Update on stents: Recent studies on the TAXUS® 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 used. 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 restenostic 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^2) and drug release kinetics (slow-release and moderate-release) but similar polymers, stent materials and drug concentrations (1.0 μg/mm^2 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^2 stent is composed of a balloon-expandable EXPRESS^2 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^2 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^2 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

	TAXUS I (Grube et al 2003)	TAXUS II (Colombo et al 2003)	TAXUS III (Tanabe et al 2003)
Published year	2003	2003	2003
Trial design	Randomized	Randomized	Single arm
Used device	TAXUS NIRx	TAXUS NIRx	TAXUS NIRx
Release kinetics	SR	SR and MR	SR
Patient number	TAXUS 31 Control 30	TAXUS SR 131, SR control 136 TAXUS MR 135, MR control 134	TAXUS 28
Lesion morphology	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
Lesion length	= 12 mm	= 12 mm	= 30 mm
Vessel diameter	3.0 to 3.5 mm	3.0 to 3.5 mm	3.0 to 3.5 mm
Primary endpoint	MACE at 30 days	Mean % stent volume obstructed by neointimal proliferation measured by IVUS at 6 months	N/A
	TAXUS IV (Stone et al 2004a)	**TAXUS V (Stone et al 2005)**	**TAXUS VI (Dawkins et al 2005)**
Published year	2004	2005	2005
Trial design	Randomized	Randomized	Randomized
Used device	TAXUS EXPRESS	TAXUS EXPRESS^2	TAXUS EXPRESS^2
Release kinetics	SR	SR	MR
Patient number	TAXUS 662 Control 652	TAXUS 577 Control 579	TAXUS 219 Control 227
Lesion morphology	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
Lesion length	10 to 28 mm	10 to 46 mm	18 to 40 mm
Vessel diameter	2.5 to 3.75 mm	2.25 to 4.0 mm	2.5 to 3.75 mm
Primary endpoint	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**
Clinical outcomes									
Acute phase				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			
Follow up		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			
Baseline QCA									
RVD				2.07 ± 0.31	2.10 ± 0.33	0.46			
Lesion length				16.6 ± 9.7	16.4 ± 9.2	0.91			
Follow-up QCA		9 months			9 months			9 months	
Late Loss (instent)				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 (instent)				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 ± 0.45 mm versus BMS, 0.95 ± 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^2 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 ≤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 ≥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 ≥80% for Primary Endpoint Achieved	Yes = 1
	No = 0
Follow-up Percentage ≥80% for Angiographic Primary Endpoint or Follow-up Percentage of ≥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		
Clinical outcomes									
Acute phase	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
Follow up	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
Baseline QCA									
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
Post-PCI QCA									
MLD (instent)	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 (instent)	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			
Follow-up QCA	6 months			6 months					
MLD (instent)	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 (instent)	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 (instent)	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 (instent)	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 (Rodoriguez-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 ≥ 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)			**RESEARCH and T-SEARCH subanalysis (Tanimoto et al 2006)**		
	SES	**BMS**	**p value**	**SES**	**PES**	**p value**
Patient number	n = 533	n = 525		n = 107	n = 92	
Trial design	Randomized trial			Non-randomized trial		
1-year follow up						
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
2-year follow up						
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
1-year to 2-year						
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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