Safety and Efficacy of Drug-Eluting Stents: On-Label and Off-Label Perspectives

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Favorable outcomes in multiple randomized trials have resulted in the widespread adoption of drug-eluting stents (DES) during percutaneous coronary intervention (PCI). However, reports of increased stent thrombosis—possibly with increased rates of late death and myocardial infarction (MI)—along with the requirement of an extended course of clopidogrel with DES, have resulted in uncertainties as to which patients should receive DES instead of bare-metal stents (BMS). In most patient and lesion subsets, DES significantly reduce neointimal proliferation (resulting in decreased angiographic restenosis), recurrent angina and ischemia, and the need for subsequent revascularization procedures. DES "off-label" indications include use in patients with multiple lesions and multiple vessels, lesions showing long diffuse disease, very small or very large vessels, true bifurcation lesions, thrombotic lesions, and conditions such as acute MI and chronic total occlusions. For now, pending more data, the risks and benefits of DES for off-label indications must be carefully considered on an individual patient basis.

[Rev Cardiovasc Med. *2008;9(1):46-61*]

Key words: Drug-eluting stents • Bare-metal stents • Percutaneous coronary intervention • Stent thrombosis

Since the introduction of percutaneous coronary intervention (PCI) for the treatment of coronary artery disease, restenosis has been the "Achilles' heel" of angioplasty, resulting in the need for repeat intervention in a significant number of patients. By the late 1990s, the implantation of bare-metal stents (BMS) during PCI had became routine on the basis of numerous studies demonstrating a dramatic reduction in the need for emergency coronary bypass surgery and a moderate but significant reduction in restenosis.[1] However, in large-scale studies, the rate of angiographic in-stent restenosis after BMS has

still ranged from 17% to 47%,[2-7] depending on lesion complexity and patient-related factors, such as diabetes. In as many as 50% of these cases, restenosis after BMS is a diffuse or proliferative process[8] that is associated with a high rate of subsequent recurrence regardless of the type of interventional management.[9]

In-stent restenosis with the need for recurrent revascularization procedures is not just a temporary inconvenience for patients; it also increases the risk of death and myocardial infarction (MI). In a series from the Cleveland Clinic of 1186 cases of in-stent restenosis in a single lesion treated with BMS, 9.5% of patients presented with acute MI (7.3% as non–ST-segment elevation MI and 2.2% as ST-segment elevation MI), and 26.4% of patients presented with unstable angina that required hospitalization before angiography.[10] In 8.9% of the patients, the stent was found to be totally occluded during angiography. Furthermore, the periprocedural death rate to treat restenosis was 0.7%. In-stent restenosis also carries a significant economic burden. More than 1.2 million PCI procedures were performed in the United States in 2003.[11] With an estimated rate of repeat culprit vessel revascularization of 14.4%,[12] the economic burden of in-stent restenosis was more than US$1.2 billion.

The introduction of drug-eluting stents (DES) has been considered a transforming breakthrough. A device combining the scaffolding properties of a metallic stent (to seal dissection planes and prevent recoil), an antiproliferative agent, and a polymer to control drug-dose release kinetics offered the promise of not only achieving a stable immediate postprocedure angioplasty result, but also of ensuring long-term efficacy and durability. In multiple randomized clinical trials, patients treated with DES (with either sirolimus or paclitaxel) have shown significant improvements in angiographic and clinical endpoints as compared with BMS control patients.[13-31] These favorable clinical outcomes have resulted in the widespread adoption of DES during PCI procedures over the past several years in the United States and around the world. However, reports of increased stent thrombosis—possibly with increased rates of late death and MI—along with the requirement of an extended course of clopidogrel with DES, have resulted in uncertainties as to which patients should receive DES instead of BMS.[32-41] The outcomes of DES have recently been categorized for "on-label" indications (in those patients and lesions for which the Food and Drug Administration [FDA] has approved commercialization of DES, based on the results of numerous randomized controlled trials) and "off-label" indications, for which there are fewer rigorous scientific data to guide stent selection. This article will review the current safety and efficacy of DES compared with the alternative of BMS for on-label and off-label indications.

Safety Concerns With DES

Recent studies have demonstrated that stents eluting potent antiproliferative and immunosuppressive agents result in delayed and incomplete endothelialization of the stent struts. As compared with BMS, DES have been associated with incomplete endothelialization from months to more than a year after implantation, as has been demonstrated with various modalities, including light microscopy and scanning electron microscopy.[42,43] Angioscopic studies performed 3 to 6 months after stent implantation have shown that only 13% of sirolimus-eluting stents (SES) (CYPHER®, Cordis Corp, Miami Lakes, FL) have complete strut coverage, compared with 100% of BMS. Thrombi were more common on SES, particularly in those with incomplete neointimal coverage.[44] In an autopsy series of 23 patients with DES implanted more than 30 days earlier, 14 had evidence of stent thrombosis. SES and paclitaxel-eluting stents (PES) (TAXUS® Express²™, Boston Scientific Corp, Natick, MA) showed delayed healing characterized by persistent fibrin deposition and less extensive endothelialization compared with BMS controls. Moreover, endothelialization was less complete in DES associated with late stent thrombosis as compared with patent DES. Local hypersensitivity reactions and strut penetration into a necrotic core were identified as risk factors for late stent thrombosis.[45] Late acquired incomplete apposition of the stent struts to the vessel wall may result as a consequence of local inflammatory reactions to either the drug or the polymer,[46] representing vascular toxicity. When mild to moderate in magnitude, incomplete stent apposition is unapparent angiographically, but it may be demonstrated during intravascular ultrasound. In severe cases, vascular toxicity with marked stent malapposition may manifest as a localized aneurysm.[46] The unopposed stent struts are not endothelialized, and, theoretically, the exposed metal and polymer may activate the coagulation system and serve as a nidus for platelet deposition and subsequent stent thrombosis. In clinical studies, however, a linkage between late incomplete stent apposition and subsequent stent thrombosis has been difficult to establish; a link is present in some studies but not others.[47,48]

Another rare phenomenon that has been described after implantation of SES is endothelial dysfunction

with severe coronary artery spasm resulting in occlusion in the distal coronary artery. This condition is reversible with intracoronary nitroglycerine.[49]

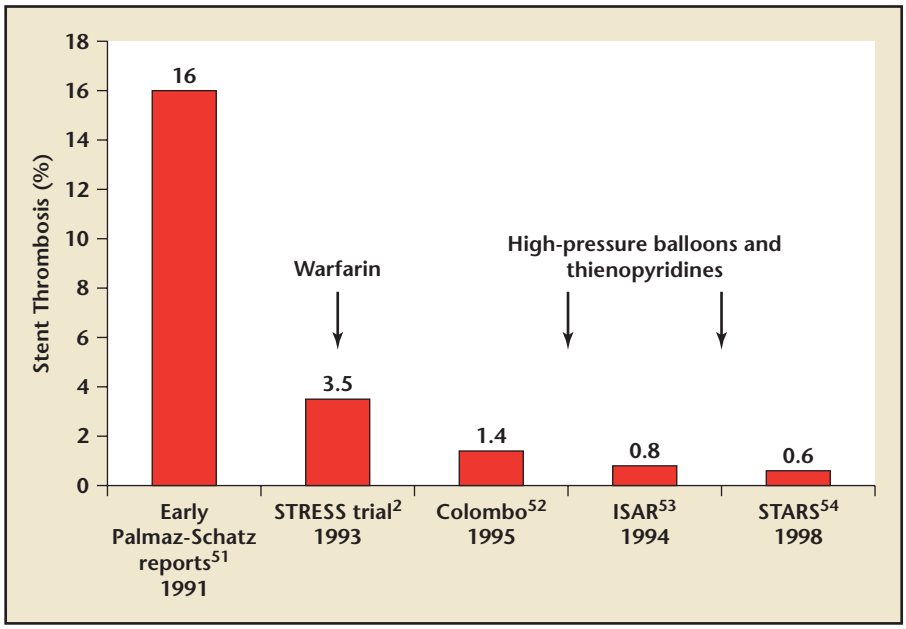
BMS strut fractures have been reported very rarely, possibly because they are difficult to identify. Stent strut fracture with DES has been reported with increasing frequency of late. Theoretically, coverage of the metal stent with polymer and drug may change its mechanical properties, stiffening the device and increasing the risk that flexion or torsional forces may result in strut fracture. In a single-center registry, it was reported that the incidence of stent fracture after SES implantation was 2.6%.[50] Focal restenosis was observed in 37% of these lesions, typically at the fracture site. In at least 2 cases, strut fractures have been associated with stent thrombosis. Significant predictors of stent fracture were saphenous vein graft location, implanted stent length, and right coronary artery location. Strut fractures have also occurred with PES, although in most reports with lower frequency than in SES, possibly due to the more open cell design of the PES stent. The true incidence and clinical consequences of stent strut fracture are unknown due to general unawareness and difficulty in recognizing this condition.

