Target Audience
This activity has been designed to meet the educational needs of cardiologists involved in the management of patients needing percutaneous coronary intervention.

Statement of Need/Program Overview
Sensitivity to safety has been a primary concern of interventional cardiologists dating back to the development of percutaneous transluminal coronary angioplasty (PTCA). The development of permanently implanted bare metal stents (BMS) led to a more effective treatment of acute vessel closure and restenosis associated with PTCA. These permanent metal implants also introduced a new life-threatening safety issue—stent thrombosis—which led to the pervasive use of dual antiplatelet therapy and optimization of stent delivery techniques in the catheterization laboratory. The advent of drug eluting stents (DES) had a welcome beneficial effect on restenosis rates when compared with BMS, but at the cost of increasing rates of late and very late stent thrombosis.

Our current knowledge of stent thrombosis has led us to better understand the patient demographics associated with this complication of DES implantation, as well as the role of different aspects of the stent delivery platform, including drugs and polymers. Recently available clinical trial and registry data show a gradient of safety among DES drug delivery platforms. The goal of this educational initiative is to present a thoughtful and comprehensive review of the clinical data on DES safety, including the recently presented COMPARE and other clinical trials.

Educational Objectives
After completing this activity, the participant should be better able to:
- Describe the different components of first- and second-generation drug delivery systems (metal scaffold, drug, and polymer), including how they affect thrombogenic potential.
- Identify the patient demographics and coronary anatomy associated with stent thrombosis.
- Compare recently presented clinical trial safety data and safety data among commercially available drug delivery platforms and bare metal stents.
- Compare drug delivery platforms in development, specifically as they relate to incremental safety enhancements.

Faculty
Dean J. Keriakes, MD, FACC, Medical Director of The Christ Hospital Heart and Vascular Center and The Linder Research Center, Cincinnati, OH.

Accreditation Statement
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and MRCME®. PIM is accredited by the ACCME to provide continuing medical education for physicians.

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Name of Faculty or Presenter	Reported Financial Relationship
Dean J. Kereiakes, MD, FACC	Grant/Research Support: Abbott Vascular, Amylin Pharmaceuticals, Cordis/Johnson & Johnson, Boston Scientific, Medtronic, Daiichi Sanyko, Inc. Consulting Fees: Abbott Vascular, Boston Scientific, Cordis/Johnson & Johnson, Eli Lilly & Co., Medpace, REVA Medical Inc. Speaker's Bureau: Eli Lilly & Co.

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Safety of Drug-Eluting Stents
Release date: January 31, 2011
Expiration date: January 31, 2012
Estimated time to complete activity: 1 hour

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This activity is supported by an educational grant from Abbott Vascular.

Safety of Drug-Eluting Stents

Dean J. Kereiakes, MD, FACC

The Christ Hospital Heart and Vascular Center, The Lindner Research Center, Cincinnati, OH

Significant evolution in catheter-based technologies for percutaneous coronary intervention has occurred since the introduction of coronary balloon angioplasty by Andreas Grüntzig in 1977. As balloon angioplasty was supplanted by bare metal stents and subsequently drug-eluting stents (DES), randomized comparative clinical trials have demonstrated a progressive decline in both angiographic and clinical restenosis with each technologic iteration. Following widespread clinical use of DES, multiple safety issues have been identified in late follow-up that have prompted efforts toward development of bioresorbable polymers and polymer-free metal platforms, as well as completely resorbable DES platforms. The ultimate goal of these efforts is to provide safe and durable coronary patency. The promise of bioresorbable DES platforms includes the additional benefits of recovery in normal autoregulatory as well as microvascular function, the capacity for late luminal enlargement/expansive remodeling, and the potential for reducing the requirement for prolonged dual antiplatelet therapy.
[Rev Cardiovasc Med. *2010;11(4):186-200 doi: 10.3909/ricm0577*]

Key words: Drug-eluting stents • Percutaneous revascularization • Stent thrombosis

Randomized comparative clinical trials have demonstrated progressive improvement in clinical and angiographic measures of restenosis with technologic iterations from balloon angioplasty to bare metal stents (BMS) and subsequently drug-eluting stents (DES) for percutaneous coronary intervention (PCI). Although BMS reduced the incidence of early (abrupt closure) as well as late (restenosis) coronary closure following PCI, the advent of DES markedly reduced both angiographic and clinical restenosis compared with BMS.[1] Indeed, multiple randomized, controlled clinical trials, clinical registries, and meta-analyses have demonstrated the benefit of DES (vs BMS) in terms of reduced restenosis for both on-label and off-label indications.[2-4] Nevertheless, specific safety

considerations related to DES have emerged that have limited the more universal adoption of DES (vs BMS) for PCI. These concerns have focused largely on issues related to 1) late (30 days-1 year) and very late (≥ 1 year) stent thrombosis; 2) the need for extended dual antiplatelet therapy (DAPT); 3) the relative safety of discontinuing DAPT following DES versus BMS; 4) stent fracture; 5) coronary aneurysm formation; and 6) late "catch-up" in-stent and in-segment luminal narrowing with re-establishment of atherothrombosis in the stented segment. The elucidation of pathophysiologic mechanisms underlying these safety concerns has prompted technologic iterations in DES platforms that have included bioresorbable polymers and polymer-free drug delivery platforms, as well as completely bioresorbable stents. In this light, it is appropriate to review these specific issues and recent developments involving coronary stent platforms.

Table 1
Academic Research Consortium Definitions for Stent Thrombosis

Likelihood of Thrombosis Following Stent Deployment	Timeline
Early	
Acute	0-24 hours
Subacute	> 24 hours-30 days
Late	> 30 days-1 year
Very Late*	> 1 year

*Includes stent thrombosis occurring after target segment revascularization.

Safety Concerns Surrounding DES

Stent Thrombosis

Although rare, stent thrombosis (ST) is a medical emergency and is frequently a catastrophic event complicated by myocardial infarction (MI) or death.[5] The clinical consequences of ST are dependent upon the volume and viability of myocardium at risk, the degree of recruitable collateral vessels, and the timeline of reperfusion therapy. The development of standardized definitions for both the time course and probabilistic likelihood of thrombosis following stent deployment by the Academic Research Consortium (ARC)[6] has greatly facilitated comparative analyses across various studies and data sets (Table 1).

