Drug-eluting stents (DES) are combination products traditionally consisting of three components (platform, polymer, and drug), each with innumerable potential design permutations (Figure 1). Currently, six DES are available in the United States (Table 1), with more than a dozen additional products being evaluated in clinical trials globally. Design objectives range from improvements in mechanical deliverability and late lumen loss to enhanced endothelial healing and safety. As combination products, however, small changes in one component may interact with other components in unexpected ways, making comparisons among various DES in specific patient populations, lesion types, and with differing adjunctive therapies both essential and complex.

Because DES are permanent coronary implants used to treat millions of patients, rare but catastrophic safety events, such as stent thrombosis (ST), have emerged as public health concerns shared by clinicians, manufacturers, regulatory authorities, and the public. Evaluation of such endpoints requires large cohorts, long follow-up, and at least some randomized data, making safety comparisons of new DES an ongoing challenge. In this article, we examine the degree to which changes in
stent platform, polymer, or drug components have produced clinical data suggesting that new design features achieve their intended objectives.

FROM FIRST TO SECOND GENERATION:
RAISING THE BAR FOR SAFETY COMPARISON

Everolimus-eluting stents (EES) (Xience V, Abbott Vascular, Santa Clara, CA; Promus, Boston Scientific Corporation, Natick, MA) currently are the most studied medical devices in history, with more than 15,000 patients in more than half a dozen randomized clinical trials (RCTs) followed for as long as 4 years. Clinical outcomes in patients treated with Xience V/Promus EES have been reported in progressively more complex patients, head to head against more DES platforms, and with longer follow-up periods than any other stent. The consistency of cumulative Xience V/Promus EES data support the contention that DES technology can produce both low late loss and very low ST, setting a pragmatic bar for comparison as new platforms emerge.

Recently published 2-year follow-up data of the SPIRIT IV1 and COMPARE2 studies show superiority of Xience V/Promus EES to the paclitaxel-eluting (PES) Taxus Express and Taxus Liberté stents (Boston Scientific Corporation), respectively. In the SPIRIT IV study, 3,687 patients with up to three noncomplex, previously untreated lesions were randomized to Xience V/Promus EES or Taxus Express PES. Two-year results uniformly favored EES: target lesion failure (TLF) (6.9% vs 9.9%; P = .003), myocardial infarction (MI) (2.5% vs 3.9%; P = .02), Q-wave MI (0.1% vs 0.8%; P = .002), ST (0.4% vs 1.2%; P = .008), and ischemia-driven target lesion revascularization (TLR) (0.4% vs 1.2%; P = .008). In the COMPARE all-comers, prospective, double-blind study, 1,800 patients were randomized 1:1 to treatment with Xience V/Promus EES or Taxus Liberté PES. The primary composite endpoint of all death, nonfatal MI, and target vessel revascularization (TVR) occurred in 9% of Xience V/Promus EES patients and in 13.7% of Taxus Liberté PES patients (relative risk [RR]: 0.66; 95% confidence interval [CI], 0.50–0.86) driven by a lower rate of MI (3.9% vs 7.5%; RR, 0.52; 95% CI, 0.35–0.77) and TVR (3.2% vs 8%; RR, 0.41; 95% CI, 0.27–0.62), in parallel with a lower rate of definite or probable ST (0.9% vs 3.9%; RR, 0.23; 95% CI, 0.11–0.49).

Comparisons of EES to sirolimus-eluting stents (SES) (Cypher, Cordis Corporation, Bridgewater, NJ) include the

### TABLE 1. DESIGN SPECIFICATIONS OF THE SIX DES THAT ARE CURRENTLY FDA APPROVED

<table>
<thead>
<tr>
<th>Stent</th>
<th>Drug (µg/cm²)</th>
<th>Polymer</th>
<th>Polymer Thickness (µm)</th>
<th>Drug Release, (28 d)</th>
<th>Metal</th>
<th>Geometry</th>
<th>Strut Thickness (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cypher</td>
<td>Sirolimus (140)</td>
<td>Durable</td>
<td>12.6</td>
<td>80%</td>
<td>SS</td>
<td>Closed cell</td>
<td>140</td>
</tr>
<tr>
<td>Taxus Express</td>
<td>Paclitaxel (100)</td>
<td>Durable</td>
<td>16</td>
<td>&lt; 10%</td>
<td>SS</td>
<td>Open cell</td>
<td>132</td>
</tr>
<tr>
<td>Taxus Liberté</td>
<td>Paclitaxel (100)</td>
<td>Durable</td>
<td>16</td>
<td>&lt; 10%</td>
<td>SS</td>
<td>Hybrid</td>
<td>97</td>
</tr>
<tr>
<td>Endeavor</td>
<td>Zotarolimus (100)</td>
<td>Durable, biocompatible</td>
<td>4.1</td>
<td>95%</td>
<td>CoCr</td>
<td>Open cell</td>
<td>91</td>
</tr>
<tr>
<td>Xience V</td>
<td>Everolimus (100)</td>
<td>Durable</td>
<td>7.6</td>
<td>80%</td>
<td>CoCr</td>
<td>Open cell</td>
<td>81</td>
</tr>
<tr>
<td>Ion</td>
<td>Paclitaxel (100)</td>
<td>Durable</td>
<td>15</td>
<td>&lt; 10%</td>
<td>PtCr</td>
<td>Closed cell</td>
<td>81</td>
</tr>
</tbody>
</table>

