Chapter 3**, long-term (3 years) clinical outcome of SES and PES in patients with acute myocardial infarction was evaluated. Although SES proved to be superior to BMS at 1 year in reducing repeat revascularization, the use of SES was no longer superior to BMS in reducing MACE in this clinical setting (the 3-year MACE rate was 25.5% in the BMS arm and 17.9% in the SES arm). Additionally, PES showed no superior benefit over BMS in reducing the incidence of MACE at medium- and long-term follow-up. These findings could be due to the increased rates of stent thrombosis in both DES groups (2.7% in the SES group and 2.9% in the PES group) as compared to the BMS group (1.6%). In **Chapter 4 and 5**, the efficacy of SES and PES implantation for small vessel disease was assessed. At 2 years, the cumulative incidence of MACE in the SES group was significantly lower than that in the PES group (10.3% vs. 23.3%,  $p = 0.02$ ). Although PES utilization (Hazard ratio [HR] 3.34, 95% CI 1.07-5.26) was identified as an independent predictor of MACE by multivariate analysis, we concluded that there is little and weak information to support this result at present. **Chapter 6** examined the 7 months angiographic and 2-year clinical outcome of patients treated with PES for aorto-ostial lesions. The late lumen loss at 7 months was 0.48mm, resulting in the target vessel revascularization rate of 14.5% along with the MACE rate of 31.2% at 2 years. The PES implantation for this complex lesion was feasible and associated with favorable angiographic results. However, the gradual increase in later adverse events suggests that DES implantation for this specific lesion remains problematic. In **Chapter 7**, SES utilization for chronic total occlusion was analyzed. Although SES was associated with favorable 1 year survival free from target lesion revascularization, the use of SES was no longer associated with significantly lower rates of target vessel revascularization (12.7% in the BMS group vs. 9.2% in the SES group) and MACE (18.3% in the BMS group vs. 15.8% in the SES group) after 3 years of follow-up compared to BMS. The efficacy of DES for another challenging clinical setting, chronic total

occlusion in post bypass surgery patients, was investigated in **Chapter 8**. Although only a small number of patients (N = 24) were enrolled, this trial suggested that DES implantation for saphenous vein graft and native coronary artery with chronic total occlusions had relatively favorable 3-year event free survival (83.9% in the saphenous vein graft and 81.8% in the native coronary artery).

## **Part 2: New concept stents for percutaneous coronary intervention**

DES have remarkably reduced the rates of ISR and repeat revascularization. However, the incidence of stent thrombosis, especially late stent thrombosis (occurs more than 1 year after stent implantation), is the most important drawback of DES. To maintain the favorable benefits of DES and resolve their drawbacks, various new concept stents have been developed. One of these stents is the MAHOROBA tacrolimus eluting stent (**Chapter 9**). This is comprised of a cobalt chromium thin strut thickness (75  $\mu\text{m}$ ) platform coated with bioabsorbable polymer containing tacrolimus, and considered as the next generation of DES. The MAHOROBA trial was the first in man study to test the safety and feasibility of this stent for de novo coronary lesions. The results of the MAHOROBA trial were reported in **Chapter 10**. The late lumen loss at 4 months was 0.99 mm and the rate of 6 months target lesion revascularization was 23.4%. We concluded that the MAHOROBA tacrolimus eluting stent failed to reduce the growth of neointimal hyperplasia and establish its effectiveness.

The bioabsorbable everolimus eluting coronary stent (BVS) is another new concept stent. The BVS is composed of a poly-L-lactic acid backbone, coated with a bioabsorbable polymer (poly-D,L-lactic acid) containing the antiproliferative drug everolimus, and designed to be fully metabolized and totally absorbed in the human body between 2 and 3 years after implantation. Once the BVS is fully absorbed, only the healed vessels are left behind with no residual prosthesis, resulting in no potential interactions with coronary artery. Therefore, the BVS has the possibility of diminishing chronic inflammation at stented lesions and accelerating endothelialization. The first in man trial (the ABSORB trial) was conducted to assess the safety and feasibility of the BVS in patient with coronary artery disease. By using the data of the ABSORB trial, we investigated the mechanical behavior of the BVS after deployment in diseased human coronary arteries. **Chapter 11** compared acute stent recoil of the BVS with that of the everolimus eluting 'metallic' stent (EES). Acute absolute recoil of the BVS and EES was  $0.20\pm 0.21$  mm and  $0.13\pm 0.21$ , respectively ( $p = 0.32$ ), Acute percent recoil of the BVS and EES was  $6.9\pm 7.0\%$  and  $4.3\pm 7.1\%$ , respectively ( $p = 0.25$ ). These results suggested that acute stent recoil of the BVS was slightly larger but insignificantly different from that of EES. In **Chapter 12**, late stent recoil of the BVS was evaluated with intravascular ultrasound, which was performed at post-procedure and 6 months follow-up. Late absolute and percent recoil of the BVS was  $0.65\pm 1.71$  mm<sup>2</sup> and  $7.60\pm 23.3\%$ , respectively. We concluded that the BVS shrank in size during the follow-up period, which may be caused by its stent design and/or intrinsic characteristics. **Chapter 13** illustrated several images of multi-slice computed tomography (MSCT) coronary angiography in a patient successfully treated with one BVS and one drug eluting metallic stent. While metallic struts hampered clear depiction of the in-stent lumen due to the "blooming effect", BVS struts were invisible, therefore clear in-stent images of

the BVS was achieved. The polymer stent could be amenable to MSCT that has recently developed as a non-invasive imaging modality and will play an important role in the future for evaluating neointimal growth and arterial remodeling of the stented segment. In **Chapter 14**, quantitative MSCT coronary angiography analysis of the BVS was performed and compared with already established quantitative intravascular analysis. We concluded that non-invasive quantitative MSCT analysis can be used to quantify luminal dimensions in patient treated with the BVS.