Large collaborative meta-analyses have demonstrated similar rates of early (< 30 days) and late (30 days-1 year) ST between DES and BMS.[7,8] However, higher rates of very late (> 1 year) ST have been demonstrated following DES (vs BMS) and the relative risk of ST may persist for years.[9] The etiology of ST is multifactorial and may vary as a function of time course following stent deployment (Figure 1).[10] For example, in addition to early (≤ 6 months-1 year) cessation of DAPT, other factors—including stent undersizing and underexpansion, longer lesion and/or stent length, the use of multiple stents, smaller target vessel diameter, depressed left ventricular function, and the acuity of the presenting clinical syndrome—have all been incriminated in the development of early and late (but not very late) ST.[11,12] Interestingly, the antiproliferative properties of DES that are responsible for reducing restenosis (vs BMS) have also been incriminated as etiologic in late or very late ST following DES, particularly in the absence of prolonged (≥ 1 year) DAPT therapy. These specific DES properties include impaired endothelialization and incomplete stent healing.[13] Multiple studies in both animal models and humans have demonstrated more frequent and extensive stent strut exposure following DES versus BMS using invasive (angioscopy or optimal coherence tomography [OCT]) imaging techniques.[14,15] Furthermore, differences in the grades of neointimal stent coverage and luminal thrombus scores have been observed between currently available DES types.[16,17] These differences in stent healing and associated thrombus have been in large part ascribed to differences in the durable polymer coatings present on early (first-generation) DES. Nonerodable polymers may precipitate thrombus formation and ST by inciting localized inflammation, hypersensitivity reactions, and apoptosis of vascular smooth muscle cells. Delayed

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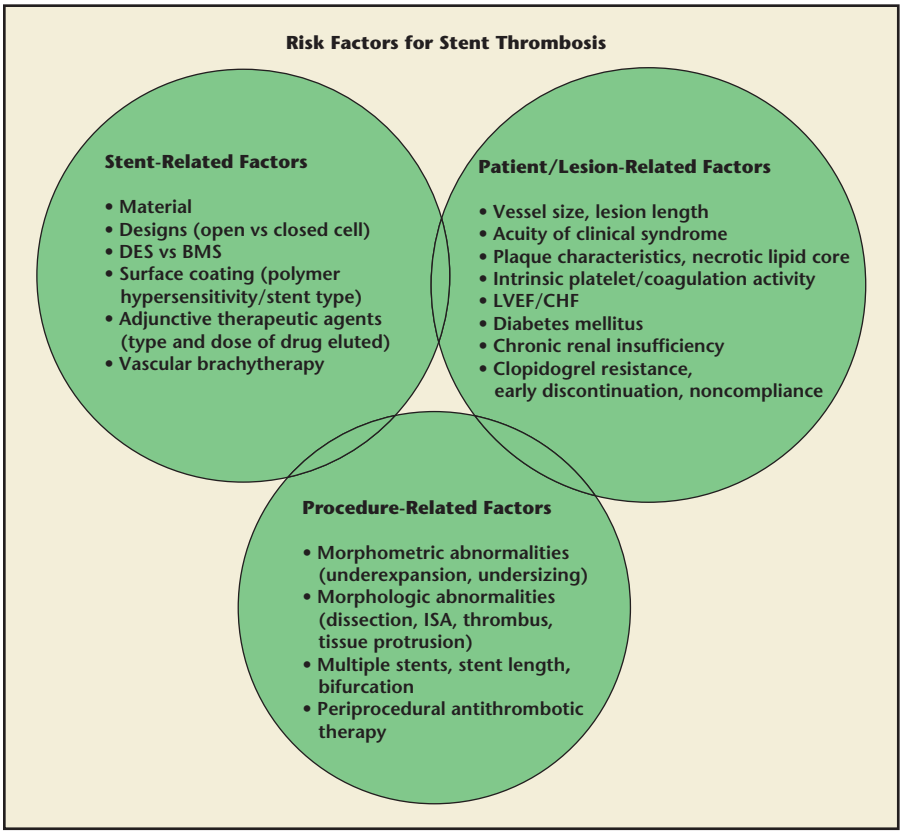


Figure 1. *Various factors that have been associated with the occurrence of stent thrombosis. BMS, bare metal stent; CHF, congestive heart failure; DES, drug-eluting stent; ISA, incomplete stent strut apposition; LVEF, left ventricular ejection fraction. Adapted with permission from Kereiakes DJ et al.*[10]

or incomplete stent healing and localized durable polymer-related inflammatory effects are likely precipitants of ST when DAPT is discontinued prematurely (< 1 year).[11] Although the clinical value of long-term DAPT (up to 12 months) following PCI for acute coronary syndromes (ACS) is well established, the optimal duration of DAPT following elective PCI with DES in clinically stable patients is the subject of controversy. Multiple studies have demonstrated that early DAPT discontinuation (< 1 year) is a significant independent risk factor for ST[11,18,19] and have prompted the US Food and Drug Administration (FDA) Advisory Panel to recommend ≥ 12 months of DAPT following DES deployment in all patients without specific contraindications or bleeding risk.[20] This recommendation was made despite the absence of any prospective, randomized trials to provide definitive evidence for benefit of prolonged DAPT and in the context of multiple other studies suggesting that the relative risk of DAPT discontinuation is maximum during the first 6 months following PCI.[21] These observations are further complicated by the fact that < 1% of patients who discontinue DAPT experience ST, whereas ST occurs commonly among individuals who are still receiving DAPT.[21,22] For example, using population-attributable risk methodology, it has been estimated that 68% to 85% of ST cannot be ascribed to clopidogrel noncompliance.[23] Although concern has been generated by the observation of a possible hyperthrombotic "rebound" phenomenon following clopidogrel discontinuation in patients treated for ACS either medically or with PCI,[24] subsequent randomized studies that evaluated serial platelet function have shown no evidence for platelet hyperaggregability or increased platelet activation following clopidogrel cessation.[25]

Definitive data on the optimal duration of DAPT for reducing ST (PCI site-specific outcome) versus death, MI, or stroke (systemic atherothrombotic outcome) await completion of adequately powered, randomized clinical trials such as the Dual AntiPlatelet study, which will enroll > 20,000 patients treated with either BMS or DES. In addition, it has recently been noted that an important minority of patients treated with clopidogrel are poorly responsive to the platelet-inhibiting effects of the drug. These hyporesponders, as defined by the presence of high on-treatment residual platelet reactivity, are at increased risk for the occurrence of major adverse cardiovascular events, including ST.[26]

The mechanisms underlying variability in clopidogrel responsiveness (beyond noncompliance) include genetic variation in specific enzymes involved in clopidogrel absorption and metabolic conversion from prodrug to active metabolite, demographic variables such as body mass index, the presence of diabetes, and the degree of glucose control and renal function.[26] Finally, drug-drug interactions at the levels of both the P-glycoprotein transporter mechanism for clopidogrel absorption as well as specific hepatic cytochrome P-450 isoenzymes (CYP2C19, 2C9, 3A4/5) may alter the level of clopidogrel active metabolite availability and thus clopidogrel-mediated platelet inhibition.[27] It is noteworthy that the newer, third-generation thienopyridine, prasugrel, and nonthienopyridine platelet P2Y12 receptor antagonist, ticagrelor, are not

