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Safety and Efficacy of Second-Generation Everolimus-Eluting Stents

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ABSTRACT: The second-generation everolimus-eluting stents (EES) are loaded with everolimus, which is a powerful analog of sirolimus; the drug carrier consists of a thin layer of durable and biocompatible fluorocopolymer, and the platform is made of cobalt-chromium alloy to allow thinner struts as well as to enhance stent radial strengh, delivery, and percutaneous coronary intervention success rates. EES are safe and efficient for the treatment of coronary artery disease in a wide range of anatomic settings, where several trials show EES superior to paclitaxel-eluting stents (PES); however, the superiority of EES over sirolimus-eluting stents (SES) is not so clear as over PES. In specific profiles of subjects such as diabetic patients, women, and patients presenting acute myocardial infarction (AMI), EES are also safe and efficient. In diabetic patients, the expected superiority of EES over PES and SES has not been confirmed. EES are equally safe and effective for women as for the general population. In the AMI setting, EES promote safety and efficacy outcomes similar to those found in non-AMI patients, as well as lower stent thrombosis rates in comparison with SES and PES. In conclusion, second-generation EES are safe and efficient for treatment of coronary artery disease in a wide range of anatomic and clinical settings.

KEYWORDS: everolimus, drug eluting stent, coronary artery disease

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Introduction

Since Gruentzig pioneered the percutaneous transluminal coronary angioplasty with balloon catheter as a treatment for chronic angina we have been fighting against in-stent restenosis. Bare metal stents (BMS) improved percutaneous coronary intervention (PCI) success rates and reduced restenosis compared with balloon angioplasty. Moreover, first-generation drug eluting stents (DES) even dramatically reduced restenosis rates. The multicenter SIRIUS trial compared sirolimus-eluting stent (SES) with BMS in native coronary arteries showing a significant reduction in the rates of target vessel failure (TVF) (BMS = 21.0% vs SES = 8.6%, $P < 0.001$) driven largely by a decrease of the need for revascularization of the target lesion (BMS = 16.6% vs SES = 4.1%, $P < 0.001$).[1] In spite of the significant reduction in late lumen loss and restenosis rates, first-generation DES increased the risk of late-stent thrombosis. The improvements in second-generation DES aimed to enhance clinical and angiographic results as well as decrease stent thrombosis by means of a better cobalt-chromium alloy stent platform and thinner struts to enhance stent radial strengh, delivery, and PCI success rates; more biocompatible polymers to decrease local inflammation and stent thrombosis; and more powerful drugs to decrease neointimal hyperplasia.

We have reviewed the literature to discuss safety and efficacy features as well as specific indications of second-generation everolimus-eluting stents (EES).

Stent Components: Drug, Polymer, and Platform

Everolimus is a sirolimus analogue that binds to cytosolic FK binding protein-12 (FKBP12) inhibiting the mammalian target of rapamycin (mTOR) pathway, which plays a main role in the cell proliferation. Extracellular stimulatory signals, growth factors (IGF), and cytokines (TNF-α) lead to the activation of AKT (protein kinase B) and subsequently of mTOR. The

Everolimus—FKBP12 complex inhibits the mTOR pathway, blocking the cell cycle at G1/S transition and, consequently, decreasing cell proliferation after vascular injury. Therefore, everolimus is able to inhibit in-stent smooth muscle cell proliferation and, consequently, prevent restenosis.[2,3]

Second-generation EES are loaded with 100 µg of everolimus per cm^2 of the stent surface area. The pharmacokinetics studies of EES show 80% of drug released at 30 days and no drug detectable after 120 days.[4] A pharmacokinetic study with SPIRIT III patients showed that blood levels dropped bellow 0.1 ng/mL 72 hours after EES deployment, and no everolimus was detected in any patient 30 days later.[5]

The drug carrier consists of a thin layer (7.8 µm) of nonadhesive, durable, and biocompatible fluorocopolymer composed of vinylidene fluoride and hexafluoropropylene monomers coated directly onto the stent metallic struts. The EES fluorocopolymer is elastomeric and experiences minimal bonding, webbing, or tearing upon expansion. Fluoropolymers have been demonstrated to resist platelet and thrombus deposition when in blood contact,[6,7] as well as low inflammatory reaction in porcine experimental models.[8]

