

Everolimus-eluting stent platforms in percutaneous coronary intervention: comparative effectiveness and outcomes

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Abstract: Despite the remarkable benefits obtained following the introduction of the first-generation drug-eluting stent (DES), concerns were raised over its long-term safety, particularly with regard to very late (beyond 1 year) stent thrombosis. Newer-generation DESs have been developed to overcome this limitation using novel stent platforms, new drugs, more biocompatible durable polymers, and bioabsorbable polymers or backbones. To date, newer-generation DESs have virtually replaced the use of first-generation DESs worldwide. In this review article, we discuss in detail the design, pharmacology, and mechanism of action of the newer-generation permanent and bioresorbable everolimus-eluting platforms. Furthermore, we present and evaluate the current evidence on the performance and safety of these devices compared to those of other available stent platforms.

Keywords: PCI, angioplasty, stent, outcome

Introduction

Percutaneous coronary intervention (PCI) has revolutionized the treatment of obstructive coronary atherosclerotic disease. Since the first case of PCI performed by Gruentzig in 1977, it has become one of the commonest procedures in medicine.¹ Despite the initial favorable outcomes, plain old balloon angioplasty (POBA) was limited by frequently occurring procedural complications, including vessel dissection, restenosis, recoil, and thrombosis. The most fearsome complication, however, was abrupt vessel closure, secondary to acute elastic recoil and plaque dissection at the site of intervention.² In 1978, Julio Palmaz developed the concept of a metal sleeve that could be placed on top of the balloon, carried to the site, and deployed by balloon expansion to support the walls of the artery, thus preventing recoil and lumen impairment. The first-in-human case to receive a Palmaz stent was reported from Sao Paulo, Brazil, in December 1987, and 7 years later, the first randomized trials demonstrated reduced revascularization and lower rates of restenosis at 6-month follow-up in the bare-metal stent (BMS) group compared to the POBA group.^{3,4}

In 2002–2003, the regulatory authorities in Europe and the USA approved drug-eluting stents (DESs) after landmark trials demonstrated significant reduction of restenosis compared with BMSs.⁵ The three fundamental stent components include the stent platform, the polymer, and the antiproliferative drug. The paclitaxel (TAXUS; Boston Scientific, Natick, MA, USA) and sirolimus (Cypher; Cordis, Johnson and Johnson Company, Warren, NJ, USA)-eluting stents (PESs and SESs, respectively) were the first DESs to be widely used. PES comprised a 316L stainless steel scaffold coated with a nonerodible biocompatible polyolefin matrix containing paclitaxel,

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an antimitotic microtubule inhibitor that halts cell division in neoplastic diseases. The SES was also made of 316L stainless steel and a permanent nonerodible polymer that was eluting sirolimus, a macrocyclic lactone produced by *Streptomyces hygroscopicus*, used in renal transplantation as immunosuppressant. Despite their widespread application, delayed healing and hypersensitivity reactions have been described in human postmortem examinations with both stents.⁶ In an attempt to increase their radial strength, these first-generation platforms were characterized by increased strut thickness (~150 µm) and width, thus reducing their flexibility and conformability. As a consequence, implantation of longer stents in distal lesions and tortuous vessels was a particularly challenging task. Stent fractures were also not an uncommon encounter, particularly when these first-generation stents were implanted at flexing points.

Design, pharmacology, and mechanism of action of everolimus-eluting stent platforms

Stent platform

Notable developments in stent platforms, including design, structure, and material composition, have resulted in major technical advances and associated beneficial clinical outcomes. The ideal stent characteristics include 1) good deliverability; 2) excellent conformability – the stent can adopt the curvature of the vessel; 3) increased radiopacity, which enables optimal implantation of overlapping stents and optimal stent positioning (particularly when treating bifurcations or ostial lesions); 4) high radial strength to prevent reflex vascular recoil; and 5) thin-strutted structure, which reduces vascular injury and minimizes the risk for late or very late stent thrombosis (ST).⁷ Bioresorbable polymers or even whole-stent platforms are desirable as, in theory, would eliminate very late ST and restore vasomotion while providing temporary vessel scaffolding to prevent recoil.⁸

The use of cobalt–chromium (CoCr) alloys in the formation of stent platforms (Xience–Vision and Multilink 8 platforms; Abbott Vascular, Santa Clara, CA, USA) allowed the reduction in strut thickness to 80–90 µm, with modest improvement in radiopacity and conformability. The increased elastic properties of CoCr, however, occur at a cost of greater recoil when compared with 316L stainless steel stents.⁹ Platinum–chromium (PtCr) alloys, consisting of at least 33% platinum (Pt), represent an attractive alternative compound given their unique properties, including biocompatibility, radiopacity, chemical stability, corrosion resistance, and radial strength. The amalgamation of chromium (Cr)

and Pt in a single alloy compound, as in the Element/Omega and Promus Premier (Boston Scientific) stent platforms,^{10–12} yielded a significant increase in radial strength and durability, allowing a subsequent reduction in strut thickness (down to 74 µm in the SYNERGY stent) while maintaining radial strength and providing improved radiopacity compared to stainless steel and CoCr alloys.⁹

Contrary to the Xience and the Promus stents, the Absorb everolimus-eluting platform (Abbott Vascular) comprises a bioresorbable scaffold (BRS) that enables vasomotion, expansive remodeling, and restoration of the vessel lumen after the dissolution of the scaffold. The scaffold consists mainly of poly-L-lactic acid (PLLA), which disappears with hydrolysis within 3 years after implantation. The scaffold coating is also bioresorbable, consisting of a 1:1 mixture of an amorphous matrix of poly-D,L-lactide and the antiproliferative drug everolimus. Because the PLLA lacks radiopaque properties, a pair of radiopaque Pt markers was placed at the proximal and distal ends of the scaffold.¹³

Everolimus as antiproliferative agent: mechanism of action

In-stent restenosis (ISR) represents the main limitation of BMSs and is secondary to neointimal hyperplasia occurring in response to local arterial injury from the PCI. Balloon- and stent-related arterial wall injury initiates a cascade of vascular healing, which includes activation, proliferation, and migration of vascular smooth muscle cells, as well as increased production of extracellular matrix components.¹⁴ The presence of a foreign body, as the stent struts, prompts an excessive healing response, resulting in neointimal hyperplasia. Therefore, antiproliferative agents that safely inhibit vascular smooth muscle cell proliferation underlie the rationale and goal of DESs currently used in clinical practice.¹⁵ Two classes of antiproliferative agents have proven successful in preventing neointimal hyperplasia and ISR: paclitaxel and the rapamycin analogs (including sirolimus, everolimus, zotarolimus, and biolimus). In addition to their antiproliferative properties, these agents have different properties (eg, hydrophilicity), which may affect their clinical efficacy. For the purposes of our review, we will only focus our description on everolimus, a rapamycin analog.

Everolimus (SDZ-RAD) is a synthetic analog of sirolimus (40-*O*-(2-hydroethyl)-rapamycin), which was initially developed to inhibit rejection of transplanted organs. The FK506-binding protein/rapamycin complex binds to a specific cell cycle-regulatory protein, the mammalian target of rapamycin (mTOR), and inhibits its activation. TOR is a

member of the phosphatidylinositol 3-kinase-related protein kinase family, which is involved with critical steps of the cell cycle, including checkpoints that govern DNA damage and repair.¹⁶ mTOR phosphorylates the phosphorylated heat-stable and acid-stable protein (Phas-1), which is a translational repressor that binds to eukaryotic translation initiation factor-4E-binding protein-1 (eIF4EBP1). This process releases the eukaryotic initiation factor eIF4F for initiation of protein translation. mTOR also stimulates p70s6k mitogen-stimulated kinase, which promotes cell cycle protein synthesis.¹⁵ Everolimus acts as an inhibitor of cellular proliferation, intervening at the late G1 phase of the cell cycle and preventing the cells from entering the S (proliferation) phase.¹⁷ Thus, its immunosuppressive potential relies on preventing lymphocyte and smooth muscle cell proliferation mediated by inflammatory cytokines and growth factors. To date, it has been successfully used in combination with multiple drugs to prevent rejection in heart transplant recipients and in reduction of the severity and incidence of cardiac allograft vasculopathy.¹⁸ A stent-based delivery of everolimus was found to selectively clear macrophages in rabbit atherosclerotic plaques by autophagy, an mTOR inhibition-dependent and novel mechanism to induce cell death in mammalian cells.¹⁹ Due to its molecular and chemical structure, the lipophilic properties of everolimus are increased compared to sirolimus, leading to a more rapid absorption into the arterial wall.²⁰

Kinetics of drug release

Local delivery, modulated release, and absorption of everolimus by the arterial wall are key steps in the

inhibition of neointimal hyperplasia. Drug release kinetics is a critical component of device efficacy and safety in terms of preventing recurrent adverse events. Invariably, antiproliferative agents are coupled to a matrix polymer that acts as a reservoir to ensure uniform distribution and drug retention during deployment. The polymer type, composition, and design define the kinetics of drug release following stent implantation for a period that ranges from weeks to months. First-generation DESs contained synthetic nonresorbable (permanent or durable) polymers, such as poly-*n*-butyl methacrylate and polyethylene vinyl acetate with sirolimus and a poly(styrene-*b*-isobutylene-*b*-styrene) copolymer with paclitaxel,²¹ which were subsequently associated with adverse allergic reactions, delayed healing, and incomplete endothelialization, thus increasing the risk for late and very late ST compared to BMSs.^{22–24} Hence, research has been directed toward the modification of polymers aiming at improvement of long-term DES safety. The target of further development has been 1) the reduction of the total polymer mass on the stent (eg, polymer thickness of 12.6 μ m for the first-generation Cypher vs 7.0 μ m for the Promus Element vs 4 μ m for the SYNERGY, with no polymer for the Cre8); 2) selective application of the polymer on the abluminal stent area, which allows rapid endothelialization of the luminal segment, avoiding excessive neointimal proliferation on the abluminal side; 3) increased biocompatibility and the advent of an everolimus-eluting stent (EES) with bioresorbable polymer (SYNERGY stent, Boston Scientific); Table 1 shows the comparison of different commercially available EES platforms.