### **Part 3: New imaging modality for coronary intervention**

Optical coherence tomography (OCT) is an analogue of intravascular ultrasound with an ultra-high resolution superior to any current available imaging modalities. An excellent image of patients presenting with ISR of PES was displayed in **Chapter 15**. **Chapter 16** provided ex vivo validation of OCT with respect to diameter measurements. OCT-based dimensional values proved to correlate extremely well with the real luminal diameter of the phantom (accuracy = -0.03, precision = 0.02, relative standard deviation = 1.8%,  $r = 1.000$ ). Although the measurement accuracy of OCT has been established in postmortem human coronary arteries, in vivo quantitative OCT analysis has not been evaluated, because in vivo intracoronary imaging is complicated due to the presence of blood and motion artifact during cardiac cycle. **Chapter 17** revealed that inter-observer variability for lumen dimensions measured by quantitative OCT analysis was extremely low and in a similar range for both ex vivo and in vivo studies.

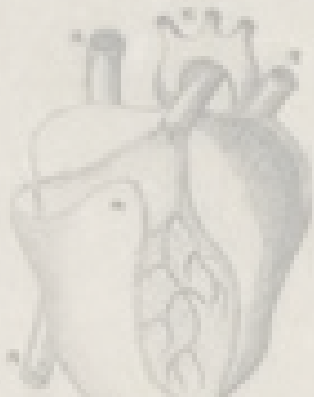
### **Conclusions**

Although both SES and PES have been demonstrated to be significantly effective in reducing the rates of restenosis and repeat revascularization, even if patients are at high risk for ISR, long term effects of these devices for these patients remain uncertain. Long term follow-up are needed to definitively address the efficacy and safety of DES in complex patients and lesions. The increased risk of thrombosis is the most notable drawback of DES, but the mechanism of this catastrophic complication has not been fully understood. To overcome of this drawback, new concept stents have been developed. The bioabsorbable drug eluting polymer stents, which is designed to be fully metabolized and absorbed in the human body, have the possibility to accelerate good endothelialization at the stented segment and reduce the rate of stent thrombosis. Further developments in this technology and larger sample size trials are warranted to evaluate the efficacy and safety of this device. OCT is a novel imaging modality with an ultra-high resolution, which permits the observation and analysis of detailed coronary structures, and can help to understand the mechanism of ISR and late stent thrombosis in the DES era.

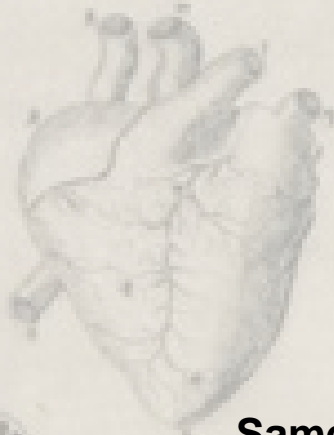


心篇圖

四脈管及心囊

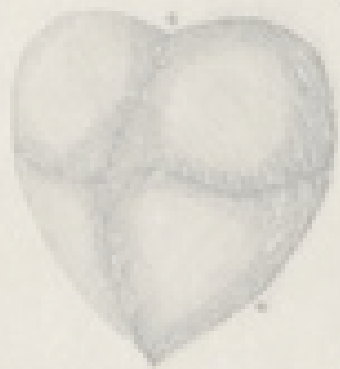


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Samenvatting en Conclusies

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## SAMENVATTING EN CONCLUSIES

### Deel 1: Doelmatigheid van medicijn-gecoate stents in complexe patiënten en vernauwingen

Sinds de introductie van percutane coronaire interventies als een behandelingsoptie voor coronaire atherosclerose, is coronaire restenose een belangrijk en groot probleem. Om het probleem van restenose te voorkomen is er uitgebreid en extensief onderzoek gedaan naar mogelijke risicofactoren die dit veroorzaken en bij welke patiëntengroepen dit voor zou kunnen komen. In het tijdperk van metalen stents (wat bare metal stent in het Engels betekent, afgekort BMS), een acuut myocard infarct, kleine coronaire vaten, ostiale vernauwingen en chronisch totale afsluitingen bleken hoge risico indicatoren voor in-stent restenoses (ISR) te zijn. In hoofdstuk 1, worden de klinische effecten van sirolimus-gecoate (Engels: sirolimus-eluting stents, afgekort SES) en paclitaxel-gecoate stents (Engels: paclitaxel-eluting stents, afgekort PES) op patiënten met deze risicofactoren onderzocht en beschreven.

In **hoofdstuk 2** beschouwen we 4 studies die de klinische voordelen op de middellange-termijn (tussen 6 en 10 maanden) onderzochten van SES tegen BMS gestente patiënten na een acuut myocard infarct. Deze beschouwing is uitgevoerd als een meta-analyse op de resultaten van deze studies. In de SES arm ondergingen 2.3% van de gestente vaten een herbehandeling (wat een reductie is van 80% t.o.v. de BMS groep). De totale reductie van cardiale gebeurtenissen (Engels: major adverse cardiac events, afgekort MACE) na stenting was 10.8% (dit is een 50% relatieve reductie t.o.v. de BMS arm). Er werden geen angiografische tromboses gevonden in de SES behandelde patiënten. Deze resultaten suggereren dat SES implantatie een veilige behandeloptie is en restenose kan voorkomen in deze patiëntenpopulatie.

In **hoofdstuk 3**, worden de lange-termijn effecten van de bovenstaande groep onderzocht en beschouwd. Hoewel de behandeling met SES superieur was t.o.v. BMS na 1 jaar m.b.t. reductie van herhaalde behandelingen, het gebruik van SES was niet beter om het aantal gevallen van MACE te reduceren voor deze patiënten (na 3 jaar bedroeg de MACE in de SES groep 17.9% t.o.v. 25.5% voor de BMS groep). In additie, PES gestente patiënten hadden geen voordeel t.o.v. BMS gestente patiënten m.b.t. reductie van MACE op de middellange- en lange-termijn. Dit zou veroorzaakt kunnen zijn door een toename van stent trombose in de medicijn-gecoate stent patiënten (Engels: drug-eluting-stents, afgekort DES) (2.7% in de SES groep, 2.9% in de PES groep en 1.6% in de BMS groep).

