

STATE-OF-THE-ART PAPERS

Coronary Stents

Current Status

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Coronary artery stents revolutionized the practice of interventional cardiology after they were first introduced in the mid-1980s. Since then, there have been significant developments in their design, the most notable of which has been the introduction of drug-eluting stents. This paper reviews the benefits, risks, and current status of Food and Drug Administration-approved drug-eluting stents. (J Am Coll Cardiol 2010;56:S1-42) © 2010 by the American College of Cardiology Foundation

In 1964, Charles Theodore Dotter and Melvin P. Judkins described the first angioplasty (1). Thirteen years later, Andreas Grüntzig performed the first balloon coronary angioplasty (2), a revolutionary treatment that led to the birth of a new specialty, interventional cardiology. Since that first procedure, there have been extensive developments and advances that have culminated in percutaneous coronary intervention (PCI) being 1 of the most frequently performed invasive medical procedures in clinical practice today.

Coronary stents, which were first developed in the mid-1980s (3), have ultimately replaced “plain old balloon angioplasty” (POBA) as the preferred method of performing PCI, after the observed improvements in angiographic and clinical outcomes seen with their use (4,5). The majority of PCI procedures now involve a coronary stent, and therefore, interventional cardiologists are faced with a wide choice of coronary stents to implant. This choice ranges from conventional bare-metal stents (BMS) and drug-eluting stents (DES) that are widely used in contemporary practice to newer stents such as DES with biodegradable polymers, DES that are polymer-free, DES with novel coatings, dedicated bifurcation stents, self-expanding stents, and biodegradable stents.

Part 1 of this review discusses the current status of coronary stents and examines some of the unresolved issues surrounding their implantation in contemporary practice. Part 2 will review the vast array of new coronary stents that are currently undergoing evaluation in pre-clinical and clinical trials.

The Need for Coronary Stents and the Early Period

There is no dispute that POBA was a pioneering treatment; however, its success was hindered by the problems of acute vessel closure and restenosis (4–6). These problems led to the development of a second revolutionary treatment, the coronary stent, which was first implanted by Sigwart et al. (3) in 1986 (Fig. 1) (7). This bare metal, self-expanding stent, known as the “Wall” stent was able to provide a scaffold that prevented acute vessel closure and late constrictive recoil (3). Although these initial stents proved effective as “bailout” devices in cases of abrupt or threatened vessel closure, thereby reducing rates of emergency coronary artery bypass surgery (CABG) (8), development was ultimately hampered by the risk of subacute thrombotic coronary artery occlusion, which was observed in up to 18% of cases within 2 weeks of implantation (9). This novel, stent-specific hazard prompted the use of complex anticoagulation regimens that were associated with increased bleeding and prolonged hospitalization (10). Overall, the early success and complication rates seen with these initial coronary stents were not always competitive with those of routine POBA.

Coronary stenting only became a widely accepted technique after the publication of the landmark BENESTENT (Belgian Netherlands Stent) trial (11) and the STRESS (Stent Restenosis Study) (12), together with evidence indicating that stenting was safe in the absence of anticoagulation therapy with the use of dual antiplatelet therapy (DAPT) (13–15) and/or adequate stent deployment (16).

By 1999, coronary stenting was performed in 84.2% of PCI procedures (17); however, despite their obvious advantages, there were associated problems and concerns. Most notably, and in addition to the risk of subacute thrombosis, which has already been alluded to, an iatrogenic problem emerged in the form of in-stent neointimal hyperplasia (18–20). This intrastent growth of scar tissue, which was

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**Abbreviations
and Acronyms**

| |
|---|
| ACS = acute coronary syndrome |
| BMS = bare-metal stent(s) |
| CABG = coronary artery bypass grafting |
| CAD = coronary artery disease |
| CI = confidence interval |
| CoCr = cobalt chromium |
| CTO = chronic total occlusion |
| DAPT = dual antiplatelet therapy |
| DES = drug-eluting stent(s) |
| EES = everolimus-eluting stent(s) |
| FDA = Food and Drug Administration |
| HR = hazard ratio |
| ISA = incomplete stent apposition |
| ISR = in-stent restenosis |
| IVUS = intravascular ultrasound |
| MACE = major adverse cardiovascular events |
| MI = myocardial infarction |
| MVD = multivessel disease |
| PCI = percutaneous coronary intervention |
| PES = paclitaxel-eluting stent(s) |
| POBA = plain old balloon angioplasty |
| RR = relative risk |
| SES = sirolimus-eluting stent(s) |
| ST = stent thrombosis |
| STEMI = ST-segment elevation myocardial infarction |
| SVG = saphenous vein graft |
| TLR = target lesion revascularization |
| TVR = target vessel revascularization |
| UPLMS = unprotected left main stem |
| ZES = zotarolimus-eluting stent(s) |

the result of proliferation and migration of vascular smooth muscle cells, and as demonstrated in Figure 2 was directly linked to stent implantation, resulted in restenosis rates of 20% to 30% (21). It was the attempts to minimize this in-stent neointimal hyperplasia, and thereby reduce rates of repeat revascularization, that ultimately lead to the development of another revolutionary treatment: the DES. The dramatic reduction in restenosis rates seen with the use of these DES compared with BMS (22–26) has been the major driving force behind the exponential growth of PCI as a treatment for patients with coronary artery disease (CAD). After the outstanding results from the early pivotal trials with DES, there was an increased confidence to use PCI, so that its use has expanded to lesions subsets that were only previously considered suitable for CABG (27–29). This increased confidence lead to a rapid and unprecedented uptake in their use, so that by 2005, 80% to 90% of all revascularization procedures in the U.S. were performed using a DES (30). In 2006, concerns were raised over the safety profile of these stents (31–33), resulting in an immediate worldwide downturn in their use. These concerns proved a vital stimulus to focus research, and have ultimately lead to the development of newer stents and improved safety, resulting in a resurgence in the use of DES; however, current rates (~75%) are still below those of 2005 (34).

DES Initial Phase: “The Rosy Period”

Sirolimus-eluting stents (SES). In the late 1990s, numerous pre-clinical studies reported that sirolimus (previously called rapamycin),

the cytokine- and growth-factor-mediated proliferation of lymphocytes and smooth muscle cells, resulting in reduced neointimal proliferation (Fig. 3) (35–38). Despite its promise, problems remained over the ability to locally deliver sirolimus at an appropriate and sustained concentration necessary to inhibit neointimal proliferation. Failures with both oral administration and local delivery using special delivery balloons led to the development of a coronary stent with a drug coating, the DES. The first human DES implant was performed by J. Eduardo Sousa in Sao Paulo in December 1999 at the start of the 2 first-in-man studies that recruited a total of 45 patients and reported minimal in-stent neointimal proliferation through to 12-month follow-up (39–41). This research culminated in the development and commercial launch of the stainless steel Cypher SES (Cordis, Warren, New Jersey), the specification of which is summarized in Table 1. The Cypher SES was initially evaluated in the pivotal RAVEL (Randomized Study With the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions) study, which randomly assigned 238 patients with relatively low risk lesions to treatment with the Cypher SES or BMS controls. At 1-year follow-up, the rate of binary stenosis was 0.0% and 26.6% for patients treated with Cypher SES and BMS, respectively (42). These results were subsequently confirmed in the much larger SIRIUS (Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) trial that enrolled 1,058 patients with more complex lesions than were seen in the RAVEL study. This study again demonstrated significantly lower rates of target lesion revascularization (TLR) and major adverse cardiovascular events (MACE) after treatment with the Cypher SES compared with BMS controls at 9-month, 2-year, and now 5-year follow-up (43–45).

After these initial randomized studies, which ultimately lead to regulatory approval, the performance of the Cypher stent has been assessed in: 1) different patient types, for example, diabetic patients; 2) different clinical settings, including primary PCI for ST-segment elevation myocardial infarction (STEMI); and 3) different lesion types including chronic total occlusions (CTO), saphenous vein grafts (SVG), small coronary vessels, and complex lesions. The results of the most important randomized controlled trials comparing SES and BMS in these different clinical settings are summarized in Table 2 (42–75). As clearly demonstrated, when compared with BMS, the use of SES results in significant reductions in angiographic in-stent late loss, in-stent angiographic (binary) restenosis, and repeat revascularization at both short- and long-term follow-up, with results consistent across numerous different patient and lesion types. Furthermore, meta-analyses of patient data from the initial approval trials reaffirms the sustained advantage of SES over BMS in terms of reduced repeat revascularization, together with comparable rates of death and myocardial infarction (MI) at long-term follow-up (Table 3) (22–26,76).

a macrolide antibiotic that was approved for use as an immunosuppressant to prevent organ rejection, was able to inhibit



Figure 1 First Human Coronary Stent Implantation, March 1986

(A) A restenotic lesion after balloon angioplasty. (B) The self-expanding WALLSTENT. (C) Immediate results after stenting. (D) Angiographic results at 11-year follow-up. Reproduced with permission from Carrie et al. (7).

In addition to randomized data, registries have evaluated the performance of the Cypher stent in the setting of the real-world. The first of these registries was the single-center RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) registry, which enrolled 508 consecutive patients who were treated with the Cypher SES

irrespective of lesion complexity. Running concurrently with the RESEARCH registry was the multicenter ARTS-II (Arterial Revascularization Therapies Study) registry, which assessed the Cypher stent in 607 patients with 2- and 3-vessel CAD. Results from both registries at short- and long-term follow-up, which now extends to 4 and 5 years,

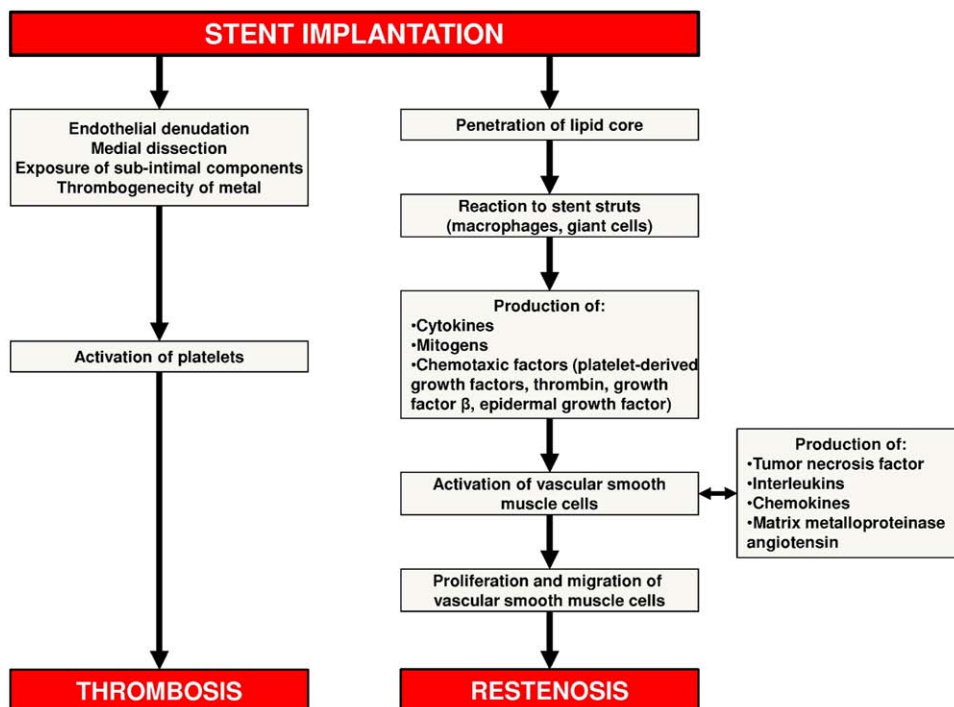
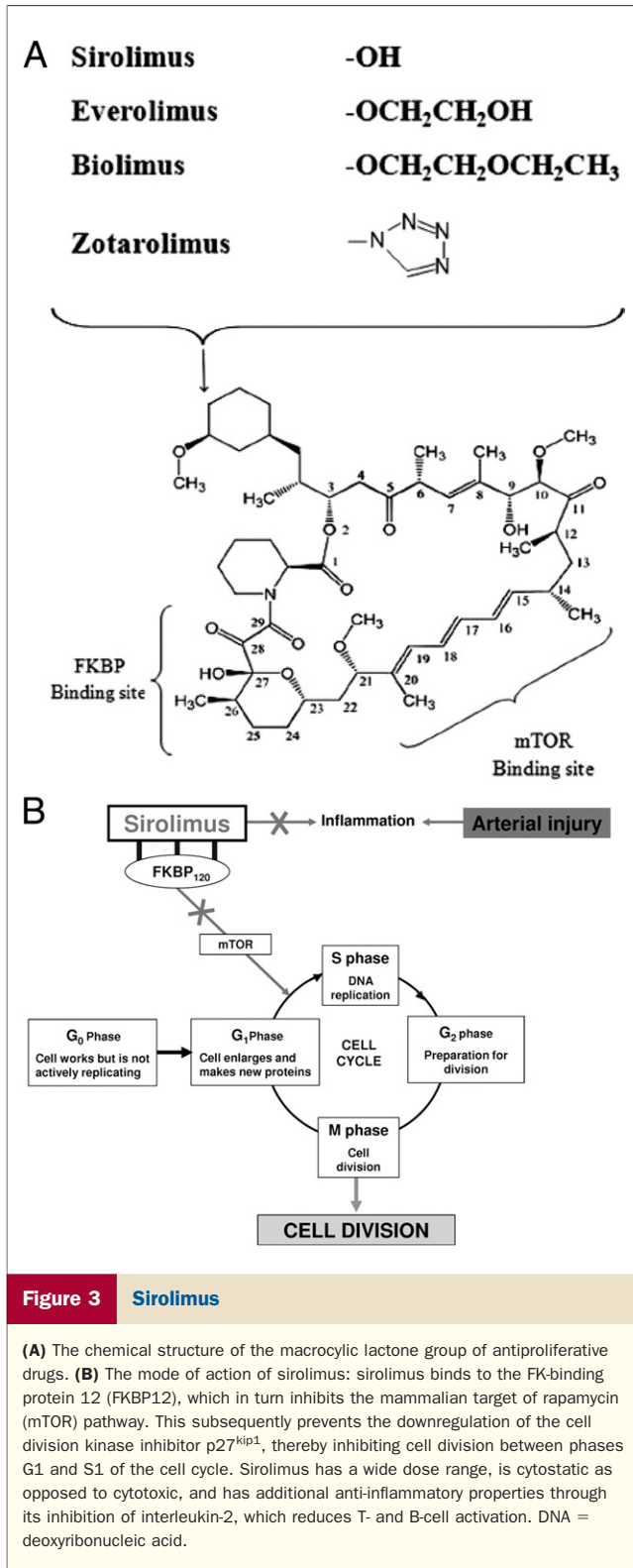


Figure 2 Pathway Leading to In-Stent Restenosis After Stent Implantation



respectively, for the RESEARCH and ARTS-II registries (Fig. 4) (77), mirrors those from other registries and the previously noted randomized studies and meta-analyses, by continuing to demonstrate significantly lower rates of

Table 1 Specifications of the Food and Drug Administration-Approved Drug-Eluting Stents

| Stent | Drug (Concentration [$\mu\text{g}/\text{cm}^2$]) | Drug Mechanism | Polymer | Polymer Thickness, μm | Release Kinetics, 28 Days | Metal | Geometry | Strut Thickness, μm | Crimped Profile, mm^* | Maximum Cell C/D, mm^* |
|---------------|--|--|--|----------------------------------|---------------------------|-------|-------------|--------------------------------|--------------------------------|---------------------------------|
| CYPHER | Sirolimus (140) | Inhibits mTOR, cytostatic | Polyethylene co-vinyl acetate and poly-n-butyl methacrylate | 12.6 | 80% | SS | Closed cell | 140 | 1.198 | 9.5/3.0 |
| TAXUS Express | Paclitaxel (100) | Microtubule inhibitor, cell cycle arrest in G0/G1 and G2/M | Poly(styrene-b-isobutylene-b-styrene) | 16.0 | <10% | SS | Open cell | 132 | 1.245 | 11.9/3.8 |
| TAXUS Liberté | Paclitaxel (100) | Microtubule inhibitor, cell cycle arrest in G0/G1 and G2/M | Poly(styrene-b-isobutylene-b-styrene) | 16.0 | <10% | SS | Hybrid | 97 | 1.219 | 13.7/4.4 |
| Endeavor | Zotarolimus (100) | Inhibits mTOR, cytostatic | Phosphorylcholine | 4.1 | 95%† | CoCr | Open cell | 91 | 1.130 | 19.8/6.3 |
| Xience V | Everolimus (100) | Inhibits mTOR, cytostatic | Polyvinylidene fluoride co-hexafluoropropylene and poly-n-butyl methacrylate | 7.6 | 80% | CoCr | Open cell | 81 | 1.055 | 12.6/4.0 |

*Based on a 3-mm stent. †Drug release at 14 days.
C/D = circumference/diameter; CoCr = cobalt chromium; mTOR = mammalian target of rapamycin; SS = stainless steel.

Table 2 Summary of Major Randomized Trials of SES Versus BMS in Different Clinical Settings

| Trial or First Author (Ref. #) | No. of Patients | Clinical Setting | Follow-Up, Months | In-Stent Late Loss (SES vs.), mm | Binary In-Stent Restenosis (SES vs.), % | MACE (SES vs.), % | Death (SES vs.), % | MI (SES vs.), % | TLR (SES vs.), % | Definite/ Probable ST (SES vs.), % |
|--------------------------------|---------------------------------|---|-------------------|----------------------------------|---|---|------------------------------|-------------------------------|---|------------------------------------|
| RAVEL (42,46) | SES (n = 120) vs. BMS (n = 118) | Elective simple lesions | 6*/12† 60 | -0.01 vs. 0.80‡ NA | 0.0 vs. 26.6‡ NA | 5.8 vs. 28.8‡ 25.8 vs. 35.2§ | 1.7 vs. 1.7 12.1 vs. 7.1 | 3.3 vs. 4.2 8.9 vs. 6.9 | 0.0 vs. 23.7§ 10.3 vs. 26.0‡ | 0.0 vs. 1.7 1.7 vs. 2.5 |
| C-SIRIUS (47) | SES (n = 50) vs. BMS (n = 50) | Canadian approval trial | 8*/9† | 0.12 vs. 1.02‡ | 0.0 vs. 45.5‡ | 4.0 vs. 18.0 | 0.0 vs. 0.0 | 2.0 vs. 4.0 | 4.0 vs. 18.0 | 2.0 vs. 2.0 |
| E-SIRIUS (48) | SES (n = 175) vs. BMS (n = 177) | Elective long lesions, small vessels, overlapped stents | 8*/9† | 0.20 vs. 1.05‡ | 3.9 vs. 41.7‡ | 8.0 vs. 22.6‡ | 1.1 vs. 0.6 | 4.6 vs. 2.3 | 4.0 vs. 20.9‡ | 1.1 vs. 0.0 |
| SIRIUS (43,45) | SES (n = 163) vs. BMS (n = 159) | U.S. pivotal approval trial | 8*/12† 60 | 0.17 vs. 1.00‡ NA | 3.2 vs. 35.4‡ NA | 8.3 vs. 23.2‡ 20.3 vs. 33.5‡ | 1.3 vs. 0.8 8.4 vs. 8.4 | 3.0 vs. 4.2 6.2 vs. 6.5 | 4.9 vs. 20.2‡ 9.4 vs. 24.2‡ | 0.4 vs. 1.1 1.2 vs. 1.8 |
| DIABETES (49,51) | SES (n = 80) vs. BMS (n = 80) | Diabetes | 9*/24† 48 | 0.09 vs. 0.67‡ NA | 3.9 vs. 31.7‡ NA | 12.8 vs. 41.3‡¶ NA | 2.6 vs. 3.8¶ 4.1 vs. 6.5¶ | 3.8 vs. 8.8 4.1 vs. 10.4 | 7.7 vs. 35.0‡ 8.1 vs. 37.7‡ | 3.8 vs. 2.5# 3.8 vs. 3.8# |
| DESSERT (52) | SES (n = 75) vs. BMS (n = 75) | Diabetes | 8*/12† | 0.14 vs. 0.96‡ | 3.6 vs. 38.8‡ | 22.1 vs. 44.0§ | 4.4 vs. 2.9 | 16.2 vs. 20.0 | 5.9 vs. 30.0‡ | 1.4 vs. 1.5 |
| SCORPIUS (53) | SES (n = 98) vs. BMS (n = 102) | Diabetes | 8*/12† | 0.22 vs. 0.99‡ | 8.8 vs. 42.1‡ | NA | 5.3 vs. 4.1 | 4.3 vs. 5.2 | 5.3 vs. 21.1‡ | 2.1 vs. 2.1 |
| Diaz de la Llera et al. (54) | SES (n = 60) vs. BMS (n = 60) | STEMI | 12 | NA | NA | 6.7 vs. 11.1 | 5.0 vs. 3.6 | 6.7 vs. 5.4 | 0.0 vs. 5.7** (Death+MI) | 3.4 vs. 1.8# |
| MISSION! (55,56) | SES (n = 158) vs. BMS (n = 152) | STEMI | 9*/12† 36 | 0.19 vs. 0.95‡ NA | 2.3 vs. 22.6‡ NA | NA NA | 1.3 vs. 2.6 4.4 vs. 6.6 | 5.7 vs. 9.2 7.6 vs. 11.2 | 3.2 vs. 11.2§ 6.3 vs. 12.5 | 1.3 vs. 2.0 3.1 vs. 2.0 |
| PASEO (57,58) | SES (n = 90) vs. BMS (n = 90) | STEMI | 12 48 | NA NA | NA NA | 11.1 vs. 24.4§ 36.7 vs. 21.1§ | 3.3 vs. 6.7 7.8 vs. 12.2 | 4.4 vs. 6.7 8.9 vs. 13.3 | 3.3 vs. 14.4§ 5.6 vs. 21.1§ | 0.0 vs. 1.1†† 1.1 vs. 2.2†† |
| SESAMI (59,60) | SES (n = 160) vs. BMS (n = 160) | STEMI | 12 36 | 0.18 vs. 0.85§ NA | 9.3 vs. 21.3§ NA | 6.8 vs. 16.8§ 12.7 vs. 21.0§ | 1.8 vs. 4.3 3.2 vs. 5.0 | 1.8 vs. 1.8 2.5 vs. 2.5 | 4.3 vs. 11.2§ 7.0 vs. 13.5§ | 1.2 vs. 0.6†† 1.9 vs. 1.3†† |
| STRATEGY (61,62) | SES (n = 87) vs. BMS (n = 88) | STEMI | 8 60 | 0.22 vs. 0.60‡ NA | 7.5 vs. 28§ NA | 18.4 vs. 31.8§ 29.9 vs. 43.2 | 8.0 vs. 9.1 18.0 vs. 16.0 | 6.9 vs. 9.1 22.0 vs. 25.0 | 5.7 vs. 20.5§ 10.3 vs. 26.1§** (Death+MI) | 0.0 vs. 2.3# 7.0 vs. 8.0‡† |
| TYPHOON (63,64) | SES (n = 355) vs. BMS (n = 357) | STEMI | 8*/12† 48 | 0.14 vs. 0.83‡ NA | 3.5 vs. 20.3§ NA | 5.9 vs. 14.6‡ NA | 2.3 vs. 2.2 4.0 vs. 6.4 | 1.1 vs. 1.4 4.8 vs. 4.0 | 5.6 vs. 13.4‡ 7.2 vs. 15.2§ | 2.4 vs. 3.6 4.4 vs. 4.8 |
| Pache et al. (65) | SES (n = 250) vs. BMS (n = 250) | Elective all-comers | 6*/12† | 0.14 vs. 0.94‡ | 8.3 vs. 25.5‡ | 13.6 vs. 22.4§** | 2.8 vs. 2.0 | 4.6 vs. 2.8 | 7.2 vs. 18.8‡** | 0.8 vs. 0.4 |
| PRISON II (66,68) | SES (n = 100) vs. BMS (n = 100) | Chronic total occlusion | 6*/12† 60 | 0.05 vs. 1.09‡ NA | 7.0 vs. 36.0‡ NA | 5.0 vs. 24.0‡ 12.0 vs. 36.0‡ | 0.0 vs. 1.0 5.0 vs. 5.0 | 2.0 vs. 3.0 8.0 vs. 7.0 | 5.0 vs. 21.0‡ 12.0 vs. 30.0§ | 2.0 vs. 0.0‡† 8.0 vs. 3.0‡† |
| GISSOC II-GISE (69) | SES (n = 78) vs. BMS (n = 74) | Chronic total occlusion | 8*/24† | 0.20 vs. 1.57‡ | 8.2 vs. 67.7‡ | 17.6 vs. 50.0‡ | 2.7 vs. 1.3 | 2.7 vs. 5.1 | 8.1 vs. 44.9‡ | 1.4 vs. 1.3 |
| SES-SMART (70,71) | SES (n = 129) vs. BMS (n = 128) | Small vessels | 8 24 | 0.16 vs. 0.90‡ NA | 4.9 vs. 49.1‡ NA | 9.3 vs. 31.3‡ §§ 12.6 vs. 33.1‡ §§ | 0.0 vs. 1.6 0.8 vs. 3.9 | 1.6 vs. 7.8§ 1.6 vs. 10.2§ | 7.0 vs. 21.1§ 7.9 vs. 29.9‡ | 0.8 vs. 3.1# 0.8 vs. 3.1# |
| SCANDSTENT (72,73) | SES (n = 163) vs. BMS (n = 159) | Complex disease | 6*/7† 36 | 0.02 vs. 1.01‡ NA | 2.0 vs. 30.6‡ NA | 4.3 vs. 29.9‡ 12.3 vs. 37.6‡ | 0.6 vs. 0.6 5.6 vs. 1.9 | 1.2 vs. 3.1 3.7 vs. 9.6 | 2.5 vs. 29.3‡ 4.9 vs. 33.8‡ | 0.6 vs. 3.8 1.2 vs. 4.4 |
| RRISC (74,75) | SES (n = 38) vs. BMS (n = 37) | Saphenous vein grafts | 6 32 | 0.38 vs. 0.79§ NA | 11.3 vs. 30.6§ NA | 15.8 vs. 29.7 57.9 vs. 40.5 | 2.6 vs. 0.0 28.9 vs. 0.0‡ | 2.6 vs. 0.0 18.4 vs. 5.4 | 5.3 vs. 21.6§ 23.7 vs. 29.7 | 0.0 vs. 0.0 5.0 vs. 0.0†† |