**Abbreviations:** CoCr, cobalt chromium; PtCr, platinum chromium; SS, stainless steel.
“Preclinical and observational evidence also suggests that thinner struts may reduce restenosis and facilitate endothelialization.”

EXCELLENT, ISAR-TEST 4,3 SORT OUT-4, and BASKET-PROVE4 trials. ISAR-TEST 4 was an open-label randomized controlled trial (RCT) comparing a novel biodegradable polymer DES to Cypher SES and Xience V/Promus EES. A substudy randomized 1,304 patients with de novo coronary lesions and ischemia (1:1) to Xience V/Promus EES or Cypher SES. At 2 years, the combined endpoint of cardiac death, target vessel MI, or TLR was similar between groups (Cypher SES, 18.8%; Xience V/Promus EES, 16%; \( P = .23 \)), whereas TLR favored Xience V/Promus EES (Cypher SES, 13.5%; Xience V/Promus EES, 9.9%; \( P = .06 \)). Definite or probable ST was numerically lower in Xience V/Promus EES, although it was not significant (Cypher SES, 1.9%; Xience V/Promus EES, 1.4%; \( P = .52 \)). The SORT-OUT 4 single-blind, RCT of Xience V/Promus EES versus Cypher SES in an all-comers population of 2,774 patients demonstrated noninferiority of Xience V/Promus EES to Cypher SES in the combined primary endpoint of major adverse cardiac events (MACE) (Cypher SES, 5.2%; Xience V/Promus EES, 4.9%; \( P = .01 \) for noninferiority). The individual components of the combined endpoint were not significantly different between groups, with the exception of definite ST, which was significantly lower in Xience V/Promus EES (Xience V/Promus EES, 0.1%; Cypher SES, 0.7%; \( P = .05 \)).

Lastly, the EXCELLENT study was a prospective, open-label, 2 x 2 RCT comparing Xience V/Promus EES to Cypher SES, as well as comparing 6 months to 1 year of dual-antiplatelet therapy. In the EXCELLENT study, 1,443 patients with native coronary stenoses > 50% and evidence of myocardial ischemia were randomized 3:1 to Xience V/Promus EES or Cypher SES. In an analysis pooling subgroups treated with 6 months versus 1 year of dual-antiplatelet therapy and comparing Xience V/Promus EES to Cypher SES, Xience V/Promus EES was noninferior to Cypher SES in the primary endpoint of in-segment loss at 9 months (Xience V/Promus EES, 0.1 ± 0.36 mm; Cypher SES, 0.05 ± 0.34 mm; \( P = .023 \) for noninferiority). Consistent with the SORT-OUT 4 and ISAR-TEST 4 studies, definite or probable ST was numerically lower in the Xience V/Promus EES group (Xience V/Promus EES, 0.4%; Cypher SES, 0.8%; \( P = .281 \)), although it was not significant.

Compared to first-generation PES/SES, the EES was designed with thinner cobalt chromium (CoCr) struts with open-cell geometry, a biocompatible polyvinylidene fluoride–based durable polymer, and the -limus analogue everolimus in a low total dose eluted 80% over 28 days.1 It is intriguing to speculate on whether it is one of these features alone or the combination of all three that has resulted in a large and consistent body of clinical data suggesting that EES represent a true advance over first-generation DES—with equivalent or improved efficacy and improved safety.

**NEW STENT SCAFFOLDS: IS THINNER SAFER?**

Stent scaffold design variables (such as material, cell length, cell pattern, and strut thickness) continue to have a key role in determining performance, including deliverability, side branch access, and in DES, the surface area for drug delivery. Preclinical and observational evidence also suggests that thinner struts may reduce restenosis and facilitate endothelialization.5-7 To allow for adequate radial strength and low recoil while reducing strut thickness, many platform designs have moved from stainless steel to CoCr or platinum chromium (PtCr).