In de **hoofdstukken 4 en 5** wordt de effectiviteit van SES en PES stents geïmplantieerd in kleine coronaire vaten onderzocht. Na 2 jaar, was de cumulatieve frequentie van MACE in de SES groep significant lager dan in de PES groep (10.3% t.o.v. 23.3%,  $p=0.02$ ). Hoewel het gebruik van PES (risico verhouding [HR] 3.34, 95% betrouwbaarheidsinterval [CI] 1.07-5.26) was geïdentificeerd als een onafhankelijke risicofactor voor MACE bij het toepassen van multivariable analyse, is onze conclusie dat de huidige beschikbare informatie onvoldoende is om dit te kunnen onderbouwen.

**Hoofdstuk 6** onderzoekt de 7 maanden angiografische en 2 jaars klinische uitkomsten van patiënten die zijn behandeld met PES voor aorta-ostiale vernauwingen. Het late verlies van lumen (Engels: late lumen loss) na 7 maanden bedroeg 0.48mm wat tot gevolg had dat in 14.5% van de patiënten revascularisatie nodig was en dat bij 31.2% van de patiënten MACE incidenten gerapporteerd werden na 2 jaar. Het implanteren van PES stents was echter goed mogelijk in deze groep met complexe vernauwingen en de angiografische resultaten waren goed. Echter de graduele toename in late nadelige gebeurtenissen suggereren dat DES implantatie voor deze specifieke groep problematisch blijft.

In **hoofdstuk 7** wordt het gebruik van SES voor chronische totale occlusies onderzocht. In de SES behandelde patiënten waren minder revascularisaties nodig na 1 jaar voor de behandelde stenoses, echter nieuwe behandelingen voor het gestente coronaire vat op zich was niet langer significant lager (12.7% in de BMS groep t.o.v. 9.2% in de SES groep) en ook het aantal incidenten van MACE (18.3% in de BMS groep t.o.v. 15.8% in de SES groep) na 3 jaar was niet lager vergeleken met de BMS behandelde groep.

Een andere uitdagende en lastige patiëntengroep is de totale chronische occlusies van vaten die reeds eerder behandeld zijn met een bypass-operatie. **Hoofdstuk 8** onderzoekt de effectiviteit van een behandeling met DES stents voor deze groep. Hoewel er maar een kleine groep patiënten op deze wijze is behandeld ( $n=24$ ) lijkt deze studie te suggereren dat DES implantatie voor zowel veneuze bypasses als lima or rima na 3 jaar een voordeel oplevert m.b.t. overleving (83.9% voor de veneuze bypasses en 81.8% in de lima's en rima's).

## Deel 2: Nieuwe stent ontwerpen voor percutane coronaire interventies

Het gebruik van DES heeft geleid tot een opmerkelijke daling van ISR en noodzakelijke herbehandelingen. Echter, het meest belangrijke negatieve effect van het gebruik van DES zijn incidenties van stent trombose, in vele gevallen later dan na 1 jaar. Om dit probleem te voorkomen en de positieve eigenschappen van DES te behouden, zijn verschillende nieuwe stent ontwerpen ontwikkeld. Één van deze nieuwe stents is de MAHORоба tacrolimus gecoat-stent (**hoofdstuk 9**). Deze is gemaakt van een mengsel van kobalt en chroom en de stent struts hebben een dikte van 75 micron. De struts zijn gecoat met een bioafbreekbare polymeer die tacrolimus bevat en deze ontwerpen worden gezien als de nieuwe generatie DES. De MAHORоба studie was de eerste studie in mensen die de veiligheid en toepasbaarheid van dit nieuwe stent ontwerp voor de novo coronaire vernauwingen onderzocht.

De resultaten van de MAHORоба worden in **hoofdstuk 10** gepresenteerd. Het verlies van lumen na 4 maanden bedroeg 0.99mm and revascularisatie was nodig bij 23.4% van de patiënten. De conclusie was dat deze nieuwe stent niet bijdroeg in verlaging van het aantal gevallen van restenose en dus niet effectief was. De bioafbreekbare everolimus-gecoat stent (BVS) is een ander nieuw ontwerp. Deze stent is gemaakt van poly-l-lactic acid en heeft een coating van alweer een bioafbreekbare polymeer (poly-D, L-actin acid) die het medicijn everolimus bevat dat weefsel groei zou moeten remmen. Deze stent zou na 2 á 3 jaar volledig moeten zijn afgebroken in het menselijk lichaam. Dit heeft als voordeel dat er geen artificieel implantaat achterblijft en dus geen nadelige effecten meer zou moeten hebben voor het coronaire vat. De BVS stent heeft dus mogelijk als voordeel dat het een chronische onsteking in de gestente regio's zou kunnen voorkomen en het zou de re-endothelialisatie van de behandelde vernauwing kunnen bespoedigen. De eerste studie in mensen (de ABSORB studie) met deze stent betrof het bestuderen van de veiligheid en de toepasbaarheid van dit ontwerp. De data verkregen uit de ABSORB studie is gebruikt om de mechanische eigenschappen van deze stent te onderzoeken na implantatie in zieke coronaire vaten.