In the early days of BMS, before the recognition of the importance of adequate technique and antiplatelet therapy, stent thrombosis occurred in as many as 16% of patients (Figure 1).[51] With the conversion from heparin to warfarin, stent thrombosis rates fell to 3% to 4%, although hemorrhagic and vascular complications markedly increased.[2] Subsequently, with better implantation techniques (high-pressure implantation and intravascular ultrasound guidance)[52] and dual antiplatelet therapy (aspirin and a thienopyridine, without warfarin), the risk of stent thrombosis declined significantly, to about 1%, and typically occurred within the first 1 to 2 weeks after implantation.[52-55] Recent publications, including registries and meta-analyses, have suggested that DES may be associated with increased rates of stent thrombosis, especially beyond 1 year, as compared with BMS.[34,36,37,39-41,56] These studies have all had significant limitations, however, including insufficient numbers of patients, absence of concurrent controls, limited duration of follow-up, incomplete monitoring, and lack of access to original source data.[57] Long-term clinical follow-up of carefully controlled and systematically monitored randomized trials provides the best level of evidence to assess the safety and efficacy of DES, although to date, many such studies have been underpowered for low-frequency safety events, which requires that results be combined and analyzed in meta-analyses. Moreover, the level of evidence from randomized trials examining the safety and efficacy of DES is currently more robust for on-label than off-label indications.

Definitions of Stent Thrombosis

Another issue that has led to confusion when interpreting the safety of DES is the difficulty and lack of uniformity across studies in defining stent thrombosis. Angiographic or autopsy confirmation of thrombus within or adjacent to the stent is the most certain definition of stent thrombosis, but this approach underestimates the true frequency. The protocols of all the DES randomized controlled trials used a more liberal definition for late stent thrombosis, counting unexplained deaths within 30 days as stent thrombosis, as well as MIs attributable to the target vessel without angiographic confirmation. However, the definitions varied from study to study, and have clearly provided an imprecise estimate of

Figure 1. *Progressive and marked reduction in the rates of bare-metal stent thrombosis by improvements in stent implantation technique and adjunct pharmacotherapy. STRESS, Stent Restenosis Study Investigators; ISAR, Intracoronary Stenting and Anti-thrombotic Regimen; STARS, Stent Anticoagulation Restenosis Study Investigators.*



the true rate of stent thrombosis.[57] Moreover, most of the pivotal randomized trials included only "primary" stent thromboses (those due to the original stent implanted) in the prespecified protocol definition, excluding those secondary events that occurred after an intervening target vessel revascularization (TVR) for restenosis. Although this practice more accurately directs the occurrence of stent thrombosis to the originally implanted stent, it falsely excludes other true thrombotic episodes using the intention-to-treat principle.

In an attempt to provide uniformity and consistency to this field, the Academic Research Consortium (ARC), representing interventional cardiologists, investigators of DES trials, members of the FDA, and industry representatives, proposed a set of consensus definitions for stent thrombosis.[58] The ARC definition considers several distinct reportable time points: acute stent thrombosis (0 to 24 hours after stent implantation); subacute stent thrombosis (from > 24 hours up to 30 days); late stent thrombosis (from 30 days to 1 year); and very-late stent thrombosis (more than 1 year after stent implantation). The ARC definitions recognize 3 levels of evidence: definite, probable, and possible stent thrombosis. *Definite* (or confirmed) stent thrombosis is defined as the occurrence of an acute coronary syndrome, combined with either angiographic or pathologic confirmation of stent thrombosis. *Probable* stent thrombosis is defined as unexplained death within 30 days of implantation or any MI in the territory of the implanted stent at any time in the absence of any other obvious cause. *Possible* stent thrombosis includes all unexplained deaths occurring at least 30 days after the procedure. ARC does not differentiate between primary and secondary thrombotic episodes and includes both in the definition.[58] Because revascularization procedures are more common with BMS than DES, secondary thromboses after interim procedures are more common with BMS,[57] thus masking the true incidence of stent thrombosis due to the original device, although more accurately reflecting the true clinical implications of the stent choice to the patient. For the same reasons, stent thrombosis rates using the ARC definitions will be higher than the protocol definitions. Most investigators believe that the ARC "possible" category is too nonspecific for stent thrombosis, and prefer to use the ARC definite or probable composite as the best compromise for estimating the occurrence of stent thrombosis.

On-Label Use of DES

The FDA-labeled indications for DES refer to stent use in a single de novo lesion in a native coronary artery in patients with stable coronary artery disease. For the polymer-based SES stent, the lesion may be up to 30 mm long, with a reference vessel diameter of 2.5 to 3.5 mm. For the polymer-based PES, the lesion may be up to 28 mm long, with a reference vessel diameter of 2.5 to 3.75 mm. Accordingly, the FDA-approved range for stent diameters is 2.5 to 3.5 mm for each device, with a stent length of up to 33 mm for SES and 32 mm for PES. These "on-label" approval indications by the FDA were based directly on the results of the pivotal studies done in the United States—the Sirolimus-Eluting Stent in de Novo Native Coronary Lesions (SIRIUS) trial for the SES[15] and the TAXUS IV trial for the PES[28]—with supporting data from additional randomized trials performed outside the United States.[57] "Off-label" indications refer to DES use for all lesions and patients not included in the FDA-approved label, such as use in patients with multiple lesions and multiple vessels, lesions showing long diffuse disease, very small or very large vessels, true bifurcation lesions, and thrombotic lesions, and patients with acute MI, chronic total occlusions, stenoses in saphenous venous grafts, and arterial bypass conduits, among other conditions.

All of the completed randomized trials to date have been underpowered for low-frequency safety events. Therefore, several meta-analyses comparing the results of DES and BMS from these trials have been performed to increase the power to evaluate the early and long-term outcomes of DES. These meta-analyses may be categorized as being performed on a trial level or a patient level. Trial-level meta-analyses[39,41,59] have relied on estimates of event rates from limited published results, abstracts, and online summaries, and thus are inherently less accurate than true patient-level meta-analyses, in which all the individual patient baseline and outcome data are available for entry into a single database, allowing time-to-event data calculations and multivariate analyses. Stone and colleagues[57] performed a patient-level pooled meta-analysis of data from 9 double-blind placebo-controlled trials in which 5261 patients were randomly assigned to receive either DES or BMS in single, de novo coronary lesions with follow-up available through median times of 4.0 years for the 4 SES trials (n = 1748) and 3.2 years for the 5 PES trials (n = 3513). Data were pooled from the original databases, with events as defined and adjudicated by the clinical events committees for each study. Of note, the results of this analysis differed from those of the earlier trial-level meta-analyses, which had previously

reported increased rates of composite death or Q-wave MI[39] or of noncardiac mortality[41] with SES compared with BMS, likely due to incomplete data availability. As a result, this review will rely on the results from the more accurate patient-level meta-analyses.

The SES was compared with an otherwise identical BMS, the Bx VELOCITY® stent (Cordis Corp, Miami Lakes, FL), in 4 randomized trials: Randomized Study with the Sirolimus-eluting Velocity Balloon-Expandable Stent (RAVEL),[13,15,18,19] Sirolimus-Eluting Stent in De Novo Native Coronary Lesions (SIRIUS),[15] European Sirolimus-Eluting Stent in De Novo Native Coronary Lesions (E-SIRIUS),[18] and Canadian Sirolimus-Eluting Stent in De Novo Native Coronary Lesions (C-SIRIUS).[19] The protocol designs among these 4 trials had only minor differences. Each trial randomized patients with de novo single lesions and target vessel diameters of 2.5 to 3.5 mm[13,15] or 2.5 to 3.0 mm,[18,19] and lesion lengths of less than 18 mm[13] or 15 to 32 mm.[15,18,19] All of the patients received clopidogrel for at least 2 months (3 months in SIRIUS), and angiographic follow-up was performed in a cohort of patients at 8 months (except for RAVEL at 6 months). In total, 878 patients were treated with SES, and 870 received a BMS, with follow-up data up to 4 years.

PES was compared with an otherwise identical BMS in the 5 trials in the TAXUS series.[26-28,30,60] The stent platform of the TAXUS stent evolved from the NIR (Medinol Ltd, Jerusalem, Israel) stent to the Express, and then to the Express[2] (both Boston Scientific). The included lesions had a reference vessel diameter of 2.25 to 4.0 mm and a length of up to 46 mm, with the exact lesion requirements varying in the 5 trials. In all the TAXUS studies, clopidogrel was administered for at least 6 months, and routine angiographic follow-up was performed in a cohort of patients in each study at 9 months (except for TAXUS I at 6 months). In total, 1749 patients were treated with PES and 1757 received BMS. Follow-up data were available for up to 4 years (median, 3.2 years) at the time of the meta-analysis.