Differences are nonsignificant unless indicated. Stent thrombosis defined per Academic Research Consortium definitions, unless indicated. All trial acronyms are listed in the Online Appendix. *Angiographic follow-up. †Clinical follow-up. ‡p < 0.001. §p < 0.05. ||Ischemia driven. ¶Cardiac. #Protocol-defined ST. **Target vessel revascularization. ††Definite ST only. ‡‡Definite, probable, and possible. §§Major adverse cardiovascular and cerebrovascular events.

BMS = bare-metal stent(s); MACE = major adverse cardiovascular events (a composite of death, myocardial infarction, and target lesion revascularization); MI = myocardial infarction; NA = not available; SES = sirolimus-eluting stent(s); ST = stent thrombosis; STEMI = ST-segment elevation myocardial infarction; TLR = target lesion revascularization.

Table 3 Rates of Death, MI, and TLR From Recent Meta-Analyses of DES Compared to BMS

| First Author (Ref. #) | Number of Patients | Longest Follow-Up, yrs | Death (DES vs. BMS) | MI (DES vs. BMS) | TLR (DES vs. BMS) |
|--------------------------------|------------------------------|------------------------|---------------------|------------------|-------------------|
| SES vs. BMS | | | | | |
| Stettler et al. (22) | 8,646 (4,643 SES, 4,003 BMS) | 4 | HR: 1.0 | HR: 0.81* | HR: 0.3† |
| Stone et al. (24) | 1,748 (878 SES, 870 BMS) | 4 | 6.7% vs. 5.3% | 6.4% vs. 6.2% | 7.8% vs. 23.6%† |
| Kastrati et al. (26) | 4,958 (2,486 SES, 2,472 BMS) | 5 | 6.0% vs. 5.9% | 9.7% vs. 10.2%‡ | HR: 0.43§† |
| PES vs. BMS | | | | | |
| Stettler et al. (22) | 8,330 (4,327 PES, 4,003 BMS) | 4 | HR: 1.03 | HR: 1.0 | HR: 0.42† |
| Stone et al. (24) | 3,513 (1,755 PES, 1,758 BMS) | 4 | 6.1% vs. 6.6% | 7.0% vs. 6.3% | 10.1% vs. 20.0%† |
| Other | | | | | |
| Stettler et al. (22) | 8,970 (4,643 SES, 4,327 PES) | 4 | HR: 0.96 | HR: 0.83* | HR: 0.70* |
| Kirtane et al. (76), on-label | | | HR: 1.05 | HR: 1.03 | HR: 0.54† |
| Kirtane et al. (76), off-label | 9,470 (4,867 DES, 4,603 BMS) | 5 | HR: 0.84 | HR: 0.83 | HR: 0.42† |

Differences nonsignificant unless indicated. * $p < 0.05$. † $p < 0.001$. ‡Combined death or MI. §Combined death, MI, or TVR. DES = drug-eluting stent(s); HR = hazard ratio; PES = paclitaxel-eluting stent(s); TVR = target vessel revascularization; other abbreviations as in Table 2.

MACE and TLR after the use of the Cypher SES compared with historical BMS controls (77–81). **Paclitaxel-eluting stents (PES).** The TAXUS PES (Boston Scientific, Natick, Massachusetts) was developed almost simultaneously with the SES, gaining regulatory approval ~12 months later (Table 1, Fig. 5). Its evaluation has followed a

pattern similar to that of the SES, and its first assessment, in the randomized TAXUS I study, reported no binary restenosis at 6-month follow-up (82). Subsequent randomized studies, the most important of which are summarized in Table 4, have demonstrated a significantly lower rate of late loss, angiographic binary restenosis, and repeat revascularization with

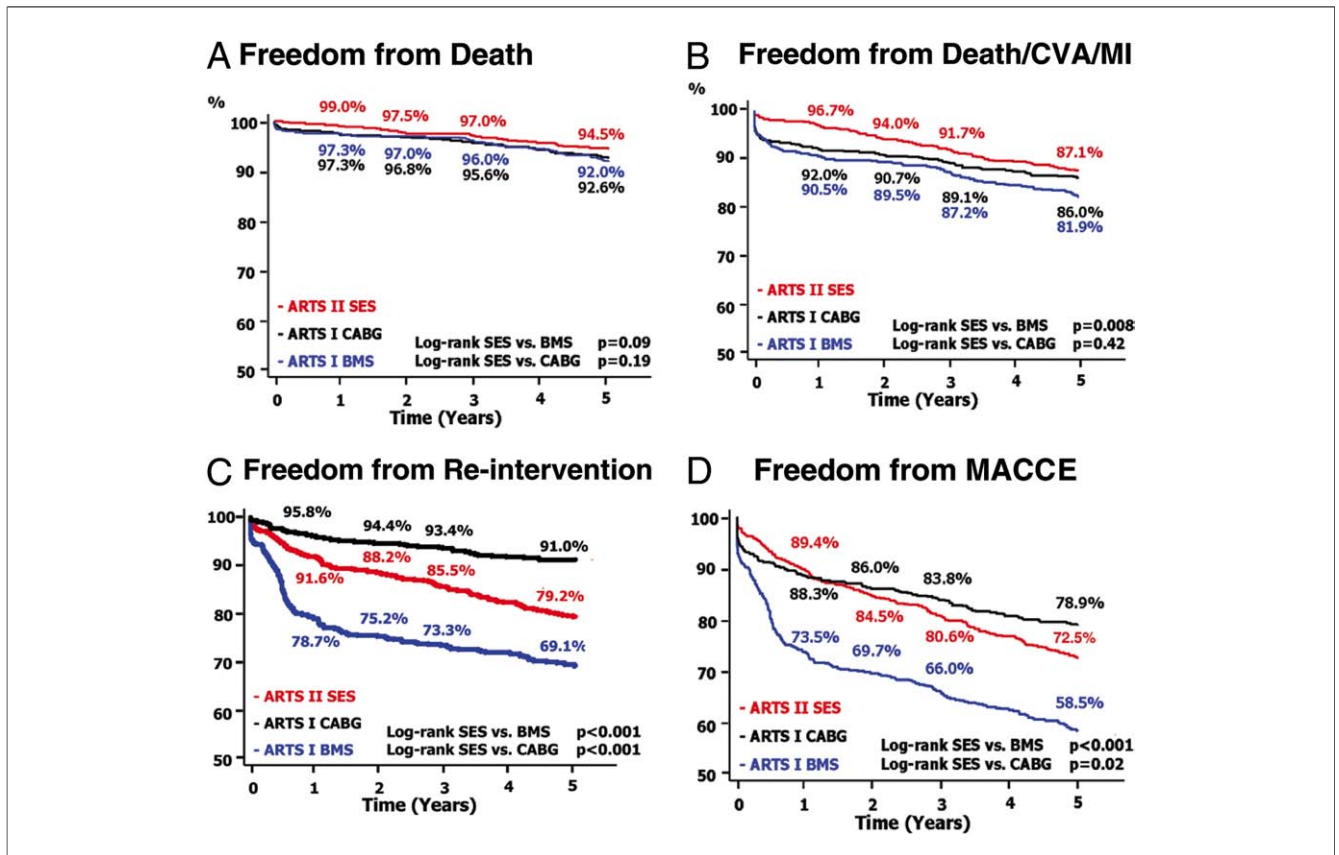


Figure 4 Long-Term Clinical Outcomes of SES, BMS, and CABG in ARTS I and II

Long-term clinical outcomes compared for patients treated with sirolimus-eluting stents (SES [red lines]), bare-metal stents (BMS [blue lines]), and coronary artery bypass graft surgery (CABG [black lines]) in the ARTS (Arterial Revascularization Therapy Studies) I and II (77). Kaplan-Meier estimates for freedom from (A) death, (B) death, cerebrovascular accident (CVA), and myocardial infarction (MI), (C) repeat revascularization, and (D) overall major adverse cardiovascular and cerebrovascular events (MACCE). Reproduced with permission from Serruys et al. (77).

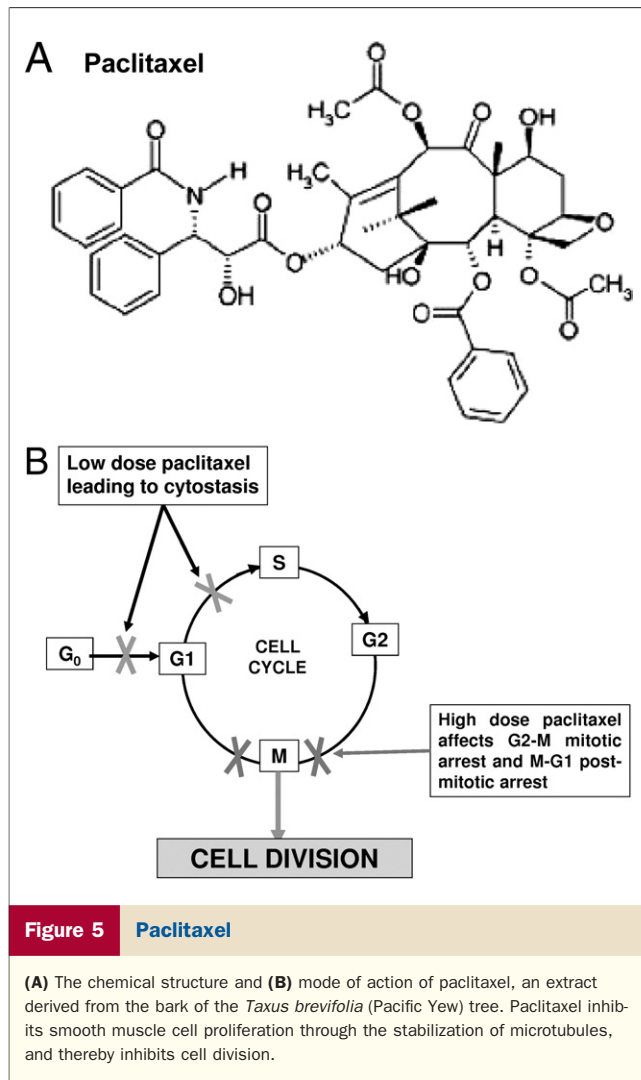


Figure 5 Paclitaxel

(A) The chemical structure and (B) mode of action of paclitaxel, an extract derived from the bark of the *Taxus brevifolia* (Pacific Yew) tree. Paclitaxel inhibits its smooth muscle cell proliferation through the stabilization of microtubules, and thereby inhibits cell division.

PES compared with BMS that is consistent across different patient groups including those with simple lesions, STEMI, lesions in the unprotected left main stem (UPLMS), and complex lesions (57,82–96). In addition, patient-level meta-analysis of the initial PES approval trials has confirmed the comparable safety and superior efficacy of PES compared with BMS out to 4-year follow-up (Table 3) (22,24).

In a fashion similar to the SES, the TAXUS PES stent has been assessed in an unrestricted single-center registry that used the PES as the default stent for all PCI in 576 consecutive real-world patients. Two-year results from the T-SEARCH (Taxus Stent Evaluated at Rotterdam Cardiology Hospital) registry demonstrate similar efficacy in terms of suppression of neointimal growth and reduction of restenosis when compared with historical controls treated with SES (97,98).

TAXUS EXPRESS VERSUS TAXUS LIBERTÉ. The first PES to be approved by the Food and Drug Administration (FDA) was the TAXUS PES Express stent. This was subsequently superseded by the TAXUS PES Liberté stent, which was

designed to be more deliverable and conformable and to provide a more homogenous drug distribution (99). Table 1 summarizes the main physical properties of both stents, both of which have the same polymer and dose of paclitaxel; however, the Liberté stent has a more uniform cell geometry (Fig. 6) (99), allowing more enhanced and uniform drug delivery, thinner struts (97 μm vs. 132 μm), a smaller profile, and separate stent designs depending on stent diameter. Stents with a diameter of 2.25 to 2.5 mm have a 2-cell design, whereas stents with a diameter >2.75 mm have a 3-cell design. The superiority of the Liberté stent was confirmed through the multicenter noninferiority TAXUS ATLAS (TAXUS Liberté-SR Stent for the Treatment of De Novo Coronary Artery Lesion) clinical trial, which enrolled 871 patients treated with the TAXUS Liberté stent who were compared with a historical population of patients treated with the TAXUS Express-SR stent from the TAXUS IV and V trials (99). In spite of similar inclusion criteria, patients receiving the Liberté stent had treatment for significantly more complex baseline lesions. Nevertheless, the primary end point of 9-month target vessel revascularization (TVR) occurred in 7.0% and 8.0% of patients treated with the Express and Liberté stents, respectively, achieving the pre-specified criteria for noninferiority ($p = 0.049$). There were no significant differences in other clinical outcomes.

Two additional multicenter studies confirmed the improved outcomes with the newer Liberté stent. These were the TAXUS ATLAS Small Vessels study and the TAXUS ATLAS Long Lesions study.

The TAXUS ATLAS Small Vessels study, which compared the performance of the 2.25-mm TAXUS Liberté stent in 261 patients with 75 historical controls from the TAXUS V study who had had a lesion treated with a single 2.25-mm TAXUS Express stent (100). In addition to meeting the noninferiority primary end point of 9-month in-segment diameter stenosis, compared with the Express stent, the Liberté stent was shown to significantly reduce the rate of 9-month angiographic restenosis (18.5% vs. 32.7%, $p = 0.02$) and TLR at 12 months (6.1% vs. 16.9%, $p = 0.004$). Moreover, at 3-year follow-up, the use of the TAXUS Liberté led to a significant reduction in TLR (10.0% vs. 22.1%, $p = 0.008$) and MACE (19.5% vs. 32.4%, $p = 0.03$), together with a numerically lower composite of death/stroke and MI (6.5% vs. 7.4%, $p = 0.79$) (101).

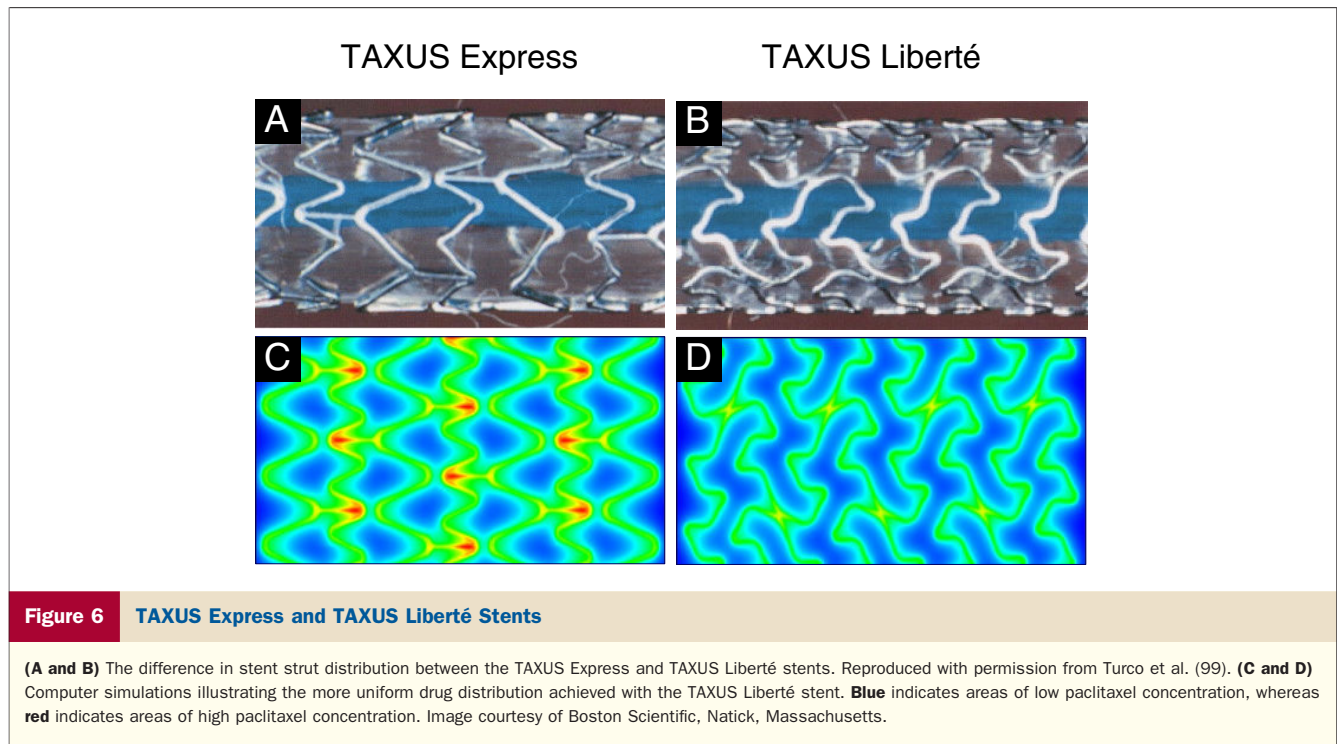
The TAXUS ATLAS Long Lesions study compared the performance of the 38-mm long TAXUS Liberté stent in 150 patients with lesions between 26 mm and 34 mm in length with that of 145 historical control patients from the TAXUS IV and V studies with similar length lesions treated with a least 1 Express stent (100). In addition to meeting the noninferiority primary end point of 9-month in-segment diameter stenosis, compared with the Express stent, the Liberté stent was also shown to significantly reduce the risk of MI at both 12-month follow-up (1.4% vs.