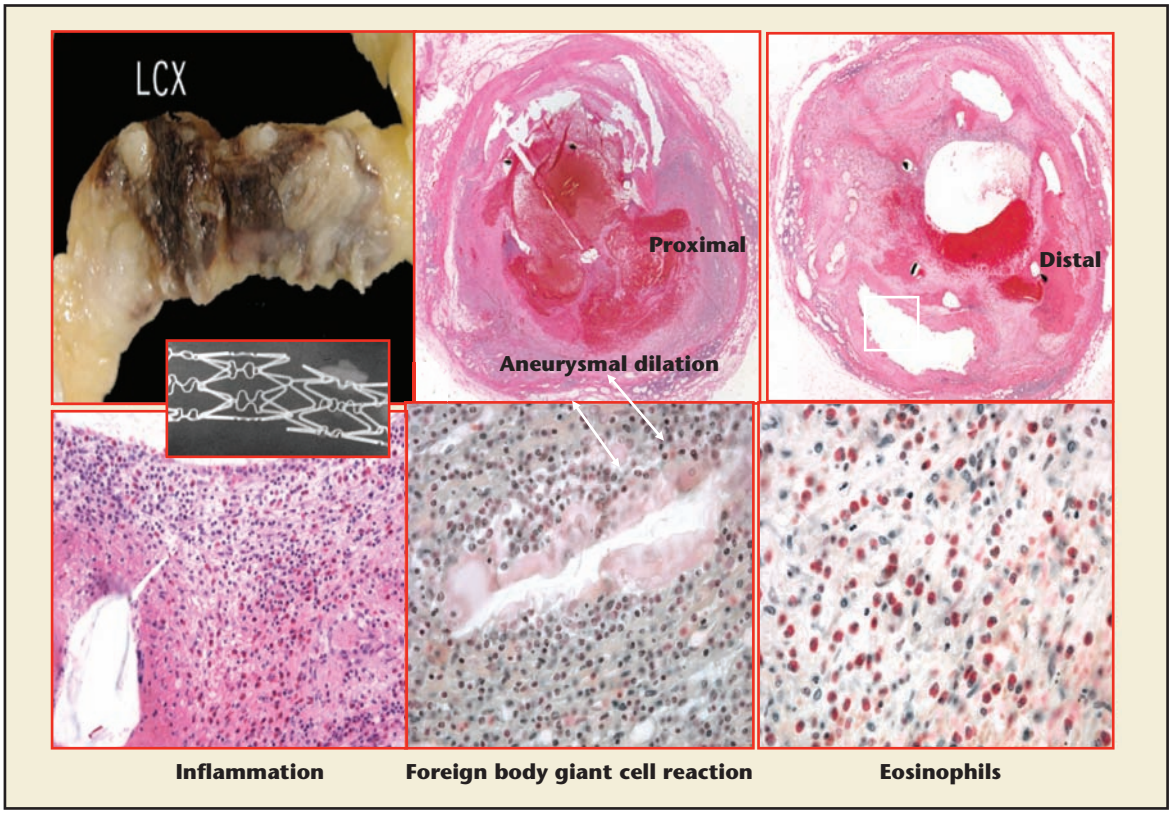
influenced by the genetic polymorphisms that affect clopidogrel metabolism. Similarly, individuals who are unresponsive to clopidogrel are almost invariably responsive to either prasugrel or ticagrelor. These observations have prompted great interest in genomic testing for specific genotypes that have been demonstrated to be associated with either reduced clopidogrel absorption (TT variant of the *ABCB1* or *MDR1* gene) or diminished conversion of clopidogrel prodrug to active metabolite (CYP2C19*2, *3, *4, and *5 alleles). Active metabolite generation is maximally reduced in CYP2C19*2 homozygotes (*2/*2) and intermediate in heterozygote carriers (*1/*2) of the *2 allele. Although the *2 allele (*2-*5 accounts for ~ 90% of nonfunctioning alleles in white subjects) may be present in approximately 25% of the general population, an increased prevalence (30%-40%) has been observed in both Asians and black Americans. Indeed, the high prevalence of genetic polymorphisms involving *CYP2C19* among black Americans has been implicated pathophysiologically in the increased prevalence of ST observed in this population.[28]

Durable Polymer-Related Issues

Both the first-generation sirolimus-eluting stent (SES) and the paclitaxel-eluting stent (PES) use durable, nonerodable polymers that may be pathophysiologically linked to late clinical outcomes following stent deployment. The SES poly n-butyl methacrylate/polyethylene vinyl acetate polymer has been associated with granulomatous and hypersensitivity reactions in both animal models and humans (Figure 2).[13,29] Similarly, the PES poly (styrene-isobutylene-styrene) polymer has been associated with medial necrosis, positive vessel remodeling, and excessive fibrin deposition. In comparative studies, despite having

Both the first-generation sirolimus-eluting stent and the paclitaxel-eluting stent use durable, nonerodable polymers that may be pathophysiologically linked to late clinical outcomes following stent deployment.

Figure 2. *Both gross* (upper frames) *and histologic pathologic* (lower frames) *findings following circumflex (LCX) coronary stent thrombosis involving a sirolimus-eluting stent. Polymer-related inflammatory changes, including eosinophilia and grant cell reaction, are observed. Thrombotic coronary occlusion* (upper middle frame) *is present. Image courtesy of Renu Virmani, MD, CVPath Institute, Inc. (Gaithersburg, MD).*



a greater in-stent late lumen loss following PES (vs SES) by quantitative coronary angiography, PES have demonstrated more frequent in-stent thrombus and more heterogeneous neointimal coverage by angioscopy.[16] Polymer-related inflammatory changes have been incriminated in the occurrence of very late DES thrombosis despite neointimal coverage and prolonged DAPT as demonstrated by OCT. Histopathologic evaluations have suggested that the development of atherothrombosis and yellow plaque in the stented coronary segment may be accelerated following first-generation DES deployment compared with BMS and may in part be explained by polymer-related inflammation. Finally, the histopathologic response to first-generation DES may be influenced by the acuity of the presenting clinical syndrome and the nature of plaque being treated. For example, DES struts embedded into the necrotic core of a thin-cap fibroatheroma responsible for ACS may demonstrate impaired healing and endothelial coverage and more frequent mural thrombus than DES deployed for chronic stable coronary disease.[30] Concern that the necrotic core may serve as a reservoir for lipophilic drug eluted from the DES and thus disturb the intended programmed DES pharmacokinetic profile has been expressed. These histopathologic observations may underlie the late angiographic observation of increased mural thrombus following DES for ST-elevation MI (STEMI), as well as the clinical observation of increased risk for late and very late DES thrombosis following PCI for ACS.[31]

Stent Fracture

Stent strut fracture appears to be an uncommon late complication of DES deployment. Although the exact incidence is unknown, reported rates vary widely from 1% to 2% of angiograms from randomized clinical trials to 1.0% to 7.7% of observational studies and 29% of autopsy series.[32] Multivariable analyses have identified stent type, stent length or overlap, implant duration, right coronary target vessel, and target site angulation as predictors of subsequent stent fracture. Stent fractures can range in severity from a single strut (grade I) through multiple strut fractures with an associated gap (grade V).[33] Although the majority of patients who have stent fracture appear to remain asymptomatic, affected patients may present with ST, in-stent restenosis, aneurysm, or pseudoaneurysm formation, or they may require target lesion revascularization. The extent or prevalence of symptoms appears to parallel the grade of stent fracture.