Both DES markedly reduced the 4-year rates of angiographic restenosis, target lesion revascularization (TLR), and TVR as compared with their BMS counterparts (Table 1 and Figure 2). The differences in the rates of clinical restenosis (TLR) between the 2 stents peaked at approximately 1 year, and then remained stable through the 4 years of follow-up (Figure 2, first row). No catch-up phenomenon was observed, confirming the durability of the clinical efficacy of both DES during prolonged

Table 1
Clinical Outcomes of DES Versus BMS With 4 Years of Follow-Up From 9 Double-Blind Randomized Trials

	SES (n = 878)	BMS (n = 870)	*P* Value	PES (n = 1755)	BMS (n = 1758)	*P* Value
Death	6.7%	5.3%	.23	6.1%	6.6%	.68
Cardiac	3.5%	2.7%	.40	2.4%	3.0%	.51
Noncardiac	3.3%	2.7%	.40	3.8%	3.7%	.98
MI	6.4%	6.2%	.86	7.0%	6.3%	.66
Q-wave	2.1%	1.3%	.19	1.4%	1.1%	.42
Non–Q-wave	4.5%	5.0%	.55	5.8%	5.3%	.92
Death or any MI	11.6%	10.4%	.44	12.4%	11.8%	.97
Death or Q-wave MI	8.2%	6.4%	.14	7.3%	7.5%	.93
Cardiac death or MI	8.8%	8.2%	.69	8.9%	8.5%	.82
Stent thrombosis (protocol)	1.2%	0.6%	.20	1.3%	0.9%	.30
Subacute (0 to 30 days)	0.5%	0.1%	.23	0.5%	0.6%	.79
Late (> 30 days to 1 year)	0.1%	0.5%	.18	0.2%	0.1%	.28
Very late (> 1 to 4 years)	0.6%	0	.025	0.7%	0.2%	.028
Target lesion revascularization	7.8%	23.6%	< .001	10.1%	20%	< .001
Target vessel revascularization	12.1%	27.5%	< .001	17.2%	24.7%	< .001

DES, drug-eluting stents; BMS, bare-metal stents; SES, sirolimus-eluting stents; PES, paclitaxel-eluting stents; MI, myocardial infarction.
Adapted with permission from Stone GW et al.[57]

Figure 2. *Event-free survival in patients randomized to the sirolimus-eluting CYPHER stent versus bare-metal stents (left graphs in each panel) and to the paclitaxel-eluting TAXUS stent versus bare-metal stents (right graphs in each panel). Percentages at the end of each of the curves represent the 4-year Kaplan-Meier estimates of event-free survival, and in parentheses are the associated numbers of actual events. First row: Freedom from ischemic target lesion revascularization. Second row: Freedom from all-cause death. Third row: Freedom from myocardial infarction. Fourth row: Freedom from protocol-defined stent thrombosis.*

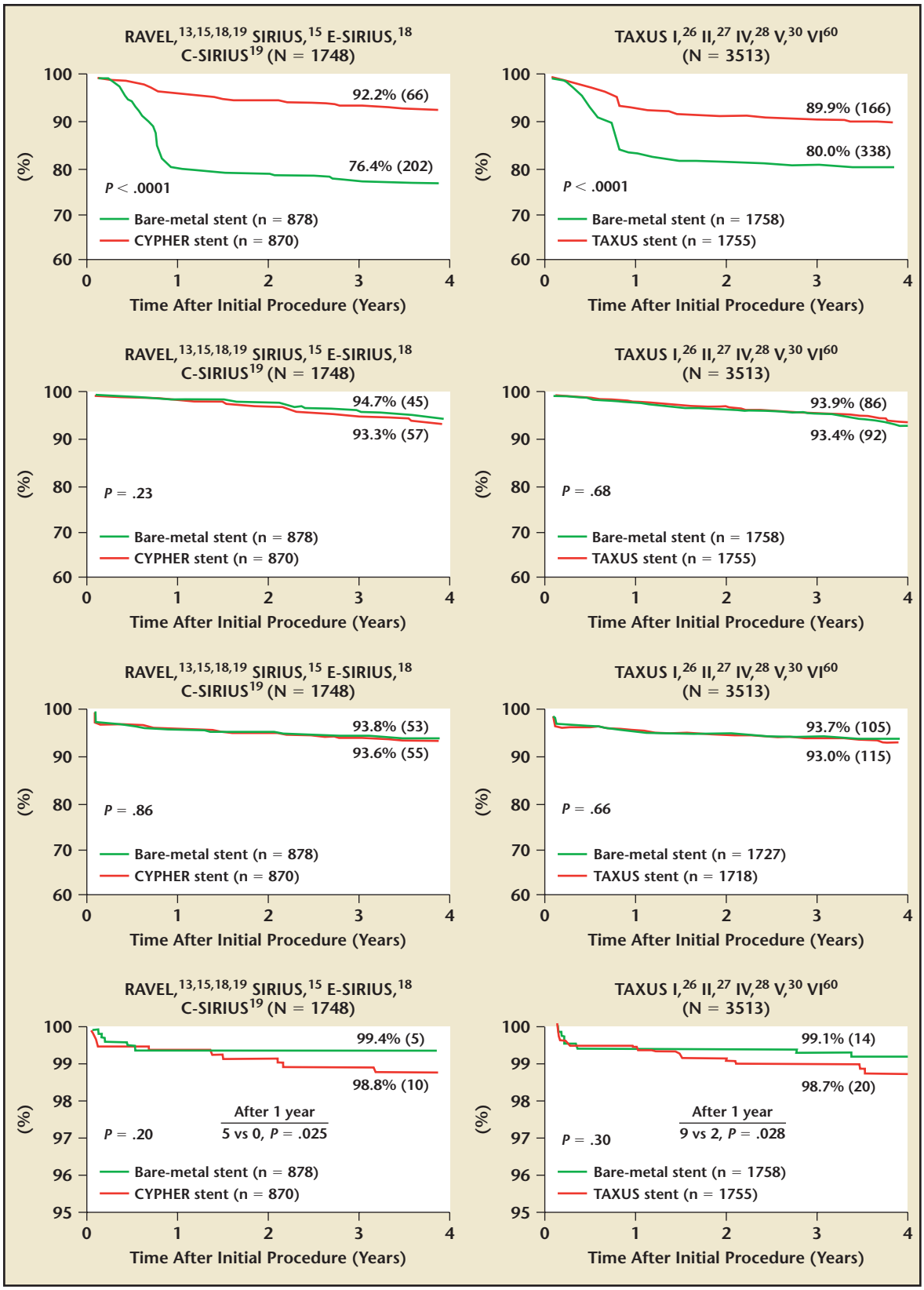


Table 2
Late Angiographic Outcomes* of DES Versus BMS From 9 Double-Blind Randomized Trials

	SES (n = 658)	BMS (n = 670)	*P* Value	PES (n = 1352)	BMS (n = 1342)	*P* Value
Late loss (mm)						
In-stent	0.14 ± 0.42	0.99 ± 0.66	< .001	0.41 ± 0.54	0.90 ± 0.59	< .001
In-segment	0.17 ± 0.44	0.75 ± 0.64	< .001	0.31 ± 0.50	0.67 ± 0.58	< .001
Binary restenosis						
In-stent	2.6%	36.6%	< .001	10.1%	29.4%	< .001
In-segment	6.4%	37.8%	< .001	14.0%	31.7%	< .001

*At 6 months for RAVEL, TAXUS-I, and TAXUS-II; 8 months for SIRIUS, E-SIRIUS, and C-SIRIUS; and 9 months for TAXUS-IV, TAXUS-V, and TAXUS-VI.
DES, drug-eluting stents; SES, sirolimus-eluting stents; BMS, bare-metal stents; PES, paclitaxel-eluting stents; RAVEL, Randomized Study with the Sirolimus-eluting Velocity Balloon-Expandable Stent; SIRIUS, Sirolimus-Eluting Stent in De Novo Native Coronary Lesions; E-SIRIUS, European Sirolimus-Eluting Stent in De Novo Native Coronary Lesions; C-SIRIUS, Canadian Sirolimus-Eluting Stent in De Novo Native Coronary Lesions.
Adapted with permission from Stone GW et al.[57]

follow-up. As shown in Table 2, among the patients undergoing routine angiographic follow-up, both DES greatly reduced late luminal loss and binary restenosis as compared with BMS: both in-stent (within the stent margins) and in-segment (which includes the reference vessel margins 5 mm proximal and distal to the stent edges).[57] The superiority of both DES over BMS in reducing restenosis and the need for clinical revascularization procedures was maintained in multiple subgroups, including men and women, patients with and without diabetes mellitus, small and large vessels, short and long lesions, and the use of single or overlapping stents.