Table 4 Summary of Major Randomized Trials of PES Versus BMS in Different Clinical Settings

| Trial or First Author (Ref. #) | No. of Patients | Clinical Setting | Follow-Up, Months | In-Stent Late Loss (PES vs.), mm | Binary In-Stent Restenosis (PES vs.), % | MACE (PES vs.), % | Death (PES vs.), % | MI (PES vs.), % | TLR (PES vs.), % | Definite/Probable ST (PES vs.), % |
|-----------------------------------|-----------------------------------|------------------------|-------------------|----------------------------------|---|--|--------------------------------|-----------------------------|--------------------------------------|-----------------------------------|
| TAXUS-I (82) | PES (n = 31) vs. BMS (n = 30) | Simple lesions | 6*/12† | 0.36 vs. 0.71 | 0.0 vs. 10.4 | 3.3 vs. 10.0‡ | 0.0 vs. 0.0 | 0.0 vs. 0.0 (Q-wave only) | 0.0 vs. 10.0§ | 0.0 vs. 0.0 |
| TAXUS-II Slow release (83,84) | PES (n = 131) vs. BMS (n = 136) | Simple lesions | 6*/12† 60 | 0.31 vs. 0.79 NA | 2.3 vs. 17.9 NA | 10.9 vs. 22.0¶# 20.4 vs. 27.6‡‡‡ | 0.0 vs. 1.5 2.4 vs. 1.5†† | 2.4 vs. 5.3 4.7 vs. 7.1 | 4.7 vs. 12.9¶ 10.3 vs. 18.4¶ | 0.7 vs. 0.0** 2.7 vs. 0.8** |
| TAXUS-II Moderate release (83,84) | PES (n = 135) vs. BMS (n = 134) | Simple lesions | 6*/12† 60 | 0.30 vs. 0.77 NA | 4.7 vs. 20.2 NA | 9.9 vs. 21.4¶# 15.1 vs. 27.6‡¶†† | 0.0 vs. 0.0 1.6 vs. 1.5†† | 3.8 vs. 5.4 5.3 vs. 7.1 | 3.8 vs. 16.0¶ 4.5 vs. 18.4 | 0.7 vs. 0.0** 1.7 vs. 0.8** |
| TAXUS-IV (85,86) | PES (n = 662) vs. BMS (n = 652) | Pivotal approval trial | 9 60 | 0.39 vs. 0.92 NA | 5.5 vs. 24.4 NA | 8.5 vs. 15.0 †††† 24.0 vs. 32.0‡ †† | 2.4 vs. 2.2 10.0 vs. 11.2 | 3.5 vs. 3.7 7.2 vs. 7.4 | 3.0 vs. 11.3 ‡‡ 9.1 vs. 20.5 ‡‡ | 0.8 vs. 1.1 2.1 vs. 2.3 |
| TAXUS-V (87,88) | PES (n = 577) vs. BMS (n = 579) | Complex lesions | 9 60 | 0.49 vs. 0.90 NA | 13.7 vs. 31.9 NA | 15.0 vs. 21.2¶††††† NA | 0.5 vs. 0.9†† 10.2 vs. 8.5 | 5.4 vs. 4.6 9.3 vs. 5.6¶ | 8.6 vs. 15.7¶‡‡ 17.0 vs. 23.2¶‡‡ | 0.7 vs. 0.7** 2.4 vs. 1.5¶ |
| TAXUS-VI (89,90) | PES (n = 219) vs. BMS (n = 227) | Long complex lesions | 9 60 | 0.39 vs. 0.99 NA | 9.1 vs. 32.9 NA | 16.4 vs. 22.5 31.3 vs. 27.8#†† | 0.0 vs. 0.9†† 2.8 vs. 3.2†† | 8.2 vs. 6.2 11.2 vs. 8.2 | 6.8 vs. 18.9 14.6 vs. 21.4¶ | 0.5 vs. 0.9** 0.9 vs. 0.9** |
| HORIZONS-AMI (91,92) | PES (n = 2,257) vs. BMS (n = 749) | STEMI | 13*/12† 24 | 0.41 vs. 0.82 NA | 8.2 vs. 21.0 NA | 8.0 vs. 7.9§§ 11.0 vs. 11.2§§ | 3.5 vs. 3.5 4.3 vs. 5.2 | 3.6 vs. 4.4 5.7 vs. 6.1 | 4.3 vs. 7.2¶‡‡ 6.8 vs. 11.6 ‡‡ | 3.1 vs. 3.3 4.1 vs. 4.1 |
| PASEO (57,58) | PES (n = 90) vs. BMS (n = 90) | STEMI | 12 48 | NA NA | NA NA | 11.1 vs. 24.4¶ 21.1 vs. 36.7¶ | 4.4 vs. 6.7 8.9 vs. 12.2 | 3.3 vs. 6.7 7.8 vs. 13.3 | 4.4 vs. 14.4¶ 6.7 vs. 21.1¶ | 1.1 vs. 1.1 1.1 vs. 2.2 |
| PASSION (93,95) | PES (n = 310) vs. BMS (n = 309) | STEMI | 12 60 | NA NA | NA NA | 8.8 vs. 12.8†††† 18.3 vs. 22.0†††† | 4.6 vs. 6.5 8.9 vs. 11.5†† | 1.7 vs. 2.0 6.5 vs. 4.3 | 5.3 vs. 7.8 7.3 vs. 10.5 | 1.4 vs. 2.3 3.9 vs. 3.4 |
| Erglis et al. (96) | PES (n = 53) vs. BMS (n = 50) | UPLMS | 6 | 0.22 vs. 0.60 | 5.7 vs. 22.0¶ | 13.2 vs. 30.0 | 1.9 vs. 2.0 | 9.4 vs. 14.0 | 1.9 vs. 16.0¶ | 0.0 vs. 0.0 |

Differences are nonsignificant unless stated. Stent thrombosis as per Academic Research Consortium definition, unless indicated. All trial acronyms are listed in the Online Appendix. *Angiographic follow-up. †Clinical follow-up. ‡Major adverse cardiovascular events a composite of death, MI, TVR, and ST. §Percutaneous revascularization only. ||p < 0.001. ¶p < 0.05. #Major adverse cardiovascular events a composite of death, MI, and TVR. **Protocol-defined ST. ††Cardiac death. ‡‡Ischemia driven. §§Major adverse cardiovascular events a composite of death, MI, stroke, and ST. |||Definite ST only.

UPLMS = unprotected left main stem; other abbreviations as in Tables 2 and 3.



6.5%, $p = 0.002$) and 3-year follow-up (2.9% vs. 10.4%, $p = 0.01$). Moreover, at 3-year follow-up, the use of the Liberté stent led to a 78% reduction in cardiac death (1.5% vs. 6.7%, $p = 0.03$), with no reported stent thrombosis (ST) (101).

SES versus PES. Several randomized studies, which are summarized in Table 5, have formally compared outcomes between patients treated with SES or PES for: 1) unselected patients populations; 2) specific patient groups such as diabetic patients or patients with STEMI; and 3) specific lesion types such as UPLMS lesions, long lesions, or lesions in small vessels (102–117). Of note, results at short-term angiographic follow-up demonstrate superior reductions in late loss and binary restenosis with the use of SES; however, long-term angiographic follow-up, which is limited to the SIRTAX (Sirolimus Eluting Versus Paclitaxel Eluting Stents for Coronary Revascularization) study, indicates a greater delayed late loss with SES in that, at 5 years, there was no longer a significant difference in late loss between SES and PES (107). With respect to clinical outcomes, a meta-analysis of 16 randomized trials of SES versus PES, which included 8,695 patients and, where possible, patient-level data, reported significant reductions in TLR (hazard ratio [HR]: 0.74, 95% confidence interval [CI]: 0.63 to 0.87, $p < 0.001$) and ST (HR: 0.66, 95% CI: 0.46 to 0.94, $p = 0.02$) with SES, whereas no significant differences in death (HR: 0.92, 95% CI: 0.74 to 1.13, $p = 0.43$), or MI (HR: 0.84, 95% CI: 0.69 to 1.03, $p = 0.10$) were noted at a median of 2-year follow-up (118).

Angiographic measures of DES effectiveness. As suggested by the discussion in the preceding text, angiographic measures such as late lumen loss and binary angiographic

stenosis are commonly used surrogates of clinical effectiveness in DES trials (119). Of the 2, binary angiographic stenosis appears a more favorable variable as it requires a single measurement and not, as in the case of late loss, 2 separate measurements several months apart. In addition, the relationship between late loss and TLR is dependent on vessel size, with more late loss being accommodated in larger vessels before triggering a TLR (so-called headroom); conversely, binary angiographic stenosis is independent of vessel size (120).

The relationship between late loss and the risk of binary restenosis has been described as monotonic; in other words, incremental changes in late loss are associated with a predictable increased risk of binary restenosis (121). Conversely, a curvilinear relationship has been described between late lumen loss and TLR, namely, the increased risk of TLR is not linear over the entire range of late lumen loss (122). Using data from the TAXUS IV trial, Ellis et al. (122) demonstrated that the normally low risk of TLR is only significantly increased once late lumen loss reaches a threshold >0.5 to 0.6 mm. This nonlinear relationship serves to explain why significant differences in late loss during follow-up do not invariably translate into differences in clinical outcomes. For example, in the REALITY (Comparison of the Cypher Sirolimus Eluting and the Taxus Paclitaxel Eluting Stent Systems Trial), the significantly higher late lumen loss at 8 months with PES (PES vs. SES: 0.31 mm vs. 0.09 mm, $p < 0.001$) did not translate into any significant difference in restenosis rate (PES 11.1% vs. SES 9.6%, $p = 0.31$) or TLR (PES 6.1% vs. SES 6.0%, $p > 0.99$) at 12 months (105). Moreover, because of this

Table 5 Summary of Major Randomized Trials (>100 Patients in Each Group) Comparing SES to PES in Different Clinical Settings

| Trial (Ref. #) | No. of Patients | Clinical Setting | Follow-Up, Months | In-Stent Late Loss (SES vs. PES), mm | Binary In-Stent Restenosis (SES vs. PES), % | MACE (SES vs. PES), % | Death (SES vs. PES), % | MI (SES vs. PES), % | TLR (SES vs. PES), % | Definite/Probable ST (SES vs. PES), % |
|------------------------|-------------------------------------|----------------------------|-------------------|--------------------------------------|---|------------------------|------------------------|---------------------|----------------------|---------------------------------------|
| DES-DIABETES (102,103) | SES (n = 200) vs. PES (n = 200) | Diabetic patients | 9 | 0.13 vs. 0.53* | 3.4 vs. 18.2* | 2.0 vs. 8.0† | 0.0 vs. 0.5 | 0.5 vs. 0.5 | 2.0 vs. 7.5† | 0.5 vs. 0.0 |
| | | | 24 | NA | NA | 3.5 vs. 12.5† | 0.0 vs. 1.5 | 0.5 vs. 1.0 | 3.5 vs. 11.0† | 1.0 vs. 0.0 |
| ISAR-DIABETES (104) | SES (n = 125) vs. PES (n = 125) | Diabetic patients | 9 | 0.19 vs. 0.46* | 4.9 vs. 13.6† | NA | 3.2 vs. 4.8 | 4.0 vs. 2.4 | 6.4 vs. 12.0 | 0.0 vs. 0.1 |
| REALITY (105) | SES (n = 701) vs. PES (n = 685) | Unselected | 8‡/12§ | 0.09 vs. 0.31* | 7.0 vs. 8.3 | 10.7 vs. 11.4 | 2.3 vs. 1.3 | 5.1 vs. 6.0 | 6.0 vs. 6.1 | 0.7 vs. 1.9¶ |
| SIRTAX (106,107) | SES (n = 503) vs. PES (n = 509) | Unselected | 8‡/9§ | 0.12 vs. 0.25* | 3.2 vs. 7.5† | 6.2 vs. 10.8† # | 1.0 vs. 2.2 | 2.8 vs. 3.5 | 4.8 vs. 8.3†# | 2.0 vs. 1.8 |
| | | | 60 | 0.30 vs. 0.37 | NA | 21.3 vs. 24.2 | 10.9 vs. 9.4 | 6.6 vs. 6.9 | 14.9 vs. 17.9 | 4.6 vs. 4.1 |
| SORT-OUT II (108) | SES (n = 1,065) vs. PES (n = 1,065) | Unselected | 18 | NA | NA | 10.0 vs. 11.6 ** | 3.8 vs. 3.9 | 4.2 vs. 5.1 | 4.5 vs. 5.9 | 2.6 vs. 2.8 |
| TAXI (109,110) | SES (n = 102) vs. PES (n = 100) | Unselected | 6 | NA | NA | 6.0 vs. 4.0 | 0.0 vs. 0.0 | 2.0 vs. 3.0 | 2.0 vs. 1.0 | 1.0 vs. 0.0¶ |
| | | | 36 | NA | NA | 17 vs. 11 | 7.0 vs. 3.0 | 3.0 vs. 6.9 | 5.0 vs. 1.0 | 2.0 vs. 2.0¶ |
| PROSIT (111,112) | SES (n = 154) vs. PES (n = 154) | STEMI | 6‡/12§ | 0.19 vs. 0.43† | 5.0 vs. 12.0 | 5.8 vs. 11.7 (+ST) | 3.2 vs. 5.8 | 0.0 vs. 1.9 | 2.6 vs. 6.5 | 0.0 vs. 1.3¶ |
| | | | 36 | NA | NA | 12.3 vs. 18.8** (+ST) | 6.5 vs. 10.4 | 2.6 vs. 3.9 | 3.9 vs. 8.4** | 0.6 vs. 1.9 |
| ISAR-LEFT MAIN (113) | SES (n = 305) vs. PES (n = 302) | UPLMS | 6–8‡/24§ | NA | 19.4 vs. 16.0 | 20.6 vs. 21.3 | 8.7 vs. 10.4 | 4.6 vs. 5.4 | 10.7 vs. 9.2 | 1.0 vs. 0.3 |
| LONG-DES II (114) | SES (n = 250) vs. PES (n = 250) | Long lesions | 6 | 0.09 vs. 0.45* | 2.9 vs. 11.7† | 12.0 vs. 17.2 | 0.8 vs. 0.0 | 8.8 vs. 10.8 | 2.4 vs. 7.2† | 0.8 vs. 0.0¶ |
| ISAR-SMART 3 (115) | SES (n = 180) vs. PES (n = 180) | Small vessels, nondiabetic | 6–8‡/12§ | 0.25 vs. 0.56* | 8.0 vs. 14.9† | 5.0 vs. 5.6 (Death/MI) | 1.7 vs. 2.2 | 3.9 vs. 3.3 | 6.6 vs. 14.7† | 0.0 vs. 0.0 (30 days) |
| ISAR-DESIRE (116) | SES (n = 100) vs. PES (n = 100) | In-stent restenosis | 6 | 0.10 vs. 0.26† | 11.0 vs. 18.5 | NA | 2.0 vs. 1.0 | 1.0 vs. 2.0 | 8.0 vs. 19.0†** | NA |
| ISAR-DESIRE 2 (117) | SES (n = 225) vs. PES (n = 225) | SES in-stent restenosis | 6–8‡/12§ | 0.40 vs. 0.38 | 19.0 vs. 20.6 | 20.4 vs. 19.6 | 3.4 vs. 4.5 | 2.7 vs. 1.8 | 16.6 vs. 14.6 | 0.4 vs. 0.4†† |

Differences are nonsignificant unless indicated. Stent thrombosis Academic Research Consortium definition unless indicated. All trial acronyms are listed in the Online Appendix. *p < 0.001. †p < 0.05. ‡Angiographic follow-up. §Clinical follow-up. ||Cardiac death. ¶Protocol-defined ST. #Ischemia driven. **Target vessel revascularization. ††Definite only. Abbreviations as in Tables 2, 3, and 4.

relationship, late lumen loss is regarded as having only limited use in isolation in the assessment of clinical effectiveness among different DES, particularly if absolute levels are low.

Benefits of DES. Extensive data exist confirming the benefits of DES in terms of reduced rates of restenosis compared with BMS. Results from the largest meta-analysis to date, which included >18,000 patients from 38 DES trials, indicated a reduction in TLR of 70% ($p < 0.0001$) with the use of SES, and 58% ($p < 0.001$) with the use of PES, when compared with BMS out to 4 years of follow-up (Table 3) (22). This corresponded to a number needed to treat, to prevent a single revascularization, of only 7 and 8 patients for SES and PES, respectively. Several other similar meta-analyses have also been performed, and their results are summarized in Table 3 (23–26).

Importantly, these impressive results are not only confined to the select patients treated for on-label indications, but also have consistently been reproduced in registries and randomized controlled trials that have included those with patients receiving DES for off-label indications (76,78,123). Of note, a recent large meta-analysis by Kirtane et al. (76) that included >9,000 patients suggests that the benefit in terms of reduced restenosis from DES use appears to be at least as great as in patients treated for off-label indications (HR: 0.46, 95% CI: 0.34 to 0.52, $p < 0.01$) as opposed to on-label indications (HR: 0.54, 95% CI: 0.48 to 0.62, $p < 0.01$).

Risks of DES. MORTALITY. The concerns that DES increased mortality stemmed from the presentation and publication of 4 studies. 1) A meta-analysis performed by Nordmann et al. (31) using aggregate trial data from 17 randomized studies of patients treated with SES, PES, and BMS that demonstrated a statistically significant increase in noncardiac mortality between 2 and 3 years after SES implantation. 2) The single-center BASKET-LATE (Basel Stent Kosten Effektivitats Trial), which randomly assigned 746 unselected patients to either SES or BMS, and reported a higher rate of death and MI between 7 and 18 months after the index PCI among patients treated with SES compared with BMS (adjusted HR: 2.2, $p = 0.03$). No significant difference was seen in the rates of ST or thrombosis-related events between groups; however, ultimately the study was underpowered to detect ST events, and limited angiographic evidence was available to confirm that events were actually due to ST (124). 3) The pooled analysis of published data from the Cypher SES trials, RAVEL, SIRIUS, E-SIRIUS (European-Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions), and C-SIRIUS (Canadian-Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions) by Camenzind et al. (32), that showed a statistically significant 2.4% increased risk of death and Q-wave MI with the use of SES compared with BMS (6.3% vs. 3.9%, $p = 0.03$). Much criticism was directed at the use of the peculiar end point of death and Q-wave MI, and the use of aggregate trial data. A subsequent analysis of the same studies by Spaulding et al. (23) using patient-level data

indicated that there were no significant differences in death/MI between groups (11.4% SES vs. 10.1% BMS, $p = 0.4$). 4) The 3-year results of SCAAR (Swedish Angiography and Angioplasty Registry), which reported results from ~20,000 patients treated with BMS or DES between 2003 and 2004, and demonstrated a higher overall risk of death for patients receiving DES (adjusted relative risk [RR]: 1.18; 95% CI: 1.04 to 1.35) (33). Subsequent extended analyses to incorporate data from 2005, however, demonstrated a 31% reduction in events during the first 6 months with DES, and no difference in events between DES and BMS during long-term follow-up. That may have been the result of DES use increasing from 22% to 53% of PCI procedures from 2003 to 2005, together with operators traversing the learning curve with DES, and thereby selecting lesions and patients more appropriately, and being more meticulous with ensuring adequate stent deployment, and compliance to DAPT (125). Most recently, data from the registry, extended to include new patients treated in 2006 and now including just under 48,000 patients, showed a similar long-term incidence of death or MI among DES and BMS patients. Moreover, DES were also shown to have a reduced rate of restenosis among high-risk patients (125,126).

In the aftermath of these studies, which caused widespread concern, several patient-based meta-analysis were performed that reassuringly demonstrated the overall comparable outcomes between DES and BMS in terms of death and MI, at both short- and long-term follow-up (Table 3). The largest of these studies, by Stettler et al. (22), reported a similar risk of death for patients treated with SES, PES, or BMS; the risk of MI, although comparable between PES and BMS ($p = 0.99$), was significantly lower with SES compared with BMS ($p = 0.03$) (22). Additional meta-analyses were performed at a similar time by Stone et al. (24), Spaulding et al. (23), Kastrati et al. (26), and Mauri et al. (25), and now more recently by Kirtane et al. (76). All reiterated the safety of DES by demonstrating the absence of any significantly increased risk of death and/or MI with the use of DES compared with BMS.

In addition to the data from randomized controlled trials, observation data comparing DES to BMS have been published from numerous registries, which in total include >400,000 patients. The largest single registry published to date includes 262,700 patients from the Medicare registry and demonstrates lower rates of adjusted and unadjusted death, MI, and repeat revascularization after treatment with DES compared with BMS out to 30 months of follow-up (123). A similar advantage in favor of DES was also reported by Kirtane et al. (76) in a meta-analysis of >30 registries, which included >180,000 patients followed up for 12 to 48 months. These data reflect some of inherent differences between randomized studies and observation studies, which provide a better reflection of real-world practice and, owing to the large numbers of patients recruited, may be able to detect differences in infrequent events. Conversely, however, they can be affected by a

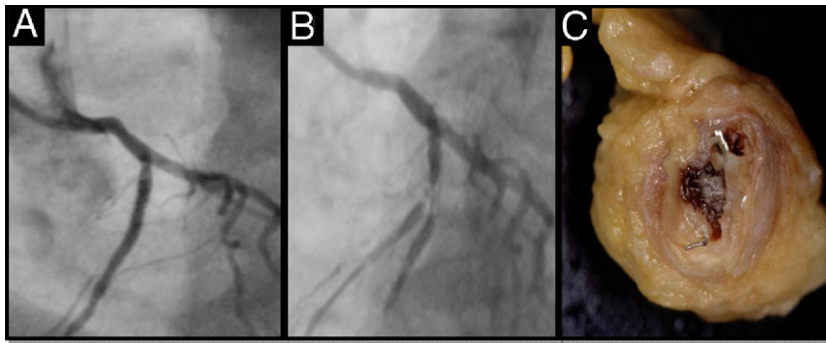


Figure 7 Stent Thrombosis

(A) Drug-eluting stent implantation in the proximal left anterior descending artery, complicated by (B) stent thrombosis occurring 7 months later, shortly after discontinuation of dual antiplatelet therapy. (C) Gross pathology example of stent thrombosis.

selection bias and/or incomplete risk adjustment due to unmeasured baseline population differences, factors that may account for the previously noted reductions in mortality and MI.

