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STATE-OF-THE-ART PAPERS

# Stent Thrombosis With Drug-Eluting Stents

## Is the Paradigm Shifting?

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**First-generation drug-eluting stents (DES), which impart the controlled release of sirolimus or paclitaxel from durable polymers to the vessel wall, have been consistently shown to reduce the risk of restenosis and target vessel revascularization compared with bare metal stents (BMS). However, stent thrombosis (ST) emerged as a major safety concern with first-generation DES early after their adoption in clinical practice, requiring prolonged dual antiplatelet therapy. Pathological studies have shown that first-generation DES are associated with delayed arterial healing and polymer hypersensitivity reactions resulting in chronic inflammation, predisposing to late and very late ST. Second-generation DES have been developed to overcome these issues with improved stent designs and construction and the use of biocompatible and bioabsorbable polymers. Meta-analyses have shown that the thin-strut, fluoropolymer-coated cobalt-chromium everolimus-eluting stent (CoCr-EES) may be associated with lower rates of definite ST than other DES and, unexpectedly, even lower than BMS. The thin-strut structure of the stent platform, the thromboresistant properties of the fluoropolymer, and the reduced polymer and drug load may contribute to the low rate of ST with CoCr-EES. The notion of DES being safer than BMS represents a paradigm shift in the evolution of percutaneous coronary intervention. The relative safety and efficacy of fluoropolymer-coated CoCr-EES, DES with bioabsorbable polymers, and fully bioresorbable scaffolds are the subject of numerous ongoing large-scale trials.**
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Although first-generation Cypher sirolimus-eluting stents (SES) (Cordis Corp., Miami Lakes, Florida) and Taxus paclitaxel-eluting stents (PES) (Boston Scientific, Natick, Massachusetts) significantly reduce the risk of target vessel revascularization compared with bare-metal stents (BMS) (1,2), concern has been raised over their ongoing propensity for very late stent thrombosis (ST) (3). These safety concerns prompted the development of second-generation drug-eluting stents (DES), which use different drugs, more biocompatible or bioabsorbable polymers, and different stent platforms. On their introduction, second-generation DES were most commonly compared with first-generation DES in noninferiority randomized controlled trials (RCTs) (4), which did not have sufficient statistical power to explore possible differences in ST rates between devices. In this review, we therefore analyze the relative risk of ST, death, and myocardial infarction (MI) of first-generation DES, second-generation DES, and BMS that have been extensively investigated in RCTs. We did not analyze in detail all studies enrolling patients with ST-segment elevation MI because this issue was recently addressed by a dedicated analysis (5).

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## ST With First-Generation DES

Although RCTs initially did not raise any safety issues with first-generation DES (1,2), a subsequent report of 4 cases of angiographically confirmed ST late after elective implantation of SES or PES raised concerns of a possible very late ST risk with DES (6). However, it was not until 2006, at the annual meeting of the European Society of Cardiology in Barcelona, that the firestorm over first-generation DES was ignited, spreading concern among the media and public as well as interventional cardiologists (7). During this congress, a meta-analysis performed on aggregate data pooled from trial programs comparing SES or PES versus BMS suggested an increased risk of mortality and MI with first generation DES compared to BMS (8). The controversy regarding the safety of DES was fueled by additional real-world studies that showed an increased risk of late ST and MI in patients treated with first-generation DES after discontinuation of dual antiplatelet therapy (DAPT) (3) and a steady accrual of ST at a rate of 0.6% per year with no evidence of plateau after 4-year follow-up (9). Pathological studies showed that the durable polymer of first-generation DES could result in chronic inflammation,

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**Abbreviations and Acronyms**

**ARC** = Academic Research Consortium

**BMS** = bare-metal stent(s)

**CoCr-EES** = cobalt-chromium everolimus-eluting stent(s)

**DAPT** = dual antiplatelet therapy

**DES** = drug-eluting stent(s)

**FDA** = Food and Drug Administration

**MI** = myocardial infarction

**PC-ZES** = phosphorylcholine polymer-based fast-release zotarolimus-eluting stent(s)

**PCI** = percutaneous coronary intervention

**PES** = paclitaxel-eluting stent(s)

**PtCr-EES** = platinum-chromium everolimus-eluting stent(s)

**RCTs** = randomized controlled trials

**Re-ZES** = C10/C19/PVP polymer-based slow-release zotarolimus-eluting stent(s)

**SES** = sirolimus-eluting stent(s)

**ST** = stent thrombosis

with delayed hypersensitivity reactions, chronic fibrin deposition, and consequent poor endothelial healing of the vessel wall with increased thrombotic risk (10).