Coronary Artery Aneurysms

Coronary artery aneurysms are a rare complication of coronary stenting, with a reported prevalence of between 0.3% and 6.0% after DES or BMS deployment.[34] Non–DES-specific factors included in the etiology of coronary aneurysms include oversizing of balloons and stents, high-pressure balloon inflations, and arterial deep wall injury due to residual dissection. DES-specific factors include the elution of antiproliferative drugs, negative coronary remodeling, and polymer-related inflammatory/hypersensitivity reactions. Coronary aneurysms may be associated with restenosis, ST, or distal thrombus embolization.

New-Generation DES

The durable fluorocopolymer used on the second-generation everolimus-eluting stents (EES) appears to be more inert and more biocompatible than the first-generation DES polymers. Measures of endothelial and microvascular function may be improved following EES versus first-generation DES deployment and may be more similar to those observed following BMS deployment.[35] Similarly, EES (vs first-generation DES) may be associated with more rapid and complete endothelial stent coverage. These physiologic and histologic observations may underlie the more clinically relevant observation of lower risk for ST following EES compared with first-generation DES implantation. For example, in both large-scale randomized trials as well as patient-level meta-analyses from multiple randomized trials, EES have been associated with a significantly lower incidence of ST through 2-year follow-up when compared with either the first- or second-generation PES (Figure 3).[36,37] All components of ST (early, late, very late) using the ARC definitions were proportionately reduced by EES (vs PES). The relative benefit of EES (vs PES) for reduction in ST is supported by a pooled, patient-level analysis of the SPIRIT II, SPIRIT III, SPIRIT IV, and COMPARE randomized clinical trials, which compared an EES with a PES. A multivariable regression analysis of this 6789-patient database (EES n = 4247; PES n = 2542) identified randomly assigned stent type (EES) to be a significant independent predictor of freedom from ST (vs PES).[36] A recent subgroup analysis from this pooled data set suggests that the relative benefit of EES (vs PES) for reduction in ST may be even more marked in patients treated for ACS versus those with stable coronary artery disease.[36] Finally, the ability to safely discontinue thienopyridine treatment following 1 year of DAPT may be enhanced in EES- versus PES-treated patients as reflected by a comparison of the SPIRIT IV and COMPARE randomized,

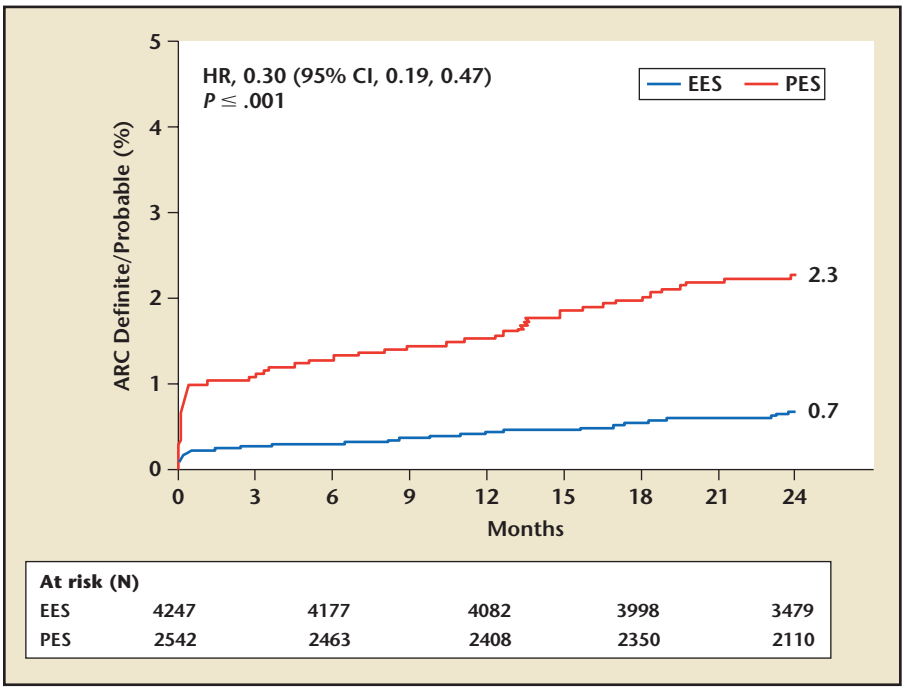


Figure 3. *Pooled patient-level analysis of stent thrombosis (ARC definite/probable) to 2-year follow-up by randomly assigned stent type from the SPIRIT II, SPIRIT III, SPIRIT IV, and COMPARE trials. Treatment with EES (vs PES) was associated with significant reduction in risk of stent thrombosis. Stent thrombosis refers to ARC definite/probable definition. ARC, Academic Research Consortium; CI, confidence interval; EES, everolimus-eluting stent; HR, hazard ratio; PES, paclitaxel-eluting stent. Data from Kedhi E et al.*[36]

controlled trial outcomes to 2 years (Figure 4).[38,39] In the SPIRIT IV trial, 63% of subjects (vs ~ 13% in COMPARE) remained on clopidogrel at 2 years. The relative increase in ARC definite/probable ST between 1- and 2-year follow-up in EES-treated patients was 0.13% in SPIRIT IV and 0.2% in COMPARE versus 0.17% and 1.3%, respectively, in PES-treated patients (Figure 4).[38,39] The relatively higher rate of ST between 1- and 2-year follow-up in the COMPARE trial may reflect the lower prevalence of late (2-year) thienopyridine compliance as well as the relative clinical acuity of patients enrolled (~ 60% ACS, ~ 25% STEMI, ~ 23% non-STEMI) in the COMPARE trial.

Aggregate data from multiple sources suggest that BMS has a continued low-level risk for very late (> 1 year) ST of approximately 0.15% to 0.2% per year.[40,41] Late follow-up of almost 10,000 EES-treated patients from the SPIRIT II, SPIRIT III, SPIRIT IV, and COMPARE randomized trials,[36] as well as the XIENCE V USA registry,[42] suggests that the incidence of late (30 days-1 year) and very late (> 1 year) ST is between 0.13% and 0.4%, and may be influenced by the complexity and acuity of patients treated. For example, in the XIENCE V USA registry of 4887 real world patients treated with an EES and followed through 1 year, ST (ARC definite/probable) was observed in 0.34% of patients (0.22% early, 0.11% late) with a standard risk profile compared with 0.84% of the entire study cohort.[42] Standard risk characteristics included lesion length ≤ 28 mm; reference vessel diameter 2.5 to 4.25 mm; absence of chronic total occlusion, bypass graft lesion, and bifurcation with side branch ≥ 2 mm; ostial or left main lesion; > 2 lesions stented in the same vessel or > 2 vessels treated; acute MI; renal insufficiency; left ventricular ejection fraction < 30%; in-stent restenosis target lesion; or planned staged procedure. These criteria (standard risk) applied to 36% (n = 1827) of the XIENCE V USA cohort. DAPT compliance to 1 year in the cohort was 79%. Total (early and late) ARC definite/probable ST rates to 1-year follow-up from multiple real world all-comers trials (including XIENCE V USA) demonstrate that rates are lowest following EES implantation (Figure 5). Finally, the capacity to safely interrupt DAPT may be enhanced following EES deployment as suggested by the XIENCE V USA registry experience. DAPT interruption beyond 90 days was associated with a low incidence of late ST, particularly in the standard risk cohort (Figure 6).