Both EES Xience V (Abbott Vascular, North Chicago, Illinois) and Promus (Boston Scientific, Natick, Massachussets) are made of cobalt chromium alloy and have exactly the same design as well as the same strut thickness (81 µm). The thin cobalt-chromium EES struts facilitate rapid reendothelialization and are proven to be as fracture-resistant as the large stainless steel struts. The Xience Prime (Abbott Vascular) is also made of cobalt chromium, and its strut thickness is also the same 81 µm but with small differences in stent design and a different stent delivery system (balloon catheter) to enhance stent radial strengh and flexibility as well as deliverability. The new Xience Xpedition (Abbott Vascular) has the same design, alloy, and strut thickness as the Xience Prime; however, it has a new stent delivery system to improve pushability and trackability. The new Promus Element (Boston Scientific) is made of platinum chromium alloy and has the same drug and polymer coating as the Promus Element. The PLATINUM trial was a randomized and multicenter study that compared Promus Element with Promus in 1530 patients and showed no difference in cardiac death, acute myocardial infarction (AMI), target lesion revascularization (TLR), and definite or probable stent thrombosis between both EES[9]; therefore, the PLATINUM trial demonstrated successful transfer of the Promus drug and polymer coating to the Promus Element platinum chromium platform, which was designed for improved deliverability and radiopacity. The EES models mentioned, specifically the Xience V and Promus, were the most worldwide implanted EESs, as well as the most evaluated EESs in the majority of clinical trials to be discussed below.

Clinical Studies

De novo lesions. The outcomes of second-generation everolimus-eluting stents in de novo lesions were evaluated by several studies that will be discussed below.

The SPIRIT IV is a randomized study that evaluated EES versus paclitaxel eluting-stent (PES) in 3687 patients with stable coronary artery disease undergoing PCI of up to 3 lesions in 3 vessels. Patients with unstable coronary syndromes, AMI, thrombus, chronic occlusions, vein graft lesions, and true bifurcation lesions were excluded. The primary end point of target lesion failure (TLF) composed of composite cardiac death, target vessel myocardial infarction, or ischemia-driven TLR at 1 year was reduced by 38% with EES (EES = 4.2% vs PES = 6.8%, relative risk [RR] = 0.62, 95% confidence interval [CI] = 0.46–0.82, P = 0.001). The 1-year rates of stent thrombosis (EES = 0.3% vs PES = 1.1%, P = 0.004), all AMI (EES = 1.9% vs PES = 3.1%, P = 0.02), and TLR (EES = 2.5% vs PES = 4.6%, P = 0.001) were also reduced with EES in comparison with PES.[10] These results were sustained at the 2-year follow-up. Treatment with EES reduced the 2-year rates of TLF (EES = 6.9% vs PES = 9.9%, P = 0.003), all AMI (EES = 2.5% vs PES = 3.9%, P = 0.02), Q-wave MI (EES = 0.1% vs PES = 0.8%, P = 0.002), stent thrombosis (EES = 0.4% vs PES = 1.2%, P = 0.008), and ischemia driven TLR (EES = 4.5% vs PES = 6.9%, P = 0.004), with nonsignificant differences in the rates of all cause and cardiac mortality.[11]