Off-label indications. The current on-label indications for DES use, as approved by the U.S. FDA are limited to simple lesions: for SES, de novo lesions ≤ 30 mm in length in native coronary arteries with reference vessel diameters of 2.5 to 3.5 mm, and for PES de novo lesions ≤ 28 mm in length in native coronary arteries 2.5 to 3.75 mm in diameter. It follows that off-label indications represent a higher-risk population with more complex lesion morphologies and unstable clinical presentations.

One of the criticisms of early DES trials was that they enrolled stable patients treated with DES for on-label indications. For example, the meta-analyses by Stettler et al. (22), Stone et al. (24), Spaulding et al. (23), Kastrati et al. (26), and Mauri et al. (25) included patients who were treated for essentially stable de novo lesions, which had a mean lesion length of 23 to 24 mm, a mean vessel diameter of 2.7 mm, and were suitably treated with an average of 1.2 to 1.4 stents. There were concerns that the comparative results between DES and BMS seen in these studies did not reflect real-world practice in which 70% to 75% of DES are implanted for off-label indications (127,128).

Unfortunately, the lack of any dedicated trials comparing off-label DES and BMS added to these concerns, and the FDA Circulatory System Devices Advisory Panel that met in December 2006 concluded that there was a need for a comprehensive assessment of the safety and efficacy of off-label DES use (129). This prompted numerous studies, many of which were observational, that ultimately demonstrated that the use of DES for off-label indications was associated with poorer clinical outcomes in terms of death, MI, and repeat revascularization when compared with DES use for on-label indications (127,130–132). Of equal importance are the results from registries and randomized controlled trials that suggest that, for off-label indications,

the use of a DES is no worse than the use of a BMS (76,133–136), with some studies, such as the Medicare and STENT (Strategic Transcatheter Evaluation of New Therapies) registry actually demonstrating significantly improved outcomes with the use of a DES (123,131). These findings suggest that the overall poor outcome with off-label use is most likely related to patient or lesions characteristics, rather than to specific shortcomings of DES.

ST. ST has emerged as 1 of the major safety concerns with stenting in today's clinical practice (Fig. 7). Fortunately, it is a rare, but it remains a devastating unpredictable event that has a significant morbidity and mortality (137); the clinical consequences are highly dependent on the myocardial area at risk, its viability, the degree of recruitable collaterals, and the speed of reperfusion therapy. The overall prognosis from ST is poor: 10% to 30% of patients with definite ST will die, whereas a proportion will experience an unexpected out-of-hospital death.

Early anecdotal reports of ST occurring in the months and years after implantation of a DES (138–140) were substantiated by subsequent studies reporting an annual risk of ST ranging from 0.2% in post-marketing surveillance registries, to 0.5% in trials of multivessel PCI (141–144). The infrequent nature of ST, together with concerns regarding mortality among patients treated with DES, lead to large collaborative meta-analyses, performed using the standardized Academic Research Consortium (ARC) definitions, that demonstrated similar rates of overall ST between DES and BMS (Table 6) (22–26,145). In particular, no difference between DES and BMS was seen for early ST (<30 days) or late ST (30 days to 1 year); however, significantly higher rates of very late ST (>1 year) were seen with DES. Furthermore, registry data from the Rotterdam-Bern group ($n = 8,146$), the SCAAR (Swedish Angiography and Angioplasty Registry) registry ($n = 21,717$), and the Pinto Slottow et al. registry ($n = 8,000$) have all indicated that the risk of very late ST persists at an annual rate of between 0.36% and 0.6%/year to at least 5 years after

Table 6 Rates of Overall, Early, Late, and Very Late Stent Thrombosis From Recent Meta-Analyses Comparing DES to BMS

| First Author (Ref. #) | No. of Patients | Longest Follow-Up, yrs | Overall ST, DES vs. BMS | Early ST, DES vs. BMS | Late ST, DES vs. BMS | Very Late ST, DES vs. BMS |
|------------------------|-------------------------------|------------------------|-------------------------|-----------------------|----------------------|---------------------------|
| SES vs. BMS | | | | | | |
| Spaulding et al. (23)* | 1,748 (878 SES, 870 BMS) | 4 | 3.6% vs. 3.3% | 0.5% vs. 0.5% | 0.3% vs. 1.3%† | 2.8% vs. 1.7% |
| Stettler et al. (22)* | 8,646 (4,643 SES, 4,003 BMS) | 4 | HR: 1.00 | HR: 1.02 | HR: 1.14 | HR: 1.43 |
| Stone et al. (24)‡ | 1,748 (878 SES, 870 BMS) | 4 | 1.2% vs. 0.6% | 0.5% vs. 0.1% | 0.1% vs. 0.5% | 0.6% vs. 0.0%† |
| Kastrati et al. (26)‡ | 4,958 (2,486 SES, 2,472 BMS) | 5 | HR: 1.09 | — | — | 0.6% vs. 0.05%† |
| PES vs. BMS | | | | | | |
| Stettler et al. (22)* | 8,330 (4,327 PES, 4,003 BMS) | 4 | HR: 1.38 | HR: 0.95 | HR: 1.61 | HR: 3.57 |
| Stone et al. (24)‡ | 3,513 (1,755 PES, 1,758 BMS) | 4 | 1.3% vs. 0.9% | 0.5% vs. 0.6% | 0.2% vs. 0.1% | 0.7% vs. 0.2%† |
| Mauri et al. (25)* | 2,797 (1,400 PES, 1,397 BMS) | 4 | 3.2% vs. 3.5% | 0.5% vs. 0.5% | 0.9% vs. 0.9% | 1.8% vs. 2.1% |
| Other | | | | | | |
| Stettler et al. (22)* | 8,970 (4,643 SES, 4,327 PES) | 4 | HR: 0.71§ | HR: 1.05§ | HR: 0.68§ | HR: 0.39§ |
| Roukoz et al. (145)‡ | 10,727 (5,534 DES, 5,193 BMS) | 5 | 1.4% vs. 1.3% | 0.8% vs. 0.9% | 0.3% vs. 0.4% | 0.7% vs. 0.1%† |

Difference nonsignificant unless indicated. Stent thrombosis defined by *Academic Research Council definitions or †p < 0.05. ‡study protocols. §SES vs. PES. Abbreviations as in Tables 2 and 3.

DES implantation (146–150). The results at 2-year follow-up from both the ARRIVE (The TAXUS Peri-Approval Registry: A Multi-Centre Safety Surveillance) and the STENT registry indicate that the risk of ST is higher for patients treated with DES for off-label indications compared with on-label indications (130,131).

Uncertainty exists over the exact cause of ST; however, numerous factors have been implicated in increasing the risk of a ST event (Table 7). Of note, data from large-scale registries demonstrate that the multivariate predictors of ST change during follow-up (146,147,151,152). In addition to the early cessation of DAPT, numerous other procedural-related factors such as stent undersizing, lesion length >28 mm, dissection, multiple stent implantation, calcification, and small vessel diameter have been shown to be important factors in the development of early/late but not very late ST (151,152). Conversely, patient factors such as previous

brachytherapy and renal failure appear to be more influential in very late ST. This variation in the cause of ST may explain the relatively higher rates of early ST when compared with late/very late ST. For example, in the Dutch Stent registry of 21,009 patients, 437 patient had documented ST of which 32.0%, 41.2%, 13.3%, and 13.5% was categorized as acute, subacute, late, and very late ST, respectively (151).

Two of the most prominent device concerns with the use of DES that deserve additional consideration are their ability to potentially delay endothelialization and induce hypersensitivity reactions through the presence of a drug polymer.

IMPAIRED ENDOTHELIALIZATION BY ANTIPROLIFERATIVE DRUGS. The antiproliferative properties of DES impair and/or delay endothelialization so that blood is exposed to thrombogenic stent struts, potentially precipitating ST (138,153–156). Animal studies using scanning electron microscopy have previously demonstrated a greater area of exposed stent struts with the use of DES (SES 3.08 mm², PES 3.54 mm²) compared with BMS (0.12 mm²) (157). More recently, human studies using optical coherence tomography have also demonstrated differences between different types of DES, with the second generation zotarolimus-eluting stent (ZES) having significantly lower rates of uncovered stent struts when compared with SES at both overlapping sites (0.06% vs. 5.4%) and nonoverlapping sites (0.03% vs. 8.7%) (158). Similar results have been reported by Kim et al. (159), whereas Barlis et al. (160) demonstrated a higher rate of near complete (>95%) strut coverage in a stent with a biodegradable polymer when compared with a stent with a durable polymer (SES [89.3% vs. 63.3%, p = 0.03]). Incomplete strut coverage can also be demonstrated on angiography, and has been seen as late as 2 years after implantation of SES (161,162). The restitution of a healthy but not hyperproliferative endothelial lining remains a target of ongoing current research.

Table 7 Precipitants of Stent Thrombosis

| Precipitant of Stent Thrombosis | |
|---------------------------------|--|
| Patient factors | <ul style="list-style-type: none"> Percutaneous coronary intervention for acute coronary syndrome/ST-segment elevation myocardial infarction Diabetes mellitus Renal failure Impaired left ventricular function Premature cessation of dual anti-platelet therapy Clopidogrel nonresponsiveness Prior brachytherapy |
| Lesion characteristics | <ul style="list-style-type: none"> Lesion/stent length Vessel/stent diameter Complex Lesions (bifurcation lesions, chronic total occlusions) |
| Procedural factors | <ul style="list-style-type: none"> Inadequate stent expansion Incomplete stent apposition Stent deployment in necrotic core |
| Device factors | <ul style="list-style-type: none"> Hypersensitivity to drug coating or polymer Incomplete endothelialization Stent design |

POLYMER. Conventionally, DES are coated with permanent polymers that facilitate drug release and remain long after drug elution is complete. These permanent polymers can cause delayed healing, impaired stent strut endothelialization, and a hypersensitivity reaction, which can culminate in ST (153,157,163–165). Data from histopathology studies also indicate that these nonerodable polymers can precipitate ST by inducing localized vascular inflammation, hyper eosinophilia, thrombogenic reactions, and apoptosis of smooth muscle cells (164–166). Of note, the Cypher SES is coated in a nonerodable poly(ethylene co-vinyl acetate) and poly(n-butyl methacrylate) polymer that has been shown to induce granulomatous and hypersensitivity reactions in animal models and humans (167,168). Similarly, the first-generation TAXUS PES stent has a durable poly(styrene-*b*-isobutylene-*b*-styrene) polymer that is associated with medial necrosis, positive remodeling, and excessive fibrin deposition, which likely contribute to the deleterious pathologic changes that can be seen with the TAXUS stent (168).

The potential of these first-generation stents to cause ST due to a permanent polymer has led to extensive research into developing new polymers. These developments have led to the second-generation DES that have more biocompatible nonerodable polymers, which have been shown in animal studies to have a greater degrees of re-endothelialization compared with first-generation stents (157). Research has also led to the design of the newer DES that are described in Part Two of this article, and have biodegradable polymers, novel coatings, or are completely polymer free.

DURATION OF ANTIPLATELET THERAPY. Although the clinical value and cost effectiveness of long-term clopidogrel (up to 12 months) with BMS after PCI for acute coronary syndrome (ACS) is well established (169–171), the optimal duration of DAPT after DES implantation remains an issue of contention. Central to the discussion are repeated studies that demonstrate that premature (<1 year) discontinuation of DAPT is 1 of the most significant independent predictors of ST (142,151,172,173), with poor patient compliance, surgery, bleeding complications, poor patient education, allergy to clopidogrel, and cost the most frequently cited reasons for cessation (146,172). It was this association between “early” discontinuation of DAPT and ST that led guidelines’ authorities and the U.S. FDA advisory panel to recommend 12-month DAPT after DES implantation for all patients without contraindications and bleeding risk (128,174). However, these recommendations were made in the absence of any prospective randomized trials evaluating whether prolonged DAPT actually reduced rates of ST.

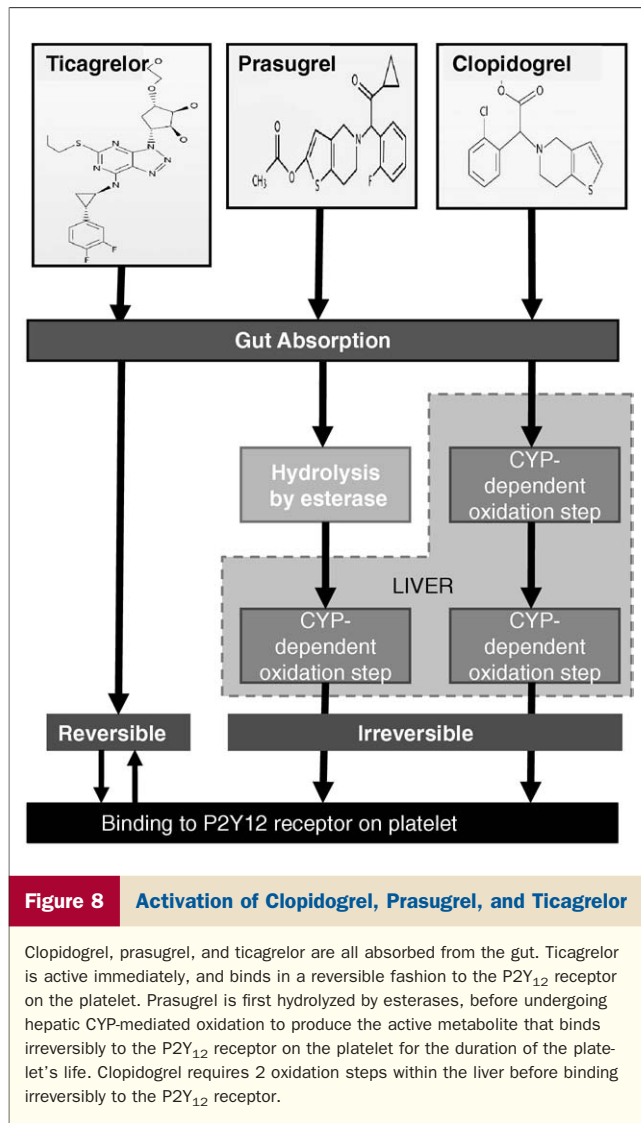
This association of cessation of DAPT and ST is complicated by studies that demonstrated that discontinuation of clopidogrel is only a major independent predictor of ST in the first 6 months after PCI, and not beyond. The median time interval for a ST event after the discontinuation of clopidogrel has been shown to be 9 days (interquar-

tile range 5.5 to 22.5) within the first 6 months of the PCI, compared with 104.3 days (interquartile range 7.4 to 294.8) for the period after (173,175). Further complicating the issues are a lack of randomized data and reliance on observational studies, some of which indicate that discontinuing clopidogrel after 6 months does not increase the risk of ST (175,176), whereas others demonstrate that long-term DAPT might be associated with reductions in death and MI (177,178). Other important facts to consider are that <1% of patients who discontinue DAPT experience a ST (179), whereas ST events commonly occur among patients who are still receiving DAPT (173). For example, in the Rotterdam-Bern study, 87% of patients with early ST and 23% of patients with late ST were still taking DAPT at the time of the event (146). Further clouding matters is a possible hyperthrombotic rebound phenomena after clopidogrel discontinuation. That has been suggested by, among others, Ho et al. (180), who observed a clustering of adverse events in the 90-day period after the cessation of clopidogrel in 3,137 ACS patients who were treated either medically or with PCI.

Current registry data assessing long-term use of DAPT show conflicting results. Park et al. (181) reported no benefit in terms of reduced clinical outcomes or ST events in 2,851 patients treated with DES who received DAPT for >12 months. More recently, however, the smaller TYCOON (Two-Year Clopidogrel Need Study) registry has reported more positive results among 443 patients treated with DES who received DAPT for 12 months ($n = 173$) or 24 months ($n = 274$). At 4-year follow-up, there was no difference in clinical outcomes; however, significantly lower rates of very late ST (2% vs. 0%, $p = 0.03$) and overall ST (3% vs. 0.4%, $p = 0.02$) were seen in the group receiving prolonged DAPT. A major limitation of the study was failure to assess the potentially adverse effects of prolonged DAPT in these patients (182).

It is hoped that several on-going randomized trials will provide additional data to help establish the optimal duration of DAPT. The ISAR-SAFE (Intracoronary Stenting and Angiographic Results: Safety And Efficacy of 6 Months Dual Anti-platelet Therapy After Drug Eluting Stenting) study and the OPTIMIZE (Optimized Duration of Clopidogrel Therapy Following Treatment With the Endeavor Zotarolimus-Eluting Stent (ZES) in the “Real-World”) study are both currently randomizing patients treated with DES to either standard therapy of 12 months of DAPT or shorter periods of DAPT ranging from 3 months (OPTIMIZE) or 6 months (ISAR-SAFE) (183,184). Conversely, the DAPT (Dual Anti-Platelet Therapy Trial) will compare outcomes of >20,000 patients treated with BMS and DES who are randomly allocated to DAPT therapy for either 12 or 30 months (185).

These concerns may be rendered immaterial if the initial promise from newer antiplatelet agents, which have recently been assessed in randomized controlled trials, is maintained (Fig. 8). Prasugrel represents a novel antiplatelet agent



that is a more effective inhibitor of the P2Y₁₂ platelet adenosine diphosphate receptor, compared with both ticlopidine and clopidogrel. This results in its antiplatelet activity peaking 60 min after oral administration, compared with 2 to 6 h with clopidogrel (186). In the recent TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38) trial that randomized >13,000 patients with ACS, use of prasugrel was associated with a significant reduction in the primary end point (a composite of cardiac death/nonfatal MI/nonfatal stroke), and rates of MI, TVR, and ST ($p < 0.001$ for all), when compared with standard therapy with clopidogrel. Of note, the risk of major life-threatening and fatal bleeding was significantly higher with prasugrel (187). A pre-specified substudy analysis involving >12,000 patients who received a stent reported significantly reduced rates of ST in patients receiving prasugrel (1.13% vs. 2.35%, HR: 0.80, $p = 0.03$), with at least as great a

reduction in ST seen in patients treated with a DES (HR: 0.36) compared with a BMS (HR: 0.52) (188).

Ticagrelor is a cyclopentyl triazolopyrimidine and functions as an orally active reversible inhibitor of the platelet adenosine diphosphate receptor P2Y₁₂. In the recently published PLATO (Platelet Inhibition and Patient Outcomes) study, use of ticagrelor compared with clopidogrel in 18,624 patients with ACS resulted in a 16.0% reduction in the primary end point, which was a composite of death from vascular causes, MI, or stroke (9.8% vs. 11.7%, HR: 0.84; 95% CI: 0.77 to 0.92; $p < 0.001$). Moreover, rates of ST among patients receiving a stent were also significantly lower in those treated with ticagrelor compared with clopidogrel (1.3% vs. 1.9%, $p = 0.009$). Rates of major bleeding were comparable; however, patients treated with ticagrelor had high rates of non-CABG-related major bleeding (4.5% vs. 3.8%, $p = 0.03$), which included more instances of fatal intracranial bleeding (189,190). Conversely, patients treated with ticagrelor had a lower risk of CABG major bleeding, which is the likely consequence of its reversibility that enables it to dissipate before surgery.

CLOPIDOGREL RESISTANCE/NONRESPONDERS. In recent times, resistance to aspirin and/or clopidogrel, which may occur in as many as 44% of patients (191,192), has emerged as a potential risk factor for adverse cardiac events, particularly ST (193-195). The underlying mechanism of this nonresponsiveness is not completely understood, but is likely to occur through a combination of clinical, cellular, and genetic factors, together with potential drug interactions (196).

The assessment of clopidogrel resistance has been advanced after developments in patient tests. Importantly, several studies in patients undergoing elective or urgent PCI have reported a correlation between the reactive platelet response to adenosine diphosphate, assessed using the point-of-care assay VerifyNow (Accumetrics, San Diego, California), and clinical outcomes ranging from periprocedural MI to 1-year MACE (197-201). These results indicate the potential importance of platelet function testing; however, in the absence of large-scale clinical trials, these tests can only be regarded as research tools at present.

Despite the potential to identify patients with clopidogrel resistance, no definitive treatment has been fully established, and in view of the potentially fatal consequences, this represents a major clinical problem. Simple measures include ensuring adequate patient compliance and evaluating possible drug interactions. Additional strategies that have been suggested include the following. 1) Use an increased maintenance dose of clopidogrel of 150 mg/day, which may improve clinical outcomes without significantly increasing bleeding (202,203). This treatment for clopidogrel resistance is currently being assessed in the randomized GRAVITAS (Gauging Responsiveness With A VerifyNow assay—Impact on Thrombosis and Safety) study (204). Further anecdotal support for this strategy is provided by

the PCI cohort in the randomized CURRENT-OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events—Optimal Anti-platelet Strategy for Interventions) study, which has recently reported the safety and clinical benefits of administering 150 mg/day clopidogrel for 7 days after PCI in patients with ACS or STEMI treated before PCI with a 600-mg loading dose of clopidogrel. The use of the higher dose of clopidogrel led to significant reductions in both definite ST and MI at 30-day follow-up, without any significant increase in stroke or major, fatal, or CABG-related bleeding (205,206). 2) Use additional antiplatelet agents such as glycoprotein IIb/IIIa inhibitors during PCI, and cilostazol, a phosphodiesterase III inhibitor, during maintenance (207–209). 3) Use alternative P2Y₁₂ receptor antagonists such as prasugrel or ticagrelor.

Operator technique. The importance of operator technique in ensuring adequate stent deployment cannot be overstated in maximizing the benefit and minimizing the risk associated with stent implantation. Specifically, suboptimal or incomplete stent expansion is associated with increased rates of restenosis and TVR, and is a possible precipitant of ST (16,151,210–212).

One of the most common causes of suboptimal stent deployment is stent undersizing, which is aggravated by the use of direct stenting, and by relying solely on coronary angiography to assess stent size together with the underuse of intravascular ultrasound (IVUS). Previous studies demonstrate that reference vessel diameters vary significantly depending on the method of measurement used. For example, Briguori et al. (213) reported a difference between IVUS and angiography of >1.0 mm in 71% and 49% of cases with vessel size diameters <2.75 mm and >2.75 mm, respectively.