In view of the rare incidence of ST and the conflicting evidence, several pooled analyses and meta-analyses were performed to address the safety of first-generation DES (11–14). As shown in Table 1, these studies collectively established no significant differences in the risk of death or MI between first-generation DES and BMS but an increased risk of very late ST with both SES and PES compared with BMS. On the basis of this mounting evidence regarding the ongoing propensity of DES ST over time, the Food and Drug Administration (FDA) assigned an expert panel to review the available evidence. Eventually, the advisory panel released a statement acknowledging a small but significant increased risk of very late ST with DES while recognized them as safe and effective for on-label indications (15). The absence of a significant difference in mortality or MI between first-generation DES and BMS despite the increased risk of very late ST with DES may be explained by the fact that in-stent restenosis is not always a benign phenomenon, presenting as acute MI in 3.5% to 19.4% of patients (16). Thus, a small increase in a low-frequency event (late or very late ST) with frequent, serious, life-threatening consequences may be offset by a large reduction of a more common event (restenosis), which is occasionally but less frequently associated with serious clinical consequences (17).

Nonetheless, responding to the general concerns of increased ST with DES, the FDA and societies recommended lengthening the requirement for DAPT after DES from 3 to 6 months (as studied in the pivotal approval trials) to 1 year, although little data supported this extension.

## The Academic Research Consortium Definition of ST

The lack of a uniform definition of ST provided significant uncertainty in the comparative interpretation of the results of clinical trials and meta-analyses. To standardize definitions for patients enrolled in cardiovascular trials, a formal collaboration between academic research organizations in the United States and Europe, the Academic Research Consortium (ARC), was established (18). Using ARC criteria, ST is defined according to various levels of certainty, depending on whether the level of evidence needs to be more or less restrictive (18). ST is also classified relative to the timing of occurrence after stent implantation as early (within 30 days), late (between 30 days and 1 year) and very late (beyond 1 year). Mauri et al. (19) were the first to analyze the risk of ST using both the trial protocol definitions of ST and the ARC criteria in a meta-analysis. At 4-year follow-up, there were no significant differences in the risk of ST between either SES or PES and BMS, but a different temporal trend in the risk of ST was apparent depending on whether the protocol definition or the ARC criteria were used to define ST. In the Stettler meta-analysis, using mixed treatment comparisons and comparing outcomes of PES, SES, and BMS, the authors reported that mortality was similar in the 3 groups, SES was associated with significantly lower rates of MI than both BMS and PES, and PES was associated with significantly higher rates of late plus very late definite ST than both SES and BMS.

## ST With Second-Generation DES

Second-generation DES have been developed with advanced design features, specifically thinner strut stent platforms (most commonly using a cobalt-chromium alloy) and more biocompatible polymers or bioabsorbable polymers. FDA-approved second-generation DES currently in use include Xience V, Xience Prime, and Xience Expedition (Abbott Vascular, Santa Clara, California), which are cobalt-chromium everolimus-eluting stents (CoCr-EES); Promus Element (Boston Scientific, Natick, Massachusetts), a platinum-chromium everolimus-eluting stent (PtCr-EES); Endeavor (Medtronic, Santa Rosa, California), a phosphorylcholine polymer-based fast-release zotarolimus-eluting stent (PC-ZES); and Resolute (Medtronic), a C10/C19/PVP polymer-based slow-release zotarolimus-eluting stent (Re-ZES) (Table 2).