Table 1 Comparison of different commercially available everolimus-eluting stents

Stents	Xience V	Xience PRIME/ Xience Xpedition	Promus Element	Promus Premier	SYNERGY	Absorb
Stent platform	Vision: CoCr	Multilink-8: CoCr	Element: PtCr	Promus Premier: PtCr	Element: PtCr	PLLA, based on Multilink-8
Strut thickness	81 μ m	81 μ m	81 μ m	81 μ m	74 μ m	158 μ m
Connectors between hoops	3	3	2	2 (4 between the 3 proximal hoops)	2	3
Polymer	Primer layer PBMA Drug matrix layer A semicrystalline random copolymer: PVDF-HFP	Primer layer PBMA Drug matrix layer A semicrystalline random copolymer: PVDF-HFP	Primer layer PBMA Drug matrix layer A semicrystalline random copolymer: PVDF-HFP	Primer layer PBMA Drug matrix layer A semicrystalline random copolymer: PVDF-HFP	PLGA	PDLLA
Manufacturer	Abbott Vascular, Santa Clara, CA, USA	Abbott Vascular, Santa Clara, CA, USA	Boston Scientific, Natick, MA, USA	Boston Scientific, Natick, MA, USA	Boston Scientific, Natick, MA, USA	Abbott Vascular, Santa Clara, CA, USA

Abbreviations: CoCr, cobalt–chromium; PBMA, poly(*n*-butyl methacrylate); PDLLA, Poly D, L lactide; PLGA, poly(D,L-lactide-co-glycolide); PLLA, poly-L-lactic acid; PtCr, platinum–chromium; PVDF-HFP, poly(vinylidene fluoride-co-hexafluoropropylene).

Comparative efficacy and safety of EESs

Preclinical trials

Everolimus has been effective in reducing neointimal hyperplasia in a rabbit's iliac artery model when administered orally.²⁵ After implantation of a Vision BMS, oral everolimus (1.5 mg/kg the day before, followed by 0.75 mg/kg/day for 28 days) reduced neointimal thickness from 0.12 ± 0.03 mm to 0.07 ± 0.03 mm ($P=0.005$). After 28 days, 86.7% of the luminal stent surface was endothelialized in the everolimus-treated animals (96.8% in the control ones, $P<0.006$).²⁶ Similar results were observed after 28 days in a porcine model comparing the EES with the Multi-link Vision BMS and the Cypher SES. Results were similar between EES and SES.²⁵

BMSs versus EESs

Everolimus has been previously tested in the PLLA-coated stainless steel S-stent (Biosensors International, Singapore), which was effective in the first human experience with EES stents for the treatment of coronary lesions (FUTURE I Trial) of 42 patients randomized in a 2:1 analogy to EES ($n=27$) vs BMS ($n=15$). Patients with recent myocardial infarction (MI), diabetes, left main coronary artery disease, ostial lesions, bifurcation lesions, or presence of thrombus were excluded. The 6-month late lumen loss (LLL) was significantly reduced in the EES group; EES: 0.10 mm vs BMS: 0.85 mm ($P<0.001$).^{27,28} There was a 70% release of the $197 \mu\text{g}/\text{cm}^2$ everolimus within 30 days and 85% within 90 days. A pooled analysis of 106 patients enrolled in both FUTURE I and its expanded sequel FUTURE II clinical trials demonstrated the beneficial effect of EES regardless of vessel size.²⁹

In the SPIRIT I trial, which was the first-in-human study of the CoCr EES (Xience V), 60 people in nine centers in Europe were randomly assigned to either Multi-link Vision BMS ($n=32$) or Xience V EES ($n=28$).³⁰ The study included patients with either unstable angina or silent ischemia presenting with a single de novo significant lesion (50%–99%), in vessels with a reference diameter of 3.0 mm that could be covered by a single stent of 18 mm length. Patients with ongoing MI, unprotected left main coronary artery disease, ostial lesions, lesions within 2 mm from a bifurcation, moderate-to-severe calcification, angiographically visible thrombus, and left ventricular ejection fraction (LVEF) $<30\%$ were excluded. At 6 months follow-up, LLL (0.10 ± 0.21 mm vs 0.87 ± 0.37 mm, $P<0.001$), diameter stenosis ($16 \pm 8\%$ vs $39 \pm 14\%$, $P<0.001$), and binary angiographic stenosis (0% vs 25.9%, $P<0.05$) were all reduced within the EES group.^{30–32} At 6 months and

2 years,³² there were no statistically significant differences in clinical outcomes, although the study was only powered for angiographic outcomes. No cases of ST were observed.

More recently, in the Xience or Vision Stents for the Management of Angina in the Elderly (XIMA) multicenter randomized trial,³³ a total of 800 patients were randomized to BMS ($n=401$) or EES ($n=399$) for treatment of stable angina (32%) or acute coronary syndrome (ACS) (68%). Rates of dual antiplatelet therapy (DAT) at 1 year were 32.2% for patients in the BMS group and 94.0% for patients in the EES group. The primary end point occurred in 18.7% of patients in the BMS group versus 14.3% of patients in the EES group ($P=0.09$). There was no difference in all-cause mortality (7.2% vs 8.5%; $P=0.50$), major hemorrhage (1.7% vs 2.3%; $P=0.61$), or cerebrovascular accident (1.2% vs 1.5%; $P=0.77$). MI (8.7% vs 4.3%; $P=0.01$) and target vessel revascularization (TVR, 7.0% vs 2.0%; $P=0.001$) occurred more often in patients in the BMS group. The randomized Everolimus-Eluting Stents Versus Bare-Metal Stents in ST-Segment Elevation Myocardial Infarction (EXAMINATION) trial,³⁴ comparing 1,498 ST-elevation MI (STEMI) patients receiving either EES ($n=751$) or BMS ($n=747$), demonstrated significantly lower rates of target lesion revascularization (TLR; 2.9% vs 5.6%; $P=0.009$) and definite ST (0.8% vs 2.1%; $P=0.03$) at 2 years in the EES group versus the BMS group. In the Basel Stent Kosten Effektivitäts Trial PROspective Validation Examination (BASKET-PROVE) multicenter, randomized trial,³⁵ 2,314 patients, with lesions needing stents at least 3.0 mm in diameter, were randomly assigned to receive CoCr EES (Xience V, $n=774$), SES (Cypher Select, $n=775$), or the CoCr (Vision, $n=765$) BMS. At 2 years of follow-up, no significant differences in cardiac death or nonfatal MI were observed with EES (2.6%), SES (3.2%), and BMS (4.8%) ($P_{\text{logrank}}=0.06$). TVR was similar between EES and SES groups but significantly lower than in the BMS group (EES: 3.1%, SES: 3.7%, BMS: 8.9%; $P_{\text{logrank}}<0.001$). Ergo, the EES proved to be beneficial, even in high-caliber arteries with low rates of restenosis after bare-metal stenting. The superiority of EES over BMS was also shown in a recent meta-analysis,³⁶ which showed hazard ratios (HRs) of 0.67 (0.49–0.91), 0.71 (0.55–0.92), 0.42 (0.22–0.78), and 0.29 (0.20–0.42) for cardiac death, MI, definite ST, and TVR, respectively.