In **hoofdstuk 11** vergelijken we de acute stent krimp van deze BVS stent met die van een metalen stent die een vergelijkbare structuur heeft en ook met everolimus is gecoat (EES). De acute krimp van de BVS was  $0.20 \pm 0.21$ mm tegen  $0.13 \pm 0.21$ mm voor de EES stent ( $p=0.32$ ). Relatief bedroeg de krimp voor de BVS stent  $6.9 \pm 7.0$  tegen  $4.3 \pm 7.1$ % voor de EES,  $p=0.25$ ). Deze resultaten suggereren dat de acute krimp voor de BVS groter is dan die voor de metalen stent, maar dit verschil is statistisch niet significant.

In **hoofdstuk 12** wordt de late krimp van de BVS stent onderzocht met intravasculair ultrageluid (IVUS). De behandelde coronairen werden met IVUS bekeken, post-implantatie, na 6 maanden en na 2 jaar. De late absolute krimp van de BVS stent bedroeg  $0.65 \pm 1.71$ mm<sup>2</sup> en relatief is dit  $7.60 \pm 23.3$ %. Hieruit concludeerden we dat de BVS stent krimp tijdens de follow-up periode wat veroorzaakt zou kunnen zijn door het ontwerp zelf en/of intrinsieke karakteristieken.

**Hoofdstuk 13** illustreert aan de hand van verschillende beelden gemaakt met een multi-slice computed tomograaf (MSCT) de verschillen tussen een BVS en een metalen stent gemaakt in één patiënt die met beide stents behandeld is. In deze beelden valt te zien dat de metalen struts het zicht verhinderen op het lumen, wat niet geldt voor de BVS stent. Deze struts zijn niet zichtbaar te maken met röntgenstraling, wat wellicht in de toekomst een voordeel zou kunnen zijn om met de non-invasieve MSCT mogelijk een follow-up te kunnen doen. MSCT zal in de toekomst een grote rol gaan spelen als beeldmodaliteit om het proces van neo-intima groei en vasculaire remodelling te kunnen bestuderen.

In **hoofdstuk 14** wordt kwantitatieve MSCT vergeleken met kwantitatieve intravasculaire technieken. We concludeerden dat non-invasieve kwantitatieve MSCT analyses gebruikt kunnen worden bij patiënten behandeld met een BVS stent.

## Deel 3: Nieuwe beeldvormende modaliteiten voor coronaire interventies

Optical coherence tomography (OCT) is een techniek die verwant is met en vergelijkbaar is aan IVUS maar met het voordeel dat het de coronaire vaatwand in een hele hoge resolutie (10 maal zo hoog als IVUS) zichtbaar kan maken. Een excellent voorbeeld kan worden gevonden in **hoofdstuk 15**.

**Hoofdstuk 16** presenteert een ex-vivo validatie studie waarin gevalideerd wordt hoe nauwkeurig de diameter metingen met OCT zijn. OCT gebaseerde metingen bleken extreem goed te correleren met de gebruikte gouden standaard, e.g. een fantoom (accuracy = -0.03, precision = 0.02, relatieve standaard deviatie = 1.8%,  $r = 1$ ). Hoewel de meetnauwkeurigheid van OCT is vastgesteld voor ex-vivo humane coronaire vaten, in-vivo kwantitatieve OCT validatie is niet onderzocht. Dit omdat in-vivo

gebruik van OCT wordt bemoeilijkt door bloed en bewegingen van de catheter tijdens de cardiale cyclus.

**Hoofdstuk 17** laat zien dat de inter- en intra-onderzoeker variabiliteit voor het meten van lumen dimensies m.b.v. kwantitatieve OCT extreem laag is voor een vergelijkbare reeks in- en ex-vivo studies.

## **Conclusies**

Hoewel het gebruik van SES en PES hebben aangetoond dat ze effectief zijn in het reduceren van restenoses en benodigde herhaalde behandelingen, zelfs voor patiënten in hoge risico groepen voor ISR, zijn de lange termijn effecten van deze stents voor deze patiënten groepen onzeker. Lange termijn vervolg onderzoeken zijn nodig om definitief vast te kunnen stellen dat het gebruik van DES veilig en effectief is voor gebruik in complexe patiënten groepen en vernauwingen. Het verhoogde risico op stent trombose is de meest prominente negatieve eigenschap van DES. Het mechanisme hierachter is echter nog steeds niet helemaal begrepen. Om deze eigenschap te overkomen zijn nieuwe stent ontworpen. De bioabsorbeerbare polymeer-gecoate stents welke volledig door het lichaam afbreekbaar zijn bieden de mogelijkheid tot een goede re-endothelialisatie van het gestente deel van het coronaire vat en tot het reduceren van stent trombose. Verdere ontwikkelingen van deze technologie en studies met grotere patiënten aantallen zijn noodzakelijk om de verdere veiligheid en effectiviteit van dit nieuwe ontwerp te kunnen evalueren. OCT is een nieuwe beeldvormende intravasculaire techniek met een extreem hoge resolutie. Dit biedt de mogelijkheid om met grote detailweergave coronaire sturcturen te observeren en analyseren. Dit zou kunnen leiden tot een vergrote kennis van de onderliggende redenen die resulteren in stent trombose in het DES tijdperk.