The cumulative 4-year rates of death from any cause in the SES group did not differ significantly from that in the BMS group (6.7% vs 5.3%; $P = .23$); the differences in 4-year mortality between the PES group and the BMS group was also not significant (6.1% vs 6.6%; $P = .68$) (Table 1; Figure 2, second row). Nor were there significant differences between either of the DES and their control BMS when comparing either cardiac or noncardiac mortality, or in the cumulative combined rates of death and MI (Table 1). The cumulative 4-year rates of MI were also similar in the SES and BMS groups (6.4% vs 6.2%; $P = .86$) and in the PES and BMS groups (7.0% vs 6.3%; $P = .66$), with no significant differences in the rates of either Q-wave or non–Q-wave MI (Table 1; Figure 2, third row).

From stent implantation through 4 years of follow-up, the rates of protocol-defined primary stent thrombosis among patients with SES did not differ significantly from the rates among patients with BMS (1.2% vs 0.6%; $P = .20$). Similarly, there were no significant differences in the 4-year cumulative rates of primary stent thrombosis between PES and BMS (1.3% vs 0.9%; $P = .30$) (Table 1; Figure 2, fourth row). However, between 1 and 4 years, the rates of primary stent thrombosis in the SES group and the BMS group were 0.6% versus 0%, respectively ($P = .025$, consistent with 1 extra event per 489 patient years). Similarly, the rates of primary stent thrombosis after 1 year in the PES group and the BMS group were 0.7% versus 0.2%, respectively ($P = .028$, consistent with 1 extra event per 557 patient-years).

There are at least 2 reasons why the increased rate of very late stent thrombosis with DES compared with BMS does not translate into increased death or MI. The first is that by preventing restenosis, DES actually reduce death and MI as compared with BMS. Several trials have emphasized that restenosis may present as death or MI, and the procedures required to treat restenosis also result in death or MI.[10,61,62] To directly test this hypothesis, Stone and colleagues[63] performed a blinded analysis of 4 randomized TAXUS trials (N = 3445), measuring the incidence of death or MI within 1 week of either the occurrence of a stent thrombosis or TLR in the 4 years after PES or BMS device implantation. Stent thrombosis occurred in 34 patients (1.0%), 31 (91.1%) of whom died or had an MI within

. . . by preventing restenosis, DES actually reduce death and MI as compared with BMS.

1 week. Stent thrombosis occurred in 14 BMS and 20 PES patients, resulting in 12 and 19 deaths or MIs within 1 week, respectively. In contrast, TLR was required in 425 patients (12.3%), 15 (3.5%) of whom died or had an MI within 1 week. TLR was performed in 290 BMS patients and 135 PES patients, resulting in 11 and 4 deaths or MIs within 1 week, respectively. In total, 23 patients in both the BMS and PES groups died or had an MI within 1 week of either stent thrombosis or TLR. Thus, stent thrombosis, although infrequent, results in a high rate of death and MI, whereas the more frequently occurring TLR is associated with a finite but lower rate of death and MI that counterbalances what otherwise might have been an increased risk of adverse events with DES.

The second reason that stent thrombosis, as defined in the pivotal randomized DES trials, does not result in an increased rate of death and MI is that this risk is counterbalanced by an increased rate of secondary thrombotic events that occur after TLR in BMS patients. Mauri and colleagues[58] analyzed the raw data from the 4 randomized clinical trials with SES (878 SES patients vs 870 BMS patients)[13,15,18,19] and 4 randomized PES trials (1400 SES patients vs 1397 BMS patients),[26-28,30] readjudicating the stent thrombosis according to the ARC definitions. With consideration of both primary and secondary thrombotic events, the cumulative 4-year incidence of definite or probable stent thrombosis as defined by the ARC was 1.5% in the SES group versus 1.7% in the BMS group (P = .70), and 1.8% in the PES group versus 1.4% in the BMS group (P = .52). The incidence of definite or probable events occurring 1 to 4 years after implantation was 0.9% in the SES group versus 0.4% in the BMS group, and 0.9% in the PES group versus 0.6% in the BMS group (P = NS for both comparisons). Of note, very late stent thrombosis events (> 1 year) occurred in all 4 stent groups; nearly 40% of the cases of very late stent thrombosis were among patients who received BMS. Thus, by intention-to-treat standards, stent thrombosis is not increased with DES; the increased primary risk of stent thrombosis with DES is offset by a reduced risk of secondary thrombotic events as compared with BMS.

Off-Label Use of DES

Even before the introduction of DES, BMS were commonly used to treat a wide spectrum of "off-label" lesions and patients. The lesions included those showing multivessel disease or small vessels, lesions with diffuse disease, ostial lesions, bifurcation lesions, and restenotic lesions. The patients were at high risk, with conditions such as acute MI and diseased saphenous vein grafts. It has been estimated that approximately 60% of stent use is in such "off-label" indications.[64] Whether DES are more effective and as safe as BMS in these settings has been a matter of great debate. Data from randomized trials and registries can be used to consider stent selection decisions for off-label use.

Outcomes with DES for on-label and off-label indications. Three recent studies have attempted to compare the outcomes following on-label and off-label use of DES.[64-67] These studies have varied in their definitions of off-label DES use and the completeness with which baseline characteristics were collected to accurately make this determination. Nonetheless, the results are generally concordant.

The American College of Cardiology National Cardiovascular Data Registry (ACC-NCDR), a national multicenter database of PCI procedures, was used to examine the frequency and in-hospital outcomes of off-label DES use from the second quarter of 2003 to the end of the fourth quarter of 2004.[64] A total of 408,033 DES procedures were included; 24% of the procedures were performed for one of the following off-label indications: acute MI, in-stent restenosis, bypass graft intervention, and chronic total occlusions. The mortality rates of each of the off-label–treated patients were actually lower than expected from the ACC-NCDR mortality model.

In the DEScover US-based multicenter registry,[66] off-label use of SES was defined as stenting of a restenotic lesion, lesions in a bypass graft, lesion length greater than 30 mm, or reference-vessel diameter less than 2.5 mm or greater than 3.5 mm. For PES, the lesion criteria were identical except for lesion length greater than 28 mm and reference-vessel diameter less than 2.5 mm or greater than 3.75 mm as the criteria for off-label indications. The researchers further defined "untested use" for conditions for which the safety and effectiveness of DES have not been established, specifically left main and ostial lesions, bifurcations, and totally occluded vessels. DES use in the presence of acute MI was defined as off-label, untested, or standard, based on lesion characteristics and regardless of the presence of the infarction per se, although such indications technically are off-label according to the FDA. Of 5541 patients receiving DES from January 2005 to June 2005 at 140 hospitals in this registry, 2953 (53.3%) were treated per the on-label indication, 1398 (25.2%) were off-label, and 1190 (21.5%) were for untested lesion types. Periprocedural and in-hospital outcomes were similar among the

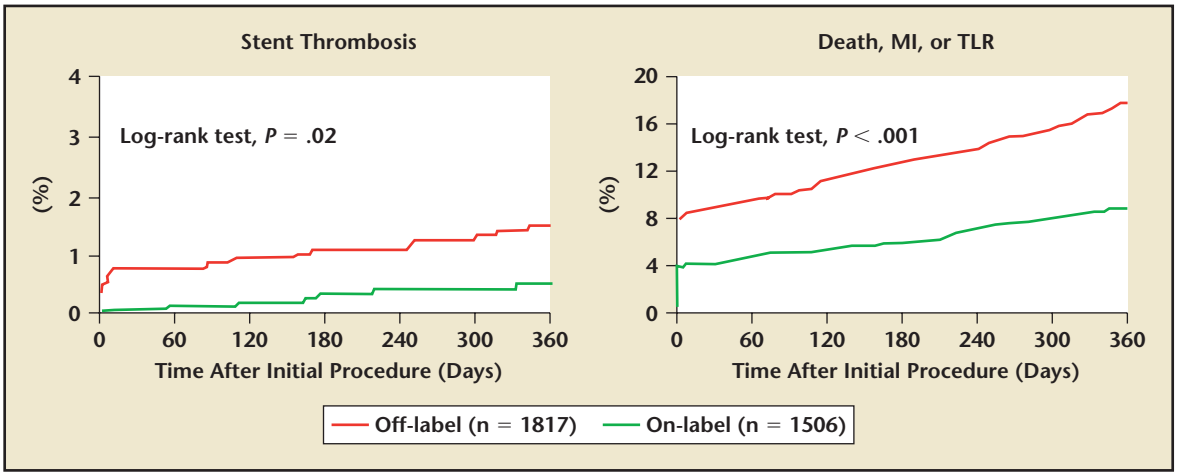
3 groups. At 30-day follow-up, however, the composite endpoint of death, MI, and stent thrombosis was significantly higher with off-label use than with on-label use (2.5% vs 1.0%; adjusted hazard ratio [HR], 2.08; 95% confidence interval [CI], 1.24-3.48; $P = .005$) but not untested use (1.6% vs 1.0%; adjusted HR, 1.45; 95% CI, 0.79-2.67; $P = .23$). At 1 year, the trend remained (7.6% vs 4.4%), with a small increase in the adjusted hazard ratio of 1.49 (95% CI, 1.13-1.98; $P = .005$) in off-label use compared with on-label use. No differences in 1-year death rates were present between on-label and untested use (4.4% vs 4.3%; P = NS). Stent thrombosis rates were very low in all groups at all time points. Both off-label and untested indications were associated with increased rates of repeat TVR.