As alluded to, IVUS has an important role to play in optimizing stent implantation that extends beyond just minimizing the risk of stent undersizing. Intravascular ultrasound is considerably more accurate than angiography in determining in-stent dimensions, identifying incomplete stent apposition (ISA), and stent-edge dissections.

CLINICAL IMPLICATIONS. Studies indicate that the main clinical consequences of stent underexpansion are restenosis, ST, and stent fracture.

RESTENOSIS. In BMS studies, minimum stent area was identified as the single most powerful predictor of in-stent restenosis (ISR), with an inverse correlation between post-procedural minimum stent area and both angiographic restenosis and TVR (214,215). After the arrival of DES and the subsequent reduction in TVR, less importance was given to adequate stent deployment. Importantly, observational studies have indicated that not only is minimum stent area still an independent predictor of ISR in patients having DES, but also that the rate of stent underexpansion with DES may be as high as 30% (216–218). This finding reiterates the importance of maximizing final minimal stent area/diameter with noncompliant balloon inflation, thereby



Figure 9 Stent Malapposition

Stent malapposition is seen from the 11 o'clock to 9 o'clock position using Fourier domain optical coherence tomography (Terumo Corp., Tokyo, Japan). Reproduced with permission from Okamura et al. (222).

reducing suboptimal stent deployment, which may result in improved clinical outcomes. Unfortunately, at present, no randomized data exist investigating this with DES.

ST. Minimum stent area and suboptimal stent expansion represent major post-procedural predictors of ST (211,219,220). Retrospective data from Fuji et al. (211) indicate that lesions leading to ST after successful implantation of a SES stent more often have stent underexpansion, a small minimum stent area, and a residual edge stenosis. The importance of IVUS assessment after stent deployment is reaffirmed by registry data from >7,000 patients treated with BMS indicating that only approximately one-fifth of patients experiencing subacute ST had an optimum PCI result as assessed by IVUS. Moreover, analysis of these thrombosed stents indicates inadequate lumen dilation (final lumen <80% reference lumen), edge dissection, ISA, and plaque prolapse in 78%, 17%, 9%, and 4% of cases, respectively (221).

Incomplete stent apposition can be acute if detected at the time of the procedure, or late if detected at follow-up (Fig. 9) (222). Acute ISA can resolve itself, or if detected at the time of stent implantation, can be treated immediately with balloon dilation. Late ISA can be persistent (present after procedure and at follow-up) or acquired, if only detected on follow-up (223). Some studies (219) but not all (224,225) have suggested that ISA is associated with an increased risk of ST. Moreover, a recent meta-analysis has demonstrated that the risk of late acquired ISA is significantly higher for DES compared with BMS (OR: 4.36, 95% CI: 1.74 to 10.94), whereas the risk of late/very late ST is significantly higher for patients with ISA when compared

with patients who do not have ISA (OR: 6.51, 95% CI: 1.34 to 34.91) (226).

This difference in ISA between DES and BMS may be due to the effect of the antiproliferative drug on the vessel wall, causing positive remodeling, or a result of the decrease in plaque volume behind the stent struts (227). It has also been demonstrated using optical coherence tomography in patients before PCI and at 9-month follow-up that lesions with plaque rupture, thrombus, lipid-rich plaque, and thin-capped fibroatheroma have a greater incidence of ISA than do patients not having those features at baseline (83% vs. 30%, $p < 0.001$) (228).

It remains unclear exactly how ISA leads to ST. It may be the result of chronic inflammation and delayed healing, causing tissue necrosis and erosion around the stent (153). The link between inflammation, ISA, and ST has been reaffirmed by a histopathology study of ST eosinophil counts demonstrating that not only is very late ST associated with a greater degree of inflammation than other types of ST (early, late, BMS), but also eosinophil counts appear to correlate with the degree of ISA (167). Finally, ISA may serve as a trigger for thrombosis by allowing fibrin and platelet deposition behind stent struts (229).

Stent fracture. Stent fracture remains an uncommon late complication of DES implantation (230,231) whose true incidence among first-generation DES remains unknown; however, rates of 1% to 2%, 1% to 7.7%, and as high as 29% have been reported in randomized, observational, and autopsy studies, respectively (232–235). Notably, the majority of stent fractures have been reported with the Cypher SES, whereas stent fractures with TAXUS PES and BMS have been seen very rarely. This difference may be related to the increased radio-opacity of the Cypher SES, its closed cell design, and/or the greater neointimal coverage seen with the PES and BMS that may strengthen and stabilize the struts to withstand the mechanical forces that result in stent fracture. Overall, stent fractures can range from a single strut fracture (grade I) through to multiple strut fractures (grade V).

There are a number of suspected causes for stent fractures that include both mechanical and lesion-based factors.

MECHANICAL FACTORS. Stent fracture may be the consequence of an excessive mechanical vessel wall stress that occurs from extreme repetitive contraction and flexion of the vessel (233). Of note, this may actually be a protective mechanism for stress relief within the vessel.

LESION FACTORS. Predictors for stent fractures have included lesions located in the right coronary artery and/or lesions in very tortuous or severely calcified vessels. Additional factors increasing the risk of stent fracture include implantation of long and/or overlapping stents (Fig. 10), underlying diffuse disease, SVG, and treatment of CTO (230,235–237). In a recent autopsy study, longer stent length, use of the Cypher stent, and longer stent duration were all identified as independent predictors of stent fracture (235).

Patients with stent fractures may remain asymptomatic; however, they may present with ACS, ST, or recurrent angina due to clinical restenosis; overall, 70% to 80% of patients with a stent fracture will present with ISR or ST (230,231,233,238). The extent of symptoms appears to be related to the grade of the stent fracture, with few symptoms occurring as a result of grade I to grade IV stent fractures, whereas grade V stent fractures are associated with the most adverse clinical events (235). There are no data on definitive treatment; however, repeat PCI, which is the current preferred strategy, appears to provide prompt symptom relief (230,231). Some suggest treatment using a short stent, together with extending DAPT beyond 12 months (239).

Coronary artery aneurysms. Coronary artery aneurysms are a rare complication of stenting, whose true incidence, clinical course, and treatment are largely unknown (Fig. 11). Nevertheless, studies report an incidence between 0.3% and 6.0% after DES and BMS implantation (240). There are a number of postulated causes for these coronary artery aneurysms, some of which are specific for DES. In general, mechanical causes include the use of oversized balloons or stents, high-pressure balloon inflations, and atherectomy—all of which can cause residual dissection and deep arterial wall injury eventually leading to aneurysm formation (241–243). Of note for DES, the elution of antiproliferative drugs and/or presence of a polymer can lead to delayed re-endothelialization, inflammatory changes in the medial wall, ISA, and hypersensitivity reactions, all of which can result in coronary artery aneurysm formation (240). Data on coronary aneurysms are derived mainly from case reports indicating a variable clinical course that is similar irrespective of whether the aneurysm is after BMS or after DES implantation. In particular, aneurysms have been detected from as early as 3 days after DES implantation (244) and as late as 9 years after BMS implantation (245).

Coronary artery aneurysms can be associated with restenosis (246), whereas turbulent and sluggish blood flow in the area of the aneurysm, coupled with a metallic stent, can predispose patients to the risk of ST and/or distal embolization (247,248). Currently, there are no definitive data on the best management of patients with coronary artery aneurysms, treatment of which is complicated by some aneurysms resolving spontaneously (249), whereas others lead to life-threatening complications. In addition to the use of long-term DAPT to minimize the risks of ST, therapeutic options that can be considered include the use of coils and cardiac surgery.

Second-Generation DES

The initial coronary stents were composed of 316L stainless steel since this material is radio-opaque and provides adequate radial strength to maintain arterial scaffolding with minimal acute recoil. An alternative to stainless steel is cobalt chromium (CoCr), which exhibits superior radial

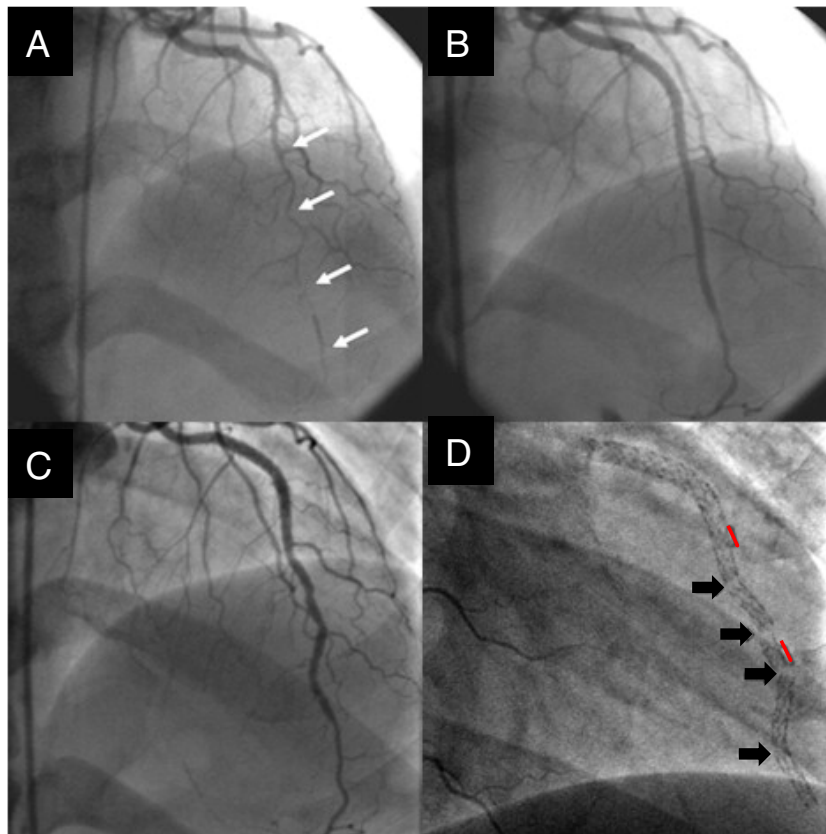


Figure 10 Stent Fracture

(A) A long, diffusely diseased left anterior descending artery is treated with 3 sirolimus-eluting stents (white arrows). (B) The initial angiographic result is excellent; however, at (C) 3-months' follow-up, an irregular appearance is seen, and is the result of (D) 4 stent fractures (black arrows) occurring adjacent to regions of stent overlap (red lines). Reproduced with permission from Popma et al. (236).

strength and improved radio-opacity, allowing for thinner stent struts that may reduce restenosis (250–252). Thinner struts can also lead to a reduction in device profile and, hence, an improvement in stent deliverability to the target lesion. The 2 second-generation DES that are currently approved by the U.S. FDA utilize CoCr, and elute “limus” drugs with the aid of more biocompatible polymers than are found on the first-generation DES.

Endeavor ZES. The second-generation Endeavor ZES (Medtronic, Minneapolis, Minnesota) uses the CoCr Driver stent platform loaded with a permanent “biomimetic” phosphorylcholine polymer (Table 1), which although not biodegradable is biostatic and biocompatible, being a natural component of the cell membrane. The polymer, which releases ~95% of the sirolimus analogue, zotarolimus, within 14 days of stent deployment, causes less inflammation compared with the polymers on the Cypher SES stent.

Both animal studies and in vivo studies using angioscopy and optical coherence tomography have shown a greater endothelial coverage of struts with ZES compared with SES and PES (157,253–255). Angioscopy has demonstrated levels of neointimal coverage with ZES that are superior to

that SES and comparable to that seen with BMS (253). Similarly, the mean percentage of covered struts seen by optical coherence tomography 3 months after implantation of ZES, SES, and BMS has been reported in separate studies as 99.9%, 85%, and 99.9%, respectively (254,255).

Clinical data on ZES are available from the Real-World E-Registry, and from numerous other trials ranging from the first-in-man ENDEAVOR I study to randomized trials comparing ZES to BMS, SES, and PES (Table 8) (256–269). Data from the “all-comers” E-Registry at 12 months of follow-up, and a pre-specified subgroup of patients who had extended follow-up for 2 years in the E-Five (Endeavor Stent Registry) study, demonstrate comparable outcomes between the randomized ENDEAVOR studies and real-world patients.

The superiority of ZES compared with BMS was demonstrated in the 1,197-patient, randomized ENDEAVOR II study, which reported significantly lower in-stent late loss and angiographic binary restenosis at 9-month follow-up with ZES, together with significantly lower TLR out to 5 years of follow-up. Rates of death, MI, and ST remained comparable between both stents throughout follow-up (258,259).

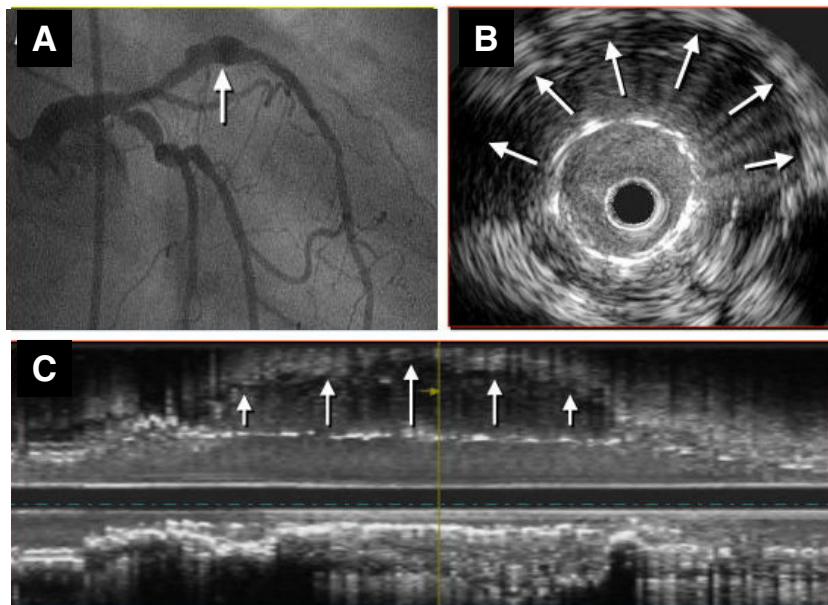


Figure 11 Coronary Artery Aneurysms

A coronary aneurysm (white arrows) is seen on (A) coronary angiography and on (B) cross-sectional and (C) longitudinal intravascular ultrasound. The aneurysm has led to extensive stent malapposition (B and C). Reproduced with permission from Alfonso et al. (246).

In the comparison with other DES, data have indicated a relatively poorer performance of ZES compared with PES and SES at short-term follow-up, as indicated by significantly higher late loss and numerically greater TLR (260,264). Results at longer follow-up have been more reassuring after the observed reductions in the absolute difference in TLR between ZES and SES/PES. For example, in the ENDEAVOR III study, the 2.8% absolute difference in TLR between ZES and SES at 1 year was reduced to 1.6% at 5 years (260,262), whereas in the ENDEAVOR IV study, the absolute difference in TLR between ZES and PES was 1.3% and 0.5% at 1 year and 3 years, respectively (264,265). Although at only medium-term follow-up, these results suggest the absence of the “late-catch” phenomenon with ZES.

Conflicting results have been observed when comparing ZES to SES and PES for early and late ST; however, despite this, a consistent benefit has been seen with ZES in terms of reduced very late ST (Fig. 12). Although these current trials are underpowered to detect differences in ST, these inconsistencies with ZES serve to reaffirm data that indicate the lack of association between in-stent late loss and ST (270); moreover, they reiterate the complex pathophysiology underlying ST. The only adequately powered study that will provide definitive data on the safety and efficacy between ZES and SES is the fully enrolled PROTECT (Patient Related Outcomes With Endeavor Versus Cypher Stenting Trial) study. This study has randomly assigned 8,800 “all-comers” patients to treatment with either the ZES or SES, and will report a primary end point of definite/probable ST at 3-year follow-up (271).

Xience V everolimus-eluting stent (EES). The Xience V EES (Abbott Vascular, Santa Clara, California) consists of the Multilink Vision CoCr platform with a nonerodable biocompatible polymer and $100 \mu\text{g}/\text{cm}^2$ everolimus, a synthetic derivative of sirolimus (40-O-[2-hydroxyethyl]-rapamycin). The 6- to 8- μm -thick polymer is composed of acrylic and fluorinated polymers and releases $\sim 80\%$ of the drug within 30 days, with nearly all the drug released within 4 months (Table 1). This stent is also marketed by Boston Scientific as the Promus stent. In the U.S., the Abbott supply agreement for the Promus stent continues until 2012 when the Promus stent will be replaced by the Promus Element stent.

Clinical data consist of both real-world registries, and randomized trials comparing EES to BMS and PES. Results have consistently demonstrated the safety and efficacy of the EES, together with low rates of ST out to long-term follow-up (Table 9) (272–282).

In brief, the randomized SPIRIT (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System) II, III, IV studies and the COMPARE (Second-Generation Everolimus-Eluting and Paclitaxel-Eluting Stents in Real-Life Practice) study have all compared EES and PES. Two-year follow-up of the SPIRIT II study was the first study to demonstrate “delayed” restenosis with everolimus, a phenomenon previously observed with other DES (283,284); however, this did not appear to have any detrimental effect on clinical outcomes. In fact, at 3-year follow-up, a greater absolute difference in cardiac death, MI, TLR, and MACE in favor of EES was observed when compared with results at both 1- and 2-year follow-up

Table 8 The Most Prominent Randomized Trials and Registries of the Second-Generation ZES

| Trial (Ref. #) | No. of Patients | Follow-Up, Months | In-Stent Late Lumen Loss (ZES vs.), mm | Binary In-Stent Restenosis (ZES vs.), % | Death (ZES vs.), % | Myocardial Infarction (ZES vs.), % | Target Lesion Revascularization (ZES vs.), % | TVF (ZES vs.), % | Definite/Probable ST (ZES vs.), % |
|--------------------------|---|-------------------|--|---|---------------------|------------------------------------|--|------------------|-----------------------------------|
| Randomized trials | | | | | | | | | |
| ENDEAVOR I (256,257) | ZES (n = 100) | 12 | 0.61 | 5.4 | 0.0 | 1.0 | 2.0 | 2.0 | 1.0 |
| | | 60 | — | — | 4.1 | 1.0 | 3.1 | 5.2 | 1.0 |
| ENDEAVOR II (258,259) | ZES (n = 598) vs. BMS (n = 599) | 9 | 0.61 vs. 1.03* | 9.4 vs. 33.5* | 1.2 vs. 0.5 | 2.7 vs. 3.9 | 4.6 vs. 11.8*† | 7.9 vs. 15.1* | 0.5 vs. 1.2 |
| | | 60 | — | — | 6.2 vs. 7.6 | 3.8 vs. 4.8 | 7.5 vs. 16.3*† | 15.4 vs. 24.4* | 0.9 vs. 1.7 |
| ENDEAVOR III (260,262) | ZES (n = 323) vs. SES (n = 113) | 8‡/9§ | 0.60 vs. 0.15* | 9.2 vs. 2.1 | 0.6 vs. 0.0 | 0.6 vs. 3.5 | 6.3 vs. 3.5† | 12.0 vs. 11.5 | 0.0 vs. 0.0 |
| | | 60 | — | — | 5.2 vs. 13.0 | 1.0 vs. 4.6 | 8.1 vs. 6.5† | 17.9 vs. 18.5 | 0.7 vs. 0.9 |
| ENDEAVOR IV (264,265) | ZES (n = 773) vs. PES (n = 775) | 8‡/12§ | 0.67 vs. 0.42* | 13.3 vs. 6.7 | 1.1 vs. 1.1 | 1.6 vs. 2.7 | 4.5 vs. 3.2† | 6.6 vs. 7.2¶ | 0.9 vs. 0.1 |
| | | 36 | — | — | 4.0 vs. 4.5 | 2.2 vs. 4.9 | 6.5 vs. 6.0† | 12.4 vs. 16.1 | 1.1 vs. 1.6 |
| ZEST (266) | ZES (n = 880) vs. SES (n = 880) vs. PES (n = 880) | 12 | — | — | 0.7 vs. 0.8 vs. 1.1 | 5.3 vs. 6.3 vs. 7.0 | 4.9 vs. 1.4 vs. 7.5* | — | 0.7 vs. 0.0 vs. 0.8 |
| SORT-OUT III (267) | ZES (n = 1,162) vs. SES (n = 1,170) | 9 | — | — | 2.0 vs. 2.0 | 1.4 vs. 0.5 | 4.0 vs. 1.0*† | — | 1.1 vs. 0.2 # |
| | | 18 | — | — | 4.4 vs. 2.7 | 2.1 vs. 0.9 | 6.1 vs. 1.7*† | — | 1.1 vs. 0.5# |
| Registry data | | | | | | | | | |
| E-Registry (268) | ZES (n = 7,832) | 12 | — | — | 2.4 | 1.6 | 4.5 | 7.2 | 1.1 |
| E-Five Registry (269) | ZES (n = 2,116) | 12 | — | — | 1.7 | 1.2 | 4.5 | 6.7 | 0.6 |
| | | 24 | — | — | 2.9 | 1.5 | 5.1 | 7.9 | 0.7 |

Differences nonsignificant unless indicated. All trial acronyms are listed in the Online Appendix. *p < 0.001. †Ischemia-driven. ‡Angiographic follow-up. §Clinical follow-up. ||p < 0.05. ¶p < 0.001 for noninferiority. #Definite only. ST = stent thrombosis; TVF = target vessel failure (a composite of cardiac death, target vessel myocardial infarction, or target vessel revascularization); ZES = zotarolimus-eluting stent; other abbreviations as in Tables 2 and 3.