Although it has been suggested that the "biomimetic" phosphorylcholine polymer used in one zotarolimus-eluting stent (ZES) confers relative safety for reduction in ST, randomized comparative clinical trials provide a discordant viewpoint. For example, in the ENDEAVOR III randomized trial, which compared a ZES to an SES, the incidence of ARC definite/probable ST to 1-year follow-up was numerically increased following ZES deployment (0.3% vs 0% following SES).[43] Similarly, in the Scandinavian Organization of Randomized Trials With Clinical Outcomes (SORT-OUT) III randomized trial, which compared the ZES with an SES,[44] ARC definite ST was increased at 9-month follow-up in ZES-treated patients (hazard ratio, 4.62; 95% confidence interval, 1.33-16.1; P = .02). In the ENDEAVOR IV trial, which compared the ZES with a PES,[45] ARC definite/probable ST was

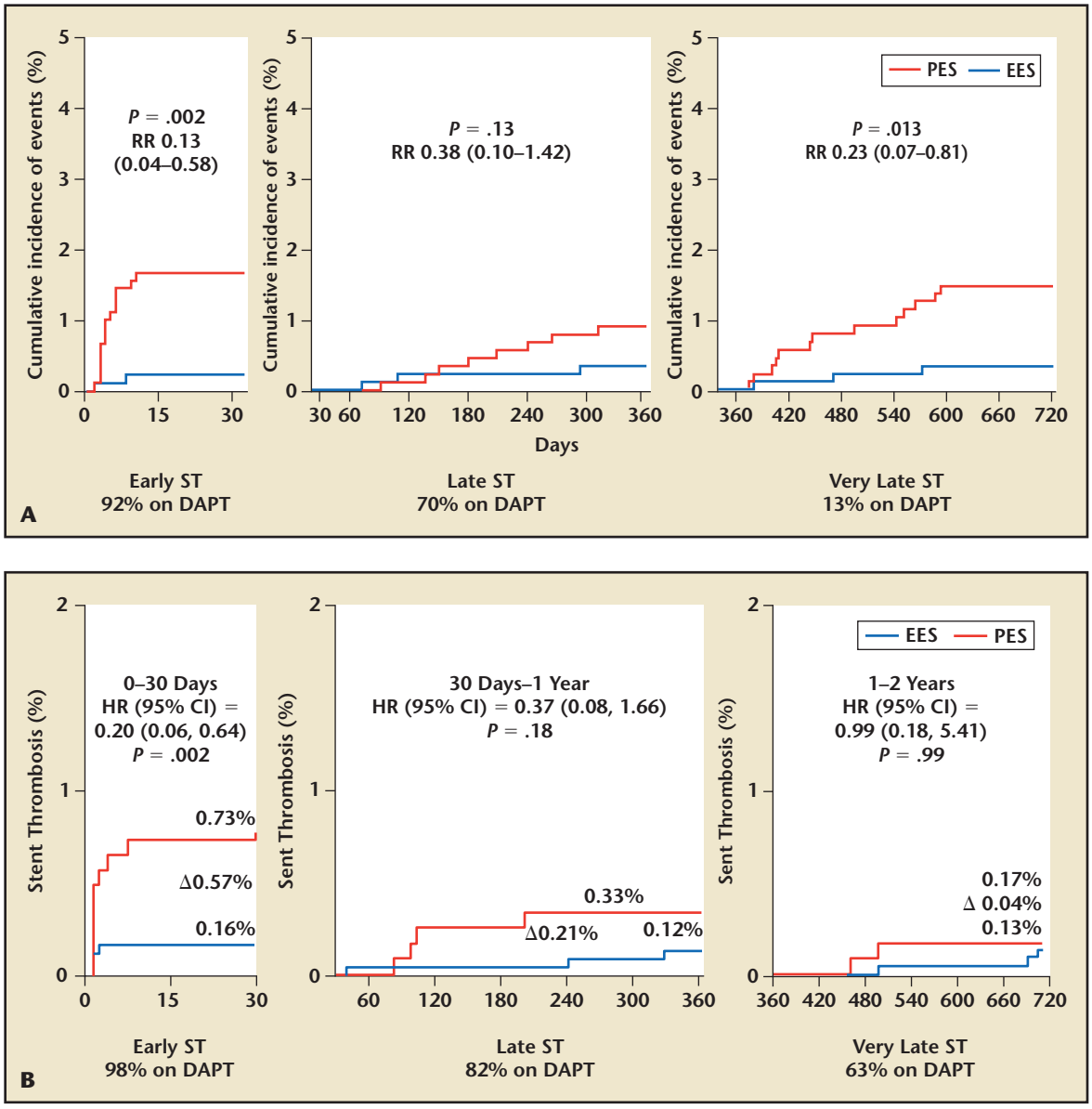


Figure 4. ***(A)*** *Kaplan-Meier curves for early, late, and very late ST stratified by randomly assigned stent type (EES vs PES) to 2-year follow-up in the COMPARE trial. Rates of DAPT compliance at teach time intervals are shown. ST refers to ARC definite/probable definition.* ***(B)*** *Kaplan-Meier curves for early, late, and very late ST by randomly assigned stent type (EES vs PES) to 2-year follow-up in the SPIRIT IV trial. Rates of DAPT compliance by time interval are shown. ARC, Academic Research Consortium; CI, confidence interval; DAPT, dual antiplatelet therapy; EES, everolimus-eluting stent; HR, hazard ratio; PES, paclitaxel-eluting stent; RR, relative risk. Adapted from Stone G[38] and Smits P[39] with permission from Cardiosource.*

numerically increased at 1-year follow-up among ZES-treated patients (6 events) compared with PES treatment (1 event). Interestingly, a landmark analysis at 1 year (1- to 3-year follow-up) demonstrated a reversal in this relative ratio of events with advantage for ZES (vs PES) beyond 1 year. Iteration in durable polymer from phosphorylcholine to the 3-component (C-10, C-19, PVP) polymer provided extended zotarolimus release kinetics with lower angiographic late lumen loss and reduced binary (> 50%) angiographic as well as clinical restenosis for the DES platform. Although efficacy endpoints appear to be improved following the ZES, a large-scale, randomized all-comers trial comparing ZES with EES demonstrated an increased incidence of definite (1.2 vs 0.3%; $P = .01$) or definite/probable (1.6% vs 0.7%; $P = .05$) ST following ZES versus EES