The COMPARE study randomized 1800 all-comer patients to EES or PES (Libertè platform). The primary end point of major adverse cardiovascular events (MACE) at 1 year was reduced by 31% with the EES compared with PES (EES = 6.2% vs PES = 9.1%, P = 0.02), driven by reductions in stent thrombosis (EES = 0,7% vs PES = 2,6%, P = 0.002), AMI (EES = 2,8% vs PES = 5,4%, P = 0.007) and TLR (EES = 1.7% vs PES = 4.8%, P = 0.0002). At 2 years, significantly fewer EES patients were on dual antiplatelet therapy (11.4% vs 15.4%, P = 0.02). The primary composite of all death, AMI, and TVR occurred in 9.0% of EES patients and 13.7% of PES patients (RR = 0.66, 95% CI = 0.50–0.86) driven by a lower rate of AMI (EES = 3.9% vs PES = 7.5%, 95% CI = 0.35–0.77) and TVR (EES = 3.2% vs PES = 8.0%, 95% CI = 0.27–0.62), in parallel with a lower rate of definite or probable stent thrombosis (EES = 0.9% vs PES = 3.9%, 95% CI = 0.11–0.49). Differences significantly increased between the 1- and 2-year follow-up for the primary composite end point (P = 0.04), TVR (P = 0.02) and definite or probable stent thrombosis (P = 0.02). The clinical benefits of EES over PES regarding both safety and efficacy were maintained at 2 years. Moreover, there was an increase in benefits in terms of both safety and efficacy between the 1- and 2-year follow-up.[12,13] In the SORT OUT IV trial, 2774 unselected patients with coronary artery disease were randomized to EES or SES. The primary 9-month composite end point composed of cardiac death, AMI, definite stent thrombosis, and target vessel revascularization (TVR) occurred in a similar proportion in both groups, but the event rates were lower than expected (EES = 4.9% vs SES = 5.2%, 95% CI = 0.67–1.31 and P for noninferiority = 0.01). At the 18-month follow-up, the

primary end points rates remained comparable in both groups (EES = 7.2% vs SES = 7.6%, 95% CI = 0.71–1.23). Definite stent thrombosis at the 9-month follow-up was lower in the EES group (EES = 0.1% vs SES = 0.7%, 95% CI = 0.05–1.02) and the difference was sustained to the 18-month follow-up (EES = 0.2% vs SES = 0.9%, 95% CI = 0.07–0.88). At 2 years, there was no composite end point significant difference between EES and SES groups (EES = 8.3% vs SES = 8.7%, 95% CI = 0.73–1.22); however, the rate of definite stent thrombosis was lower in the EES group (0.2% vs 0.9%, 95% CI = 0.07–0.80, $P = 0.02$).[14,15]

The EXCELLENT trial compared the angiographic outcomes of EES and SES in a prospective, randomized, open-label and multicenter study, which demonstrated the noninferiority of EES compared with SES in preventing late loss at 9 months. Clinical follow-up was available in 1428 patients and 9-month angiographic follow-up in 924 patients (1215 lesions). The primary end point of the study was in-segment late loss at 9 months (EES = 0.11 ± 0.38 mm vs SES = 0.06 ± 0.36 mm, P for noninferiority = 0.0382). The in-stent late loss was also noninferior (EES = 0.19 ± 0.35 mm vs SES = 0.15 ± 0.34 mm, P for noninferiority = 0.0121). The incidence of clinical end points was not statistically different between the 2 groups, including TLF (EES = 3.75% vs SES = 3.05%, $P = 0.53$) and stent thrombosis at 12 months (EES = 0.37% vs SES = 0.83%, $P = 0.38$). EES was noninferior to SES in inhibition of late loss after stenting, which was corroborated by similar rates of clinical outcomes.[16]

The RESOLUTE All Comers trial randomized 2292 patients at 17 hospitals in Europe and Israel for EES or zotarolimus-eluting stent (ZES). The 1-year results showed that ZES was noninferior to EES with respect to the primary end point of TLF (EES = 8.3% vs ZES = 8.2%, $P < 0.001$ for noninferiority), which was defined as a composite of cardiac death, AMI, or ischemia-driven TLR. The rates of cardiac death, AMI, and TLR (EES = 3.4% vs ZES = 3.9%, $P = 0.50$) were also equivalent for both DES. Nevertheless, definite stent thrombosis (EES = 0.3% vs ZES = 1.2%, $P = 0.01$) and definite/probably stent thrombosis (EES = 0.7% vs ZES = 1.6%, $P = 0.05$) were lower for the EES at 1 year. The 2-year follow-up showed similar patient-related events of combined all deaths, myocardial infarction, and TLR (EES = 20.5% vs ZES = 20.6%; 95% CI = –3.2 to 3.5, $P = 0.958$), as well as similar stent-related events of TLF (EES = 10.7% vs ZES = 11.2%, 95% CI = –2.1 to 3.1, $P = 0.736$). Three patients in each group (0.3%) had very late (after 1 year) stent thrombosis. The 2-years data evidenced that the overall noninferiority result was sustained even after cessation of dual antiplatelet therapy. Furthermore, the low rate of very late stent thrombosis seems to have been achieved without a major increase in late TLR.[17,18]