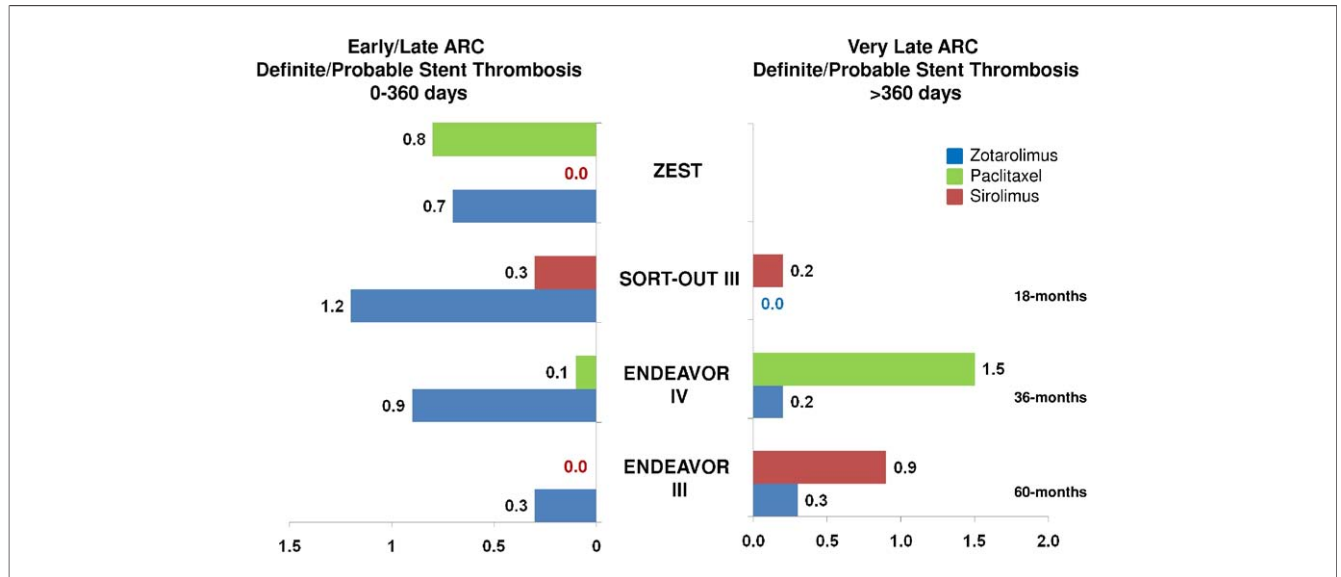


Figure 12 Rates of Stent Thrombosis Comparing ZES to SES or PES

Rates of early/late and very late definite/probable stent thrombosis in randomized trials comparing the Endeavor zotarolimus-eluting stent (ZES [blue bars]) to either the sirolimus-eluting stent (SES [red bars]) or paclitaxel-eluting stent (PES [green bars]). Rates of early/late stent thrombosis are consistently higher with the ZES; however, conversely, very late stent thrombosis rates are consistently lowest with ZES. No differences are significant. ARC = Academic Research Consortium.

(Fig. 13) (275). Similarly, in the larger SPIRIT III study, the benefit of EES over PES increased during follow-up, and at 3 years, use of EES lead to significant reductions in target vessel failure, target lesion failure, and MACE (278). Recently, 2 important randomized studies assessing EES have reported 12-month outcomes. The SPIRIT IV study, which enrolled 3,690 patients, represents the largest randomized trial comparing 2 DES; and the COMPARE study, which recruited 1,800 patients, was the first randomized all-comers trial of the EES (279,281). Both studies demonstrated significantly superior efficacy and safety with EES compared with PES. In addition, whereas nonsignificantly lower rates of ST have been observed in the SPIRIT

II and III studies, the SPIRIT IV and COMPARE studies were the first to demonstrate a significant reduction in ST between 2 DES. At 12-month follow-up, rates of definite/probable ST for EES and PES were 0.29% versus 1.06% ($p = 0.003$), and 0.7% versus 2.6% ($p = 0.002$) in the SPIRIT IV and COMPARE studies, respectively.

Some have suggested that the superiority of EES has only been demonstrated because it has not been compared with the SES, which historically is regarded as the most efficacious first-generation DES (22,105,106). Important data on this issue will be provided by the EXCELLENT (Efficacy of Xience/Promus Versus Cypher in Reducing Late Loss After Stenting) study, which plans to randomize 1,400

Table 9 The Most Prominent Randomized Trials and Registries of the Second-Generation EES

| Trial (Ref. #) | No. of Patients | Follow-Up, Months | In-Stent Late Lumen Loss (EES vs.), mm | Binary In-Stent Restenosis (EES vs.), % | Death (EES vs.), % | Myocardial Infarction (EES vs.), % | Target Lesion Revascularization (EES vs.), % | MACE (EES vs.), % | Definite/Probable ST (EES vs.), % |
|------------------------|-------------------------------------|-------------------|--|---|--------------------|------------------------------------|--|-------------------|-----------------------------------|
| SPIRIT FIRST (272,273) | EES (n = 27) vs. BMS (n = 29) | 6 | 0.10 vs. 0.87* | 0.0 vs. 25.9† | 0.0 vs. 0.0 | 3.8 vs. 0.0 | 3.8 vs. 21.4‡ | 7.7 vs. 21.4 | 0.0 vs. 0.0 |
| | | 60 | — | — | 0.0 vs. 7.4 | 8.3 vs. 0.0 | 8.3 vs. 28.0‡ | 16.7 vs. 28.0 | 0.0 vs. 0.0 |
| SPIRIT II (274,276) | EES (n = 223) vs. PES (n = 77) | 6 | 0.11 vs. 0.36* | 1.3 vs. 3.5 | 0.0 vs. 1.3 | 0.9 vs. 3.9 | 2.7 vs. 6.5 | 2.7 vs. 6.5 | 0.5 vs. 1.3 |
| | | 48 | — | — | 4.9 vs. 9.9 | 3.6 vs. 7.5 | 5.9 vs. 12.7 | 7.7 vs. 16.4 | 1.0 vs. 3.0 |
| SPIRIT III (277,278) | EES (n = 669) vs. PES (n = 333) | 8§/12 | 0.16 vs. 0.30† | 2.3 vs. 5.7 | 1.2 vs. 1.2 | 2.8 vs. 4.1 | 3.4 vs. 5.6 | 6.0 vs. 10.3† | 1.1 vs. 0.6 |
| | | 36 | — | — | 2.6 vs. 4.1 | 3.7 vs. 6.3 | 5.4 vs. 8.9‡ | 9.1 vs. 15.7† | 1.3 vs. 1.7 |
| SPIRIT IV (279) | EES (n = 2,458) vs. PES (n = 1,229) | 12 | — | — | 1.0 vs. 1.3 | 1.9 vs. 3.1† | 2.5 vs. 4.6†† | 4.2 vs. 6.9*‡ | 0.3 vs. 1.1† |
| | | 24 | — | — | 1.7 | 3.5 | 1.9 | 5.3 | 0.65 |
| SPIRIT V (280) | EES (n = 2,663) | 12 | — | — | 3.0 | 4.4 | 3.0 | 7.5 | 0.79 |
| | | 24 | — | — | 2.0 vs. 1.6 | 2.8 vs. 5.3† | 2.0 vs. 5.3* | 6.2 vs. 9.1† | 0.7 vs. 2.6† |
| COMPARE (281) | EES (n = 897) vs. PES (n = 903) | 12 | — | — | 2.0 vs. 1.6 | 2.8 vs. 5.3† | 2.0 vs. 5.3* | 6.2 vs. 9.1† | 0.7 vs. 2.6† |

Differences nonsignificant unless indicated. All trial acronyms are listed in the Online Appendix. * $p < 0.001$. † $p < 0.05$. ‡Ischemia driven. §Angiographic follow-up. ||Clinical follow-up. EES = everolimus-eluting stent(s); other abbreviations as in Tables 2 and 3.

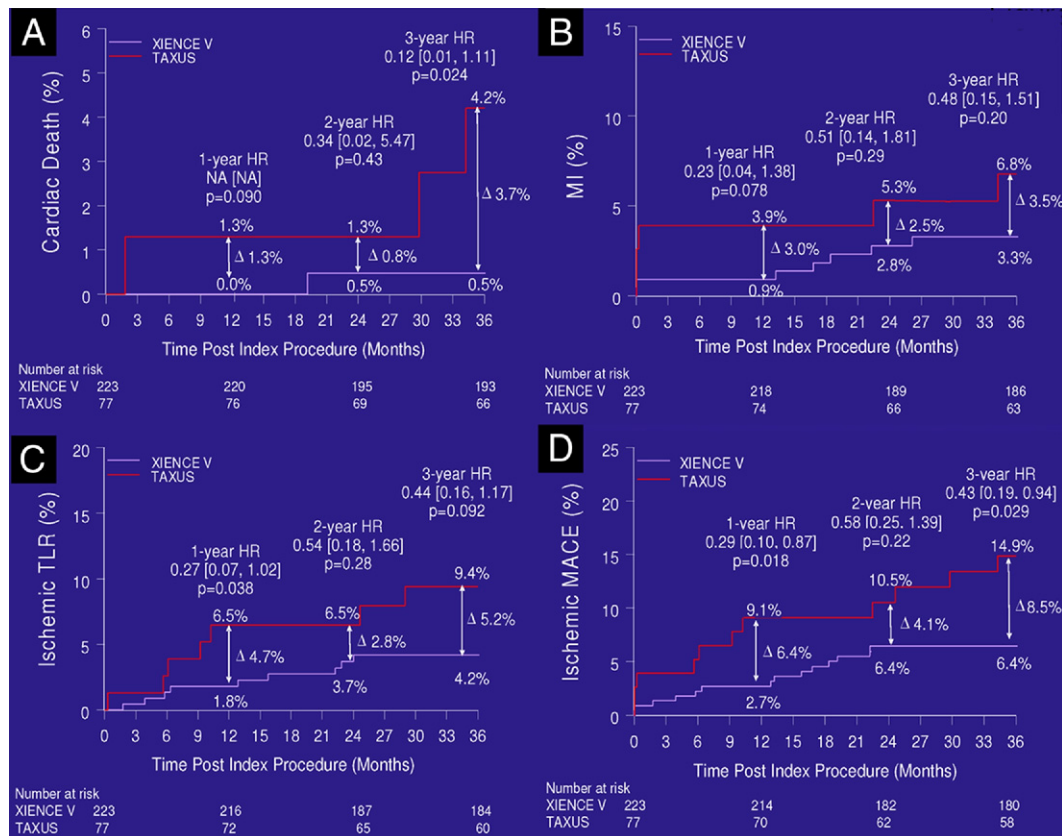


Figure 13 Clinical Outcomes in the SPIRIT II Trial

The delayed restenosis observed with the XIENCE V everolimus-eluting stent (EES [white lines]) between 1 year and 2 years may explain the reduction in the absolute difference in (A) cardiac death, (B) myocardial infarction (MI), (C) ischemic target lesion revascularization (TLR), and (D) ischemic major adverse cardiovascular events (MACE) seen between EES and the TAXUS paclitaxel-eluting stent (PES [red lines]) at 2-year follow-up. However, events rates remained lower with EES, and a much larger absolute difference between both stents was observed at 3-year follow-up. Reproduced with permission from Garg et al. (275). HR = hazard ratio.

patients to treatment with either EES or SES (285). The study will also investigate the optimal duration of DAPT by comparing outcomes in patients randomly assigned to 6 months or 12 months of DAPT.

The Xience PRIME EES, which represents the latest development of the Xience V stent, has recently gain regulatory approval in Europe. This modified EES has a CoCr platform; however, this is mounted on a new enhanced stent delivery system that enables the stent to be more flexible and deliverable. Furthermore, the stent balloon has higher rate burst pressures, and shorter balloon tapers to minimize the risk of edge dissections. The stent is being evaluated in the prospective, multicenter, nonrandomized SPIRIT PRIME study in 500 patients at 75 hospital centers, with the aim of gaining U.S. FDA approval.

Issues of Today

Role of BMS in Contemporary Practice

Despite the benefits of DES, there is still a role for BMS in the management of patients with CAD. Although reports

indicate that DES are used in >75% of PCI procedures in the U.S. (34), their use varies widely from hospital to hospital, and in some U.S. states, DES use is actually less than BMS use. For example, recent data indicate that only 49% of PCI cases in Arkansas used a DES, with rates dropping down to 35% for rural hospitals (286). Irrespective of the specific reasons for this disparity, this report confirms the BMS are still used in contemporary practice. Ultimately, the decision to implant a BMS is guided by both clinical and economic factors.

Clinical justification for stent selection. The overall net clinical benefit of a stent can be summarized after considering the stent's beneficial and adverse effects. The benefits of DES are their significant reduction in repeat revascularization compared with use of a BMS, whereas their adverse effects relate to the increased risk of very late ST and the requirement for prolonged DAPT (22–26). Importantly, the net benefit cannot be assessed by simply determining the difference between these 2 outcomes, as they both have a different incidence and clinical consequence. For example, in a study by Stone et al. (287), the rate of ST and TLR was

3.1% (DES:BMS 1.4:1) and 12.3% (DES:BMS 0.47:1), respectively, whereas the rate of death and MI within 7 days for these events was 91.1% for ST and 3.5% for TLR. Therefore, to assess the overall net clinical benefit, actual mortality must be considered. Extensive data exist to confirm that DES not only significantly reduce restenosis compared with BMS, but do so without increasing the risk of mortality or MI. Thus, the overall net clinical benefit favors DES.

It must be appreciated, however, that this benefit in favor of DES is not universal, and in certain patients and lesions this net benefit may ultimately favor a BMS. The advantage of a DES in terms of reducing restenosis is dependent on lesion characteristics, and the observed benefit is greater in lesions at higher risk for restenosis. For example, the absolute difference in rates of repeat revascularization between DES and BMS for lesions in vessels <3 and >3 mm in diameter in the BASKET trial at 3-year follow-up was 9.1% and 2.0%, respectively (288). Similarly, in the Ontario registry, Tu et al. (289) reported a significantly lower rate of TVR with the use of DES compared with BMS among diabetic patients who had lesions that were >20 mm long in vessels <3 mm in diameter (DES vs. BMS 7.2% vs. 17.6%, HR: 0.38, 95% CI: 0.24 to 0.60, $p < 0.001$; number needed to treat to prevent TVR = 10). Conversely, no significant difference in TVR was seen between DES and BMS when patients were not diabetic and had lesions <20 mm long in vessels >3 mm in diameter (DES vs. BMS 5.3% vs. 5.9%, HR: 0.87, 95% CI: 0.52 to 1.47, $p = 0.61$; number needed to treat to prevent TVR = 167) (289). The risk of ST is also variable and may be increased for patients who are not willing to, or are unlikely to, comply with DAPT, or for patients awaiting elective surgery (146,172). Therefore, for patients whose risk of restenosis is relatively low (i.e., nondiabetic, large vessel >3 mm in diameter), and/or the risk of ST is relatively high (inability to comply with long-term DAPT), a BMS maybe more appropriate. Ultimately, an evaluation of the overall risk/benefit ratio should play a key role in the clinical decision whether to implant a BMS or DES.

Cost effectiveness. Unfortunately, the discussion of stent selection cannot be made without considering the cost effectiveness of both therapies, in view of the additional initial expense associated with using a DES. Numerous cost-effectiveness analyses have been performed with conflicting results. Of note, many studies group patients treated with different DES together as 1 population, which ultimately can affect the accuracy of cost-effectiveness calculations for individual stents.

Some studies indicate that DES may be cost effective or even cost saving with specific patients, such as those who have lesions with a high risk for restenosis such as diabetic patients, long lesions, and lesions in vessels with small diameters. In the BASKET study, for example, DES were

more effective and less expensive for vessels <3.0 mm diameter. For vessels >3.0 mm diameter, although the overall cost per quality-adjusted life-year gained was €39,641 (\$59,392), subgroup analysis revealed that the cost per quality-adjusted life-year gained was €6,863 (\$10,282) for off-label use, €3,471 (\$5,200) for lesions ≥ 24 mm in length, and €300 (\$450) for patients ≥ 65 years of age (290). Conversely, other studies report an incremental cost-effectiveness ratio of >200,000 Canadian dollars per quality-adjusted life year—indicating DES are not cost effective (291).

Importantly, the use of angiographic follow-up in randomized controlled trials and a short period of follow-up are 2 major factors that can bias results in favor of DES. Nevertheless, a recent systematic review evaluated 19 different cost-effectiveness studies that mainly reported results at 1 year, and concluded that the cost effectiveness of DES was unfavorable compared with that of BMS. That was primarily because, although the use of DES was associated with a higher initial cost (€700 [\$1,060]), they did not increase life expectancy, produced only a small relative reduction in rates of repeat procedures, and led to only a short duration of improved quality of life (291).

Further data suggesting DES are not cost effective come from analysis at 1 year of the outcomes from patients in France enrolled in the TYPHOON (Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty), which reported the mean aggregate 1-year costs were €1,142 (\$1,711) higher per patient in the SES group compared with the BMS group. The incremental cost-effectiveness ratio was €7,321 (\$10,972) per TVR avoided (292).

By restricting follow-up to 1 year, previous cost-effectiveness studies have the potential to miss accounting for the costs incurred with very late ST, thereby introducing bias against BMS. To investigate the impact of long-term follow-up, Bischof et al. (293) performed an analysis using a Markov model to speculate on the cost effectiveness of using DES in the U.S. Medicare setting at 1 to 3 years of follow-up. Their results suggested that DES were not cost effective compared with BMS when used in unselected patients with CAD in the setting of Medicare (293).

In the United Kingdom, the National Institute of Clinical Excellence has taken into account the differences in cost between DES and BMS, and the differences in the risk of restenosis for specific lesions. Therefore, they have recommended DES in cases where lesions are >15 mm in length, in vessels <3.0 mm in diameter, provided the cost difference between BMS and DES is £300 or less (€330 [\$500]) (294).

The increasing development of DES in the developing world and the expiry of the patent for sirolimus are both likely to lead to reductions in the cost of DES, completely altering the cost-effectiveness evaluations that have previously been performed.

Diabetes Mellitus

Diabetic patients are known to have an aggressive form of atherosclerosis with less favorable long-term survival after PCI compared with that of nondiabetic patients. Moreover, diabetes mellitus is frequently identified as an independent predictor of ISR (295,296), although the underlying mechanisms for this are poorly understood. Implicated factors include the greater degree of the vascular inflammation and endothelial dysfunction seen in diabetic patients (297,298) together with poor glycemic control (299) and insulin resistance that can aggravate restenosis through the direct growth factor-like effect of insulin on vascular smooth muscle and neointimal cells (300).

BMS versus DES. REGISTRY DATA. The most recent registry data come from the MDACR (Massachusetts Data Analysis Center Registry) and the SCAAR registry, which have reported results for 5,051 and 19,004 diabetic patients, respectively. The MDACR, which reported the results of propensity-matched diabetic patients treated with either BMS or DES, demonstrated significantly lower rates of death, MI, and repeat revascularization with DES at 3-year follow-up (301). The SCAAR registry only assessed patients treated with DES and demonstrated that, overall, patients with diabetes were at higher risk of restenosis compared with nondiabetic patients. Interestingly, this was only true for patients treated with SES and ZES; the rate of restenosis for patients treated with PES was not influenced by diabetic status. Ultimately, no mortality difference was demonstrated between the different DES (302).

RANDOMIZED DATA. The evaluation of diabetic patients with the use of DES is hampered by the distinct lack of dedicated randomized trials. At present, only 10 randomized trials enrolling 1,662 patients have been conducted with DES to specifically assess outcomes in diabetic patients: 4 Cypher SES versus BMS, 5 Cypher SES versus TAXUS PES, and 1 Cypher SES versus ZES (49–53,102–104,303–308). There are no dedicated randomized trials assessing the performance of EES in diabetics, and data are derived from the diabetic patient subgroup ($n = 1,185$; 786 EES, 399 PES) of the SPIRIT IV trial (279) and the diabetic subgroup of the SPIRIT V study, which randomly assigned 324 patients to EES ($n = 215$) or PES ($n = 104$) (309). Similarly, the only data comparing ZES and PES are derived from 477 diabetic patients (241 ZES, 236 PES) in a subgroup analysis of the ENDEAVOR IV study (310).

SAFETY. Pooled analyses of diabetic subgroups from randomized trials comparing SES to BMS and PES to BMS among diabetic patients have demonstrated conflict results. Spaulding et al. (23) reported significantly higher mortality with the use of SES compared with BMS at 4-years follow-up (12.2% vs. 4.4%, $p = 0.004$); however, the authors acknowledge that this result may have been a play of chance, particularly in view of the small number of actual deaths in the diabetic subgroup (SES 23 vs. BMS 10). At

the same length of follow-up, Kirtane et al. (311) reported comparable mortality between PES and BMS (PES 8.4% vs. BMS 10.3%, $p = 0.61$), and reassuringly, a collaborative network analysis by Stettler et al. (312) that included 3,850 patients demonstrated no significant difference in mortality between SES, BMS, and PES in the treatment of diabetic patients who received DAPT for >6 months.

Among different DES, no differences in mortality or MI have been noted. A recent meta-analysis (313) of 5 dedicated randomized trials comparing SES to PES—the ISAR-DIABETES (Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefit From Paclitaxel-Eluting and Sirolimus-Eluting Stents?), DES-DIABETES (Drug-Eluting Stents in Patients With Diabetes Mellitus), and DiabeDES (Diabetes and Drug Eluting Stent) trials, and studies by Kim et al. (303) and Tomai et al. (307)—that in total enrolled 1,069 patients, with follow-up of as long as 2 years, reported no significant difference between SES and PES with respect to mortality (OR: 0.78, 95% CI: 0.30 to 2.07) or the risk of MI (OR: 0.88, 95% CI: 0.33 to 2.38). No significant differences in mortality, MI, or ST were reported at 12-month follow-up between either ZES and PES, or between EES and PES in the SPIRIT IV study. In the SPIRIT V diabetic cohort, treatment with EES led to a significantly lower risk of the composite of cardiac death/MI (3.7% vs. 9.6%, $p = 0.04$), which was driven by the significantly lower rate of MI with EES (309). The rate of ST was 0.0% for EES and 1.9% for PES.