EESs versus PESs

The SPIRIT II trial was a multicenter, multinational trial that was conducted in 28 centers of Europe, India, and New Zealand. The trial randomized 300 patients in a 3:1 ratio to Xience V EES ($n=223$) vs Taxus PES ($n=77$). The primary end point was once

again angiographically defined LLL at 6-month follow-up. In contrast to the SPIRIT I trial, the protocol of the study was not as restrictive, allowing for patients with more complex disease to be included: patients could present with two separate de novo lesions in two different vessels with reference vessel diameters ranging between 2.5 mm and 4.25 mm, whereas the maximum lesion length was not to exceed 28 mm. Once again, patients presenting with acute MI, LVEF <30%, aorto-ostial or left main coronary artery lesions, heavy calcifications, and visible thrombus in the angiogram were excluded from the study.³⁷ The trial was powered to demonstrate noninferiority of EES relative to PES. At 6 months, the in-stent LLL was 0.11 ± 0.27 mm in the EES arm, as compared to 0.36 ± 0.39 mm in the PES arm ($P < 0.001$).³⁷ The 5-year clinical follow-up was completed in 244 patients (81%).³⁸ At 5-year follow-up, 19.5% of patients were on thienopyridine in the EES arm, compared to 30.5% in the PES arm. Cardiac mortality was significantly lower in the EES group than in the PES group (1.5% vs 7.3%; $P = 0.015$). There was a trend toward lower cardiac death and MI (4.8% vs 11.4%) and lower ischemia-driven (ID) TLR (ID-TLR; 4.7% vs 9.4%) with EES than with PES. Hence, there was a reduction in ID major adverse cardiovascular events (MACEs) for EES vs PES (ID-MACE: 8.0% vs 18.1%; $P = 0.018$). In addition, the Academic Research Consortium-defined ST rate was numerically lower in the EES group compared to the PES group (0.9% vs 2.8%).

The SPIRIT III trial^{39,40} was exclusively conducted in US centers, enrolling 1,002 patients, randomized in a 2:1 ratio into the EES study group (Xience V, $n = 669$) vs PES group (Taxus, $n = 333$). The inclusion criteria were similar to those of SPIRIT II. Similarly, the primary end point was mainly angiographic, namely LLL at 8 months, which was significantly less in the EES group compared with that in the PES group (0.14 ± 0.41 mm vs 0.28 ± 0.48 mm; $P = 0.004$). EES was noninferior to PES with regard to target vessel failure (TVF) at 9 months (7.2% vs 9.0%, respectively; $P_{\text{noninferiority}} < 0.001$). At 5 years,⁴⁰ TVF was reduced in the EES group (19.3% vs 24.5%; $P = 0.05$). Furthermore, MACEs were significantly reduced among patients treated with EES vs those on PES at 9 months (4.6% vs 8.1%; $P = 0.03$), 1 year (6.0% vs 10.3%; $P = 0.02$), and 5 years (13.2% vs 20.7%; $P = 0.007$), due to the occurrence of fewer MIs and TLRs.

In the large SPIRIT IV trial,⁴¹ 3,687 patients with stable coronary artery disease were enrolled. Patients underwent PCI for up to three distinct lesions. SPIRIT IV was a pivotal study for US Food and Drug Administration approval of the EES, which randomly assigned patients to receive either EES or PES. Despite the broader inclusion criteria than

studies for first-generation DES approval, patients with ACSs, visible thrombus, chronic occlusions, vein graft lesions, and true bifurcation lesions were excluded. At 1 year, the primary end point target lesion failure (TLF), defined as a composite of cardiac death, target vessel MI, or ID-TLR, was significantly lower with EES than with PES (3.9% vs 6.6%; $P < 0.001$). Rates of postprocedure adverse events, such as ST (0.3% vs 1.1%; $P = 0.003$), MI (1.9% vs 3.1%; $P = 0.02$), and TLR (2.3% vs 4.5%; $P < 0.001$), were also lower with EES than with PES. Of interest, in a subgroup analysis of diabetic patients, no significant difference was observed in 1-year TLF rates (6.4% vs 6.9%; $P = 0.080$), suggesting that the mechanisms of restenosis or the response to antiproliferative agents may vary in diabetic patients. The 3-year follow-up results of the SPIRIT IV study were particularly encouraging because they demonstrated sustained reductions in TLF, MI, and ST in the EES arm.⁴² More importantly, at 3 years, both all-cause mortality (3.2% vs 5.1%; $P = 0.02$) and the composite of death/MI (5.9% vs 9.1%; $P = 0.001$) were reduced with EES compared to the outcomes with PES use.

The SPIRIT trials were subsequently complemented by the All-comers Everolimus-Eluting Stents and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice (COMPARE) trial,⁴³ which enrolled 1,800 patients who were subsequently randomly assigned to EES ($n = 897$, Xience V) vs PES ($n = 903$, Taxus Liberté). The primary end point, MACE, defined as a composite of death, MI, or TVR was lower with EES compared with PES at 1 year (6.2% vs 9.1%; $P = 0.02$), equally driven by reductions in ST (0.7% vs 2.6%; $P = 0.002$), MI (2.8% vs 5.4%; $P = 0.007$), and TLR (1.7% vs 4.8%; $P < 0.001$).^{43,44} The EES group maintained the significantly reduced MACE rates at 2-year follow up (9% vs 13.7%; $P = 0.002$).

EESs versus zotarolimus-eluting stents

In the 2-year follow up of the The Real-World Endeavor Resolute Versus Xience V Drug-Eluting Stent Study in Twente (TWENTE) trial,⁴⁵ a randomized study assigning all-comers to zotarolimus-eluting stent (ZES; Endeavor Resolute; Medtronic Vascular, Santa Rosa, CA, USA; $n = 697$) vs EES (Xience V, $n = 694$), there was no significant difference in the composite end point of TVF (cardiac death, target vessel MI, or TVR) in the two groups (ZES 10.5% vs EES 9.8%; $P = 0.65$), although there were fewer TLRs in the EES group (ZES 2.6% vs EES 4.9%; $P = 0.03$). Of note, only 5.4% of patients were still on DAT past the first 12 months.

In the DUTCH PEERS⁴⁶ multicenter, randomized study in the Netherlands, 1,811 all-comer patients were randomly

assigned in a 1:1 ratio to receive either CoCr ZES (Resolute Integrity; Medtronic) or PtCr EES (Promus Element; Boston Scientific). The primary end point of TVF was a composite of safety (cardiac death or target vessel-related MI) and efficacy (TVR) at 12 months, analyzed by intention to treat (with a noninferiority margin of 3%–6%). The primary end point occurred in 55 (6%) of 905 patients in the ZES group and 47 (5%) of 905 in the EES group ($P_{\text{noninferiority}}=0.006$). We noted no significant between-group differences in individual components of the primary end point. Definite ST occurred in three (0.3%) patients in the ZES group and six (0.7%) patients in the EES group ($P=0.34$). Longitudinal stent deformation was seen only in the Promus Element EES group (9 [1.0%] of 905 EES patients vs 0 of 905 ZES patients; $P=0.002$; nine of 1,591 [0.6%] EESs implanted became deformed), but this was not associated with any adverse events.

In another multicenter Randomized Comparison of a Zotarolimus-Eluting Stent With an Everolimus-Eluting Stent for Percutaneous Coronary Intervention (RESOLUTE All-comers) noninferiority all-comers (excluding only STEMI) trial, Serruys et al⁴⁷ demonstrated no difference in 12-month TLF (cardiac death, target vessel MI, TLR) in 2,992 patients, with 66.3% off-label indications, randomized to either ZES (n=1,140) or EES (n=1,152) PCI (ZES: 8.2%, EES: 8.3%; $P_{\text{noninferiority}} < 0.001$). At 4-year follow-up, the rates of TVF (15.2% vs 14.6%; $P=0.68$), cardiac death (5.4% vs 4.7%; $P=0.44$), target vessel MI (5.3% vs 5.4%; $P=1.00$), clinically indicated TLR (7.0% vs 6.5%; $P=0.62$), and definite/probable ST (2.3% vs 1.6%; $P=0.23$) were similar with the Resolute ZES (R-ZES) and EES.

In a recent propensity-matched study of 400 diabetic patients, Miyazaki et al⁴⁸ showed no significant differences in MACE (death, MI, and TVR) in all-comer diabetics treated with R-ZES (n=128) or EES (n=128) (ZES: 20.9% vs EES: 25.3%; $P=0.47$). In a recent meta-analysis by Piccolo et al⁴⁹ comparing the R-ZES and EES (five trials that included a total of 9,899 patients), similar risks in TVR, definite ST, cardiac death, and target vessel MI were shown. Compared with EES, R-ZES had similar risks of TVR (HR = 1.06; 95% confidence interval [CI]: 0.90 to 1.24; $P=0.50$), definite or probable ST (HR = 1.26; 95% CI: 0.86 to 1.85; $P=0.24$), cardiac death (HR = 1.01; 95% CI: 0.79 to 1.30; $P=0.91$), and target-vessel MI (relative risk [RR]: 1.10; 95% CI: 0.89 to 1.36; $P=0.39$).