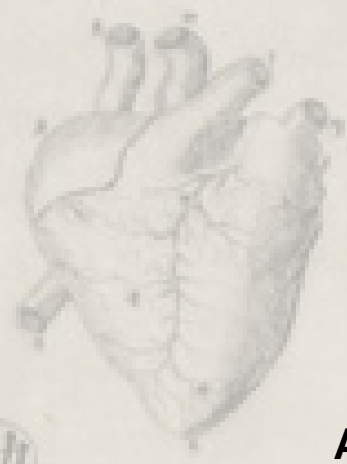


心篇圖

四脈管及心囊

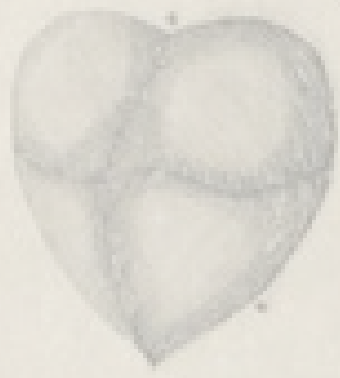


剖心囊視冠脈



Acknowledgements

全形



心障膜



勃

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### Beginning

One day in March 2004, Dr. Kengo Tanabe (One of Japanese predecessors) invited me for a drink. He was the first preceptor as I started my career for physician. We have been working together in the same hospital throughout my career. I could be very nervous because he would point out some mistakes in my clinical practice. However, my fears turned out to be groundless. Dr. Tanabe asked me whether I had a good mind to go to the Netherlands for clinical research on coronary intervention. At that time, I realized that I was a candidate for a next Japanese fellow at the Thoraxcenter. This offer was a big chance for me, since Prof. Serruys have a world-wide reputation for interventional cardiology and ex-fellows have been leading the field. I remember that I could only be pleased with his offer.

September 2004, just after the ESC in Munich, I met Prof. Serruys for the first time and had a short interview with him in the Cardialysis, accompanied with Dr. Tanabe and Dr. Jiro Aoki (my predecessor). As Prof. Serruys started to discuss recent topics on interventional cardiology with Dr. Tanabe, I could only become silent, even though I had prepared a lot to introduce myself. I clearly remember that only I could do was shaking hands with Prof. Serruys and telling it was a great pleasure to meet him. Even now, I have no idea how Prof. Serruys evaluated me at that time, but he allowed me to be a research fellow at the Thoraxcenter, one of the famous institutions in the world, from June 2005.

After that, Dr. Kazuhiro Hara (my current boss, a respected leader and great cardiologist) and Prof. Yuji Ikari (member of my committee, a mentor of initiating me into clinical research) provided financial support with me. Dr. Ken Kozuma (a pioneer of Japanese fellows at the Thoraxcenter) gave me valuable advices on what I should experience in Rotterdam. Without their supports, I could not get an opportunity to learn at the Thoraxcenter. I would like to express my deepest gratitude to all of them.

I arrived at Rotterdam with my pregnant wife at the end of May 2005. I felt a little bit anxious because this was the first time to live abroad on a long term. Dr. Jiro Aoki and Dr. Keiichi Tsuchida (my Japanese colleague at the Thoraxcenter) kindly welcomed us and took some daily essentials to our flat. They also cheered me up by their smile and relieved my concerns. Second day in Rotterdam, Dr. Jiro Aoki took me to Prof. Serruys' house. This was the first visit his house, but at this time, I could not imagine that I would go there hundreds of times.

My room at the Thoraxcenter was Kamer 922 in the H building, which was placed at the entrance of the orthopedics ward. All fellows and staffs warmly welcomed me. However, everyone must have been surprised that my spoken English was terrible and listening skills were more horrible. In addition, it was very difficult to adapt myself to the new surroundings, mainly because I was silent and not talkative (a so-called "typical" Japanese). One of what I did not want to do was to take a phone call, even in my house. It is still a traumatic experience of my life.

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### **Cardialysis**

Cardialysis, the best core-lab in the world, I believe. A lot of cutting edge information from the world is there. I have learned numerous things in the Cardialysis, how to create and manage clinical trials, how to analyze various imaging modalities, and how to interpret raw data from clinical trials.

Marie-Angele Morel, a woman with great smile. When I faced many difficulties, you always guided me in the right direction. When I was at a loss what to do, you kindly taught me what I should do first. Without your support, I was already killed by Prof. Serruys. I greatly appreciate your kindness.

Monique Schuijjer, a very kind lady with receptiveness. You have always assisted me. I had many opportunities to work with you (ABSORB, MAHOROBA, SPIRIT, etc.). Without your help, I could not have written many chapters of my thesis. I wish all the success in your future.

Paul Cummins, an upbeat Irish man, the managing editor of EuroIntervention. Whenever I went to the Cardialysis, I visited at your office. I recall many pleasant talks with you. But, I beg a favor of you, Paul. Please speak English more slowly.

I would like to thank all great statisticians (Marco Bressers, Tessa Rademaker and Dick Goedhart), Gerrit-Anne van Es, Peter-Paul Kint, Janette Symons, Yvonne Teunissen, Yvonne van Lint, Connie van der Wiel and others for their assistance.

### **Device companies**

During my fellowship, I have achieved good relationships with many device companies.

Eizo Nishimura, a very famous sales representative of Cordis Cardiology Japan, Johnson & Johnson KK. Thank you very much for your valuable supports to me.

Susan Veldhof, a worker belonging to the Abbott Europe. With your kind support, I could produce several manuscripts regarding the BVS. I hope this device can be a main stream in the field of interventional cardiology soon.

I need to clearly state that a Japanese group had struggled in the Netherlands to develop a new drug eluting stent, which consists of all made-in-Japan products. The name of its group is Kaneka Corporation. This new device was named 'MAHOROBA'. Unfortunately, MAHOROBA failed to show its expected performance in diseased human coronary arteries. However, I strongly believe that Kaneka Corporation can develop a new amazing device in the near future by using its technical strength and general ability. I would like to thank Hiroshi Sakurai, Kohei Fukaya, Takuji Nishide, Hiroyasu Higuchi and Hiromi Maeda for providing a chance to join in the first-in-man trial with me. I think we are so-called 'blood brothers'. We need to move forward hand in hand steadily.

### **My family**

Finally, I would like to acknowledge to my family.