EFFICACY. Clinical data indicate the superior performance of the SES with respect to BMS and both PES and ZES. The 4 dedicated randomized trials comparing SES to BMS (DECODE [A Randomized Study With the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent in the Treatment of Diabetics Patients With Native Coronary Artery Lesions], SCORPIUS [German Multicenter Randomized Single Blind Study of the CYPHER Sirolimus-Eluting Stent in the Treatment of Diabetic Patients With De Novo Native Coronary Artery Lesions], DESSERT [Diabetes Drug-Eluting Sirolimus Stent Experience in Restenosis Trial], and DIABETES [Diabetes and Sirolimus-Eluting Stent]) have collectively enrolled ~600 patients, and have all demonstrated significant reductions in their primary end point of in-segment late loss at between 6 and 9 months of follow-up. Furthermore, although not powered to detect differences in clinical outcomes, they have also all shown significant reductions in TLR at follow-up of between 8 and 48 months.

Similarly, 4 of the 5 dedicated randomized trials comparing SES to PES have demonstrated significant reductions in in-segment late loss for SES compared with PES. With respect to reintervention, no significant difference has been shown in any of the individual trials apart from the DES-DIABETES study, which reported a somewhat unexpected 75% reduction in reintervention at 2 years for SES

compared with PES (SES 3.5% vs. PES 11%, OR: 0.25, 95% CI: 0.08 to 0.77, $p = 0.004$). Meta-analysis of these 5 trials, which include a total of 1,069 patients with follow-up of as long as 2 years, has indicated that overall treatment with SES is associated with significant reductions in restenosis (OR: 0.29, 95% CI: 0.18 to 0.47) and reintervention (OR: 0.47, 95% CI: 0.28 to 0.77), compared with PES (313).

The DiabeDES III study is the only randomized comparison involving treatment with ZES. This study randomly allocated 127 diabetic patients to either ZES or SES, and demonstrated significantly lower late lumen loss with SES (0.14 mm vs. 0.74 mm, $p < 0.001$) at 10-month follow-up (308). In the subgroup of diabetic patients returning for angiographic follow-up in the ENDEAVOR IV study ($n = 86$), a trend toward higher in-stent late loss was seen in patients treated with ZES compared with SES (0.81 vs. 0.56, $p = 0.073$), whereas no notable differences in 1-year TLR were seen (310). Similarly, in the SPIRIT IV study, despite significant reductions at 1 year in TLR, TVR, MACE, and target vessel failure among nondiabetic patients treated with EES compared with PES, no significant differences in any of these outcomes were seen among diabetic patients (279). In the SPIRIT V study, EES was shown to be noninferior and subsequently superior to PES with respect to in-stent late loss at 9 months (0.19 mm vs. 0.39 mm, $p_{\text{noninferiority}} < 0.0001$, $p_{\text{superiority}} = 0.0001$); rates of repeat revascularization remained comparable between both stents (309). Some of these results are at variance with the meta-analysis by Kastrati et al. (313), and therefore, reiterate that there is presently no clear evidence to indicate that “limus”-based DES are superior to paclitaxel in the treatment of coronary lesions in diabetic patients.

DES versus CABG for diabetic patients. The CARDia (Coronary Artery Revascularization in Diabetes Trial) is the only randomized trial comparing the management of diabetes with multivessel disease (MVD) between CABG and PCI; however, because of poor recruitment, it was discontinued early after enrolling only 510 of the desired 600 patients, and is therefore largely underpowered. The ultimately negative noninferiority trial found no significant difference in 1-year mortality (3.2% PCI vs. 3.3% CABG, $p = 0.83$) or the 1-year composite clinical end point of death, nonfatal MI, or nonfatal stroke (10.2% for PCI vs. 11.8% for CABG); however, repeat revascularization was required more frequently in the PCI group (9.9% vs. 2.0%, $p = 0.001$). Although PCI was performed with DES in only 71% of cases, even these patients had higher rates of repeat revascularization when compared with CABG (7.3% vs. 2.0%, $p = 0.013$) (314).

More recently, the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) study, although not a dedicated randomized trial of diabetic patients, did enroll 452 diabetic patients (221 CABG, 231 PCI). Results demonstrated a higher rate of major adverse cardiovascular and cerebrovascular events (MACCE) for patients treated with PCI that was mainly

driven by significant higher rates of repeat revascularization. Overall, the presence of diabetes increased mortality for both revascularization strategies (315). Further information about the optimal treatment for diabetic patients with MVD will be known with the results of the ongoing FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial (316).

STEMI

Invasive reperfusion therapy has improved the prognosis of patients with STEMI (317,318), and new recommendations from the American College of Cardiology/American Heart Association (ACC/AHA) indicate that DES are a reasonable alternative to BMS for these patients (319). There have been concerns, however, that the use of DES in this setting may predispose to a higher risk of ST (143,320,321), which may result from the following: 1) the trapping of thrombus behind stent struts and subsequent thrombus resolution, which can lead to an increased risk of ISA; 2) the protrusion of stent struts into underlying necrotic core due to overlying plaque rupture; 3) a delay in arterial healing (e.g., greater incomplete stent strut endothelialization and persistent fibrin deposition) that has been recognized at the culprit site in patients with STEMI compared with patients treated for stable angina (322); and 4) high risk of adverse events for patients noncompliant to DAPT, as suggested by results from the PREMIER (Prospective Registry Evaluating Myocardial Infarction: Events and Recovery) study, which reported a significantly increased 11-month mortality among the 13.6% of patients who discontinued DAPT 30 days after their revascularization for ACS or STEMI (172).

Clinical data on outcomes from primary PCI are limited at present by the short duration of follow-up in most studies. The largest randomized primary PCI trial to date, the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) study, has reported angiographic data and clinical outcomes at 13 and 24 months, respectively, among 3,006 STEMI patients treated with PES or BMS. At 13 months, there were significant reductions in in-stent late loss and binary restenosis with PES (91). At 24 months of clinical follow-up, the use of PES was associated with significant reductions in the respective primary and second efficacy end point of ischemia-driven TLR ($p < 0.001$) and ischemic TVR ($p < 0.001$). In addition, there were no significant differences at 24 months between PES and BMS in the primary safety end point, a composite of death, MI, stroke or ST (PES 11.0% vs. BMS 11.2%, $p = 0.90$), or all-cause mortality, cardiac death, reinfarction, or definite/probable ST (92).

A previous meta-analysis by Kastrati et al. (323) of 2,786 patients undergoing primary PCI reported no significant difference in terms of death, MI, or ST between BMS or DES, and significant reductions in the risk of reintervention

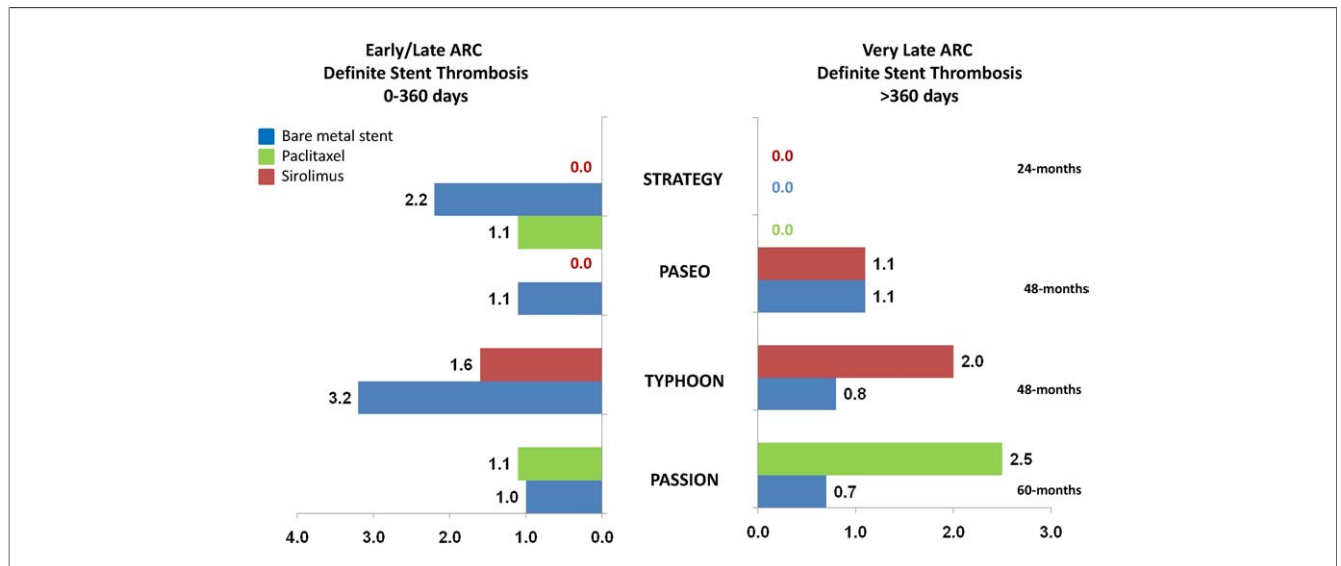


Figure 14 Rates of Stent Thrombosis Comparing DES to BMS

Rates of early/late and very late definite stent thrombosis (ST) in randomized trials comparing paclitaxel-eluting stents (green bars) and sirolimus-eluting stents (red bars) to bare-metal stents (blue bars) among patients undergoing primary percutaneous coronary intervention at long-term follow-up. Although no differences are significant, the rates of early/late ST are numerically higher with bare-metal stents, whereas the rates of very late ST are numerically greater with drug-eluting stents. ARC = Academic Research Consortium.

with DES (HR: 0.38, 95% CI: 0.29 to 0.50, $p < 0.001$). Unfortunately, follow-up was limited to 2 years (323).

More recently, Brar et al. (324) performed a much larger meta-analysis of 13 randomized trials that included 7,352 patients followed up for a maximum of 2 years. Results again demonstrate no significant difference between BMS and DES in terms of mortality (RR: 0.89, 95% CI: 0.70 to 1.14), MI (RR: 0.82, 95% CI: 0.64 to 1.05), and ST (RR: 0.97, 95% CI: 0.73 to 1.28), whereas the use of DES led to a significant reduction in repeat TVR (RR: 0.44, 95% CI: 0.35 to 0.55, $p < 0.001$). Notably, this benefit in reduced TVR was consistent in patients irrespective of whether DAPT was given for <6 months or >6 months, or whether follow-up was for 1 year or >1 year. Another important observation was that the benefit seen with DES treatment was greater for patients at highest risk of restenosis (324). A concurrent meta-analysis of 18 registries that included $>26,000$ patients was performed by the same group, and has shown similar results, with comparative outcomes in terms of death and MI between DES and BMS and significant reductions in terms of repeat revascularization with DES at up to 3-year follow-up (324).

Long-term follow-up data (≥ 4 years) that are available from 1 registry and 4 randomized studies have shown conflicting results. The randomized TYPHOON study, the PASEO (Paclitaxel or Sirolimus-Eluting Stent Versus Bare Metal Stent in Primary Angioplasty) study, and the STRATEGY (Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare Metal Stent in Myocardial Infarction) study, which all randomly assigned STEMI patients to treatment with either DES and

BMS, have all shown positive results in favor of using DES with respect to reduced rates of repeat revascularization, and comparable safety at between 4- and 5-year follow-up (58,62,64). Specifically, the TYPHOON study, which randomly allocated 715 STEMI patients to treatment with either BMS or SES, demonstrated no significant differences in rates of death, cardiac death, and MI at 4-year follow-up, whereas rates of TLR and TVR were significantly lower in the SES group. With respect to ST, although the overall rate was comparable between groups (SES 3.6% vs. BMS 4.0%, $p = 0.82$), very late ST was numerically higher with SES (2.0% vs. 0.8%) (Fig. 14) (64). These results need to be interpreted with caution, considering the extensive exclusion criteria used during enrollment (only 35% of screened patients were enrolled) (63) and that complete follow-up was available for only 70% of patients.

At variance with these results are data from a large single-center registry of 1,738 patients by Kukreja et al. (325) and the 5-year follow-up results of the 619-patient PASSION (Paclitaxel-Eluting Stent Versus Conventional Stent in Myocardial Infarction With ST-Segment Elevation) randomized trial (95). Kukreja et al. (325) reported no overall significant differences between DES (SES, $n = 185$; PES, $n = 1,022$) and BMS ($n = 531$) in all-cause mortality (BMS 16.4% vs. SES 11.4% vs. PES 12.9%) or repeat revascularization (8.0% vs. 7.0% vs. 6.9%, respectively) at a median follow-up of 1,185 days. Moreover, although there were no differences in overall, early, or late ST rates, there were no cases of very late ST in the BMS group compared with a rate of 2.7% and 0.9%, respectively, in the SES group ($p = 0.001$) and the PES group ($p = 0.03$).

Similarly, in the PASSION study, which had considerably fewer exclusion criteria compared with the TYPHOON study and enrolled 60% of patients who were screened, no significant differences were observed in overall MACE, mortality, reinfarction, and TLR between patients treated with PES or BMS out to 5-year follow-up. Overall rates of definite/probable ST were comparable (PES 3.9% vs. BMS 3.4%, $p = 0.85$); however, rates of late/very late ST were approximately 3 times higher among patients treated with PES (3.2% vs. BMS 1.1%, $p = 0.09$) (Fig. 14). Again, these results must be interpreted with caution considering the relatively small sample size and the lack of power to detect differences in ST.

Multivessel CAD

The debate over the optimal method of revascularizing patients with MVD has raged for many years and continues to this day. The importance of this patient subgroup cannot be underestimated considering the increasing age and multiple comorbidities of patients currently being investigated for CAD, and the correspondingly higher number of patients with MVD ultimately requiring revascularization (326). Historically, CABG has been the accepted treatment for MVD (327); however, advances in the percutaneous treatment of CAD have made PCI a more attractive alternative (28,77,328). Despite this, observational data from real-world practice indicate that for two-thirds of patients with complex CAD, cardiac surgery remains the preferred method of revascularization, findings that have been supported by a recent prospective randomized trial (28,329).

BMS versus CABG. A meta-analysis of the 4 randomized trials comparing outcomes at 5-year follow-up in patients with MVD treated with either a BMS or CABG showed a similar rate of the composite of death, stroke, and MI (PCI 16.7% vs. CABG 16.9%; HR: 1.04, 95% CI: 0.86 to 1.27, $p = 0.69$); a numerically higher rate of stroke with CABG (PCI 3.1% vs. CABG 3.9%; HR: 1.16, 95% CI: 0.73 to 1.83, $p = 0.54$); and a significantly higher rate of repeat revascularization with the use of a BMS (29.0% vs. 7.9%; HR: 0.23, 95% CI: 0.18 to 0.29; $p < 0.001$) (330). A much larger meta-analysis by Bravata et al. (331) that included 23 randomized controlled trials comparing PCI (POBA or BMS; $n = 5,019$) with CABG ($n = 4,944$) showed that despite a significantly higher rate of procedure-related stroke after CABG (1.2% vs. 0.6%, $p = 0.002$), and more frequent repeat revascularization after PCI (absolute risk difference 24% at 1 year and 33% at 5 years), there was no difference in survival between percutaneous and surgical intervention. More recently, Hlatky et al. (332) performed a collaborative analysis using patient data from trials comparing POBA and BMS to CABG and reported somewhat similar findings, with significantly higher stroke rates at 90 days after CABG, significantly higher repeat revascularization after PCI, and no overall significant difference in terms

of mortality at a median of 5.9 years of follow-up (PCI 15% vs. CABG 16%, HR: 0.91, 95% CI: 0.82 to 1.02, $p = 0.12$). **BMS versus DES.** The development of DES led to significant reductions in the rates of restenosis and repeat revascularization when compared with BMS. Consequently, if PCI is selected, there is little debate over whether to use a DES or a BMS; in fact, some would argue that patients with MVD where a DES cannot be used should be offered surgical revascularization. Currently, no dedicated prospective randomized trials have been performed comparing DES and BMS for patients specifically with MVD, and data supporting the use of DES in these patients, as opposed to BMS, come from the extrapolation of data from registries, nondedicated trials, and subgroup analyses. The ARTS-II study recruited 607 patients with 2- or 3-vessel disease treated with DES, who were then compared with patients with 2- or 3-vessel disease treated with BMS who were recruited in the ARTS-I study. At 5-year follow-up, there was no significant difference in survival (DES 94.5% vs. BMS 92.0%), whereas the use of DES led to significant reductions in repeat revascularizations (20.8% vs. 30.9%, $p < 0.001$) and overall MACCE (27.5% vs. 41.5%, $p < 0.001$) (Fig. 4) (77).

At variance with these results is the risk-adjusted outcomes among 60,000 patients undergoing PCI or CABG in the New York cardiac registry (333). Results suggested a significantly higher risk-adjusted survival among the CABG group (HR: 0.64, 95% CI: 0.56 to 0.74), with the difference being most pronounced in patients with 3-vessel disease and proximal left anterior descending artery disease. Complete risk adjustment was impossible to achieve, particularly as clinical judgment could not be adjusted for in this complex cohort of patients.

DES versus CABG. Data comparing the outcomes in patients with MVD treated with DES and CABG were initially derived from the addition of DES arms to the initial BMS-CABG trials, to allow a comparison of outcomes between DES and historical CABG cohorts. This was performed in the ARTS-II study, which at 5 years again demonstrated no significant difference in survival between DES and CABG (DES 94.5% vs. CABG 92.6%), but significantly higher rates of repeat revascularization (20.8% vs. 9.0%, $p < 0.001$) and MACCE (27.5% vs. 21.1%, $p = 0.02$) with the use of DES (Fig. 4) (77). A similar approach was performed in the ERACI-III (Argentine Randomized Study: Coronary Angioplasty With Stenting Versus Coronary Bypass Surgery in Multi-vessel Disease) study, which added 225 DES patients to the 500 patients (225 BMS, 225 CABG) in the ERACI-II study. At 1-year follow-up, freedom from adverse events was significantly greater among patients treated with DES (88.0% vs. 80.5% CABG, $p = 0.038$), whereas at 3-year follow-up, event rates were equal (77.3%, $p = 1.0$). This convergence was largely driven by the significantly higher TVR in the PCI cohort at 3 years (5.8% vs. 14.2%, $p < 0.002$). Of note, mortality was highest in the

cohort treated with CABG at both 1-year follow-up (3.1% vs. 7.6%, RR: 0.41, 95% CI: 0.17 to 0.97) and 3-year follow-up (5.7% vs. 9.8%, RR: 0.59, 95% CI: 0.31 to 1.14) (334).

Observation data, again from the New York cardiac registry, of 17,400 patients reported similar rates of unadjusted survival at 18 months between DES and CABG in patients with 3-vessel (93.7% vs. 93.4%, $p =$ not significant) and 2-vessel (95.0% vs. 94.9%, $p =$ not significant) disease. However, after adjustment of variables that are difficult to adjust for, such as the judgment of the treating physician, outcomes in favor of CABG were obtained (94.0% vs. 92.7%, $p = 0.03$; and 96.0% vs. 94.6%, $p = 0.003$ for 3- and 2-vessel disease, respectively) (335,336).

The only randomized data comparing DES to CABG in patients with MVD comes from the previously discussed CARDia trial, and the SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) study (28,314). The SYNTAX study was a large, prospective, multicenter, “all-comers” trial that assessed outcomes in 1,800 patients with either left main (705 patients: PCI 357, CABG 348) or 3-vessel disease (1,095 patients: PCI 546, CABG 549) randomly allocated to treatment with either PCI (with PES) or CABG (28). The all-comers study design and the use of the SYNTAX score allowed the study to address the important limitations of previously conducted randomized trials comparing PCI and CABG. These limitations included patient selection; for example, in studies comparing BMS to CABG, only 4% of those initially screened were eventually randomized (330), with a common exclusion being patients with impaired left ventricular function (327). Second, all patients with MVD are not the same, and the previous trials did not include any methods of categorizing the extent of MVD or the lesion complexity to allow results to be put into context and stratified according to disease severity.

Among patients with triple-vessel disease, the overall respective rates of death (4.1% vs. 6.5%; $p = 0.07$), cardiac death (2.3% vs. 4.5%; $p = 0.05$), stroke (2.3% vs. 1.7%; $p = 0.47$), MI (2.8% vs. 6.1%; $p = 0.009$), repeat revascularization (7.5% vs. 17.4%; $p < 0.001$), and MACCE (14.4% vs. 23.8%; $p < 0.001$) favored CABG at 2-year follow-up. Moreover, as shown in Figure 15, when outcomes are stratified according to disease complexity using the SYNTAX score, outcomes between PCI and CABG are only comparable among patients in the lowest SYNTAX score tercile (≤ 22) (337).