CoCr-EES have undergone the most extensive clinical investigation. RCTs and observational studies have consistently shown low rates of ST with CoCr-EES, with some studies showing significantly lower rates of ST with CoCr-EES than with PES or SES (4,20,21). However, all these studies were insufficiently powered to reliably detect differences in ST, and therefore several meta-analyses have been performed to address this issue (Table 1). In the meta-analysis by Baber at al. in which 13 RCTs with 17,101 patients were included, CoCr-EES significantly reduced definite/probable ST and MI compared with pooled PES, SES, and Re-ZES after a median follow-up of 21 months (22). However, treatment effects for each endpoint varied by DES comparator, with the largest difference apparent for CoCr-EES versus PES, intermediate for CoCr-EES versus Re-ZES, and smallest for CoCr-EES versus SES. In the meta-analysis by de Waha et al. (23) in which CoCr-EES were compared with SES in 5 RCTs with 7,370 patients,

**Table 1** Main Meta-Analyses Comparing Clinical Outcomes With Different Types of Drug-Eluting Stents and Bare-Metal Stents

| First Author, Year | No. of Studies | No. of Patients | DES Comparators | Length of Follow-Up | Main Results for Death and MI | Main Results for ST |
|---|---|---|---|---|---|---|
| Per-protocol definition of ST | | | | | | |
| Stone, 2007 | 9 | 5,261 | BMS/PES/SES | 4 yrs | No difference | Increased rates of very late ST with SES or PES compared with BMS |
| Ellis, 2007 | 4 | 3,445 | BMS/PES | 3 yrs | NA | Increased rates of ST between 6 months and 3 yrs with PES compared with BMS |
| Kastrati, 2007 | 14 | 4,958 | BMS/SES | 5 yrs | No difference | No difference |
| ARC definition of ST with first-generation DES | | | | | | |
| Mauri, 2007 | 8 | 4,545 | BMS/PES/SES | 4 yrs | NA | No difference |
| Stettler, 2007 | 38 | 18,023 | BMS/PES/SES | 4 yrs | Lower rates of MI with SES than BMS or PES | Increased rates of late and very late ST with PES compared with both SES and BMS<br>No difference between SES and BMS |
| ARC definition of ST with second-generation DES | | | | | | |
| Baber, 2011 | 13 | 17,101 | CoCr-EES vs. pooled PES, SES, and Re-ZES | 21 months* | Lower rates of MI with CoCr-EES compared with pooled other DES | Lower rates of ST with CoCr-EES compared with pooled other DES |
| De Waha, 2012 | 8 | 11,167 | CoCr-EES vs. SES | 13 months* | No difference | Trend for lower rates of ST with CoCr-EES |
| Palmerini, 2012 | 11 | 16,775 | CoCr-EES vs. pooled PES, SES, and Re-ZES | 2 yrs | NA | Lower rates of ST with CoCr-EES compared with pooled other DES |
| Palmerini, 2012 | 49 | 50,844 | BMS/PES/SES/ CoCr-EES/PtCr-EES/ Re-ZES/PC-ZES | 2 yrs | NA | Lower rates of ST with CoCr-EES than BMS and PES |
| Bangalore, 2012 | 77 | 117,762 | BMS/PES/SES/EES/ Re-ZES/PC-ZES | 2.1 yrs* | Lower rates of MI with SES, ZES, and CoCr-EES but not with PES compared with BMS | Lower rates of ST with CoCr-EES compared with other DES and BMS |

*Median follow-up.

ARC = Academic Research Consortium; BMS = bare-metal stent(s); CoCr-EES = cobalt-chromium everolimus-eluting stent(s); DES = drug-eluting stent(s); MI = myocardial infarction; NA = not available; PC-ZES = phosphorylcholine polymer-based zotarolimus-eluting stent(s); PES = paclitaxel-eluting stent(s); Re-ZES = Resolute zotarolimus-eluting stent(s); SES = sirolimus-eluting stent(s); ST = stent thrombosis.

no significant differences in the risks of death, MI, or definite/probable ST were apparent between CoCr-EES and SES after a median follow-up of 13.3 months, although a trend toward a reduction in definite/probable ST was apparent in favor of CoCr-EES (23).