EES versus SESs

Although randomized trials between EES and PES have shown overall favorable results for EES, fewer clinically apparent differences were evident when EES and SES

were compared. The All-comers Scandinavian Organization for Randomized Trials with Clinical Outcome IV (SORT OUT IV) trial⁵⁰ enrolled 2,774 patients randomly assigned to either EES (Xience V, n=1,390) or SES (Cypher Select Plus, n=1,384) and followed through the Danish Civil Registration System. At 9 months of follow-up, no significant differences were observed between the two groups in terms of MACE (EES: 4.9% vs SES: 5.2%; $P_{\text{noninferiority}}=0.01$), although definite ST occurred in fewer patients with EES compared with SES at both 9 months (0.1% vs 0.7%; $P=0.05$) and 18 months (0.2% vs 0.9%; $P=0.03$). Three Korean randomized controlled studies demonstrated a trend toward reduced LLL among patients treated with SES vs those treated with EES,^{51,52} whereas EES appeared to link to more favorable clinical outcomes among diabetics.⁵³

The multicenter Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) trial⁵² aimed to demonstrate the noninferiority of EES compared with SES in preventing LLL at 9 months. Patients with left main coronary artery disease, recent (<72 hours) MI, STEMI, cardiogenic shock, or LVEF <25% were excluded. A total of 1,443 patients undergoing PCI were randomized in a 3:1 ratio to receive EES (Xience V) or SES (Cypher Select). In-segment LLL at 9 months was 0.11 ± 0.38 mm and 0.06 ± 0.36 mm for EES and SES, respectively ($P_{\text{noninferiority}}=0.038$, using a noninferiority margin of 0.1 mm). Another randomized study from Korea, The Percutaneous Treatment of LONG Native Coronary Lesions With Drug-Eluting Stent-III (LONG-DES-III) trial,⁵¹ compared the use of long EES (Xience V/Promus) with SES (Cypher Select) in 450 patients with long (≥ 25 mm) native coronary lesions. The primary end point of the trial was in-segment LLL at 9-month angiographic follow-up. In-segment LLL between the EES group and the SES group was 0.08 mm (95% CI: 0.02 to 0.14), a result failing to show the noninferiority of the EES ($P_{\text{noninferiority}}=0.96$ using a margin of 0.1 mm) and instead demonstrating the statistical superiority of the SES ($P_{\text{superiority}}=0.042$).

The Everolimus-Eluting Stent Versus Sirolimus-Eluting Stent Implantation for De Novo Coronary Artery Disease in Patients with Diabetes Mellitus (ESSENCE-DIABETES) randomized study compared EES (n=149) and SES (n=151) implantation in diabetic patients. The primary end point was noninferiority of angiographic in-segment LLL at 8 months. EESs were noninferior to SESs in terms of 8-month in-segment LLL (0.23 ± 0.27 mm vs 0.37 ± 0.52 mm; difference: -0.13 mm; 95% CI: -0.25 to -0.02 ; upper one-sided 95% CI: -0.04 ; $P_{\text{noninferiority}} < 0.001$; $P_{\text{superiority}} = 0.02$).

In the recent BIOFLOW-II randomized controlled trial,⁵⁴ 452 patients were randomly assigned in a 2:1 ratio to treatment with the novel ultrathin strut, biodegradable polymer Orsiro (Biotronik, Bülach, Switzerland) O-SES (298 patients, 332 lesions) or Xience Prime X-EES (154 patients, 173 lesions) in a multicenter, noninferiority trial. The biodegradable polymer SES (Orsiro) is a novel DES consisting of an ultrathin (60 µm) CoCr L605 platform covered with an amorphous silicon carbide layer and releases sirolimus from a biodegradable PLLA polymer. In terms of the primary end point, in-stent LLL at 9 months, O-SES was noninferior to X-EES (0.10±0.32 mm vs 0.11±0.29 mm; difference =0.00063 mm; 95% CI: -0.06 to 0.07; $P_{\text{noninferiority}} < 0.0001$). Both groups showed similar rates of TLF at 1 year (O-SES: 6.5% vs X-EES: 8.0%; HR =0.82; 95% CI: 0.40 to 1.68; $P_{\text{log-rank}} = 0.58$) without cases of ST. In the much larger BIOSCIENCE trial,⁵⁵ 1,056 patients were randomized to CoCr EES and 2,119 to O-SES. At 12-month follow-up, there were no significant differences in the rates of TLF (cardiac death, MI, clinically indicated TLR): O-SES: 6.7% vs EES: 6.7% ($P = 0.950$).

In the multicenter Xience V stent vs Cypher stent in Primary PCI for Acute Myocardial Infarction (XAMI) trial,⁵⁶ 625 patients were randomized (2:1 ratio) to EES or SES. At 3-year follow-up, the primary end point (cardiac death, nonfatal MI, TVR) was 8.0% for EES and 10.5% for SES ($P = 0.30$). Cardiac death was low and comparable in both groups (EES: 2.5% vs SES: 2.7%; $P = 0.86$), as was definite/probable ST (EES: 2.3% vs SES 3.2%; $P = 0.60$). In the Randomized Comparison of Everolimus-Eluting Stents and Sirolimus-Eluting Stents in Patients With ST Elevation Myocardial Infarction (RACES-MI) trial,⁵⁷ 500 STEMI patients were randomized to EES or SES. No significant difference was observed between EES and SES in MACEs (16% vs 20.8%; $P = 0.17$), cardiac death (4.4% vs 5.6%; $P = 0.53$), recurrent MI (6.4% vs 10%; $P = 0.13$), and TVR (4.8% vs 4.8%; $P = 0.99$). However, EES was associated with a significant reduction in ST (1.6% vs 5.2%; $P = 0.035$).

A recent meta-analysis⁵⁸ of 14 randomized trials (n=13,434 patients) comparing EES vs SES using the longest available follow-up data revealed that EES was associated with significantly lower risk for definite ST (odds ratio [OR]: 0.66; 95% CI: 0.38 to 0.9), TLR (OR: 0.83; 95% CI: 0.7 to 0.98), and MACE (OR: 0.86; 95% CI: 0.76 to 0.96). The direction and magnitude of the effect beyond 1 year were comparable with those observed within 1 year.

Another meta-analysis of 13 randomized studies⁵⁹ (n=17,101 patients, weighted mean follow-up: 21.7 months)

revealed that EES significantly reduced ST (RR: 0.55; 95% CI: 0.38 to 0.78; $P = 0.001$) compared to non-EES stents, an association that was independent of follow-up time or DAT duration, but that was mainly driven by randomized studies comparing EES with PES.

PtCr EES trials

The randomized Prospective, Randomized, Multicenter Trial to Assess an Everolimus Eluting Coronary Stent System PROMUS Element for the Treatment of Up to Two de Novo Coronary Artery Lesions (PLATINUM) trial¹⁰ randomly assigned 1,530 patients undergoing PCI of one or two de novo native lesions to treatment with either the standard CoCr EES Xience V (n=762) or the new PtCr PROMUS Element (n=768) stent. The primary end point was the 12-month rate of TLF, the composite of target vessel cardiac death, target vessel MI, or ID-TLR. This occurred in 2.9% vs 3.4% of patients assigned to CoCr EES versus PtCr EES, respectively (difference: 0.5%; 95% CI: -1.3% to 2.3%; $P_{\text{noninferiority}} < 0.001$; $P_{\text{superiority}} = 0.60$), suggesting similar outcomes. The Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-Safety and Effectiveness of Drug-Eluting Stents and Antiplatelet Regimen (HOST ASSURE) trial⁶⁰ aimed to compare a PtCr EES (PROMUS element, Boston Scientific) to the CoCr-based ZES (Resolute; Medtronic, Minneapolis, MN, USA). At 1 year, TLF occurred in 2.9% and 2.9% of the PtCr-EES and CoCr-ZES groups, respectively ($P_{\text{superiority}} = 0.98$; $P_{\text{noninferiority}} = 0.02$). There were no significant differences in the individual components of TLF as well as in the patient-oriented clinical outcomes.

The recent EVOLVE II randomized trial⁶¹ assessed the safety and efficacy of a novel PtCr bioresorbable polymer-coated EES (SYNERGY stent, Boston Scientific) versus the PtCr PROMUS Element Plus. The primary end point of 12-month TLF was observed in 6.7% of SYNERGY- and 6.5% PROMUS Element Plus-treated subjects by intention to treat ($P_{\text{noninferiority}} = 0.0005$).

The PLATINUM China randomized clinical trial⁶² evaluated the safety and effectiveness of the PtCr PROMUS Element EES (Boston Scientific, Marlborough, MA, USA) and compared the 9-month LLL to PES (Taxus Liberté) (PtCr EES, n=373 vs PES, n=127, 3:1 randomization). Nine-month in-stent LLL was significantly lower in the PtCr EES group (PES: 0.40±0.45 mm vs PtCr EES: 0.11±0.36 mm; $P < 0.001$). The 1-year rate of death/MI was 1.6% (2/127) for PES versus 0% (0/371) for PtCr EES ($P = 0.06$) and TVR was 4.7% (6/127) for PES versus 2.7% (10/371) for PtCr EES ($P = 0.26$). No ST occurred at 12 months in either group.