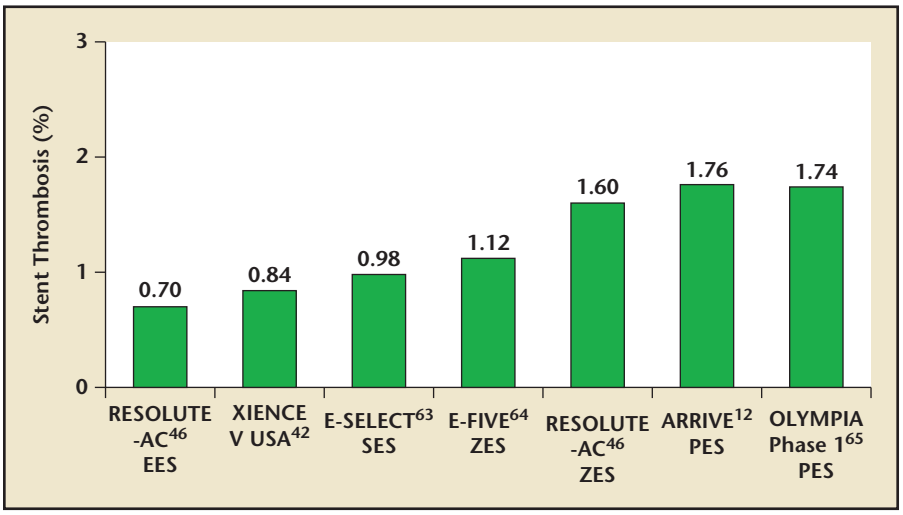


Figure 5. *Rates of definite or probable (by ARC definition) stent thrombosis to 1-year follow-up in real world all-comers clinical trials and registries. Stent thrombosis appears to be less frequent following EES deployment. ARC, Academic Research Consortium; EES, everolimus-eluting stent; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; ZES, zotarolimus-eluting stent. Data from Lasala JM et al,[12] Hermiller J,[42] Serruys PW et al,[46] Urban et al,[63] Lotan C et al,[64] and Ahmed WH et al.[65]*

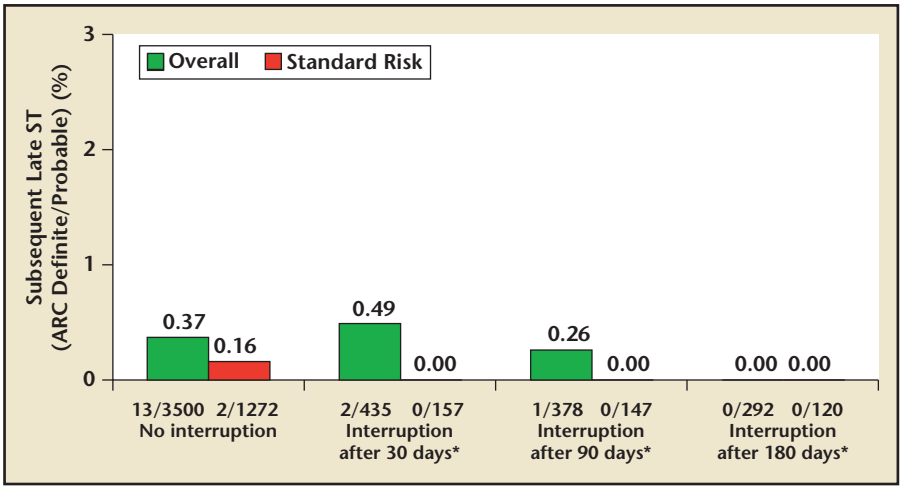


Figure 6. *Rates of late (30 days-1 year) stent thrombosis following discontinuation of dual antiplatelet therapy stratified by relative risk criteria from the XIENCE V USA (XIENCE V Everolimus-Eluting Coronary Stent System USA Post-Approval Study) registry. Standard risk criteria defined in text. *Out to 1 year. ARC, Academic Research Consortium; ST, stent thrombosis. Reprinted with permission from Hermiller J et al.[42]*

respectively.[46] Finally, comparison of an EES to an SES in both the Long-term Comparison of Everolimus-eluting and Sirolimus-eluting Stents for Coronary Revascularization (LESSON 1) 1 registry[47] and the SORT-OUT IV randomized trial[48] demonstrates higher rates of ST following SES stent deployment. Definite ST to 9 months was increased following SES (0.7% vs 0.1% EES; $P = .05$) in SORT-OUT IV.[48]

Attempts to improve upon the performance of DES that use durable polymers have included both bioresorbable polymer and polymer-free platforms. Multiple biodegradable polymer DES are commercially available outside of the United States and offer the theoretical benefit of antirestenotic properties of a standard DES with the relative late safety of a BMS following polymer resorption. Novel challenges that face the prospect of biodegradable polymer DES include polymer load and degradation time, as well as the pharmacokinetics of the antiproliferative agent eluted. Polymer degradation may be associated with immune or inflammatory reactions due to the physicochemical properties of the microcrystalline degradation fragments. These sequelae of polymer breakdown emphasize the need for adequately powered clinical trials with long-term follow-up to determine the relative safety and efficacy of biodegradable polymer DES.

Biodegradable Polymer DES

Multiple biodegradable polymer DES have been developed. These stents use various formulations of polylactide (PLA), poly-L-lactide (PLLA), or poly(lactic-co-glycolic acid), and various polymer loads ranging from surface coverage to microdots ($\geq$ 1 μm thick) on the abluminal surface.[49] To date, noninferiority of one stent (biolimus A9 eluted from PLA polymer) has been demonstrated in comparison with an SES in the 1707-patient LEADERS trial for the composite occurrence of cardiac death, MI, or ischemia-driven target lesion revascularization (IDTLR) through 2-year follow-up.[50] The absolute benefit of the biolimus A9-eluting stent (vs the SES) appears to be progressive over time as evidenced by the LEADERS trial STEMI cohort followed through 3 years. The difference between

primary endpoint events (cardiac death, MI, or IDTLR) at 1, 2, and 3 years was 1.4%, 2.4%, and 3.3%, respectively, in favor of the biolimus A9 platform. Theoretically, the avoidance of any polymer coating (polymer-free DES), including those that bioerode over 9 months, would be attractive in that it avoids any potential adverse inflammatory immune reactions to polymer and may improve stent healing with the opportunity for shorter-duration DAPT therapy.