These 2 meta-analyses were limited by the facts that they examined ST using the broad definition of definite/probable ST, rather than the more specific criteria used to define definite ST, and considered only one specific time point, thus leaving undetermined whether there might be

**Table 2** Current FDA-Approved Drug-Eluting Stents

| Commercial Name | Manufacturer | Drug Released (Concentration μg/cm$^2$) | Kinetic of Drug Release | Polymer | Platform | Strut Thickness (μm) |
|---|---|---|---|---|---|---|
| Taxus Express<br>Taxus Liberté | Boston Scientific | Paclitaxel (100) | 10% during the first 10 days* | SIBS | Stainless steel | 132<br>97 |
| Cypher | Cordis | Sirolimus (140) | 80% during the first month | PEVA, PMA | Stainless steel | 140 |
| Endeavor | Medtronic | Zotarolimus (160) | 80% during the first 10 days | MPC, LMA, HPMA, 3-MPMA | Cobalt-chrome | 91 |
| Resolute | Medtronic | Zotarolimus (160) | 80% during the first 2 months | PBMA, PHMA, PVP, PVA | Cobalt-chrome | 91 |
| Xience V<br>Xience Prime<br>Xience Expedition | Abbott Vascular | Everolimus (100) | 80% during the first month | PBMA, PVDF-HFP | Cobalt-chrome | 81 |
| Promus Element | Boston Scientific | Everolimus (100) | 80% during the first month | PBMA, PVDF-HFP | Platinum-chrome | 81 |

*The remaining 90% of the drug remains sequestered in the polymer indefinitely.

FDA= Food and Drug Administration; HPMA = hydroxypropyl methacrylate; LMA = lauryl methacrylate; MPC = methacryloyloxyethyl phosphorylcholine; 3-MPMA = 3-(trimethoxysilyl)propyl methacrylate; PBMA = poly(n-butyl methacrylate); PEVA = poly(ethylene-co-vinyl acetate); PHMA = poly(hexyl methacrylate); PVA = polyvinyl acetate; PVDF-HFP = copolymer of vinylidene fluoride and hexafluoropropylene; PVP = polyvinylpyrrolidone; SIBS = poly(styrene-b-isobutylene-b-styrene).

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time-related differences in the risk of ST between various devices. To address these issues, Palmerini et al. performed a meta-analysis of 11 RCTs with 16,775 patients (including 5 trials of CoCr-EES vs. PES, 5 trials of CoCr-EES vs. SES, and 1 trial of CoCr-EES vs. Re-ZES) (24). This study showed significantly lower rates of early, late, 1-year, and 2-year definite ST with CoCr-EES compared with other pooled DES, with no interaction apparent between the overall relative risk of definite ST and any DES comparator. The reduced risk of ST with CoCr-EES compared with first-generation DES suggested by these meta-analyses has since been confirmed in "real-world" studies. Specifically, with a median follow-up of 1.5 years in 1,342 propensity score-matched pairs of patients, CoCr-EES were found to have significantly lower rates of definite ST and MI compared with SES (20). Moreover, in a large all-comers study including 12,339 patients, the rates of definite ST were lower with CoCr-EES than either SES or PES up to 4-year follow-up, with differences in ST most pronounced after the first year from stent implantation (21).

PC-ZES represents the combination of zotarolimus, a low-profile cobalt alloy stent platform, and a biocompatible phosphorylcholine polymer as a drug carrier system. In the Endeavor clinical trials program, PC-ZES was compared with BMS (ENDEAVOR II) (25), with SES (ENDEAVOR III) (26), and with PES (ENDEAVOR IV) (27). Although no significant difference in the risk of ST between PC-ZES and either of these stent comparators emerged in these trials, some studies have suggested lower rates of death and MI with PC-ZES than SES (26) or PES (27), whereas other studies have refuted this association (28). More recently, in the large-scale, multicenter, randomized PROTECT (PROphylaxis for ThromboEmbolism in Critical Care Trial), in which 8,800 patients with coronary artery disease were enrolled (the largest comparative DES trial to date), no significant differences in death, MI, or ST were apparent between patients with SES (n = 4,400) and PC-ZES (n = 4,440). Notably, however, patients with SES tended to have less definite/probable ST in the first year than PC-ZES ($p = 0.06$), while very late ST rates between the first and third year were greater with SES than PC-ZES (1.1% vs. 0.3%; $p < 0.001$) (29).