Everolimus-eluting BRSs

Despite improvements in the safety profile of DESs,⁶³ LLL, late ST, and permanent vessel caging remain inherited limitations. BRSs provide temporary support to the vessel wall and subsequently disappear in approximately 3 years. The only everolimus BRS currently approved for clinical use in Europe is the Absorb v1.1 (bioresorbable vascular scaffold [BVS]; Abbott Vascular) made of PLLA, which degrades gradually over time via hydrolysis.

The initial experience with BVS implantation in de novo simple lesions has been promising, with acceptable long-term outcomes (MACE: 3.4%) in the ABSORB Cohort A,⁶⁴ a study of 30 patients with single de novo lesions who were treated with Absorb v1.0. At 5 years follow-up, there was an increase in minimal luminal diameter and area, which was primarily attributed due to a persistent reduction in plaque area size. The ABSORB⁶⁵ multi-imaging modality study (45 patients [Cohort B1] and 56 patients [Cohort B2]) revealed unchanged LLL after the first year of Absorb 1.1 implantation, whereas on intravascular ultrasound, the mean lumen, scaffold, and vessel areas showed enlargement up to 2 years. In the ABSORB II randomized controlled trial,⁶⁶ 335 patients treated with Absorb v1.1 were compared to 166 patients treated with a permanent metallic EES (Xience, Abbott Vascular). The ABSORB II included patients with one, or maximum two, de novo relatively simple lesions (ostial, left main coronary artery, bifurcation, chronic total occlusion, heavily calcified, or ISR lesions were all excluded). Despite the lower postimplantation acute lumen gain observed in lesions treated with BVS, 1-year TLF (composite of cardiac death, target-vessel MI, or clinically indicated TLR) was similar between the two groups (BVS vs EES: 5% vs 3%; $P=0.35$). The Comparison of Everolimus- and Biolimus-Eluting Stents With Everolimus-Eluting Bioresorbable Vascular Scaffold Stents II (EVERBIO II) trial,⁶⁷ a single-center, assessor-blinded study of 240 patients randomly assigned in a 1:1:1 ratio to BVS, PROMUS Element PtCr EES, and biolimus-eluting stent (Biomatrix FLEX, Biosensors, Newport Beach, CA, USA), showed no difference in angiographic LLL 9 months after stent/scaffold implantation in all-comer patients (BVS: 0.28 ± 0.39 mm; EES/BES: 0.25 ± 0.36 mm; $P=0.30$). In real-world patients, a small propensity-matched study by Costopoulos et al⁶⁸ demonstrated similar 1-year MACE (3.3% vs 7.6%; $P=0.19$) in patients treated with Absorb v1.1 versus newer-generation EES, respectively. The large “real-world” multicenter GHOST-EU registry,⁶⁹ consisting of 1,189 patients, showed a TLF rate of 3.5% at the median follow-up time of 109 days. Despite the acceptable TLF of 4.4%

at 6 months, estimated by the Kaplan–Meier method, the GHOST-EU registry revealed some worrying signals of BVS thrombosis (1.5% at 30 days; 2.1% at 6 months). In the Dutch Academic Medical Center (AMC) real-world registry,⁷⁰ 135 patients (159 lesions) treated with Absorb v1.1 and followed up for 6 months demonstrated TVR rates of 8.5%, including a 6.3% TLR rate, a 3% rate of MI, and a 3% rate of definite BVS thrombosis (three subacute and one late), concurring with the GHOST-EU findings. In the BVS Expand⁷¹ single-center registry of 200 patients, which excluded patients with STEMI and previous coronary artery bypass grafting (CABG), the 6-month rate of MACE was 3.3%, TLR 2.2%, and MI 1.7%, whereas 2.2% ($n=4$) definite BVS thrombosis cases occurred. The findings from these three studies (GHOST-EU, AMC, and BVS Expand) suggest that the current BVS generation, which is characterized by significantly thicker and wider struts ($\sim 150 \times 200$ μm) compared to new-generation DESs (80×80 μm) may be more thrombogenic, particularly when underexpanded or malapposed. In the German multicenter ASSURE (ABSORB: Postmarketing Surveillance Registry to Monitor the Everolimus-eluting Bioresorbable Vascular Scaffold in Patients With Coronary Artery Disease) registry,⁷² 183 patients treated with Absorb v1.1 were followed up for 1 year. Of note, this study excluded long lesions (defined as >28 mm) and lesions with a vessel diameter of >3.3 mm. The 1-year rate for MACE was 5%, TLR 2.8%, and MI 1.6%, whereas no scaffold thrombosis was observed. The ABSORB first registry,⁷³ a multicenter (1,200 patients), prospective global registry of “real world” patients treated with Absorb v1.1, demonstrated a 30-day MI rate of 0.8%, whereas no cardiac deaths were reported. Definite or probable scaffold thrombosis rates were 0.42%, almost a third of those reported in the GHOST EU. The Bioresorbable Vascular Scaffold-A Clinical Evaluation of Everolimus Eluting Coronary Stents in the Treatment of Patients With ST-segment Elevation Myocardial Infarction (BVS-EXAMINATION) trial⁷⁴ studied propensity-matched STEMI patients treated with BVS, CoCr EES Xience V, or BMS (290 patients in each group). The cumulative incidence of device-oriented clinical end points did not differ between the BVS and EES/BMS groups at 1 year (4.1% vs 4.1%, $P=0.994$; vs 5.9%, $P=0.306$, respectively). Definite/probable thrombosis rate in the BVS group was numerically higher at both 30 days (2.1% vs 0.3% [$P=0.059$] vs 1.0% [$P=0.324$], respectively) and 1 year (2.4% vs 1.4% [$P=0.948$] vs 1.7% [$P=0.825$], respectively), as compared with the EES or BMS groups. Several smaller registries have demonstrated the feasibility of implantation of BVS in more complex lesions,⁷⁵ such as calcified lesions⁷⁶ or

Table 2 Landmark studies in patients treated with everolimus-eluting stents/scaffolds

Study	Groups	N	Age (years)	Males (%)	DM (%)	Stable/unstable angina/NSTEMI/STEMI (%)	B2/C (%)	FU mo	All-cause mortality (%)	CV mortality (%)	MI (%)	TLR (%)	TVR (%)	Definite ST (%)	Composite (%)	Composite definition
CoCr EES vs BMS																
SPIRIT ³²	CoCr EES	28	64	70	11	78/19/0/0	59	24	N/A	0	7.6	7.7	7.7	0	15.4	Cardiac death, MI, TLR
	BMS	32	62	76	10	79/14/0/0	62	24	N/A	0	0	25	28.6	0	25.0	
XIMA ³³	CoCr EES	399	83	61	24	32/18/50	N/A	12	8.5	3.3	4.3*	N/A	2.0*	N/A	14.3	Death, MI, TVR, CVA, major TIMI bleeding
	BMS	401	84	59	26	32/18/50	N/A	12	7.2	4.7	8.7*	N/A	7.0*	N/A	18.7	Death, MI, all revascularization
EXAMINATION ³⁴	CoCr EES	751	61	83	18	0/0/0/100	N/A	24	4.3	3.7	1.9	2.9*	4.8*	0.8*	14.4	Cardiac death, MI, or clinically indicated TLR
	BMS	747	62	82	16	0/0/0/100	N/A	24	5.0	3.7	2.4	5.6*	7.9*	2.1*	17.3	Death, MI, TVR
CoCr EES vs PES																
SPIRIT ⁸¹	CoCr EES	3,350	63	68	31	74/29/0/0	19.3 [†]	36	3.2*	1.3	3.2*	6*	9.9*	0.9*	9.4*	Cardiac death, MI, or clinically indicated TLR
	PES	1,639	63	68	31	72/28/0/0	17.4 [†]	36	5.1	1.9	5.1*	8.2*	11.4*	1.9*	13*	Death, MI, TVR
COMPARE ⁴³	CoCr EES	897	63	69	17	40/12/22/26	74	12	2	1	3*	2*	2*	0.4*	6*	
	PES	903	64	72	19	41/12/24/23	74	12	2	1	5*	5*	6*	2*	9*	
EES vs ZES																
TWENTY ⁴⁵	CoCr EES	694	64	73	23	49/22/27/0	69.7	24	4.8	2.7	5.6	2.6*	5.1	0.1	11.6	Cardiac death, TV MI, TVR
	E-ZES	697	65	73	22	48/25/27/0	70.6	24	4.2	1.6	5.3	4.9*	5.6	0.9	12.9	Death, MI, clinically indicated TLR
DUTCH PEERS ⁴⁶	PtCr EES	905	65	73	17	42/15/22/22	65	12	1	1	1	2	3	0.7	6	
	CoCr ZES	906	64	73	18	41/12/27/19	66	12	2	2	2	2	3	0.3	5	
Serruys et al ⁴⁷	CoCr EES	1,152	64	77	23	36/19/34	N/A	12	2.8	1.7	13.6	3.4	4.8	0.3*	9.7	Death, MI, clinically indicated TLR
	ZES	1,140	64	77	24	34/19/35	N/A	12	1.6	1.3	13.5	3.9	4.9	1.2*	8.7	
CoCr EES vs SES																
SORTOUT IV ⁴⁰	CoCr EES	1,390	64	76	14	56/0/33/9	57	18	4.0	2.0	1.6	2.6	4.8	0.2	7.2	Cardiac death, MI, clinically indicated TVR
	SES	1,384	64	75	14	54/0/33/11	57	18	3.7	1.6	1.8	3.3	5.6	0.9	7.6	Cardiac death, TV MI, TLR
EXCELLENT ⁵²	CoCr EES	1,079	63	65	37	48/42/7/3	53	11	0.7	0.28	1.4	2.4	3.1	0.3	3.8	Cardiac death, TV MI, TLR
	SES	364	63	63	41	52/6/5	54	11	1.1	0.55	1.39	1.7	2.2	0.8	3.1	
BIOSCIENCE ⁵⁵	CoCr EES	1,056	66	77	22	31/7/27/19	N/A	12	2.6	2.1	4.4	3.1	3.7	0.4	6.7	Cardiac death, TV MI, clinically indicated TLR
	O-SES	2,119	66	77	24	31/7/27/20	N/A	12	3.3	1.9	3.9	4.0	5.2	0.9	6.7	
CoCr EES vs PtCr EES																
PLATINUM ¹⁰	CoCr EES	762	63	71	25	75/25/0	N/A	12	1.2	0.7	1.6	1.9	2.9	0.4	4.0	Cardiac death, MI, ID-TLR
	PtCr EES	768	64	72	22	76/24/0	N/A	12	1.3	0.9	0.8	1.9	2.7	0.4	4.2	Cardiac death, MI, ID-TLR
HOST ASSURE ⁶⁰	CoCr EES	1,252	64	66	32	34/38/17/11	52	12	1.6	1.4	1.4	1.2	1.8	0.25	2.9	Cardiac death, MI, ID-TVR
	PtCr EES	2,503	63	70	32	35/36/18/11	50	12	2.2	1.4	1.1	1.2	1.7	0.2	2.9	
EES vs BVS																
ABSORB II ⁶⁶	CoCr EES	166	61	80	24	75/22/0/0	49	12	1	0	1	2	5	0	5	Cardiac death, MI, ID-TVR
	BVS	335	62	76	24	77/20/0/0	46	12	0	0	4	1	2	2.6	5	