The TWENTE was a randomized trial that aimed to compare the safety and efficacy of ZES with EES. The primary end point was target vessel failure (TVF), a composite of cardiac death, MI not clearly attributable to nontarget vessels, and clinically indicated TVR. A total of 1391 patients were randomly assigned to ZES (n = 697) or EES (n = 694); acute coronary syndromes were present in 52% and off-label features in 77% of patients. At 2-year follow-up, the rates of TVF were similar in both second-generation DES groups (ZES = 10.8% vs EES = 11.6%, $P = 0.65$). There was no significant between-group difference in TVF components. The definite or probable stent thrombosis rates were relatively low and similar (ZES = 1.2% vs EES = 1.4%, $P = 0.63$). This study showed that ZES was noninferior to EES in treating "real-world" patients who usually present complex lesions, requiring off-label indications for DES[19,20] (Table 1).

The second-generation EES is more effective than the first-generation PES in de novo lesions since EES significantly reduce MACE, TLR, and stent thrombosis when compared with PES; however, when compared with SES, 2 studies revealed similar rates of MACE but statistically significant lower or tendency to lower stent thrombosis for EES. Regarding other second-generation DES, EES and ZES are clinically equivalent for the treatment of de novo lesions with sustained equivalency even after cessation of dual antiplatelet therapy.

Multivessel disease. Patients with multivessel disease represent a complex and challenging subset. The lack of dedicated studies makes subgroup analysis of large trials the best evidence to date.

The SPIRIT III and IV trials evaluated EES versus PES with broad entry criteria. The combined study population

Table 1. Studies comparing EES with other DES in *de novo* lesions.

STUDY	N	FOLLOW-UP	STENT TYPE	TLF/ MACE (%)	TLR/ TVR (%)	ST (%)
SPIRIT IV	3,687	1 year	EES	4.2*	2.5*	0.3*
			PES	6.8*	4.6*	1.1*
COMPARE	1,800	1 year	EES	6.2*	1.7*	0.7*
			PES	9.1*	4.8*	2.6*
		2 years	EES	9.0*	3.2*	0.9*
			PES	13.7*	8.0*	3.9*
SORT OUT IV	2,772	9 months	EES	4.9	1.4	0.1
			SES	5.2	1.7	0.7
		2 years	EES	8.3	2.9	0.2*
			SES	8.7	3.5	0.9*
EXCELLENT	1,428	1 year	EES	3.75	2.4	0.37
			SES	3.05	1.7	0.83
RESOLUTE	2,292	1 year	EES	8.3	3.4	0.7*
			ZES	8.2	3.9	1.6*
		2 years	EES	20.5	5.1	1.0
			ZES	20.6	5.7	1.9
TWENTE	1,391	2 years	EES	11.6	5.1	1.4
			ZES	10.8	5.6	1.2

Note: *$P < 0.05$.
Abbreviations: N, number of patients; TLF, target lesion failure; MACE, major adverse cardiac events; TLR, target lesion revascularization; TVR, target vessel revascularization; ST, stent thrombosis.

of both trials included 4689 patients who were randomly assigned 2:1 to receive EES (n = 3127) or PES (n = 1562). A total of 785 of these patients (17%) underwent multivessel PCI. Pooled analysis revealed lower TLF rates in EES treated patients compared with PES treated ones (EES = 6.0% vs PES = 12.2%, $P = 0.005$) at 1-year follow up as well as lower MACE in the EES group (EES = 6.2% vs PES = 12.5%, $P = 0.004$). No significant differences in definite or probable stent thrombosis rates were found between both DES groups (EES = 1.2% vs PES = 2.7%, $P = 0.15$).[21]