Re-ZES uses the same stent platform as PC-ZES but incorporates a different polymer system (BioLinx; Medtronic Vascular), a composite polymer with hydrophilic and hydrophobic layers that allows a more delayed release of the same zotarolimus concentration as in the original Endeavor stent. Re-ZES has been compared with CoCr-EES in the RESOLUTE-AC (Two-arm, Non-inferiority Study Comparing Resolute Stent With Xience-V Stent) (30) and TWENTE (The Real-World Resolute Versus XIENCE V Drug-Eluting Stents Study in Twente) trials (31). In both studies, no significant differences in rates of death or MI were apparent between the 2 stents. However, definite ST at 1 year was significantly less frequent with CoCr-EES than Re-ZES in the RESOLUTE-AC trial (0.3% vs. 1.2%, respectively; $p = 0.01$) (30) and numerically lower in the TWENTE trial (0% with Xience vs. 0.6% with Re-ZES; $p = 0.12$) (31). When the broader definition of definite/probable ST was considered, a borderline statistical reduction in ST was apparent with CoCr-EES compared with Re-ZES in the RESOLUTE-AC trial (0.7% vs. 1.6%, respectively; $p = 0.05$), whereas numerically higher rates of definite/probable ST were apparent with CoCr-EES compared with Re-ZES in the TWENTE trial (1.2% vs. 0.9%, respectively; $p = 0.59$).

## ST With Second-Generation DES Versus BMS: Network Meta-Analyses

Because most second-generation DES were approved in non-inferiority trials compared with first-generation DES, few studies have directly compared second-generation DES with BMS. Recently, the EXAMINATION (A Clinical Evaluation of Everolimus Eluting Coronary Stents in the Treatment of Patients With ST-segment Elevation Myocardial Infarction) trial, in which 1,504 patients with ST-segment elevation MI were randomized to CoCr-EES versus BMS, showed significantly lower rates of ST in patients treated with CoCr-EES (32). However, this trial was not powered to determine differences in ST (and this hypothesis was not prespecified), and therefore a type I error cannot be excluded.

Network meta-analysis and mixed treated comparisons are novel research methods capable of comparing different treatments using a common reference treatment, and their role in clinical research has been established (33). Two network meta-analyses have assessed the relative safety and efficacy of currently available DES and BMS (34,35). In a network meta-analysis that included 49 RCTs with 50,844 patients, Palmerini et al. investigated the risk of ST between FDA-approved DES (Xience/Promus, Endeavor, Resolute, Promus Element, Cypher, and Taxus) and BMS, analyzing the risk of definite and definite/probable ST at 1 and 2 years and in the early, late, and very late periods (35). Only studies reporting ST according to the ARC criteria were included. As shown in Figure 1, CoCr-EES were associated with significantly lower rates of 1-year and 2-year definite ST than BMS, a result not observed with other DES; the reduction in ST with CoCr-EES compared with BMS was apparent both early and late (occurring before 30 days and between 31 days and 1 year); and CoCr-EES were also associated with significantly lower 1-year rates of definite ST compared with other first- and second-generation DES, including PES, SES, PC-ZES, and Re-ZES. Potentially the most important and unexpected finding was the significantly lower risk of ST with CoCr-EES compared with BMS at 1-year and 2-year follow-up. A significant difference in definite ST between CoCr-EES and BMS was already apparent at 30 days and was also present in the period between 31 days and 1 year. These differences were also seen for the more sensitive but less specific definition of ARC definite/probable ST for up to 2 years of follow-up.