A second US-based registry, the Evaluation of Drug Eluting Stents and Ischemic Events (EVENT) registry, also found higher adverse event rates with off-label use compared with on-label DES use.[67] Of 3323 patients who received DES at 42 hospitals between July 2004 and September 2005 (51% SES, 49% PES), 54.7% had at least 1 off-label characteristic, including multilesion stenting, total stent length at or greater than 36 mm, bifurcation lesion, saphenous vein bypass graft, elevated baseline creatine phosphokinase-MB (CPK-MB), total occlusion, maximal balloon diameter greater than 4 mm, left ventricular ejection fraction less than 25%, and unprotected left main coronary artery intervention. Off-label compared with on-label DES use was associated with more acute angiographic complications, in particular, side branch occlusion and dissections. As shown in Figure 3, the event-free survival curves also diverged immediately after the procedure, and at 1 year, the composite endpoint of death, MI, or TLR was significantly more frequent with off-label use than with on-label use (17.5% vs 8.9%; adjusted HR, 2.16; 95% CI, 1.74-2.67; $P < .001$). Stent thrombosis also occurred more frequently among patients in the off-label group (1.6% vs 0.9%; HR, 2.29; 95% CI, 1.02-5.16; $P = .05$). Off-label use was the strongest independent predictor of adverse short- and long-term events.[67]

It is not surprising that off-label compared with on-label use of DES is associated with higher rates of adverse events, including death, MI, stent thrombosis, and TLR (as seen in the DEScover and EVENT registries). Off-label patients have higher rates of comorbidities, such as diabetes, significantly more diffuse atherosclerosis, and other conditions, such as depressed left ventricular function and presentation with acute MI, that adversely impact prognosis regardless of the chosen therapy. The major question to answer is how DES would fare in such patients compared with reasonable therapeutic alternatives, such as BMS use, medical therapy, or coronary artery bypass graft surgery. To address this important issue, studies have been completed in which the outcomes of patients receiving BMS or DES for off-label indications have been examined in large-scale "real world" registries. In addition, a number of randomized trials of DES for specific off-label indications have been completed or are ongoing.

Real-world registries. Observational registries typically enroll consecutive patients with limited

Figure 3. *One-year cumulative occurrence of stent thrombosis (left graph) and composite death, myocardial infarction (MI), or target lesion revascularization (TLR) (right graph) among 3323 patients receiving drug-eluting stents for either on-label use (n = 1506; thin lines) or off-label use (n = 1817; thick lines) at 42 hospitals in the Evaluation of Drug Eluting Stents and Ischemic Events (EVENT) registry. Adapted with permission from Win HK et al.* JAMA. *2007;297:2001-2009.*[67] *Copyright © 2007, American Medical Association. All rights reserved.*



exclusion criteria. Such "all comer" studies in principle represent real world practice, and include high proportions of patients with complex disease. The major limitation of registries is that the selection of one treatment versus another is not controlled. Although sophisticated statistical adjustments can be applied to attempt to correct for baseline imbalances or treatment propensities, unmeasured or unrecorded confounders cannot be corrected for, in contrast to the process of randomization, which inherently balances the rate of both measured and unmeasured covariates between treatment groups. A second major limitation of many registries is that independent monitoring of source documents is often sparse or nonexistent, and independent, blinded core laboratories and clinical event adjudication committees typically are not used—again, in contrast to well-run randomized trials. As such, bias is much more likely in registries than in randomized trials. Conversely, randomized trials apply only to the narrow range of patients and lesion types enrolled, and are subject to their own unique set of biases. Therefore, although an appropriately powered, large-scale randomized clinical trial is widely accepted as the highest level of scientific evidence on which clinical decision-making should be based, "real world" registries provide useful complementary information as long as their limitations are recognized.

Large-scale registries (in which both on-label and off-label patients and lesions have been enrolled) have provided conflicting data regarding the safety of DES in unrestricted use, although recently the conclusions from most of these studies have become concordant. The initial report from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) included all patients from 26 centers in Sweden who had received coronary stents from January 1, 2003 to December 31, 2004, and in whom complete follow-up data were available.[40] They compared the group of 6033 patients treated with DES with the group of 13,738 patients treated with BMS. Notably, the 2 groups markedly varied in baseline characteristics. For example, the BMS group had more patients with acute MI, whereas the DES group included more women, more patients with diabetes, longer lesions, more frequent involvement of the left anterior descending artery, and more frequent stenting of multiple lesions and vessels, requiring a greater number of stents and longer stents. Propensity adjusted Cox multivariate analysis was used to attempt to correct for the differences in baseline characteristics.

The primary endpoint of composite death or MI at 3 years was no different between the DES and BMS groups, either in an unadjusted analysis or after adjustment for differences in baseline characteristics. Within the first 6 months, there was a trend toward a lower unadjusted event rate in patients receiving DES compared with BMS, with 13.4 fewer such events per 1000 patients. However, after 6 months, patients receiving DES had a significantly higher event rate, with 12.7 more events per 1000 patients per year (adjusted relative risk, 1.20; 95% CI, 1.05-1.37). At 3 years, overall mortality was significantly higher in patients treated with DES rather than BMS (adjusted relative risk, 1.18; 95% CI, 1.04-1.35), and in a landmark analysis from 6 months to 3 years, the adjusted relative risk for death in this group was 1.32 (95% CI, 1.11-1.57). These findings indicated an ongoing increase in the risk of death with DES compared with BMS of approximately 0.5% per year, and an increase in the incidence of death or MI after 6 months of 0.5% to 1.0% per year. Following the publication of the SCAAR report[40] (and a government advisory), DES use plummeted in Sweden and other Nordic countries. Widespread discussion of these results in the media led to significant concern among patients and health care providers.

Surprisingly, the SCAAR investigators reversed their conclusions at the European Society of Cardiology Congress held in September 2007, based on 1 additional year of follow-up and a near doubling of the number of patients studied (including patients enrolled in 2005).[68] As presented by Stefan James, MD, of the Academic Hospital, Uppsala, Sweden, SCAAR now reported the comparative outcomes from 35,226 patients, including 21,480 treated with BMS and 13,786 treated with DES. The 4-year adjusted rates of death or MI were now almost identical between DES and BMS (relative risk, 1.01; 95% CI, 0.94-1.09), as were the adjusted rates of death (relative risk, 1.03; 95% CI, 0.94-1.14) and MI (relative risk, 1.01; 95% CI, 0.91-1.11). In the landmark analyses, there were now no significant differences in the rates of death either before 6 months (relative risk, 0.02; 95% CI, 0.78-1.07) or between 6 months and 4 years (relative risk, 1.09; 95% CI, 0.92-1.05).

The major differences between the SCAAR results from the earlier report and those from the present study can be attributed to the outcomes in the new cohort of patients enrolled in 2005. In contrast to the finding of worse late outcomes after DES compared with BMS in patients enrolled in 2003 and 2004, among the 2005 cohort, the composite incidence of death or MI was reduced with DES compared with BMS between the

time of enrollment and 6 months (relative risk, 0.69; 95% CI, 0.59-0.81), and tended to be reduced between 6 months and 2 years (relative risk, 0.93; 95% CI, 0.76-1.13). This improvement over time may be attributed to better operator technique with increasing experience and/or better patient selection. Of note, DES penetration had increased to 53% of all the patients enrolled in the 2005 cohort, suggesting that simpler lesions were now being included, perhaps allowing for more accurate statistical correction. Finally, the overall 3-year rate of clinical restenosis (reported for the single-stent cohort) was reduced from about 8% to about 4%, a 52% reduction.

Other large-scale registries have reported similar or lower rates of adverse events with DES compared with BMS. In the prospective REgistro AngiopLastiche dell'Emilia Romagna (REAL) registry of 10,629 "real-world" patients from 13 Italian centers enrolled between July 2002 and June 2005, 3064 received DES and 7565 received BMS.[69] At 2 years of follow-up, DES resulted in lower adjusted rates of TVR (9.1% vs 12.9%; $P < .0001$), and combined major adverse cardiac events (16.9 vs 21.8%; $P < .0001$), with no significant differences in the adjusted rates of death (6.8% vs 7.4%; $P = .35$) and MI (5.3% vs 5.8%; $P = .49$).

The Western Denmark Registry investigators reported the outcomes in 12,395 patients with 17,152 lesions treated with either BMS (n = 8847 patients) or DES (n = 3548 patients) between January 2002 and June 2005 at 3 high-volume hospitals caring for 3 million inhabitants of the country.[70] As seen in Table 3, the 15-month adjusted rates of mortality, MI, and stent thrombosis were similar between the 2 stent types, and TLR was significantly reduced with DES.