First, my wife, Tomoko. I can not find out right words enough to express my deepest gratitude to you. Only after a few weeks in Rotterdam, before getting used to new life in a foreign country, you confronted great difficulty. It was threatened premature delivery. You needed to be hospitalized in Sophia Ziekenhuis. I could not imagine how lonely you were and how anxious you got on the bed. Despite Dutch doctors' effort, my little daughter was born premature at a gestational age of less than 32 weeks. She was only 1530g, but full of vitality, and fortunately, intubation was unnecessary. She was transferred to IJsselland Ziekenhuis to receive intensive care nursery. I will never forget throughout my life that everyday you took your breast milk to the hospital by Metro in order to give it to her. The 2 years in Rotterdam were undoubtedly difficult for you, although you were surrounded by good friends you met there. However, you have always encouraged me with your excellent smile. Therefore, this thesis is not for me, but for you. Without your support, it would not have happened. Dear Tomoko, thank you very much again for everything.

## Acknowledgements

I named my daughter, Yui. In Japanese, the meaning of her name, Yui, is someone to tie, bind, link or relate things and people together. Indeed, she has strengthened the bond of our marriage. It has been great pleasure for us to watch her growth. Forty days after birth, Yui finally came home from IJsselland Ziekenhuis. After that, serious problems had not happened on her. Yui is now 4 years old, relatively big and very talkative. That is 'enough' for us. Yui, dear my little daughter, I hope you will become a cultural bridge between the Netherlands and Japan in the future as your name implies.

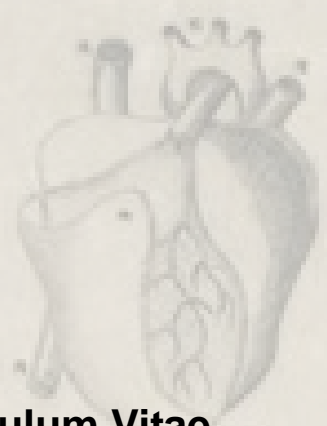
My first son, Junya, was born in November 2008 in Japan. I'm just writing this part with him crying beside me. As well as his sister came in our family in the Netherlands, Junya will make his first touch with international culture, life, people and so on in this country. This inspires me it could be a fate that we all have strong ties with the Netherlands. Dear Junya, a little boy, I wish you can bring back your memory of this first trip to the Netherlands someday (but, is it a little bit difficult for you?).

My father (Katsumi), brother (Takahiko) and in-laws (Masayoshi and Mitsue) have been always encouraging. Without their understanding, I could not have an opportunity to learn at the Thoraxcenter. Thank you very much for your physiological and material supports.

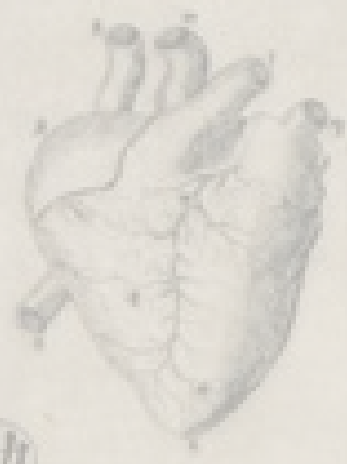
**At the end, I would like to thank all the people mentioned above again. With your supports, I could achieve this thesis. I am really happy to meet many nice people in the Netherlands.**

心篇圖

四脈管及心囊

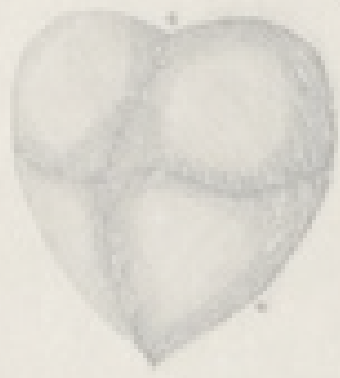


剖心囊視冠脈



Curriculum Vitae

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豎剖心視內室







## CURRICULUM VITAE

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### Education:

2000 M.D., Tohoku University School of Medicine, Sendai, Japan  
1993 Graduated from Komaba Toho High School, Tokyo, Japan

### Professional Training and Employment:

2007 Senior staff at the Division of Cardiology, Mitsui Memorial Hospital, Tokyo, Japan  
2005-2007 Research fellow at the Thoraxcenter, Erasmus MC, Rotterdam, the Netherlands  
2002-2005 Resident at the Division of Cardiology, Mitsui Memorial Hospital, Tokyo, Japan  
2000-2002 Resident in Internal Medicine, Mitsui Memorial Hospital, Tokyo, Japan

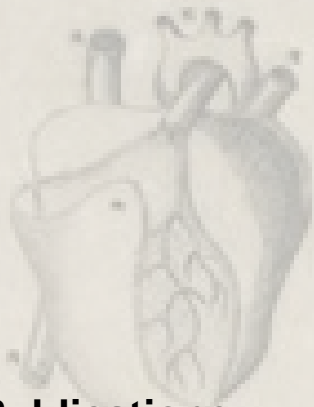
### License and Certification:

2010 Board Certified Member of the Japanese College of Angiology: Vascular Specialist  
2009 Board Certified Member of the Japanese Circulation Society  
2008 Fellow of Japanese Society of Interventional Cardiology  
2004 Board Certified Member of the Japanese Society of Internal Medicine  
2000 Japanese Medical License