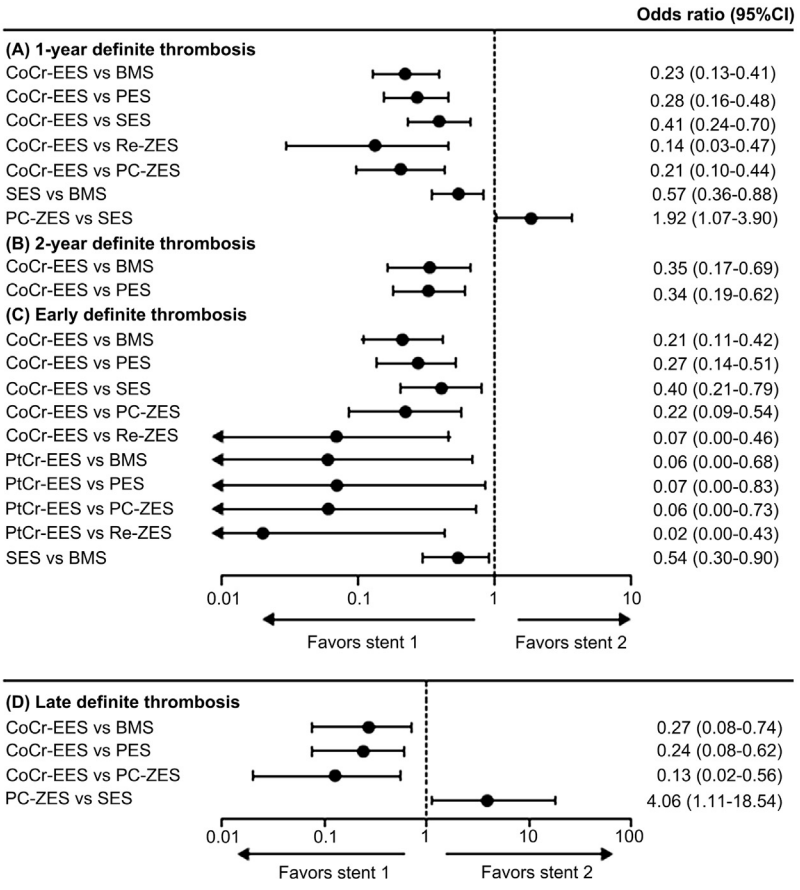


**Figure 1** **Pooled Odds Ratio and 95% Credible Intervel Determined by Network Meta-Analysis for the Risk of Definite Stent Thrombosis at Various Time Points**

Only statistically significant results are shown. **(A)** 1-year odds ratio of definite stent thrombosis; **(B)** 2-year odds ratio of definite stent thrombosis; **(C)** odds ratio of early definite stent thrombosis; **(D)** odds ratio of late definite stent thrombosis. BMS = bare-metal stent(s); CI = credible interval; CoCr-EES = cobalt-chromium everolimus-eluting stent(s); PC-ZES = phosphorylcholine polymer-based zotarolimus-eluting stent(s); PES = paclitaxel-eluting stent(s); PtCr-EES = platinum-chromium everolimus-eluting stent(s); Re-ZES = Resolute zotarolimus-eluting stent(s); SES = sirolimus-eluting stent(s); Reprinted with permission from Palmerini et al. (35).

A subsequent broader network meta-analysis by Bangalore et al. included 77 RCTs with 117,762 patients. In that study, study selection was not restricted to FDA-approved brands or to RCTs reporting ST according to the ARC criteria as in the previous network meta-analysis (34). Although rates of long-term mortality were similar between first-generation DES, second-generation DES, and BMS, rates of MI were significantly lower with SES, ZES, and CoCr-EES but not with PES compared with BMS. Data on ST, both per protocol or by ARC criteria, were consistent with the previous network meta-analysis, showing lower definite ST rates with CoCr-EES compared with other DES and BMS (35).

Although meta-analyses inherently contain flaws and should be considered hypothesis generating, the lack of heterogeneity across most of the included RCTs, the stability of results in several sensitivity analyses, and the consistency between direct and indirect estimates apparent in these network meta-analyses provide strong support of their findings, suggesting a paradigm shift from the contention of an increased risk of ST with DES compared with BMS to the converse. A large randomized trial of CoCr-EES (or other DES) compared with BMS powered for ST would be required for definitive proof of this hypothesis, however. Such a study is unlikely to be performed except possibly in patients with ST-segment elevation MI. Moreover, it should be underscored that CoCr-EES is the most extensively studied second-generation DES; other second-generation DES such as PtCr-EES or Re-ZES have been less intensely studied in terms of the number of clinical trials performed and the length of follow-up available. Further studies are therefore needed to clarify the relative safety and efficacy of different second-generation DES.