In the above mentioned COMPARE trial, 27% of the enrolled patients (n = 484) had multivessel disease. At 2-year follow-up, the benefit of EES over PES for reducing MACE was greater in multivessel (EES = 11.0% vs PES = 20.0%, $P = 0.006$) compared with single-vessel (EES = 8.0% vs PES = 12.0%, $P = 0.053$) disease patients (RR = 0.55; 95% CI = 0.35 to 0.85). It should be emphasized that the results may have been conservatively biased in favor of EES since the stent length-to-lesion length ratios were higher for EES than for PES.[13]

The COMPARE II trial was designed to evaluate non-inferiority of biolimus eluting stent (BES) with biodegradable polymer in relation to EES. From the original study population of 2700 patients, multivessel subgroup analysis of 683 patients showed similar rates of primary composite end point of cardiac death, AMI, and clinically driven TVR (BES = 8.6% vs EES = 9.1%, P not significant) at 1 year[22] (Table 2).

The ongoing BEST trial whose estimated primary completion is December 2013 was designed to evaluate

Table 2. Studies comparing EES with other DES in different anatomic settings.

SETTING	STUDY	N	FU	STENT TYPE	TLF/ MACE (%)	TLR/ TVR (%)	ST (%)
Multivessel Disease	SPIRIT III + IV	785	1 year	EES PES	6.0* 12.2*	4.2* 8.0*	1.2 2.7
	COMPARE	130	2 years	EES PES	11.0* 20.0*	– –	– –
	COMPARE II	683	1 year	EES BES	9.1 8.6	– –	– –
Left Main	LEMAX	173	1 year	EES	15.0	2.9	0.6
	PRECOMBAT II	334	18 months	EES SES CABG	8.9 10.8 6.7	6.5 8.2 2.6*	0 0.3 1.1
	EXCELLENT	275	1 year	EES SES	7.5 13.9	2.5 7.0	0.6 1.7
	ESTROFA-LM	770	3 years	EES PES	18.0 16.4	6.0 4.0	1.4 1.6
	SPIRIT V	508	1 year	EES		6.6	0.4
Bifurcation	TWENTE	362	2 years	EES ZES	11.5 12.8	– –	– –
	Herrador et al	239	1 year	EES ZES	4.9* 23.1*	3.2* 17.5*	– –
Small Vessels	SPIRIT Small Vessels	150	1 year	EES	8.1	5.1	1.5
	Kitabata et al	643	1 year	EES SES	9.1 8.6	5.6 4.8	0 1.2
	SPIRIT III + IV	1,019	1 year	EES PES	4.5* 7.9*	2.4* 5.5*	0.2* 1.2*
SVG	Kitabata et al	331	2 years	EES S+PES	18.2* 35.0*	1.1* 11.6*	0 0.8
CTO	Valenti et al	258	9 months	EES PES	8.9* 22.6*	8.0* 20.5*	0* 3.4*
	Moreno et al	207	1 year	EES SES	11.1 15.9	– –	0 3.0
In-Stent	Almalla et al	174	1 year	EES PES	4.5 13.6	1.0* 11.5*	0 2.1
Restenosis	Markovic et al	198	2 years	EES PES	18.7 15.0	13.2 9.3	2.2 1.9

Note: *$P < 0.05$.
Abbreviations: N, number of patients; FU, follow-up; TLF, target lesion failure; MACE, major adverse cardiac events; TLR, target lesion revascularization; TVR, target vessel revascularization; ST, stent thrombosis; SVG, saphenous vein graft; CTO, chronic total occlusion.

noninferiority of EES in comparison with coronary artery bypass graft (CABG) for the treatment of multivessel coronary artery disease patients.