By virtue of its density, the struts of the PtCr platform are among the thinnest of any current DES. The Ion PES (Boston Scientific Corporation) was recently approved based on the results of the PERSEUS Workhorse8 and Small Vessel9 studies. PERSEUS Workhorse was a prospective 3:1 RCT comparing the Ion PES to the Taxus Express PES in de novo coronary lesions. The Ion PES was noninferior to Taxus Express PES in the primary endpoint of 12-month TLF (Ion PES, 5.57%; Taxus Express PES, 6.14%; Bayesian probability for noninferiority, 0.9996). No differences in 12-month clinical outcomes were observed. The PERSEUS Small Vessel (2.25–2.75 mm) study was a single-arm trial comparing Ion PES to a lesion-matched historical cohort treated with bare-metal stent (BMS). The primary 9-month angiographic late loss endpoint favored Ion PES (0.38 ± 0.51 mm vs 0.80 ± 0.53 mm; \( P < .001 \)). Conclusions on rare safety endpoints such as ST, MI, and death were limited by study size and follow-up duration.

The PtCr scaffold has also been developed with everolimus (Promus Element, Boston Scientific Corporation). In the PLATINUM study10 1,530 patients undergoing percutaneous coronary intervention of de novo native coronary lesions were randomized 1:1 to Xience V EES versus Promus Element EES. The primary endpoint of 12-month TLF was not significantly different between groups (Xience V EES, 2.9% vs Promus Element EES, 3.4%; \( P = .001 \) for noninferiority), with no significant differences in cardiac death, MI, or ST at 12 months. Whether there is a benefit to reducing strut thickness of DES even further than that achievable with CoCr and PtCr remains unclear.
POLYMER

Polymer allows drug loading onto polished metal stent platforms and also provides control of drug elution. Unintended consequences\(^{11-13}\) reported with durable polymer include inflammatory and allergic reactions, incomplete endothelialization, and inhibition of recovery of normal endothelial function, with concerns that such observations relate to long-term DES safety and ST. New DES design changes include use of more biocompatible durable polymers, bioabsorbable polymers with less blood exposure, and polymer-free drug delivery systems.

The zotarolimus-eluting stent (ZES) (Endeavor, Medtronic, Inc., Minneapolis, MN) was the first DES available in the United States to use the highly biocompatible, durable phosphorylcholine polymer on a CoCr platform. A meta-analysis of ZES compared to BMS showed comparable ST rates over more than 3 years of follow-up.\(^{14}\) Late lumen loss, however, was not noninferior to either first-generation Taxus PES\(^{15}\) or Cypher SES.\(^{16}\)

To improve late lumen loss, the polymer was changed to a blend of three separate durable polymers (BioLinx, Medtronic, Inc.) with differing hydrophobicities, allowing for more sustained drug release past 120 days. Using the same platform, drug, and dose of drug, the shift from Endeavor ZES to Resolute ZES (Endeavor Resolute stent, Medtronic, Inc.) was exclusive to the polymer and the kinetics of drug delivery.

In the RESOLUTE US single-arm study\(^{17}\) of 1,402 patients with de novo coronary lesions treated with Resolute ZES, the primary endpoint of 12-month TLF was numerically lower in the Resolute ZES group than in propensity score–matched historical cohorts treated with the Endeavor ZES (Resolute ZES, 3.7%; Endeavor ZES, 6.5%; \(P < .001\) noninferiority). In the RESOLUTE all-comers study,\(^{18}\) patients were randomized 1:1 to treatment with Resolute ZES or Xience V/Promus EES. The composite primary endpoint of death, MI, and revascularization did not differ between groups (Resolute ZES, 20.6%; Xience V/Promus EES, 20.5%; \(P = .958\)) at 2 years. ST rates, while not significantly different, were almost 50% lower in the Xience V/Promus EES group (Resolute ZES, 1.9%; Xience V/Promus EES, 1% \(P = .077\)). As seen in the transition from Endeavor ZES to Resolute ZES, efficacy can clearly be altered by changing drug-elution kinetics. Whether this change results in new residual safety concerns remains controversial.