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Nonpolymeric DES

The ability to elute antiproliferative agents without polymer may be achieved by placing the medication into a nonpolymeric biodegradable carrier, by impregnating drug onto a microporous surface, or by attaching it directly to the stent surface by using covalent bonding or crystallization/chemical precipitation. There is only one polymer-free stent currently available (in Europe). It is a stainless steel platform with a microporous surface that "traps" drug and functions as a reservoir.[51] Clinical trials have demonstrated greater and more homogeneous neointimal stent strut coverage by OCT at 3 months following the polymer-free product (compared with SES) and noninferiority at 9- to 12-month follow-up compared with PES.[52,53] Interestingly, long-term follow-up from a 1331-patient observational study suggests that there is significantly less late lumen loss between 6 and 8 months and 2 years following the polymer-free stent deployment compared with either SES or PES.[53] This observation suggests that the polymer-free stent may not be affected by the "late catch-up" phenomenon observed following durable polymer DES, which has been relatively more marked following limus drug (vs paclitaxel) elution. There are other polymer-free DES currently in development. These devices use microporous surface modification, nano-thin microporous ceramic, hydroxyapatite surface coating, or, in the case of one, apply pure paclitaxel to the stent surface using a microdrop spray crystallization process.[49] Conversely, a novel polymer-free concept is exemplified by a drug-filled stent (DFS) with continuous sinusoidal technology that employs a hollow (de-cored) microtubular design in which the stent struts serve as reservoirs for drug, which elutes through small laser-drilled holes, the size and number of which control drug elution rate. This innovative design avoids drug carrier issues related to polymer biocompatibility, inflammation due to polymer degradation, or surface coating durability while providing prolonged, controlled, and tailored drug elution profiles that have not been achievable with other nonpolymeric approaches.[54] However, the residual of all nonpolymeric DES strategies remains the metallic stent scaffold, which may limit side branch access, impair microvascular responsiveness and coronary autoregulation, and provide the iatrogenic platform upon which subsequent atherothrombosis occurs. Indeed, late atherothrombotic change, including the development of neovascularization and yellow plaque within the residual BMS scaffold, has been observed by angioscopy, intravascular ultrasound (IVUS), and OCT.[55-57] The interest in avoidance of issues related to the long-term presence of an intracoronary metallic prosthesis has prompted efforts toward the development of fully biodegradable stents.

Biodegradable Stents

The attractive attributes of biodegradable stents (BDS) include the following: 1) BDS removes potential "triggers" for very late stent thrombosis such as residual polymer and nonendothelialized stent struts that may, in turn, reduce the requirement for long-term DAPT; 2) the lack of a metallic scaffold facilitates the recovery of autoregulation, normal microcirculatory function, and adaptive shear stress, as well as late luminal enlargement and expansive remodeling; 3) BDS will not restrict future revascularization treatment options for either PCI or bypass surgery; and 4) BDS eliminates issues of late side branch coverage and overhang at ostial lesions, as well as "blooming" artifact observed on noninvasive cardiovascular imaging techniques. BDS currently in development use either polymer or metal alloy. The most extensively studied polymer for this use has been PLLA, which has numerous other medical applications, including resorbable sutures, soft tissue implants, and dialysis media. PLLA is metabolized via the Krebs cycle over 12 to 18 months into carbon dioxide and water. The first PLLA stent evaluated in humans was both thermal self-expanding and balloon expandable. The initial self-expansion was

achieved by the use of heated contrast in the delivery balloon with final expansion occurring following balloon inflation. Although the initial bare polymer (non-DES) stent was evaluated in 65 total patients with impressive angiographic as well as IVUS follow-up, the failure of further development was primarily due to the use of heat to induce self-expansion and concerns related to heat-induced vascular injury.[49] This device exemplifies several obstacles to use of a polymer stent scaffold, which include lack of radiopacity, reduced radial strength, and limited capacity for deformation. Strategies devised to overcome these obstacles, including the use of radiopaque markers and increased stent strut thickness, have been used in the most extensively studied BDS, which is a bioresorbable vascular scaffold (BVS).

BVS

The BVS platform includes a PLLA backbone that is coated with a microlayer mixture (1:1) of poly-D, L-lactide (PDLLA) and everolimus (an antiproliferative drug). PDLLA enables controlled everolimus release with kinetics that parallel those of another EES. This device has a strut thickness of 150 μm and demonstrates radial strength as well as vessel recoil. Polymer mass loss through bioabsorption approximates 30% at 1 year and 60% at 18 months.[49] Platinum markers at each end of the device facilitate angiographic visualization. The initial clinical evaluation in man demonstrated no ST to 3-year follow-up and only one major adverse event in 30 subjects. Complete bioresorption of the implant was confirmed by serial IVUS and OCT evaluation. Furthermore, return to normal vessel vasoreactivity in response to methyl-ergometrine maleate or acetylcholine was observed.[58] A subsequent iterative revision of the device has been clinically evaluated in the 101-patient cohort B ABSORB trial and has demonstrated low late lumen loss at 6 months (0.19 mm) and minimal scaffold recoil/device shrinkage. Clinical events in follow-up were infrequent (1 MI, 1 target lesion revascularization) and no ST events were observed.[59] The ABSORB EXTEND multicenter registry is currently ongoing and should provide the basis for both Conformité Européene approval as well as a pivotal randomized noninferiority trial of BVS with a metal scaffold DES.

Bioresorbable Coronary Stents

Another polymer BDS currently under evaluation is an iodinated desaminotyrosyl-tyrosine ethyl ester polycarbonate stent. The tyrosine polycarbonate polymer degrades into water, carbon dioxide, and ethanol, leaving iodinated desaminotyrosil-tyrosine, which is subsequently absorbed and excreted.[60] The initial device involved a slide-and-lock balloon expandable design and was radiopaque due to iodination of the desaminotyrosine ring. Although the structural design provided radial strength comparable to a BMS, focal mechanical failure due to polymer embrittlement led to a high target lesion revascularization through 6-month follow-up in the first 27 patients undergoing clinical evaluation and prompted device redesign. The revised stent platform has a more robust polymer, a novel spiral slide-and-lock mechanism, and is coated with sirolimus, which is 95% eluted by 90 days.

Biodegradable Metallic Stent Technology

The absorbable metallic stent (AMS) is composed of 93% magnesium and 7% rare earth metals. The AMS stent has already undergone several iterations, which have included a modified magnesium alloy (AMS2) with reduced strut thickness and prolonged degradation time, as well as the incorporation of an antiproliferative drug (AMS3).[61] The magnesium alloy degrades into negatively charged inorganic salts. In the AMS2 stent, strut thickness was reduced from 165 μm to 120 μm and the cross-sectional shape of the strut was changed from rectangular to square to improve radial strength. The AMS3 stent incorporates a bioresorbable matrix for controlled antiproliferative drug release.

Conclusions

Coronary stents have improved the safety and efficacy of PCI. The advent of DES reduced late restenosis and enhanced the durability of coronary patency. Following widespread experience with first-generation DES, a propensity for late and particularly very late ST (relative to BMS) was observed and has been ascribed to delayed, incomplete healing, and inflammatory/hypersensitivity reactions to residual durable polymer. Polymer reactions have also been incriminated in the development of positive vessel remodeling and acquired late incomplete stent strut apposition. These DES-related phenomena have necessitated the extended duration of DAPT and have prompted the evolution of new-generation DES, as well as the development of bioresorbable polymer and polymer-free drug delivery platforms.