Left main coronary artery (LMCA). A multicenter registry named LEMAX enrolled 173 consecutive patients that received EES for unprotected left main coronary artery (LMCA). Out of these, 140 (81%) had involvement of the distal segment of LMCA and 129/140 (92%) were treated with provisional side branch T-stenting with a side branch stenting rate of 20%. Angiographic success was achieved in all cases. At 12 months, the cumulative rate of adverse cardiac or cerebrovascular events (MACCE) was 15%, death rate from any cause was 2.9%, stroke was 2.3%, Q-wave myocardial infarction was 1.2%, non-Q-wave myocardial infarction was 3.5%, TLR was 2.9%, and definite or probable stent thrombosis was 0.6%. Therefore, this study revealed that unprotected LMCA stenting using EES and a strategy of provisional side branch T-stenting for distal lesions is safe and effective at midterm follow-up with a relatively low rate of events and reintervention at 1 year.[23]

The PRECOMBAT-2 study assessed 334 consecutive patients who received EES for unprotected LMCA and the results were compared with those of SES and CABG from the previous randomized study PRECOMBAT performed by the same authors. The second-generation EES showed a comparable 18-month composite incidence of death, AMI, stroke, and ischemia-driven target vessel revascularization as SES (EES = 8.9% vs SES = 10.8%, 95% CI = 0.51–1.40, $P = 0.51$) and CABG (6.7%, 95% CI = 0.78–2.54, $P = 0.26$). However, the incidence of ischemia-driven target vessel revascularization in the EES group was higher than in the CABG group (EES = 6.5% vs CABG = 2.6%, 95% CI = 1.17–6.58, $P = 0.02$), but comparable to the SES group (8.2%, 95% CI = 0.64–2.06, $P = 0.65$). Late loss and restenosis rates in the branch were slightly lower in EES than in SES patients. Furthermore, a focal pattern was predominant in restenotic lesions. This study came to the conclusion that the second-generation EES had an 18-month clinical outcome similar to that of the first-generation SES but more ischemia-driven target vessel revascularization than CABG.[24]

The EXCELLENT registry evaluated the efficacy and safety of EES and SES for the treatment of LMCA in 275 patients. MACE at 1 year was comparable between the two groups (EES = 7.5% vs SES = 13.9%, hazard ratio [HR] = 0.55, $P = 0.117$). However, after multivariable or propensity score adjustment, the rate of MACE was significantly lower for EES compared with SES (multivariable adjusted HR = 0.42, $P = 0.030$; propensity score-adjusted HR = 0.43, $P = 0.037$). These results were mainly driven from the numerically lower rate of repeat revascularization in the EES group (EES = 2.5% vs SES = 7.0%, $P = 0.096$). As for hard end point of death (EES = 4.4% vs SES = 7.0%, $P = 0.383$) or AMI (EES = 0.6% vs SES = 0.0%, $P = 0.396$) and stent thrombosis (EES = 0.6% vs SES = 1.7%, $P = 0.384$), no differences were found between both DES groups. The conclusion of this study was that EES promote lower MACE rates than SES (statistically significant only after adjustment) in patients receiving unprotected LMCA stenting, the difference between the MACE rates being in favor of EES mainly driven by numerically lower rates of repeat revascularization.[25]

The ESTROFA-LM is a multicenter retrospective registry that enrolled consecutive patients with unprotected LMCA disease treated with PES or EES. A total of 770 patients have been included at 21 centers, 415 patients being treated with PES and 355 with EES. The use of 2 stents was more frequent with PES (PES = 17% vs EES = 10.4%, $P = 0.007$), whereas intravascular ultrasound (IVUS) was more frequently used in the EES group (PES = 26% vs EES = 35.2%, $P = 0.006$). The 3-year survival free rates for death and AMI were 86.1% for PES and 87.3% for EES ($P = 0.50$), whereas for death, AMI, and TLR were 83.6% for PES and 82% for EES ($P = 0.60$). Definite or probable thrombosis was 1.6% for PES and 1.4% for EES ($P = 0.80$). The use of 2 stents, age, diabetes, and acute coronary syndromes were independent predictors of mortality. In the subgroup of distal lesions, the use of intravascular ultrasound was an independent predictor of better outcome. The results showed comparable safety and efficacy for PES and EES in the treatment of LMCA disease at 3 years. The use of bifurcation stenting techniques in distal lesions was a relevant independent predictor for events; therefore, IVUS-guided PCI should be encouraged in these patients[26] (Table 2).