Patrick Serruys, MD, PhD, of Erasmus University in Rotterdam, the Netherlands, presented his single-center experience with DES at the FDA advisory panel meeting in December 2006.[71] He compiled data from 3 time intervals, in each of which a different type of stent was used exclusively. From April 2002 to February 2003, only SES were used (n = 979), and from February 2003 to December 2005, only PES were used (n = 3019). The control cohort was patients enrolled between January 2000 and April 2002, during which only BMS were available (n = 2444). Overall, 13,150 stents were implanted in 6442 patients. At 3 years of follow-up, survival from all-cause mortality was significantly higher with SES than with PES or BMS (92.1% vs 89.1% and 89.1%, respectively; $P < .01$ for both). Mortality was reduced with SES in the subgroup of nondiabetic patients. No significant differences in survival were found among the 3 stent types, except in diabetic patients.

Similarly, Wake Forest Medical Center in Winston-Salem, NC, has reported a single-center registry experience comparing results with BMS and DES. The BMS were placed in 1164 patients the year before DES became available (April 2002 to April 2003). After this time, DES were placed in 1285 comparable patients,

Table 3
Clinical Outcomes at 15 Months in Patients Treated With DES and BMS in the Western Denmark Registry

	DES (n = 3548)	BMS (n = 8847)	Unadjusted *P* Value	Adjusted* Hazard Ratio (95% CI)	Adjusted* *P* Value
Stent thrombosis (ARC)					
Definite	0.6%	0.7%	.65	—	—
Definite, probable, or possible	1.8%	2.2%	.20	0.91 (0.67-1.24)	.57
Death	4.4%	6.2%	< .001	0.90 (0.75-1.09)	.29
Cardiac	2.4%	3.8%	.002	0.88 (0.68-1.13)	.31
Myocardial infarction	3.2%	3.0%	.65	1.14 (0.89-1.45)	.31
Target lesion revascularization	4.6%	7.1%	< .0001	0.57 (0.48-0.67)	< .001

*Adjusted for age, sex, clinical indication, and procedure time.
DES, drug-eluting stent; BMS, bare-metal stents, ARC, Academic Research Consortium; CI, confidence interval.
Adapted with permission from Jensen LO et al.[70]

of whom 72% had acute coronary syndromes.[72] At 9 months, mortality was 4.9% with DES compared with 7.1% with BMS (propensity adjusted Cox multivariate hazard ratio, 0.56; 95% CI, 0.36-0.87; $P = .03$). TVR was reduced to 2.8% with DES from 8.6% with BMS ($P < .001$).

Finally, the Strategic Transcatheter Evaluation of New Therapies (STENT) investigators represent physicians at 8 US hospital centers who enrolled 7008 patients treated between 2003 and 2005 into a registry. Results from patients who received a DES (n = 5631) were compared with those who received a BMS (n = 1377). As presented by Chuck Simonton, MD, of the Sanger Clinic, PA, in Charlotte, NC, at the Transcatheter Cardiovascular Therapeutics meeting in October 2006, DES use resulted in reduced 9-month rates of death, MI, and TVR as compared with BMS (Figure 4).[73] In patients who reached the 2-year follow-up time point, DES (n = 2114) resulted in a 50% reduction in mortality as compared with BMS (n = 756) (5.9% vs 11.4%; HR, 0.50; 95% CI, 0.37-0.67; $P = .001$).

Randomized trials. Major concerns about increased late adverse event rates with DES were first seriously raised by the Basel Stent Kosten Effektivitäts Trial (BASKET). In this study, 826 consecutive patients were randomized in a 2:1 fashion to DES (n = 545) versus BMS (n = 281) and were followed clinically to examine the relative cost effectiveness of the 2 devices.[74] The BASKET-LATE phase of this investigation examined the outcomes in 746 patients who had no major adverse events by 6 months, the time at which clopidogrel was to be discontinued.[37] In the subsequent 12 months of follow-up, although there were no significant differences in the rates of stent thrombosis with DES compared with BMS (1.4% vs 0.8%; $P = .50$), there was a significant increase in the incidence of composite death or MI with DES (4.9% vs 1.3%; $P = .01$). This analysis has been criticized because it excluded from the late analysis the potentially higher risk patients who had events within the first 6 months. Indeed, when the 18-month results were reported, which included all patients in a true intention-to-treat analysis, there was no significant difference between DES and BMS in the rates of composite death or MI (8.4% vs 7.5%; $P = .63$), but TVR was required less frequently with DES (7.5% vs 11.6%; $P = .04$). By multivariate analysis, DES reduced the risk of restenosis-related TVR by 48% (HR, 0.52; 95% CI, 0.33-0.85; $P = .009$).[37]

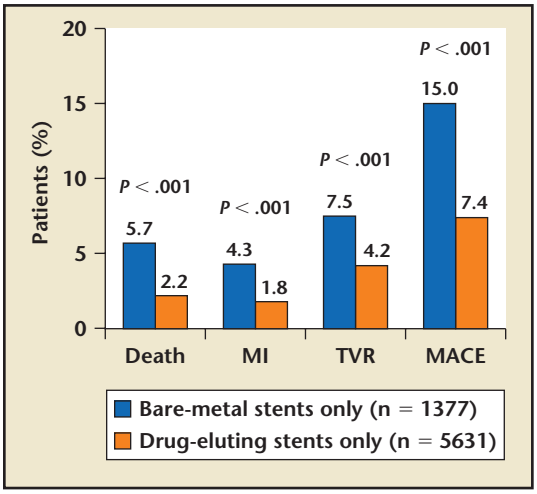


Figure 4. *Nine-month rates of death, myocardial infarction (MI), target vessel revascularization (TVR) and composite major adverse cardiac events (MACE) (death, MI, or TVR) among 7008 patients treated with bare-metal stents or drug-eluting stents at 8 US hospitals in the Strategic Transcatheter Evaluation of New Therapies (STENT) registry. See text for details. Adapted with permission from Simonton C.*[73]

Small randomized trials have been completed comparing DES with BMS for specific off-label indications, including bifurcation lesions,[75-77] chronic total occlusions,[22] in-stent restenosis lesions,[31,78,79] saphenous venous bypass grafts,[23,80] long lesions,[30,60] small vessels,[24,30] and MI.[81] For the most part, these trials have shown similar rates of death, MI, and stent thrombosis between DES and BMS, with reduced rates of TLR and TVR with DES (with 2 exceptions: routine DES implantation in the side branches of bifurcations has not been shown to be beneficial,[75-77] and concern about increased late events with DES in saphenous vein grafts was raised in 1 small study).[80] However, these trials have been underpowered to be definitive, and the results of large-scale, ongoing randomized trials are awaited.

Kastrati and colleagues[59] performed a meta-analysis of 14 randomized controlled studies (4958 patients) that compared SES with BMS with at least 1 year of follow-up. The studies included the 4 pivotal double-blind "on-label" lesion trials, as well as 10 additional trials that concentrated on specific patient and lesion subsets including diabetic patients, chronic total occlusions, small vessels, saphenous vein grafts, and acute MI. The overall risk of death and the combined risk of death or MI were not significantly different for patients receiving SES versus BMS in this meta-analysis (HRs, 1.03 and 0.97, respectively; P = NS). However, there was a marked reduction in the combined risk of death, MI, or reintervention (HR, 0.43; $P < .0001$) associated with the use of SES. There was no significant difference in the overall risk of stent

thrombosis with SES (hazard ratio, 1.09), but there was a slight increase in the risk of stent thrombosis associated with SES after the first year following the procedure (0.6% vs 0.05%; $P = .02$).

Three large-scale prospective randomized trials that have adequate power to significantly impact revascularization decisions with DES are ongoing. The Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optional Management of Multivessel Disease (FREEDOM) trial is a study sponsored by the National Heart, Lung, and Blood Institute in which 2400 patients with diabetes mellitus and either double or triple vessel coronary artery disease are being randomized to DES with either PES or SES versus coronary artery bypass graft surgery. The Synergy Between PCI and TAXUS and Cardiac Surgery (SYNTAX) trial is randomizing 1800 patients with left main and/or triple vessel disease to PES versus bypass graft surgery. Finally, the Harmonizing Outcomes with Revascularization and Stents in Acute MI (HORIZONS AMI) trial is randomizing 3400 patients with acute MI to either PES or BMS. The latter 2 trials have completed enrollment, with the results expected in 2008.

FDA Advisory Panel Recommendations

In December 2006, the Circulatory System Devices Advisory Panel of the FDA met over a 2-day period and heard numerous presentations from physician-scientists, professional societies, and stent manufacturers in an effort to characterize the risks, timing, and incidence of thrombosis with DES.[64] The panel concluded that for on-label indications, for which solid data were available from the results of numerous double-blind randomized trials, both approved DES compared with BMS are associated with a small increase in the rate of stent thrombosis that emerges after 1 year following stent implantation. However, based on the data available, this increased risk of stent thrombosis was not associated with an increased risk of death or MI, and both DES were effective in reducing angiographic and clinical restenosis, resulting in fewer revascularization procedures. The FDA panel thus concluded that concerns about stent thrombosis do not outweigh the benefits of DES as compared with BMS for on-label use.