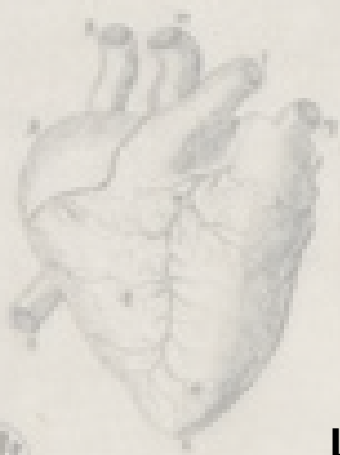


心篇圖

四脈管及心囊

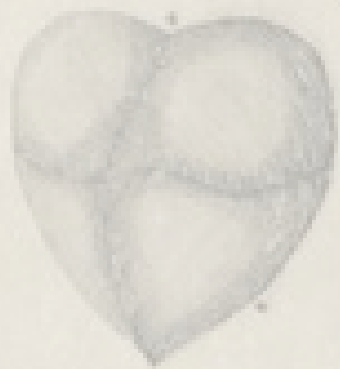


剖心囊視冠脈



List of Publications

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心障膜



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豎剖心視內室





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12. Contemporary treatment of patients with chronic total occlusion: critical appraisal of different state-of-the-art techniques and devices.  
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22. Difference of culprit plaque composition between patients with and without pre-infarction angina: an intravascular ultrasound radiofrequency analysis.  
Higashikuni Y, Tanabe K, **Tanimoto S**, Aoki J, Yamamoto H, Nakazawa G, Chihara R, Onuma Y, Otsuki S, Yagishita A, Yachi S, Nakajima H, Hara K.  
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23. Clinical and angiographic outcomes following percutaneous coronary intervention with sirolimus-eluting stents versus bare-metal stents in hemodialysis patients.  
Yachi S, Tanabe K, **Tanimoto S**, Aoki J, Nakazawa G, Yamamoto H, Otsuki S, Yagishita A, Kishi S, Nakano M, Taniwaki M, Sasaki S, Nakajima H, Mise N, Sugimoto T, Hara K.  
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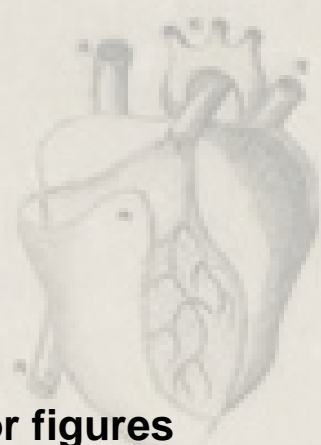
### **Abstracts (International Congress, first author)**

1. Two-year clinical outcomes after coronary stenting of very small vessels using 2.25mm sirolimus- and paclitaxel-eluting stents: a comparison between the RESEARCH and T-SEARCH registries.  
**Tanimoto S**, Rodriguez-Granillo G, Tsuchida K, Garcia-Garcia H, de Jaegere P, van Domburg R, Serruys PW.  
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2. In vivo volumetric quantification of neointima after stenting in human coronaries using optical coherence tomography (OCT).  
**Tanimoto S**, de Winter S, Bruining N, Hamers R, Serruys PW, Regar E.  
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3. Acute stent recoil of bioabsorbable everolimus eluting coronary stent: In vivo evaluation.  
**Tanimoto S**, Sianos G, van Mieghem C, Kukreja N, Ormiston JA, Serruys PW.  
TCT2006, Washington
4. Comparison of Acute Stent Recoil between Bioabsorbable Everolimus-Eluting Coronary Stent and Everolimus-Eluting cobalt chromium Stent: Insight from the ABSORB and SPIRIT Trials.  
**Tanimoto S**, Serruys PW, Thuesen L, Dariusz D, de Bruyne B, Chevalier B, Ormiston JA.  
ACC2007, New Orleans
5. Late Stent Recoil of the Bioabsorbable Everolimus Eluting Coronary Stent and its Relationship with Stent Strut Distribution and Plaque Morphology.  
**Tanimoto S**, Bruining N, Rotger D, Radeva P, Ligthart JM, van Domburg RT, Serruys PW.  
TCT2007, Wahington