The second-generation EES incorporate a thin, durable fluorocopolymer that appears to be thromboresistant and has been associated with very low rates of both late or very late ST, comparable with those observed following BMS. These observations have raised questions regarding the necessity of long-term

(beyond 6-12 months) DAPT therapy following EES deployment. Promising results have been observed in clinical evaluations and clinical experience with both bioresorbable polymer and polymer-free DES platforms, which have been developed in an attempt to avoid the late, potentially adverse events of durable polymer. Nevertheless, the residual metal alloy stent backbone (BMS) may serve as a nidus for atherothrombosis and may interfere with normal autoregulation and microcirculatory function. The development of fully bioresorbable polymer DES platforms offers the potential for restoration of normal coronary artery structure and function. Although clinical trial data using the BVS device have been extremely promising and Conformité Européene approval could be obtained in 2011, FDA approval will require both performance and follow-up from a large-scale randomized noninferiority trial involving a metallic scaffold DES.

The concept of "vascular restorative" therapy with a completely resorbable DES platform offers the promise of stenosis relief, arterial healing, and the return to normal arterial function without concerns noted previously, which surround the persistence of metal scaffold and/or durable polymer.[62] Such therapy, if achieved, will likely obviate the requirement for long-term DAPT as well. ■

Dr. Kereiakes has received grant and/or research support from Abbott Vascular, Amylin Pharmaceuticals, Cordis/Johnson & Johnson, Boston Scientific, Medtronic, and Daiichi Sanyko, Inc. He has received consulting fees from Abbott Vascular, Boston Scientific, Cordis/Johnson & Johnson, Eli Lilly & Co., Medpace, and REVA Medical Inc. He serves on the Speaker's Bureau for Eli Lilly & Co.

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Main Points

- The advent of drug-eluting stents (DES) markedly reduced both angiographic and clinical restenosis compared with bare metal stents (BMS) for percutaneous coronary intervention. However, multiple safety issues have been identified in late follow-up that have prompted efforts toward the development of bioresorbable polymers and polymer-free metal platforms, as well as completely resorbable DES platforms, with the ultimate goal of providing safe and durable coronary patency.
- Nonerodable polymers may precipitate thrombus formation and stent thrombosis (ST) by inciting localized inflammation, hypersensitivity reactions, and apoptosis of vascular smooth muscle cells. Delayed or incomplete stent healing and localized durable polymer-related inflammatory effects are likely precipitants of ST when dual antiplatelet therapy (DAPT) is discontinued prematurely.
- The durable fluorocopolymer used on the second-generation everolimus-eluting stents (EES) appears to be more inert and more biocompatible than the first-generation DES polymers. Physiologic and histologic observations may underlie the more clinically relevant observation of lower risk for ST following EES compared with first-generation DES implantation.
- Attempts to improve upon the performance of DES that use durable polymers have included both bioresorbable polymer and polymer-free platforms. Novel challenges that face the prospect of biodegradable polymer DES include polymer load and degradation time, as well as the pharmacokinetics of the antiproliferative agent eluted. Theoretically, the avoidance of polymer coating would be attractive in that it avoids any potential adverse inflammatory immune reactions to polymer and may improve stent healing with the opportunity for shorter-duration DAPT therapy.
- The ability to elute antiproliferative agents without polymer may be achieved by placing the medication into a nonpolymeric biodegradable carrier, by impregnating drug onto a microporous surface, or by attaching it directly to the stent surface by using covalent bonding or crystallization/chemical precipitation. Other polymer-free DES currently in development use microporous surface modification, nano-thin microporous ceramic, hydroxyapatite surface coating, or apply pure paclitaxel to the stent surface using a microdrop spray crystallization process.

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SELF-ASSESSMENT POST-TEST

Safety of Drug-Eluting Stents

1. Which statement regarding the current US Food and Drug Administration Advisory Panel recommendations for duration of Dual Antiplatelet Therapy (DAPT) is true?
- **a.** The panel recommends ≥ 6 months DAPT for both drug-eluting stents (DES) and bare metal stents (BMS).
- **b.** The panel recommends ≥ 12 months of DAPT following DES deployment in all patients without specific contraindications and/or bleeding risk.
- **c.** The panel recommends indefinite DAPT following DES deployment.
- **d.** The panel recommends ≥ 30 days DAPT for both BMS and DES.

2. Which of the following statements regarding DES stent thrombosis (ST) are true?
- **a.** The pathogenesis of late and very late ST may involve delayed and/or incomplete stent healing and localized polymer-related inflammation.
- **b.** The optimal duration of DAPT to prevent DES ST is unknown.
- **c.** The majority of DES ST cannot be ascribed to clopidogrel noncompliance.
- **d.** BMS and DES have similar rates of early and late ST.
- **e.** All of the above

3. Which of the following have been associated with very late DES thrombosis?
- **a.** Atherothrombosis and yellow plaque development
- **b.** Coadministration of proton pump inhibitors
- **c.** Incomplete stent healing and uncovered stent struts
- **d.** All of the above
- **e.** a + c

4. Which of the following statements is correct regarding a multivariate analysis of pooled patient-level data from multiple randomized, controlled clinical trials comparing everolimus-eluting stents (EES) versus paclitaxel-eluting stents (PES)?
- **a.** EES is an independent predictor of freedom from ST (vs PES).
- **b.** The relative benefit of EES (vs PES) for reduction in ST appears more marked in patients treated for acute coronary syndromes (vs stable coronary artery disease).
- **c.** The ability to safely discontinue thienopyridine treatment following 1 year of DAPT appears enhanced following EES (vs PES).
- **d.** None of the above
- **e.** All of the above

5. The relative increase in very late ST in PES versus EES was more marked in the COMPARE versus the SPIRIT IV trial. Which of the following are likely explanations for this observation?
- **a.** COMPARE was an all-comers trial and included a higher prevalence of subjects with acute coronary syndrome.
- **b.** COMPARE was conducted in Europe whereas SPIRIT IV was conducted in the United States.
- **c.** The prevalence of thienopyridine compliance beyond 1 year was much greater in SPIRIT IV versus COMPARE.
- **d.** a + c
- **e.** All of the above

6. The attractive attributes of biodegradable stents (BDS) include which of the following?
- **a.** BDS removes potential triggers for very late ST such as residual polymer and nonendothelialized stent struts, which may in turn reduce the requirement for long-term DAPT.
- **b.** The lack of a metallic scaffold facilitates the recovery of autoregulation, normal microcirculatory function, and adaptive sheer stress, as well as late luminal enlargement and expansive remodeling.
- **c.** BDS will not restrict future revascularization treatment options for either percutaneous coronary intervention or bypass surgery.
- **d.** All of the above
- **e.** a + c

7. Which of the following statements regarding EES are true?
- **a.** Several randomized controlled clinical trials have demonstrated lower rates of ST following EES versus PES.
- **b.** A large-scale randomized, controlled trial has demonstrated a lower rate of ST compared with the zotarolimus-eluting stent.
- **c.** Published data from all-comers registries and randomized trials have demonstrated the lowest rates of ST following EES compared with other DES.
- **d.** Rates of very late ST following EES are comparable with those of BMS.
- **e.** All of the above