Shifts away from durable polymers include attempts to minimize polymer exposure by using more directed coatings and bioabsorbable substrates. The BioMatrix Flex biolimus-eluting stent (BES) (Biosensors International, Singapore) employs a polylactic acid (PLA) polymer applied to the abluminal surface. PLA is degraded to lactic acid over approximately 6 months, leaving only the BMS scaffold. Loaded with the novel limus analogue Biolimus A9 on a stainless steel platform, this DES was tested against Cypher SES in the LEADERS study,\(^{19}\) a prospective 1:1 RCT of 1,707 all-comers patients. The 9-month primary endpoint of cardiac death, MI, or TVR showed BioMatrix BES was noninferior to Cypher SES with numerical superiority (BioMatrix BES, 9%; Cypher SES, 11%; \(P = .003\) for noninferiority). At 3-year follow-up,\(^{20}\) major adverse cardiac events trended in favor of BioMatrix BES (BioMatrix BES, 15.7%; Cypher SES, 19%; \(P = .09\)), and ST numerically favored BioMatrix BES but was not significant (BioMatrix BES, 2.2%; Cypher SES, 2.9%; \(P = .43\)). Head-to-head RCTs against second-generation DES, such as Xience V/Promus EES, have not been reported.
Although the shift to reduced exposure of a biodegradable polymer in combination with the drug biolimus appears to preserve efficacy, the intuitive potential safety advantage relative to a durable polymer remains unproven.

Attempts to eliminate polymer altogether include the use of surface texturing to create microcavities that retain drug applied directly to the metal platform. The BioFreedom BES (Biosensors International) uses such an etched stainless steel scaffold loaded with Biolimus A9. Drug tends to elute in a rapid burst because control of kinetics without polymer is challenging. Animal studies with BioFreedom BES indicate that > 95% of biolimus is eluted from the stent within 28 days. Human data so far are limited, with first-in-man reports of small cohorts showing encouraging late loss compared to PES. Safety events and clinical outcomes in these small cohorts are not interpretable. Thus, whether a polymer-free design with burst drug delivery is safer than a durable biocompatible or bioabsorbable polymer design remains to be seen.

**NOVEL APPROACHES**

Two novel stent designs with potentially revolutionary safety implications include completely bioresorbable stents and stents using endothelial progenitor cell (EPC) capture technology. The BVS is an EES with a scaffold platform (Abbott Vascular) that consists of a poly-L-lactide backbone coated with poly-D,L-lactide polymer controlling drug release. In the ABSORB cohort A study, 3-year follow-up of 30 patients implanted with BVS showed no ST, but the late loss rate at 6 months was 0.44 mm, leading to a scaffold redesign allowing for more uniform strut distribution (Figure 2). In the ABSORB cohort B study, the redesigned BVS tested in 101 patients with de novo coronary lesions displayed a 6-month angiographic late loss rate of 0.19 mm in 45 patients, comparable to the Xience/Promus EES benchmark. No ST has been reported, but the cohort size is too small to draw meaningful conclusions. Whether treatment with BVS results in restoration of normal endothelial function compared to permanent metal scaffolds, and whether this translates into improved long-term safety, will require further study.

Recruiting circulating EPCs to more quickly and completely cover stent struts has two potential mechanistic benefits: (1) downregulation of inflammatory mitotic triggers resulting in lower restenosis and (2) removing the nidus for ST. Local drug toxicity could result from interaction of the dose-response relationship and settings such as overlapping stents or use of the bifurcation crush technique, which double and triple the local dose of drug, respectively. Paclitaxel, with its steep dose-response curve, was likely one factor leading to the relabeling of Taxus PES with cautions for overlapping stents—required by the FDA on the basis of safety event rates seen in TAXUS V. Conversely, the low drug load in EES platforms may promote device safety. Two new molecular entities in DES, zotarolimus and biolimus, each have notable features. Zotarolimus in the same dose but with longer delivery kinetics significantly improved late lumen loss, as seen in the case of Endeavor ZES and Resolute ZES. Biolimus is the most lipophilic of the -limus analogues and may behave differently in burst delivery systems, such as the polymer-free BioFreedom BES. Whether either of these agents contributes to improved safety remains to be seen.

**Figure 3. Endothelial progenitor cell capture on the Genous R stent.**
four-component DES—employing drug, polymer, scaffold, and antibody. Whether more rapid and complete endothelial coverage in this construct will translate into superior early or late safety and ST represents an interesting horizon.

CONCLUSION

Safety concerns with first-generation Taxus PES and Cypher SES include rare but catastrophic events, such as ST. With second-generation CoCr scaffold Endeavor ZES and Xience/Promus EES and using durable biocompatible polymer, safety has significantly improved. Demonstrating even further benefit of new, safety-oriented modifications will require larger cohorts of more complex patients and lesions followed over longer periods of time. Nonetheless, DES are implanted in more than 1 million patients annually and innovative improvements in scaffolds, polymers, and drugs (and their combinations) continue. Proof of the role of even thinner struts, reduced polymer exposure, bioabsorbable polymers, polymer-free designs, lower drug doses, bioreabsorbable platforms, and EPC capture and strut coverage in promoting safety remains an exciting, complex, and challenging arena of clinical investigation.

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