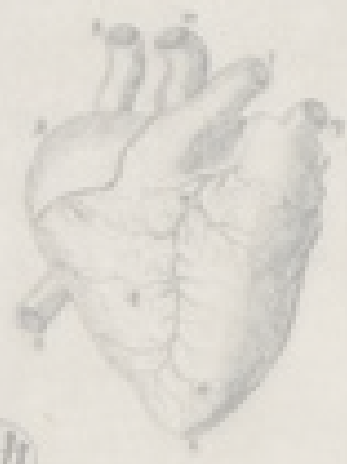


心篇圖

四脈管及心囊

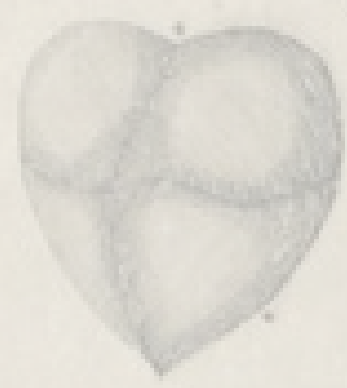


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Color figures

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心障膜

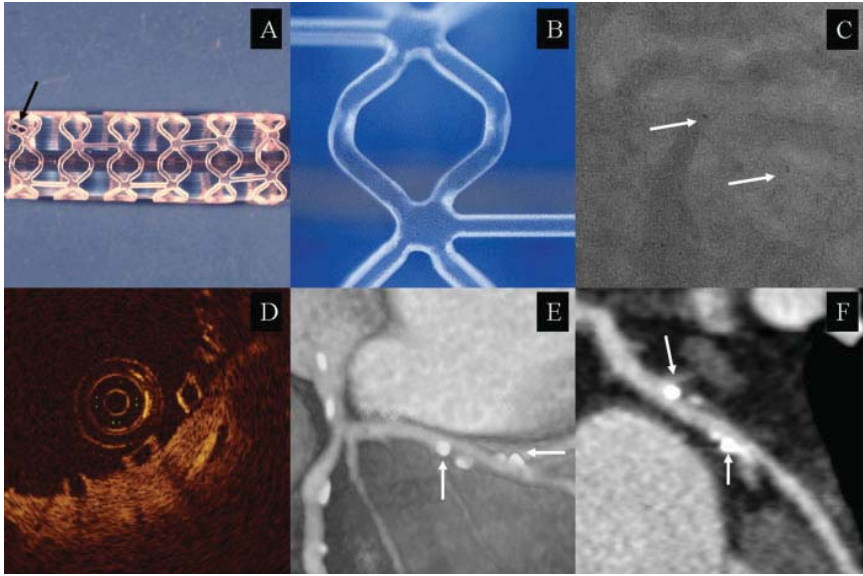


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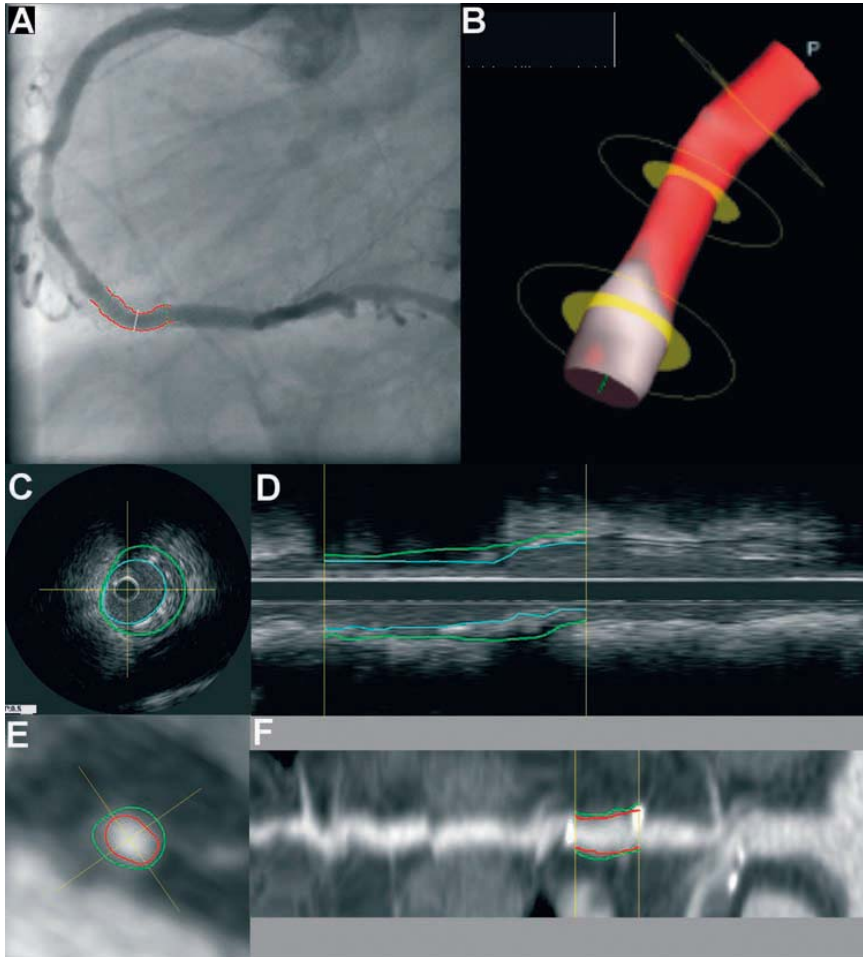
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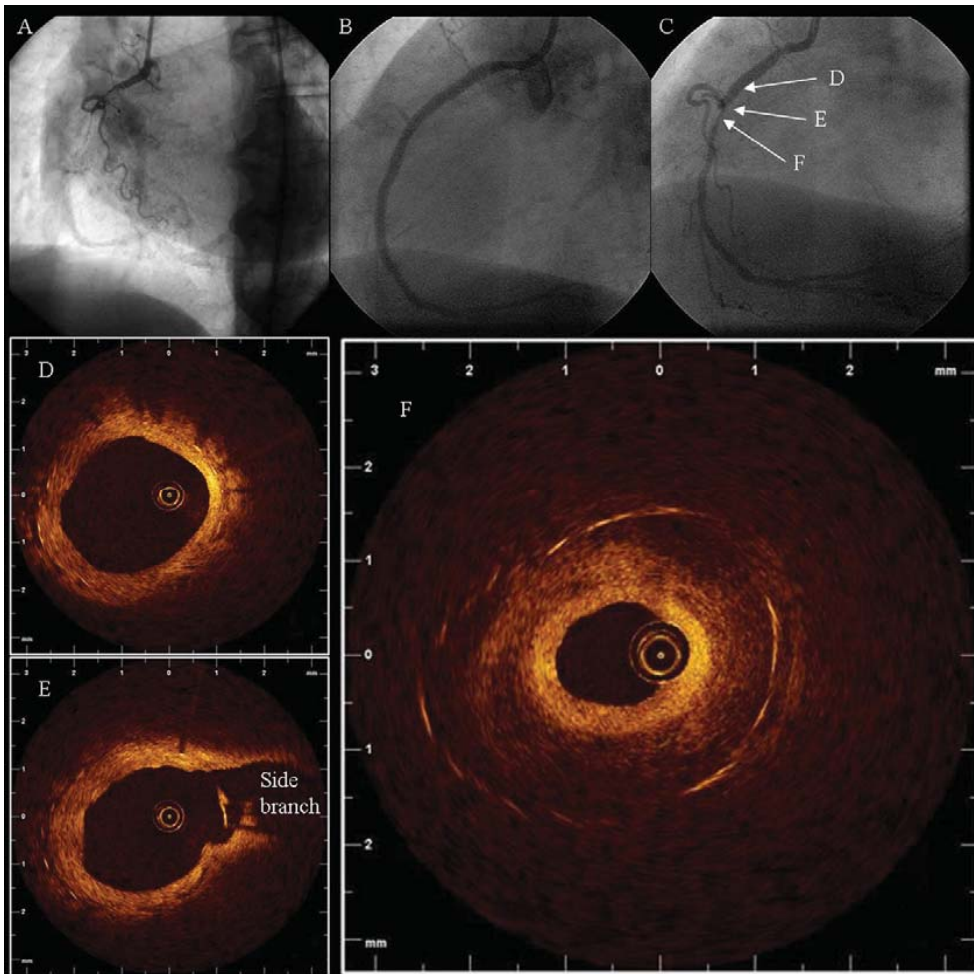


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