The FDA panel also addressed the broader use of DES in patients with more complex patients and lesions (off-label use). The panel concluded that DES use for off-label compared with on-label indications is associated with an increased risk of stent thrombosis, death, and MI. However, the panel determined that inadequate comparative trials have prevented the development of definitive recommendations regarding the safety and efficacy of DES as compared with alternative treatments (medical therapy, BMS, and surgery) in these patients. The panel recommended that, until more data are available, the DES labels should state that when DES are used off-label, patient outcomes may not be as favorable as the results observed in the clinical trials conducted to support marketing approval.[64]

Summary

DES represent a remarkable advance in the evolution of therapies to treat coronary artery disease. In most patient and lesion subsets examined, both SES and PES significantly reduce neointimal proliferation (resulting in decreased angiographic restenosis), recurrent angina and

Main Points

- In-stent restenosis with the need for recurrent revascularization procedures is not just a temporary inconvenience for patients; it also increases the risk of death and myocardial infarction (MI).
- Drug-eluting stents (DES) markedly reduce the 4-year rates of angiographic restenosis, target lesion revascularization (TLR), and target vessel revascularization as compared with bare-metal stents (BMS).
- Data from randomized trials show that the cumulative 4-year rates of death from any cause in patients with sirolimus-eluting stents do not differ significantly from those in patients with BMS.
- Stent thrombosis, although infrequent, results in a high rate of death and myocardial infarction (MI), whereas the more frequently occurring TLR is associated with a finite but lower rate of death and MI that counterbalances what otherwise might have been an increased risk of adverse events with DES.
- Approximately 60% of stent use is in "off-label" indications.
- For now, pending more data, the risks and benefits of DES for off-label indications must be carefully considered on an individual patient basis.

ischemia, and the need for subsequent revascularization procedures (both repeat PCI and bypass graft surgery). Stent thrombosis occurs in about 1 to 3 patients per 500 patient-years beyond 1 year of DES implantation, with the higher rates evident in more complex lesions and high-risk patients. Currently, all patients not at high risk for bleeding should be maintained on clopidogrel (in addition to aspirin) for at least 1 year, although whether prolonged clopidogrel use prevents late stent thrombosis is controversial, with conflicting data reported.[82,83] Nonetheless, the overall safety of DES for on-label use has been firmly established in randomized controlled trials, with both PES and SES having comparable rates with BI in long-term survival free from MI, with marked reductions in recurrent ischemia and repeat revascularization procedures. For now, pending more data, the risks and benefits of DES for off-label indications must be carefully considered on an individual patient basis. Fortunately, several large-scale trials have completed enrollment, the results of which will soon be available to guide treatment selection. Several second-generation DES will soon be approved in the United States that may further enhance the safety and efficacy profiles of stents in select patients and lesions. Finally, focused development efforts are underway to better define the causative mechanisms of early and late stent thrombosis, and to respond with improved devices incorporating changes in bioactive agents and surfaces, drug carrier systems, and pharmacotherapeutic advances. ■

References

1. Brophy JM, Belisle P, Joseph L. Evidence for use of coronary stents. A hierarchical bayesian meta-analysis. *Ann Intern Med*. 2003;138:777-786.
2. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med*. 1994;331:496-501.
3. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med*. 1994;331:489-495.
4. Lansky AJ, Roubin GS, O'Shaughnessy CD, et al. Randomized comparison of GR-II stent and Palmaz-Schatz stent for elective treatment of coronary stenoses. *Circulation*. 2000;102:1364-1368.
5. Baim DS, Cutlip DE, O'Shaughnessy CD, et al. Final results of a randomized trial comparing the NIR stent to the Palmaz-Schatz stent for narrowings in native coronary arteries. *Am J Cardiol*. 2001;87:152-156.
6. Baim DS, Cutlip DE, Midei M, et al. Final results of a randomized trial comparing the MULTI-LINK stent with the Palmaz-Schatz stent for narrowings in native coronary arteries. *Am J Cardiol*. 2001;87:157-162.
7. Holmes DR Jr, Savage M, LaBlanche JM, et al. Results of Prevention of RESstenosis with Tranilast and its Outcomes (PRESTO) trial. *Circulation*. 2002;106:1243-1250.
8. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation*. 1999;100:1872-1878.
9. Mehran R, Dangas G, Mintz GS, et al. Treatment of in-stent restenosis with excimer laser coronary angioplasty versus rotational atherectomy: comparative mechanisms and results. *Circulation*. 2000;101:2484-2489.
10. Chen MS, John JM, Chew DP, et al. Bare metal stent restenosis is not a benign clinical entity. *Am Heart J*. 2006;151:1260-1264.
11. Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2006;113:e85-e151.
12. Cutlip DE, Chauhan MS, Baim DS, et al. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. *J Am Coll Cardiol*. 2002;40:2082-2089.
13. Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med*. 2002;346:1773-1780.
14. Fajadet J, Morice MC, Bode C, et al. Maintenance of long-term clinical benefit with sirolimus-eluting coronary stents: three-year results of the RAVEL trial. *Circulation*. 2005;111:1040-1044.
15. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med*. 2003;349:1315-1323.
16. Holmes DR Jr, Leon MB, Moses JW, et al. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. *Circulation*. 2004;109:634-640.
17. Weisz G, Leon MB, Holmes DR Jr, et al. Two-year outcomes after sirolimus-eluting stent implantation: results from the Sirolimus-Eluting Stent in de Novo Native Coronary Lesions (SIRIUS) trial. *J Am Coll Cardiol*. 2006;47:1350-1355.
18. Schofer J, Schluter M, Gershlick AH, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet*. 2003;362:1093-1099.
19. Schampaert E, Cohen EA, Schluter M, et al. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). *J Am Coll Cardiol*. 2004;43:1110-1115.
20. Sabate M, Jimenez-Quevedo P, Angiolillo DJ, et al. Randomized comparison of sirolimus-eluting stent versus standard stent for percutaneous coronary revascularization in diabetic patients: the diabetes and sirolimus-eluting stent (DIABETES) trial. *Circulation*. 2005;112:2175-2183.
21. Pache J, Dibra A, Mehilli J, et al. Drug-eluting stents compared with thin-strut bare stents for the reduction of restenosis: a prospective, randomized trial. *Eur Heart J*. 2005;26:1262-1268.
22. Suttorp MJ, Laarman GJ, Rahel BM, et al. Primary Stenting of Totally Occluded Native Coronary Arteries II (PRISON II): a randomized comparison of bare metal stent implantation with sirolimus-eluting stent implantation for the treatment of total coronary occlusions. *Circulation*. 2006;114:921-928.
23. Vermeersch P, Agostoni P, Verheye S, et al. Randomized double-blind comparison of sirolimus-eluting stent versus bare-metal stent implantation in diseased saphenous vein grafts: six-month angiographic, intravascular ultrasound, and clinical follow-up of the RRISC Trial. *J Am Coll Cardiol*. 2006;48:2423-2431.
24. Ardissino D, Cavallini C, Bramucci E, et al. Sirolimus-eluting vs uncoated stents for prevention of restenosis in small coronary arteries: a randomized trial. *JAMA*. 2004;292:2727-2734.
25. Spaulding C, Henry P, Teiger E, et al. Sirolimus-eluting versus uncoated stents in acute myocardial infarction. *N Engl J Med*. 2006;355:1093-1104.
26. Grube E, Silber S, Hauptmann KE, et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions. *Circulation*. 2003;107:38-42.
27. Colombo A, Drzewiecki J, Banning A, et al. Randomized study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation*. 2003;108:788-794.
28. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med*. 2004;350:221-231.
29. Stone GW, Ellis SG, Cox DA, et al. One-year clinical results with the slow-release, polymer-based, paclitaxel-eluting TAXUS stent: the TAXUS-IV trial. *Circulation*. 2004;109:1942-1947.
30. Stone GW, Ellis SG, Cannon L, et al. Comparison of a polymer-based paclitaxel-eluting stent with a bare metal stent in patients with complex coronary artery disease: a randomized controlled trial. *JAMA*. 2005;294:1215-1223.
31. Stone GW, Ellis SG, O'Shaughnessy CD, et al. Paclitaxel-eluting stents vs vascular brachytherapy