## Mechanistic Underpinnings of Reduced ST With Second-Generation DES

Animal and human studies have identified non-erodable polymer coatings as a possible factor triggering

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hypersensitivity reactions, chronic inflammation, and persistent fibrin deposition, causing impaired endothelial healing and predisposition to very late ST (10). The fact that CoCr-EES compared with other DES and BMS have resulted in lower rates of ST in both the early as well as the late period (35) is of relevance when considering the potential mechanisms of this protective effect, which likely include more rapid and complete endothelialization as well as differences in stent alloy and architecture, strut thickness, polymer characteristics, and antiproliferative drug type, dose, and release kinetics. Specifically, the thin (81 μm), malleable cobalt-chromium stent struts, the thromboresistant fluorocopolymer (13,36), and the low polymer and drug load may contribute to the low rate of ST observed with CoCr-EES. The concept of a polymer-coated DES being safer than BMS is supported by the experimental studies of Kolandaivelu et al. (13), in which fluoropolymer-coated stents had significantly lower thrombosis and platelet deposition compared with their bare metal counterparts. In this regard, fluoro-copolymers have been shown to elicit reduced platelet aggregates in blood contact applications (36). Whether similar properties are shared by other second-generation DES deserves further investigation.

## Implications and Future Directions

The protective effect exerted by fluorocopolymers on ST challenges the notion that bioabsorbable polymers or bioabsorbable vascular scaffolds may be necessary to minimize ST; indeed, the durable polymer in this instance may be beneficial. In this regard, whereas studies have suggested lower rates of ST with DES using bioabsorbable polymers compared with permanent polymer SES only in the very late period (37), CoCr-EES have been associated with reduced rates of ST in the early, late, and very late periods compared with BMS and other first- and second-generation DES (24,35). Therefore, while the advantages of bioabsorbable polymer-based DES over first-generation permanent polymer DES are expected to emerge in the late follow-up period after biodegradation of the polymer, the presence of the thromboresistant fluoropolymer may reduce the risk of ST both in the early and late period. Large comparative trials of durable fluoropolymer-coated DES, bioabsorbable polymer-based DES, and fully bioresorbable scaffolds will be necessary to truly characterize the relative safety profiles of these very different classes of devices. Some such studies are ongoing, and others are being planned.

The lower risk of late ST with second-generation DES compared with first-generation DES also challenges current guidelines that recommend 1 year of DAPT after DES placement (38). This recommendation was not based on specific evidence-based randomized trial results, but rather relied on post-hoc analyses of observational studies performed with first-generation DES (3). More recently, a post-hoc analysis of pooled data from the SPIRIT II, III, and IV and COMPARE trials has suggested that interruption of DAPT 3 months after percutaneous coronary intervention (PCI) with CoCr-EES does not carry an increased hazard of ST compared with never interrupting DAPT up to 1 year (39). Moreover, in post-hoc analyses of real-world studies performed in the Xience V program (SPIRIT V, SPIRIT WOMEN, XIENCE V USA, and XIENCE V India) including 10,615 patients treated with CoCr-EES, there were no episodes of ST up to 1-year follow-up in patients who discontinued DAPT between 3 and 12 months (40). Similar findings were apparent when another second-generation DES (Re-ZES) was considered. Specifically, in a substudy of the RESOLUTE-AC trial, among the 851 patients with a first interruption of DAPT beyond 3 months, there were no ST events at 1 year (41). Future RCTs should investigate whether 3-month DAPT is as effective (and potentially safer, with less bleeding) as 12-month DAPT in patients treated with second-generation DES.

Similarly, important trials completed in the past decade that have examined the relative risks and benefits of PCI versus medical therapy in stable coronary artery disease (42) and PCI versus coronary artery bypass grafting in complex coronary artery disease (43) have exclusively used first-generation DES or BMS. The major generational advances in stent technology with attendant improvements in patient outcomes need to be carefully considered when interpreting the clinical implications of trials. It is a reality that major guidelines committees must rely on out-of-date studies when making recommendations. Major advances in therapies require new comparative trials. One such ongoing large-scale trial, EXCEL, is randomizing 2,600 patients with unprotected left main coronary artery disease and a low to intermediate Syntax score to coronary surgery versus PCI with CoCr-EES.

## Conclusions

Compared with first-generation DES, second-generation DES show significantly enhanced safety, representing a major advance for patients with coronary artery disease requiring revascularization.

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**Key Words:** bare-metal stent(s) ■ drug-eluting stent(s) ■ stent thrombosis.