UPLMS Disease

Using PCI for UPLMS disease was deemed inappropriate according to the 2009 ACC/AHA appropriateness criteria for coronary revascularization, which was in line with guidelines from the U.S. and Europe that both gave PCI for UPLMS a Class III indication for patients suitable for CABG (338,339). However, despite these guidelines, in 2006, approximately one-quarter of UPLMS disease was still treated by PCI (329). More recently, a white paper that

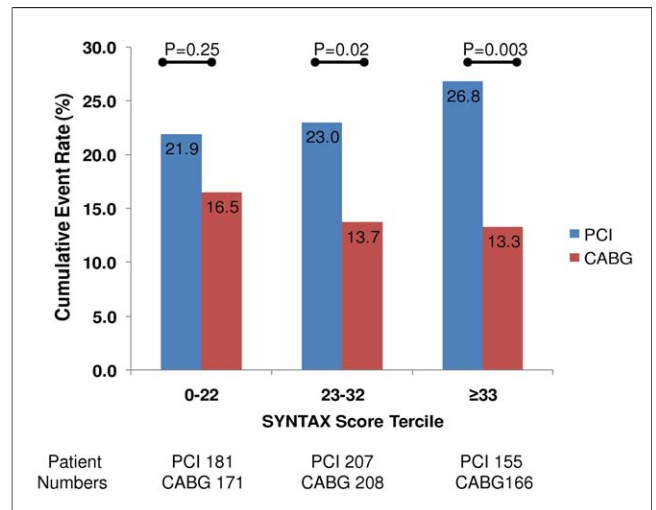


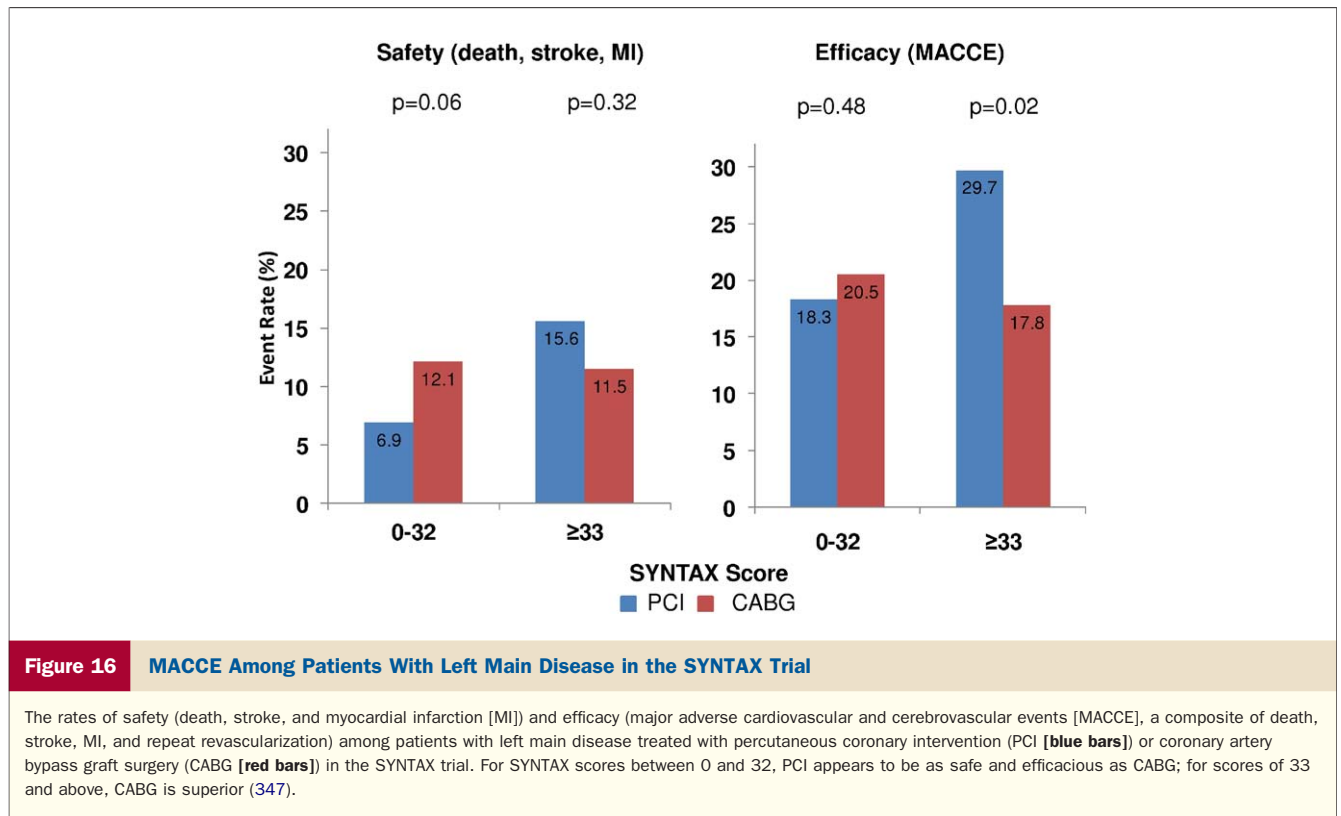
Figure 15 MACCE Among Patients With Triple-Vessel Disease in the SYNTAX Trial

The rates of major adverse cardiovascular and cerebrovascular events (MACCE [a composite of death, stroke, myocardial infarction, and repeat revascularization]) at 2-year follow-up among patients with triple-vessel disease treated with percutaneous coronary intervention (PCI [blue bars]) or coronary artery bypass graft surgery (CABG [red bars]) in the SYNTAX trial. For patients with a SYNTAX score between 0 and 22, PCI offers a suitable alternative to CABG (339).

includes a comprehensive review of the literature was published in this *Journal*, and suggests that in specific patients and lesions, PCI may offer a suitable alternative to CABG (340). Following on from this, the 2009 focused update on PCI published by the ACC/AHA has upgraded PCI for UPLMS to a Class IIb indication, and it may be considered for appropriate patients, namely, those with coronary anatomy that is associated with a low risk of procedural complication if treated by PCI and/or clinical conditions that predict an increased risk of adverse surgical outcomes (319). Unfortunately, current studies assessing outcomes in UPLMS stenting are limited by being largely observational with relatively short follow-up.

BMS versus DES. In brief, at present there is only 1 randomized trial comparing outcomes between DES and BMS for PCI of UPLMS (96). Erglis et al. (96) enrolled 103 patients randomly assigned to PCI with either PES or BMS and reported, as expected, that at 6-month follow-up, the use of DES leads to significant reductions in repeat revascularization when compared with BMS without exposing patients to any additional risk of death, MI, or ST. Further comparisons between BMS and DES in UPLMS PCI, from largely nonrandomized, observational studies with follow-up ranging from 6 months to 3 years, report similar findings. These results, however, must be taken in the context of the observational nature of the studies involved and the subsequent limitations that encompasses, such as patient selection and a lack of statistical power to demonstrate differences in events and ST (340).

SES versus PES. Three studies have assessed the outcomes of UPLMS PCI between patients treated with SES



and PES (113,341,342). The 607-patient ISAR-LEFT MAIN (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions) study represents the only dedicated randomized study, and at 1 year, there was no significant difference in the primary end point, a composite of death, MI, or TLR, between SES or PES (PES 13.6% vs. SES 15.8%, $p = 0.44$) (113). In addition, angiographic restenosis at 6- to 9-month follow-up (PES 16.0% vs. SES 19.4%, $p = 0.30$), mortality (PES 10.7% vs. SES 8.7%, $p = 0.64$), and UPLMS-specific TLR (PES 9.2% vs. SES 10.7%, $p = 0.47$) at 2-year follow-up, together with ST were all comparable between SES and PES. Longer follow-up is available from subgroup analyses of the DELFT (Drug-Eluting Stent for Left Main) registry and MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) registry. At 3-year follow-up, both studies demonstrated similar adjusted rates of death, MI, and TVR, and comparable ST (341,342).

PCI versus CABG. Consistent with the previous discussion on MVD, PCI in patients with UPLMS has shown similar safety outcomes, and consistently higher rates of repeat revascularization compared with CABG. The non-randomized MAIN-COMPARE registry that enrolled 2,240 patients (1,138 CABG and 1,102 who had PCI: 318 BMS, 784 DES) is the largest single study comparing PCI to CABG to date. At 3-year follow-up, outcomes among a propensity-matched cohort of patients were comparable in

terms of death (HR: 1.18 for PCI, 95% CI: 0.77 to 1.80, $p = 0.45$) and MACCE (HR: 1.10 for PCI, 95% CI: 0.75 to 1.62, $p = 0.61$), whereas repeat revascularization was significantly higher in the PCI group (HR: 4.76, 95% CI: 2.80 to 8.11, $p < 0.001$), with DES performing much better than BMS (26). At 5-year follow-up, overall results were unchanged (343). Of note, similar findings have also been reported out to 3-year follow-up in a meta-analysis of 3,773 patients with UPLMS undergoing revascularization by PCI or CABG (344).

The UPLMS subgroup from the SYNTAX trial (357 PCI, 348 CABG) represents the largest cohort of patients randomized to either PCI or CABG. In the overall UPLMS group at 2 years, 22.9% and 19.3% of patients treated with PCI and CABG, respectively, reached the primary end point of MACCE ($p = 0.27$), a composite of mortality (PCI 5.6% vs. CABG 6.2%, $p = 0.77$), MI (5.5% vs. 4.1%, $p = 0.45$), stroke (0.9% vs. 3.7%, $p = 0.01$), and repeat revascularization (17.3% vs. 10.4%, $p = 0.01$).

The stratification of outcomes according to the SYNTAX score has demonstrated that for patients with scores between 0 and 32, PCI with PES may be safer and as efficacious as CABG, whereas for patients with scores ≥ 33 , CABG offers a safer and more efficacious treatment, albeit at a higher risk of stroke (Fig. 16). In the overall SYNTAX study population, 421 of the 1,212 patients with UPLMS disease had a SYNTAX score between 0 and 32, indicating that approximately one-third of patients with UPLMS are suitable for PCI (345).

The results from the SYNTAX trial have fuelled the debate with respect to the management of UPLMS disease, and prompted the first dedicated UPLMS trial, the EXCEL (Evaluation of Xience Prime Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) study, which will randomize 2,500 patients to revascularization with either the Xience V PRIME EES or CABG. The trial aims to commence enrollment in late 2010 (346).

CTO

CTOs are encountered in ~15% to 30% of patients referred for coronary angiography, and generally regarded as 1 of the few remaining challenges for interventional cardiologists (347). They are associated with lower procedural success rates compared with nonocclusive lesions, with inability to cross the CTO with a wire as the most commonly cited reason for procedural failure (347).

Successful percutaneous recanalization of a CTO, compared with a failed attempt, offers the benefit of a reduction in symptoms, improved left ventricular function, and improved survival (348–351). For example, the 376-patient multicenter TOAST-GISE (Total Occlusion Angioplasty Study–Società Italiana di Cardiologia Invasiva) study reported significant reductions in mortality (1.05% vs. 7.23%, $p = 0.005$), and a greater rate of angina-free survival (88.7% vs. 75.0%, $p = 0.008$) among patients with successful CTO-PCI compared with patients who had an unsuccessful CTO-PCI attempt at 12-month follow-up (348). The long-term prognostic benefits of successful versus unsuccessful CTO intervention at both 5- and 10-year follow-up have also been demonstrated by Hoye et al. (351) (93.5 vs. 88.0%, $p = 0.02$) and Suero et al. (350) (73.5% vs. 65.1%, $p = 0.001$), respectively. In contrast, however, Prasad et al. (352), who reviewed outcomes over 25 years in a single center, reported that an unsuccessful procedure was not an independent predictor of long-term mortality; whereas de Labriolle et al. (353) also reported that patients with a successful CTO procedure had no survival benefit compared with patients having an unsuccessful procedure.

DES versus BMS. After successful recanalization of a CTO, studies demonstrate consistent improvements in clinical outcomes after implantation of a DES compared with a BMS that have been predominantly driven through reductions in repeat revascularization (66–69,354–360).

Randomized data are limited to the PRISON II (Primary Stenting of Totally Occluded Native Coronary Arteries II) study and the GISSOC II-GISE (Gruppo Italiano di Studio sullo Stent nelle Occlusioni Coronariche II–Società Italiana di Cardiologia Invasiva) study, which both compared outcomes of patients with a CTO treated with BMS or SES. The use of SES compared with BMS led to significant reductions in TLR and TVR, and comparable rates of death, MI, and ST at follow-up ranging from 6 months (PRISON II), to 24 months (GISSOC II-GISE), and out to 5 years (PRISON II) (Table 2) (66–69).

Numerous registries have also reported data from CTO subgroups, and results demonstrate a consistent significant reduction in TLR and MACE after use of DES compared with BMS at short-term follow-up of between 6 and 18 months (357–360). At longer-term follow-up, and consistent with the randomized studies, De Felice et al. (360) reported the maintenance of this advantage with DES out to 3 years among 283 patients treated with SES/PES ($n = 124$) or BMS ($n = 159$). Conversely, no significant differences in TLR or MACE were observed among 140 patients (SES 76, BMS 64) in the CTO subgroup of the RESEARCH registry at either 3- or 5-year follow-up (361,362).

A recent meta-analysis of all these studies, which included >4,000 patients with a CTO treated with either a DES ($n = 2,390$) or BMS ($n = 2,004$), confirms the superiority of DES in terms of significantly improved efficacy and comparable safety compared with BMS at a mean of 22 months of follow-up (363). It is noteworthy that a strong trend toward a higher rate of ST was observed in the DES-treated cohort (RR: 2.79, 95% CI: 0.98 to 7.97, $p = 0.06$).

SVG

SVGs have a limited durability; however, they are still frequently used as conduits in CABG. Their subsequent failure due to atherosclerosis is the most common cause of recurrent ischemia in surgically revascularized patients. Unfortunately, the optimal method of repeat revascularization in these patients is not clearly established. Repeat surgical revascularization exposes patients to an increased risk of morbidity and mortality compared with their primary operation, without evidence of prognostic gain (364,365). Moreover, PCI for SVG is associated with suboptimal results due to high rates of periprocedural MI and high rates of restenosis requiring TLR (366). The high rates of periprocedural MI are thought to relate to the poor development of fibrous caps in the SVG atheroma (367) that increases the likelihood of embolization during stent implantation. The incidence of these periprocedural MIs is reduced after the use of embolic protection devices (368–370); however, despite this, and their class I recommendation for use when technically feasible (174), analysis of the ACC National Cardiovascular Data Registry suggests that they are used in only ~22% of SVG PCI (371).

Unlike native vessel lesions, the clear clinical benefits of DES over BMS have been slow to materialize in patients with SVG. Currently there is a paucity of data investigating the benefits of BMS over DES, and what data are available, are largely retrospective (372).

Randomized data. There have been only 2 small dedicated, randomized studies comparing DES to BMS in SVG intervention, which in total have included 155 patients (74,75,373). At short-term follow-up of 6 and 18 months, respectively, both the single-center RRISC (Reduction of Restenosis in Saphenous Vein Grafts With Cypher

Sirolimus-Eluting Stent) trial, and the multicenter SOS (Stent or Surgery) study reported, as expected, significant reductions in binary restenosis and TLR after use of DES compared with BMS, together with comparable rates of death and MI (74,373). Long-term data to a median of 32 months are only available in the RRISC trial, and demonstrates catch-up in the repeat revascularization rates in patients treated with DES (75). Moreover, there was a significant increase in late mortality among patients treated with SES as compared with patients treated with BMS (29% vs. 0%, $p < 0.001$) (75). Because of their small sample sizes, both studies were very underpowered to detect true differences in clinical events.

Registry data. Twenty registries have reported results in patients with SVG PCI, including a total of 5,172 patients (3,091 DES, 2,081 BMS), with outcomes reported between 6 and 34 months of follow-up. Results have been inconsistent, with some reporting advantages for DES over BMS, (131,374–378), and some reporting no difference (379–382). The largest study to date, a subgroup of the large multicenter STENT study, has recently reported 2-year propensity score matched outcomes for 1,000 patients treated with DES or BMS. At 9-month follow-up, the use of DES was associated with significantly reduced rates of MACE (14% vs. 21%, $p = 0.001$), a lower composite of death or MI (8.7% vs. 14%, $p = 0.006$), and a lower rate of TVR (HR: 0.36, $p < 0.001$) and ST (HR: 0.22, $p = 0.009$). At 2 years, DES-treated patients had significantly better survival, whereas significant reductions in overall MACE and TVR were only noted after adjustment (383).

All trials are summarized in a recently published systematic review (372), which concluded that in comparison to BMS, DES are safe (with the exception of the RRISC trial), and offer consistently reduced late loss and angiographic stenosis. Definitive data are still needed and will be partly obtained from the results of 3 on-going randomized multicenter prospective trials. In the absence of these data, however, for the time being, current results suggest that DES offer an advantage over BMS in terms of reduced restenosis and the need for TLR.

ISR

The introduction of DES led to a significant reduction in the rates of restenosis; however, they have not been able to eliminate it, resulting in a minority of patients returning with symptoms ranging from the gradual recurrence of angina pectoris to acute presentations with ACS (384,385). Numerous factors have been suggested as the underlying mechanism of this ISR, and these include: 1) biological factors such as resistance to antiproliferative drugs and hypersensitivity reactions; 2) mechanical factors such as stent fractures, polymer peeling, and nonuniform stent strut distribution or drug deposition; and 3) technical factors, including incomplete stent expansion, geographical miss, and barotraumas to unstented segments.

BMS ISR. Historically, numerous therapies have been used in the management of ISR after BMS implantation including POBA, atherectomy, and repeat stenting. Although all these modalities produced satisfactory immediate results, their utilization was hindered by a frequent need for a subsequent repeat revascularization procedure. To address this problem, vascular brachytherapy was introduced as an adjunctive therapy after successful POBA, with subsequent randomized studies confirming that this combination was highly effective at reducing the high rates of repeat TVR after treatment of BMS ISR (386,387). The use of brachytherapy soon fell out of favor, however, not only because of procedural logistics such as the expensive equipment, but also because of results at long-term follow-up, which raised concerns over ST and demonstrated a reduction in efficacy over time with subsequent delayed restenosis and a late TVR catch-up response (388). Perhaps the most important factor, however, in the downfall of brachytherapy was the emergence of DES.

Several studies have compared the performance of DES with brachytherapy in patients with BMS ISR. All studies, ranging from nonrandomized pilot studies to the large randomized SISR (Sirolimus-Eluting Stents Versus Vascular Brachytherapy for In-Stent Restenosis) study and the TAXUS V ISR study (PES vs. brachytherapy), which individually enrolled ~400 patients, have shown a consistent benefit with treatment using DES (SES or PES) compared with brachytherapy (389–395). Of note, at long-term follow-up in the TAXUS V ISR study, a greater absolute difference in TLR was seen at 2-year follow-up in favor of PES (9-month Δ TLR 7.6% vs. 24-month Δ TLR 11.5%), without any compromise on safety (392). Similarly, in the SISR study, the significant reduction in TLR with the use of SES that was observed at 12 months was maintained out to 3-year follow-up (394).

Concurrent with the comparison between DES and brachytherapy, DES have also been compared with POBA in the treatment of ISR after BMS implantation. The first of such studies was the ISAR-DESIRE (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for In-Stent Restenosis) study that randomly assigned 300 patients with BMS ISR to treatment with SES, PES, and POBA (116). At 6-month follow-up, treatment with DES had led to significantly lower rates of in-segment angiographic stenosis (POBA 44.6% vs. SES 14.3% vs. PES 21.7%, $p < 0.05$ for SES and PES vs. POBA), whereas at 12 months, use of DES led to significantly lower rates of TVR (POBA 33% vs. SES 8% vs. PES 19%, $p < 0.05$ for SES and PES vs. POBA). Overall, rates of mortality and MI were comparable through to 12-month follow-up. A secondary analysis compared outcomes between stents, and demonstrated no significant difference between SES and PES in the rate of angiographic restenosis ($p = 0.19$), whereas use of SES

lead to significantly lower rates of TVR compared with PES ($p = 0.02$).

This advantage of DES over POBA appears to be preserved long-term, as indicated by the results of the RIBS-II (Restenosis Intra-stent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting) study that randomly allocated 150 patients with BMS ISR to treatment with SES or POBA. At 1-year follow-up (12% vs. 31%, $p < 0.005$) and 4-year follow-up (24% vs. 35%, $p = 0.02$), treatment with SES had led to a significantly lower rate of MACE, with comparable rates of death, MI, and ST. Of note, SES implantation was shown to be an independent predictor of event-free survival (396,397).

DES ISR. ISR with DES is likely to become an increasing problem, considering the expanding use of DES in contemporary practice. At present, it is estimated that there are >200,000 cases of DES ISR annually in the U.S. alone (398). Despite this, however, the optimal treatment strategy for this condition remains to be established. The lessons learned from the treatment of BMS ISR suggest that the most appropriate treatment lies with repeat stenting, rather than with brachytherapy and POBA, and this is further supported by the more focal nature of DES ISR, which is a somewhat easier morphological pattern to treat compared with BMS restenosis (399). Other treatment options besides stenting include surgical revascularization for extreme cases and the use of more novel therapies such as drug-eluting balloons, which are discussed in more detail in Part 2 of this supplement.

If stenting is selected, a question that remains under discussion is whether DES ISR should be treated with a DES eluting the same antiproliferative drug or a different class of drug. That has recently been investigated in the ISAR-DESIRE II study, which randomly allocated 450 patients with ISR after SES implantation to treatment with repeat SES implantation or PES (117). At 6-month angiographic follow-up, there were no significant differences in late loss (SES 0.40 mm vs. PES 0.38 mm, $p = 0.85$) or binary restenosis (19.6% vs. 20.6%, $p = 0.69$). Similarly, at 12-month clinical follow-up, rates of death, MI, TLR, and ST were also all comparable between treatment strategies. Therefore, patients with SES ISR can be equally effectively treated with repeat SES implantation or PES; however, it is not known whether these results are applicable to ISR occurring after implantation of a second-generation DES. Importantly, the late loss observed after SES implantation was considerably higher than that seen in other studies of SES (Tables 2 and 5), suggesting that patients experiencing SES ISR may be hyporesponsive to the antiproliferative effects of SES. It follows that further investigation is required into the problem of ISR after DES implantation to establish a definitive treatment strategy.

Conclusions

Coronary stents are an essential component of contemporary percutaneous revascularization. The introduction of DES led to significant reductions in restenosis, and al-

though their use is associated with an increased risk of late ST, no additional risk of mortality has been demonstrated. The improved outcomes with DES have led to expanding indications for PCI, which is now an accepted treatment for diabetic patients and patients with complex CAD. The persisting concerns over ST have led to improvements in stent design, and although the second-generation DES have demonstrated early improvements in safety, great anticipation remains over the newer stent technology, which is explored in Part 2: Looking Forward.

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Key Words: bare-metal stents ■ drug-eluting stents ■ sirolimus-eluting stents ■ paclitaxel-eluting stents ■ zotarolimus-eluting stents ■ everolimus-eluting stents ■ stent thrombosis ■ restenosis ■ diabetes ■ cost-effectiveness ■ stent fracture ■ left main disease ■ myocardial infarction ■ saphenous vein grafts ■ clopidogrel.

▶ APPENDIX

For a complete list of all study acronyms and their definitions, please see the online version of this article.