The EXCEL trial is the major ongoing randomized clinical trial comparing PCI and CABG for treatment of LMCA. The aim of the study is to establish the safety and efficacy of the Xience Prime or Xience V everolimus-eluting stents in subjects with unprotected LMCA disease by comparing them with CABG. The estimated enrollment is 2600 patients with unprotected LMCA disease.The clinical exclusion criteria of the EXCEL trial are prior PCI of the left main trunk at any time prior to randomization; prior PCI of any other coronary artery lesions within 1 year prior to randomization; prior CABG at any time prior to randomization; need for any concomitant cardiac surgery other than CABG; any recent myocardial infarction with CK-MB levels still elevated; subjects unable to tolerate, obtain, or comply with dual antiplatelet therapy for at least 1 year; subjects requiring or who may require additional surgery within 1 year; the presence of any clinical condition(s) that leads the participating interventional cardiologist or participating cardiac surgeon to believe that there is no clinical equipoise; pregnancy or intention to become pregnant; non cardiac comorbidities with life expectancy less than 3 years; and other investigational drug or device studies that have not reached their primary end point. The angiographic exclusion criteria are LMCA diameter stenosis $< 50\%$; SYNTAX score ≥ 33; left main reference vessel diameter < 2.25 mm or > 4.25 mm; and the presence of specific coronary lesion characteristics or other cardiac condition(s) that leads the participating interventional cardiologist or the participating cardiac surgeon to believe that

there is no clinical equipoise.[27] The importance of the EXCEL trial is mostly based on the number of subjects enrolled as well as on the characteristics of the DES in use for PCI. This trial will be the largest one comparing PCI and CABG for treatment of LMCA, even larger than the SYNTAX trial. The second-generation EES is superior to the first-generation PES used in the SYNTAX trial according to the results of the randomized trials in patients with noncomplex coronary artery disease;[28,29] however, there are few data on the comparison between EES and PES in patients with LMCA disease. Finally, it should be pointed out that the exclusion of patients with high SYNTAX scores (≥ 33) in EXCEL trial, which restricts the evaluation to the patients with low or intermediate SYNTAX scores, enhances expectation of better outcomes for PCI in the EXCEL trial rather than the ones obtained in SYNTAX trial.

The 2 trials available comparing the second-generation EES and the first-generation SES for the treatment of LMCA disease assessed a relatively small number of patients and showed no statistically significant clinical or angiographic difference between both DES. Although EES is more effective than PES in de novo lesions, the only reasonable large trial comparing EES and PES for the treatment of LMCA disease has not shown such better performance of EES over PES. Nevertheless, more data from randomized trials are required to evaluate EES in comparison with other DES for the treatment of LMCA disease. As for CABG, almost all large trials comparing DES and CABG for the treatment of LMCA disease have used first-generation DES. The only trial currently available comparing EES and CABG was similar with respect to the composite end point of death, myocardial infarction, stroke, and ischemia-driven TVR; however, there was more ischemia-driven TVR of EES in comparison with CABG. The EXCEL trial is the major ongoing randomized clinical trial comparing PCI and CABG for treatment of LMCA, and, for this trial, only EES will be used. The importance of EXCEL results reaches not only the comparison between EES and CABG, but also a broader subject, which is the comparison between DES and CABG for treatment of LMCA disease.

Bifurcation lesions. The challenge of bifurcation treatment is to combine an effective eluting agent with the best platform, which requires thin struts, high radial strength, and strut architecture to preserve side branches (open cells). Most of the studies addressing the technique for bifurcation lesions were conducted with bare metal stents or first-generation DES; thus, evidence of EES in bifurcation lesions comes from a subgroup analysis of large trials and registries.