Notes: *Statistically significant between groups ($P < 0.05$); †class C lesions only. N/A, data not available.

Abbreviations: BMS, bare-metal stent; BVS, bioresorbable vascular scaffold; CoCr, cobalt–chromium; CV, cardiovascular; CVA, cerebrovascular accident; DM, diabetes mellitus; EES, everolimus-eluting stent; FU, follow-up; ID-TLR, ischemia-driven TLR; MI, myocardial infarction; mo, months; NSTEMI, non-ST-elevation MI; O-SES, Orsiro SES; PES, paclitaxel-eluting stent; PtCr, platinum–chromium; SES, sirolimus-eluting stent; ST, stent thrombosis; STEMI, ST-elevation MI; TLR, target lesion revascularization; TVR, target vessel revascularization; TIMI, thrombolysis in myocardial infarction; TV MI, target vessel myocardial infarction; ZES, zotarolimus-eluting stent; E-ZES, Endeavor ZES.

ISR.⁷⁷ Table 2 shows the landmark studies in patients treated with EESs/everolimus-eluting scaffolds.

The main current drawback of everolimus BRS (Absorb v1.1) relates to its strut thickness and width (157×190.5 µm for the 2.5 mm and 3.0 mm scaffolds and 157×215.9 µm for the 3.5 mm scaffold), which may render it more thrombogenic, particularly when underexpanded or malapposed. Ishibashi et al⁷⁸ summarized the BRS thrombosis experience in various settings (stable angina, ACS, and STEMI). In the total population of 4,309 patients implanted with BRS (Absorb v1.1) and followed up for 10.3 months, definite/probable BRS thrombosis was seen in 1.22% of patients, of which 0.16% of cases were acute and 0.76% subacute. BRS thrombosis occurred in 0.94% of patients presenting with stable angina, 2.16% in those with ACS, and 1.22% in patients with STEMI. Large randomized controlled trials purposefully powered are needed to demonstrate whether there is truly an excess risk of device thrombosis in patients treated with BRS compared to new-generation ultrathin EES. This potentially increased risk in BRS-treated patients highlights 1) the importance of optimal scaffold implantation technique using intracoronary imaging and 2) the need for novel scaffolds with thinner struts (<100 µm).

EESs versus coronary artery bypass for multivessel disease

Two recent studies have attempted to address the question whether percutaneous or surgical revascularization is most appropriate for patients with multivessel disease, not involving the left main coronary artery. In the first study, Park et al⁷⁹ conducted a noninferiority randomized trial in 27 centers in East Asia comparing treatment of multivessel coronary disease with either EES PCI or CABG. The study, which was initially forecasted to recruit 1,776 patients, was prematurely terminated due to slow enrollment pace. The overall number of patients enrolled was 880 patients and was balanced between the two groups ($n_{\text{PCI}}=438$ and $n_{\text{CABG}}=442$) and the primary end point was the composite of death, MI, or TVR. The mean Euroscore was around 3.0 for both groups, whereas the mean SYNTAX score was ~24. Only 15.1% of patients in the PCI group and 17.9% of patients in the CABG group had a SYNTAX score ≥ 33 . At 2 years of follow-up, the primary end point occurred in 11.0% of the patients in the PCI group and in 7.9% of those in the CABG group (absolute risk difference: 3.1%; 95% CI: -0.8 to 6.9; $P_{\text{noninferiority}}=0.32$), whereas at a longer-term follow-up (median: 4.6 years), the primary end point occurred in 15.3% of the patients in the PCI group and in 10.6% of those in the CABG group (HR =1.47; 95% CI:

1.01 to 2.13; $P=0.04$). Nevertheless, these results have to be cautiously interpreted, as the study was underpowered for the primary end point. Of note, ~30% of patients in both groups had chronic total occlusions, whereas complete revascularization occurred more frequently in the CABG group than in the PCI group (71.5% vs 50.9%; $P<0.001$). No fractional flow reserve or other pressure-wire measurements were utilized to guide revascularization in either group. Among patients with diabetes, the rate of the primary end point was significantly higher among those assigned to PCI than among those assigned to CABG (19.2% vs 9.1%; $P=0.007$).

The second propensity-matched study by Bangalore et al,⁸⁰ compared PCI vs CABG in 34,819 patients with multivessel disease (excluding left main coronary artery disease). In contrast to the previous study, all-cause mortality was defined as the primary end point for this trial (9,223 PCI vs 9,223 CABG patients). At a mean follow-up of 2.9 years, PCI with EES, as compared with CABG, had similar mortality rates (HR =1.04; 95% CI: 0.93 to 1.17; $P=0.50$). Nevertheless, in the same time frame, PCI conferred higher risk for MI (HR =1.51; 95% CI: 1.29 to 1.77; $P<0.001$) and repeat revascularization (HR =2.35; 95% CI: 2.14 to 2.58; $P<0.001$), but a lower risk for stroke (HR =0.62; 95% CI: 0.50 to 0.76; $P<0.001$).

Conclusion

In the current review, we have summarized the inception and the rapid evolution of EES platforms. Several randomized controlled trials and meta-analyses have demonstrated the superior efficacy and safety of EESs, initially over BMSs and subsequently over DESs, namely, PESs and SESs. Among diabetics, these improved outcomes have not been confirmed, and future research is required to determine the differential response of this subgroup of patients to different antiproliferative drugs. Similar safety and efficacy profiles have been demonstrated between EES and the new ZES platforms. The developments of the bioresorbable polymer-coated EES SYNERGY and the everolimus-eluting BRS (Absorb v1.1) are considered revolutionary, and results from further randomized studies with larger patient numbers and broader inclusion criteria are eagerly awaited to demonstrate whether these new technologies can match or improve upon the already excellent outcomes from the CoCr and the novel ultrathin PtCr platforms in all-comer patients.

Future perspectives

Several manufacturers of everolimus-eluting BRSs are working on reducing strut thickness (<100 µm), increasing radial strength, increasing size range, reducing absorption

time to ~1 year, and improving BRS deliverability. These improved technical characteristics will enable BRS to tackle the majority of complex lesions while simultaneously minimizing procedure times and optimizing future outcomes. In the next decade, these novel scaffolds will need to go through a series of head-to-head comparisons with state-of-the-art PtCr EESs (with either durable or bioresorbable polymer) to demonstrate their superior long-term efficacy and safety, aiming to eradicate very late ST.

Disclosure

The authors report no conflicts of interest in this work.