for in-stent restenosis within bare-metal stents: the TAXUS V ISR randomized trial. *JAMA*. 2006;295:1253-1263.
32. Rodriguez AE, Mieres J, Fernandez-Pereira C, et al. Coronary stent thrombosis in the current drug-eluting stent era: insights from the ERACI III trial. *J Am Coll Cardiol*. 2006;47:205-207.
33. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA*. 2005;293:2126-2130.
34. Ong AT, McFadden EP, Regar E, et al. Late angiographic stent thrombosis (LAST) events with drug-eluting stents. *J Am Coll Cardiol*. 2005;45: 2088-2092.
35. Takano M, Ohba T, Inami S, et al. Angioscopic differences in neointimal coverage and in persistence of thrombus between sirolimus-eluting stents and bare metal stents after a 6-month implantation. *Eur Heart J*. 2006;27:2189-2195.
36. McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet*. 2004;364:1519-1521.
37. Pfisterer M, Brunner-La Rocca HP, Buser PT, et al. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. *J Am Coll Cardiol*. 2006;48:2584-2591.
38. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet*. 2007;369:667-678.
39. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents. A cause for concern. *Circulation*. 2007;115:1440-1455.
40. Lagerqvist B, James SK, Stenestrand U, et al. Long-term outcomes with drug-eluting stents versus bare-metal stents in Sweden. *N Engl J Med*. 2007;356:1009-1019.
41. Nordmann AJ, Briel M, Bucher HC. Mortality in randomized controlled trials comparing drug-eluting vs bare metal stents in coronary artery disease: a meta-analysis. *Eur Heart J*. 2006;27: 2784-2814.
42. Guagliumi G, Virmani R, Musumeci G, et al. Drug-eluting versus bare metal coronary stents: long-term human pathology. Findings from different coronary arteries in the same patient. *Ital Heart J*. 2003;4:713-720.
43. Guagliumi G, Farb A, Musumeci G, et al. Images in cardiovascular medicine. Sirolimus-eluting stent implanted in human coronary artery for 16 months: pathological findings. *Circulation*. 2003;107:1340-1341.
44. Kotani J, Awata M, Nanto S, et al. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. *J Am Coll Cardiol*. 2006;47:2108-2111.
45. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48:193-202.
46. Virmani R, Guagliumi G, Farb A, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation*. 2004;109: 701-705.
47. Cook S, Wenaweser P, Togni M, et al. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. *Circulation*. 2007;115:2426-2434.
48. Hong MK, Mintz GS, Lee CW, et al. Late stent malapposition after drug-eluting stent implantation: an intravascular ultrasound analysis with long-term follow-up. *Circulation*. 2006; 113:414-419.
49. Maekawa K, Kawamoto K, Fuke S, et al. Images in cardiovascular medicine. Severe endothelial dysfunction after sirolimus-eluting stent implantation. *Circulation*. 2006;113:e850-e851.
50. Aoki J, Nakazawa G, Tanabe K, et al. Incidence and clinical impact of coronary stent fracture after sirolimus-eluting stent implantation. *Catheter Cardiovasc Interv*. 2007;69:380-386.
51. Schatz RA, Baim DS, Leon M, et al. Clinical experience with the Palmaz-Schatz coronary stent. Initial results of a multicenter study. *Circulation*. 1991;83:148-161.
52. Colombo A, Hall P, Nakamura S, et al. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. *Circulation*. 1995;91:1676-1688.
53. Schömig A, Kastrati A, Mudra H, et al. Four-year experience with Palmaz-Schatz stenting in coronary angioplasty complicated by dissection with threatened or present vessel closure. *Circulation*. 1994;90:2716-2724.
54. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med*. 1998;339:1665-1671.
55. Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. *Circulation*. 2001;103:1967-1971.
56. Daemen J, Garcia-Garcia HM, Kukreja N, et al. The long-term value of sirolimus- and paclitaxel-eluting stents over bare metal stents in patients with diabetes mellitus. *Eur Heart J*. 2007;28: 26-32.
57. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. *N Engl J Med*. 2007;356:998-1008.
58. Mauri L, Hsieh WH, Massaro JM, et al. Stent thrombosis in randomized clinical trials of drug-eluting stents. *N Engl J Med*. 2007;356: 1020-1029.
59. Kastrati A, Mehilli J, Pache J, et al. Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. *N Engl J Med*. 2007;356: 1030-1039.
60. Dawkins KD, Grube E, Guagliumi G, et al. Clinical efficacy of polymer-based paclitaxel-eluting stents in the treatment of complex, long coronary artery lesions from a multicenter, randomized trial: support for the use of drug-eluting stents in contemporary clinical practice. *Circulation*. 2005;112:3306-3313.
61. Nayak AK, Kawamura A, Nesto RW, et al. Myocardial infarction as a presentation of clinical in-stent restenosis. *Circ J*. 2006;70:1026-1029.
62. Walters DL, Harding SA, Walsh CR, et al. Acute coronary syndrome is a common clinical presentation of in-stent restenosis. *Am J Cardiol*. 2002;89:491-494.
63. Stone GW, Ellis SG, Colombo A, et al. Offsetting impact of thrombosis and restenosis on the occurrence of death and myocardial infarction after paclitaxel-eluting and bare metal stent implantation. *Circulation*. 2007;115:2842-2847.
64. US Food and Drug Administration. Update to FDA Statement on Coronary Drug-Eluting Stents. Available at: http://www.fda.gov/cdrh/news/010407.html. Accessed October 17, 2007.
65. Rao SV, Shaw RE, Brindis RG, et al. On- versus off-label use of drug-eluting coronary stents in clinical practice (report from the American College of Cardiology National Cardiovascular Data Registry [NCDR]). *Am J Cardiol*. 2006;97: 1478-1481.
66. Beohar N, Davidson CJ, Kip KE, et al. Outcomes and complications associated with off-label and untested use of drug-eluting stents. *JAMA*. 2007;297:1992-2000.
67. Win HK, Caldera AE, Maresh K, et al. Clinical outcomes and stent thrombosis following off-label use of drug-eluting stents. *JAMA*. 2007;297:2001-2009.
68. James S. Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Paper presented at: European Society of Cardiology Congress; September 2007; Vienna, Austria.
69. Marzocchi A, Saia F, Piovaccari G, et al. Long-term safety and efficacy of drug-eluting stents. Two-year results of the REAL (REgistro AngiopLastiche dell'Emilia Romagna) multicenter registry. *Circulation*. 2007;115:3181-188.
70. Jensen LO, Maeng M, Kaltoft A, et al. Stent thrombosis, myocardial infarction, and death after drug-eluting and bare-metal stent coronary interventions. *J Am Coll Cardiol*. 2007;50: 463-470.
71. Serruys P. Thoraxcenter real world experience. Available at: http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4253oph1_09_Serruys.pdf. Accessed October 22, 2007.
72. Applegate RJ, Sacrinty MT, Kutcher MA, et al. Comparison of drug-eluting versus bare metal stents on later frequency of acute myocardial infarction and death. *Am J Cardiol*. 2007;99: 333-338.
73. Simonton C. Strategic Transcatheter Evaluation of New Therapies (STENT). Paper presented at: 18th Annual Transcatheter Cardiovascular Therapeutics Scientific Symposium; October 2006; Washington, DC.
74. Kaiser C, Brunner-La Rocca HP, Buser PT, et al. Incremental cost-effectiveness of drug-eluting stents compared with a third-generation bare-metal stent in a real-world setting: randomised Basel Stent Kosten Effektivitats Trial (BASKET). *Lancet*. 2005;366:921-929.
75. Colombo A, Moses JW, Morice MC, et al. Randomized study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation*. 2004;109:1244-1249.
76. Pan M, de Lezo JS, Medina A, et al. Rapamycin-eluting stents for the treatment of bifurcated coronary lesions: a randomized comparison of a simple versus complex strategy. *Am Heart J*. 2004;148:857-864.
77. Steigen TK, Maeng M, Wiseth R, et al, for the Nordic PCI Study Group. Randomized study on simple versus complex stenting of coronary artery bifurcation lesions: the Nordic bifurcation study. *Circulation*. 2006;114:1955-1961.
78. Holmes DR Jr, Teirstein P, Satler L, et al, for the SISR Investigators. Sirolimus-eluting stents vs

vascular brachytherapy for in-stent restenosis within bare-metal stents: the SISR randomized trial. *JAMA*. 2006;295:1264-1273.
79. Kastrati A, Mehilli J, von Beckerath N, et al, for the ISAR-DESIRE Study Investigators. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. *JAMA*. 2005;293:165-171.
80. Vermeersch P, Agostoni P, Verheye S, et al, for the DELAYED RRISC (Death and Events at Long-term follow-up AnalYsis: Extended Duration of the Reduction of Restenosis In Saphenous vein grafts with Cypher stent) Investigators. Increased late mortality after sirolimus-eluting stents versus bare-metal stents in diseased saphenous vein grafts: results from the randomized DELAYED RRISC Trial. *J Am Coll Cardiol*. 2007;50:261-267.
81. Pasceri V, Patti G, Speciale G, et al. Meta-analysis of clinical trials on use of drug-eluting stents for treatment of acute myocardial infarction. *Am Heart J*. 2007;153:749-754.
82. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA*. 2007;297:159-168.
83. Airoldi F, Colombo A, Morici N, et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. *Circulation*. 2007;116:745-754.