References

- Grüntzig AR, Senning Å, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis. *N Engl J Med*. 1979;301(2):61–68.
- Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. *N Engl J Med*. 2012;366(1):54–63.
- Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. *N Engl J Med*. 1994;331(8):496–501.
- Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med*. 1994;331(8):489–495.
- Morice MC, Serruys PW, Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med*. 2002;346(23):1773–1780.
- Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J Am Coll Cardiol*. 2006;48(1):193–202.
- Menown IB, Noad R, Garcia EJ, Meredith I. The platinum chromium element stent platform: from alloy, to design, to clinical practice. *Adv Ther*. 2010;27(3):129–141.
- Iqbal J, Onuma Y, Ormiston J, Abizaid A, Waksman R, Serruys P. Bioresorbable scaffolds: rationale, current status, challenges, and future. *Eur Heart J*. 2014;35(12):765–776.
- O'Brien BJ, Stinson JS, Larsen SR, Eppihimer MJ, Carroll WM. A platinum-chromium steel for cardiovascular stents. *Biomaterials*. 2010;31(14):3755–3761.
- Stone GW, Teirstein PS, Meredith IT, et al. A prospective, randomized evaluation of a novel everolimus-eluting coronary stent: the PLATINUM (A prospective, randomized, multicenter trial to assess an everolimus-eluting coronary stent system [promus element] for the treatment of up to Two De Novo Coronary Artery Lesions) Trial. *J Am Coll Cardiol*. 2011;57(16):1700–1708.
- Thomas MR, Birkemeyer R, Schwimbeck P, et al. One-year outcomes in 1,010 unselected patients treated with the PROMUS Element everolimus-eluting stent: the multicentre PROMUS Element European Post-Approval Surveillance Study. *EuroIntervention*. 2015;10(11): 1267–1271.
- Ormiston JA, Webber B, Ubod B, White J, Webster MW. Coronary stent durability and fracture: an independent bench comparison of six contemporary designs using a repetitive bend test. *EuroIntervention*. 2015;10(12):1449–1455.
- Gogas BD, Farooq V, Onuma Y, Serruys PW. The ABSORB bioresorbable vascular scaffold: an evolution or revolution in interventional cardiology? *Hellenic J Cardiol*. 2012;53(4):301–309.
- Welt FG, Rogers C. Inflammation and restenosis in the stent era. *Arterioscler Thromb Vasc Biol*. 2002;22(11):1769–1776.
- Costa MA, Simon DI. Molecular basis of restenosis and drug-eluting stents. *Circulation*. 2005;111(17):2257–2273.
- Carter AJ. TOR of the cell cycle: are there important implications for diabetics in the era of the drug-eluting stent? *Catheter Cardiovasc Interv*. 2004;61(2):233–236.
- Schuler W, Sedrani R, Cottens S, et al. SDZ RAD, a new rapamycin derivative: pharmacological properties in vitro and in vivo. *Transplantation*. 1997;64(1):36–42.
- Eisen HJ, Tuzcu EM, Dorent R, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med*. 2003;349(9):847–858.
- Verheye S, Martinet W, Kockx MM, et al. Selective clearance of macrophages in atherosclerotic plaques by autophagy. *J Am Coll Cardiol*. 2007;49(6):706–715.
- Kahan BD, Wong RL, Carter C, et al. A phase I study of a 4-week course of SDZ-RAD (RAD) quiescent cyclosporine-prednisone-treated renal transplant recipients. *Transplantation*. 1999;68(8):1100–1106.
- Rogers CD. Optimal stent design for drug delivery. *Rev Cardiovasc Med*. 2004;5(Suppl 2):S9–S15.
- Kotani J, Awata M, Nanto S, et al. Incomplete neointimal coverage of sirolimus-eluting stents: angioscopic findings. *J Am Coll Cardiol*. 2006;47(10):2108–2111.
- Finn AV, Joner M, Nakazawa G, et al. Pathological correlates of late drug-eluting stent thrombosis: strut coverage as a marker of endothelialization. *Circulation*. 2007;115(18):2435–2441.
- Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institution cohort study. *Lancet*. 2007;369(9562):667–678.
- Carter AJ, Brodeur A, Collingwood R, et al. Experimental efficacy of an everolimus eluting cobalt chromium stent. *Catheter Cardiovasc Interv*. 2006;68(1):97–103.
- Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J*. 2014;35(37):2541–2619.
- Grube E, Sonoda S, Ikeno F, et al. Six- and twelve-month results from first human experience using everolimus-eluting stents with bioabsorbable polymer. *Circulation*. 2004;109(18):2168–2171.
- Costa RA, Lansky AJ, Mintz GS, et al. Angiographic results of the first human experience with everolimus-eluting stents for the treatment of coronary lesions (the FUTURE I trial). *Am J Cardiol*. 2005;95(1):113–116.
- Tsuchiya Y, Lansky AJ, Costa RA, et al. Effect of everolimus-eluting stents in different vessel sizes (from the pooled FUTURE I and II trials). *Am J Cardiol*. 2006;98(4):464–469.
- Serruys PW, Ong AT, Piek JJ, et al. A randomized comparison of a durable polymer everolimus-eluting stent with a bare metal coronary stent: the SPIRIT first trial. *EuroIntervention*. 2005;1(1):58–65.
- Tsuchida K, Piek JJ, Neumann FJ, et al. One-year results of a durable polymer everolimus-eluting stent in de novo coronary narrowings (The SPIRIT FIRST Trial). *EuroIntervention*. 2005;1(3):266–272.
- Beijk MA, Neumann FJ, Wiemer M, et al. Two-year results of a durable polymer everolimus-eluting stent in de novo coronary artery stenosis (The SPIRIT FIRST Trial). *EuroIntervention*. 2007;3(2):206–212.
- de Belder A, de la Torre Hernandez JM, Lopez-Palop R, et al. A prospective randomized trial of everolimus-eluting stents versus bare-metal stents in octogenarians: the XIMA Trial (Xience or vision stents for the management of angina in the elderly). *J Am Coll Cardiol*. 2014;63(14):1371–1375.
- Sabate M, Brugaletta S, Cequier A, et al. The EXAMINATION trial (everolimus-eluting stents versus bare-metal stents in ST-segment elevation myocardial infarction): 2-year results from a multicenter randomized controlled trial. *JACC Cardiovasc Interv*. 2014;7(1):64–71.
- Kaiser C, Galatius S, Erne P, et al. Drug-eluting versus bare-metal stents in large coronary arteries. *N Engl J Med*. 2010;363(24):2310–2319.

36. Valgimigli M, Sabate M, Kaiser C, et al. Effects of cobalt-chromium everolimus eluting stents or bare metal stent on fatal and non-fatal cardiovascular events: patient level meta-analysis. *BMJ*. 2014;349:g6427.
37. Serruys PW, Ruygrok P, Neuzner J, et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. *EuroIntervention*. 2006;2(3):286–294.
38. Onuma Y, Miquel-Hebert K, Serruys PW. Five-year long-term clinical follow-up of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with de novo coronary artery disease: the SPIRIT II trial. *EuroIntervention*. 2013;8(9):1047–1051.
39. Stone GW, Midei M, Newman W, et al. Comparison of an everolimus-eluting stent and a paclitaxel-eluting stent in patients with coronary artery disease: a randomized trial. *JAMA*. 2008;299(16):1903–1913.
40. Gada H, Kirtane AJ, Newman W, et al. 5-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents: final results from the SPIRIT III trial (clinical evaluation of the XIENCE V everolimus eluting coronary stent system in the treatment of patients with de novo native coronary artery lesions). *JACC Cardiovasc Interv*. 2013;6(12):1263–1266.
41. Stone GW, Rizvi A, Newman W, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. *N Engl J Med*. 2010;362(18):1663–1674.
42. Stone G. A large scale randomized comparison of everolimus-eluting and paclitaxel-eluting stents: three-year outcomes from the SPIRIT IV trial. Presented at Transcatheter Cardiovascular Therapeutics; San Francisco, CA, USA. November 7–11, 2011.
43. Smits PC, Kedhi E, Roayaards KJ, et al. 2-year follow-up of a randomized controlled trial of everolimus- and paclitaxel-eluting stents for coronary revascularization in daily practice. COMPARE (Comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTE stent in all-comers: a randomized open label trial). *J Am Coll Cardiol*. 2011;58(1):11–18.
44. Kedhi E, Joesoef KS, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. *Lancet*. 2010;375(9710):201–209.
45. Tandjung K, Sen H, Lam MK, et al. Clinical outcome following stringent discontinuation of dual antiplatelet therapy after 12 months in real-world patients treated with second-generation zotarolimus-eluting resolute and everolimus-eluting Xience V stents: 2-year follow-up of the randomized TWENTE trial. *J Am Coll Cardiol*. 2013;61(24):2406–2416.
46. von Birgelen C, Sen H, Lam MK, et al. Third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer patients requiring a percutaneous coronary intervention (DUTCH PEERS): a randomised, single-blind, multicentre, non-inferiority trial. *Lancet*. 2014;383(9915):413–423.
47. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. *N Engl J Med*. 2010;363(2):136–146.
48. Miyazaki T, Latib A, Panoulas VF, et al. Comparison of 2-year outcomes between zotarolimus-eluting and everolimus-eluting new-generation cobalt-chromium alloy stents in real-world diabetic patients. *Catheter Cardiovasc Interv*. 2015;86(1):E11–E18.
49. Piccolo R, Stefanini GG, Franzone A, et al. Safety and efficacy of resolute zotarolimus-eluting stents compared with everolimus-eluting stents: a meta-analysis. *Circ Cardiovasc Interv*. 2015;8(4).
50. Jensen LO, Thayssen P, Hansen HS, et al. Randomized comparison of everolimus-eluting and sirolimus-eluting stents in patients treated with percutaneous coronary intervention: the Scandinavian organization for randomized trials with clinical outcome IV (SORT OUT IV). *Circulation*. 2012;125(10):1246–1255.
51. Park D-W, Kim Y-H, Song H-G, et al. Comparison of everolimus- and sirolimus-eluting stents in patients with long coronary artery lesions: a randomized LONG-DES-III (percutaneous treatment of LONG native coronary lesions with drug-eluting stent-III) trial. *JACC Cardiovasc Interv*. 2011;4(10):1096–1103.
52. Park KW, Chae I-H, Lim D-S, et al. Everolimus-eluting versus sirolimus-eluting stents in patients undergoing percutaneous coronary intervention: the EXCELLENT (efficacy of XIENCE/Promus versus Cypher to reduce late loss after stenting) randomized trial. *J Am Coll Cardiol*. 2011;58(18):1844–1854.
53. Kim W-J, Lee S-W, Park S-W, et al. Randomized comparison of everolimus-eluting stent versus sirolimus-eluting stent implantation for De Novo coronary artery disease in patients with diabetes mellitus (ESSENCE-DIABETES): results from the ESSENCE-DIABETES trial. *Circulation*. 2011;124(8):886–892.
54. Windecker S, Haude M, Neumann FJ, et al. Comparison of a novel biodegradable polymer sirolimus-eluting stent with a durable polymer everolimus-eluting stent: results of the randomized BIOFLOW-II trial. *Circ Cardiovasc Interv*. 2015;8(2):e001441.
55. Pilgrim T, Heg D, Roffi M, et al. Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): a randomised, single-blind, non-inferiority trial. *Lancet*. 2014;384(9960):2111–2122.
56. Hofma SH, Smits PC, Brouwer J, et al. Long-term follow-up of second-generation everolimus-eluting stents versus first-generation sirolimus-eluting stents in acute myocardial infarction: three-year results of the XAMI trial. *EuroIntervention*. 2015;10(11):1280–1283.
57. Di Lorenzo E, Sauro R, Varricchio A, et al. Randomized comparison of everolimus-eluting stents and sirolimus-eluting stents in patients with ST elevation myocardial infarction: RACES-MI trial. *JACC Cardiovasc Interv*. 2014;7(8):849–856.
58. Toyota T, Shiomi H, Morimoto T, Kimura T. Meta-analysis of long-term clinical outcomes of everolimus-eluting stents. *Am J Cardiol*. 2015;116(2):187–194.
59. Baber U, Mehran R, Sharma SK, et al. Impact of the everolimus-eluting stent on stent thrombosis: a meta-analysis of 13 randomized trials. *J Am Coll Cardiol*. 2011;58(15):1569–1577.
60. Park KW, Kang SH, Kang HJ, et al. A randomized comparison of platinum chromium-based everolimus-eluting stents versus cobalt chromium-based zotarolimus-eluting stents in all-comers receiving percutaneous coronary intervention: HOST-ASSURE (harmonizing optimal strategy for treatment of coronary artery stenosis-safety and effectiveness of drug-eluting stents and anti-platelet regimen), a randomized, controlled, noninferiority trial. *J Am Coll Cardiol*. 2014;63(25 pt A): 2805–2816.
61. Kereiakes DJ, Meredith IT, Windecker S, et al. Efficacy and safety of a novel bioabsorbable polymer-coated, everolimus-eluting coronary stent: the EVOLVE II randomized trial. *Circ Cardiovasc Interv*. 2015;8(4).
62. Gao R, Han Y, Yang Y, et al. PLATINUM China: a prospective, randomized investigation of the platinum chromium everolimus-eluting stent in de novo coronary artery lesions. *Catheter Cardiovasc Interv*. 2015;85(Suppl 1):716–723.
63. Stefanini GG, Kalesan B, Serruys PW, et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial. *Lancet*. 2011;378(9807):1940–1948.
64. Simsek C, Karanasos A, Magro M, et al. Long-term invasive follow-up of the everolimus-eluting bioresorbable vascular scaffold: five-year results of multiple invasive imaging modalities. *EuroIntervention*. 2014;20130724-03.
65. Bourantas CV, Farooq V, Zhang Y, et al. Circumferential distribution of the neointima at six-month and two-year follow-up after a bioresorbable vascular scaffold implantation: a substudy of the ABSORB Cohort B Clinical Trial. *EuroIntervention*. 2015;10(11):1299–1306.
66. Serruys PW, Chevalier B, Dudek D, et al. A bioresorbable everolimus-eluting scaffold versus a metallic everolimus-eluting stent for ischaemic heart disease caused by de-novo native coronary artery lesions (ABSORB II): an interim 1-year analysis of clinical and procedural secondary outcomes from a randomised controlled trial. *Lancet*. 2015;385(9962):43–54.
67. Puricel S, Arroyo D, Corpataux N, et al. Comparison of everolimus- and biolimus-eluting coronary stents with everolimus-eluting bioresorbable vascular scaffolds. *J Am Coll Cardiol*. 2015;65(8):791–801.
68. Costopoulos C, Latib A, Naganuma T, et al. Comparison of early clinical outcomes between ABSORB bioresorbable vascular scaffold and everolimus-eluting stent implantation in a real-world population. *Catheter Cardiovasc Interv*. 2015;85(1):E10–E15.

69. Capodanno D, Gori T, Nef H, et al. Percutaneous coronary intervention with everolimus-eluting bioresorbable vascular scaffolds in routine clinical practice: early and midterm outcomes from the European multicentre GHOST-EU registry. *EuroIntervention*. 2015;10(10):1144–1153.
70. Kraak RP, Hassell ME, Grundeken MD, et al. Initial experience and clinical evaluation of the absorb bioresorbable vascular scaffold (BVS) in real-world practice: the AMC single centre real world PCI registry. *EuroIntervention*. 2015;10(10):1160–1168.
71. van Geuns RJ. BVS expand: 6-month results. Presented at: EuroPCR; 2014. Available from: <http://www.pcronline.com/Lectures/2014/BVS-Expand-6-month-results>.
72. Woehrle J, Naber C, Schmitz T, et al. Beyond the early stages: insights from the ASSURE Registry on bioresorbable vascular scaffold. *EuroIntervention*. 2015;11(2):149–156.
73. Eeckhout E, Seth A, Mao VM, et al. ABSORB FIRST: an interim report on baseline characteristics and acute performance on the first 1,200 patients from a prospective, multi-center, global registry. *J Am Coll Cardiol*. 2014;64(11_S):679.
74. Brugaletta S, Gori T, Low AF, et al. Absorb bioresorbable vascular scaffold versus everolimus-eluting metallic stent in ST-segment elevation myocardial infarction: 1-year results of a propensity score matching comparison: the BVS-EXAMINATION Study (bioresorbable vascular scaffold-a clinical evaluation of everolimus eluting coronary stents in the treatment of patients with ST-segment elevation myocardial infarction). *JACC Cardiovasc Interv*. 2015;8(1 pt B):189–197.
75. Panoulas VF, Miyazaki T, Kawamoto H, Colombo A, Chieffo A. Biore-sorbable scaffolds for the treatment of complex lesions: are we there yet? *Interv Cardiol*. 2015;7(1):35–54.
76. Panoulas VF, Miyazaki T, Sato K, et al. Procedural outcomes of patients with calcified lesions treated with bioresorbable vascular scaffolds. *EuroIntervention*. 2015;10(11):20141121–01.
77. Ielasi A, Latib A, Naganuma T, et al. Early results following everolimus-eluting bioresorbable vascular scaffold implantation for the treatment of in-stent restenosis. *Int J Cardiol*. 2014;173(3):513–514.
78. Ishibashi Y, Nakatani S, Onuma Y. Definite and probable bioresorbable scaffold thrombosis in stable and ACS patients. *EuroIntervention*. Epub September 22, 2014.
79. Park S-J, Ahn J-M, Kim Y-H, et al. Trial of everolimus-eluting stents or bypass surgery for coronary disease. *N Engl J Med*. 2015;372(13):1204–1212.
80. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Xu J, Hannan EL. Everolimus-eluting stents or bypass surgery for multivessel coronary disease. *N Engl J Med*. 2015;372(13):1213–1222.
81. Dangas GD, Serruys PW, Kereiakes DJ, et al. Meta-analysis of everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease: final 3-year results of the SPIRIT clinical trials program (Clinical evaluation of the Xience V everolimus eluting coronary stent system in the treatment of patients with De Novo Native Coronary Artery Lesions). *JACC Cardiovasc Interv*. 2013;6(9):914–922.

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