The SPIRIT V Study was a 2700-patient real-world registry that provided an evaluation of the EES performance in complex lesion subsets. A subgroup analysis of patients who underwent treatment of bifurcation lesions (n = 508) was performed and showed that despite a higher patient and lesion complexity, the treatment of patients with bifurcation lesions using EES was safe and effective with low overall event rates that were similar to those without bifurcation lesions (TLR of 6.6% in patients with bifurcation lesions vs 4.7% in those with nonbifurcation lesions, $P = 0.09$), as well as comparable definite stent thrombosis rates in both bifurcation and nonbifurcation lesions groups at 1 year (bifurcation lesions = 0.4% vs nonbifurcation lesions = 0.7%, $P = 0.552$).[30]

The TWENTE trial was a noninferiority study that compared ZES with EES in a real-world setting. Acute coronary syndromes were present in 52% of 1391 patients and off-label features in 77%, which is consistent with a complex patient subset. Bifurcation lesions were present in 362 patients, and the comparison between both DES in this subset showed similar TVF rates (ZES = 12.8% vs EES = 11.5%, $P = 0.68$) at 2 years.[20]

Another study (nonrandomized) compared ZES (n = 110) and EES (n = 129) in bifurcation lesions. The 12-month follow-up found that patients treated with ZES had higher statistically significant rates of MACE than EES (ZES = 23.1% vs EES = 4.9%, $P = 0.001$), driven mainly by TLR (ZES = 17% vs EES = 3.2%, $P < 0.001$)[31] (Table 2).

In the SPIRIT III trial, transient or permanent small side branch occlusion occurred less frequently in the thin strut and polymer EES compared with the thicker strut PES (EES = 2,8% vs PES = 5,2%, $P = 0,009$).[29]

There are few data and no randomized trials designed to evaluate the use of second-generation EES in the treatment of bifurcation lesions. Although SPIRIT III is not a bifurcation trial, the results suggest lesser side branch compromising with EES than PES, especially when using provisional stent technique, which is expected due to the thinner struts and modern design of EES in comparison with the old-fashioned PES. Two studies comparing EES with other second-generation DES showed conflicting results on EES superiority. The SPIRIT V showed that EES is safe and effective for the treatment of bifurcation lesions with low overall event rates comparable to those of nonbifurcation lesions.

Small vessels. The SPIRIT Small Vessel trial was designed to evaluate the safety and efficacy of EES in 150 patients with coronary artery disease in small vessels (stent diameter = 2.25 mm). At 1-year follow-up, TLF was reported in 8.1% of patients, cardiac death in 1.5%, target vessel AMI in 1.5%, ischemia-driven TLR in 5.1%, and definite or probable stent thrombosis in 1,5%. The 8-month angiographic in-stent late loss was 0.2 ± 0.4 mm. The authors concluded that EES is safe and effective in the treatment of small coronary arteries.[32]

Another study compared the long-term clinical outcomes between EES and SES in patients with coronary artery disease in small vessels (stents ≤ 2.5 mm of diameter). A cohort of 643 patients treated with EES (220 patients with 245 lesions)

or SES (423 patients with 523 lesions) showed no significant difference between EES and SES in TLR (EES = 5.6% vs SES = 4.8%, $P = 0.68$) and TVR (EES = 5.6% vs SES = 7.6%, $P = 0.33$) rates at 1 year. MACE rates were also similar in both DES groups (EES = 9.1% vs SES = 8.6%, $P = 0.83$). Stent thrombosis was 0% in the EES group and 1.2% in the SES group ($P = 0.17$). In this study, EES demonstrated comparable clinical outcomes to those of SES in small size coronary arteries. The absence of stent thrombosis among patients treated with EES suggests a satisfactory safety profile of the second-generation EES in small vessels.[33]

A pooled analysis from the SPIRIT III and SPIRIT IV trials with 4689 patients was performed to compare EES with PES for the treatment of small (reference vessel diameter < 2.5 mm) and larger (reference vessel diameter ≥ 2.5 mm) coronary arteries. Lesion length, reference vessel diameter, and percent of diabetics were matched between stent types. The 1-year follow-up of 1019 patients with small coronary arteries disease showed significant lower rates of MACE (EES = 4.5% vs PES = 7.9%, $P = 0.04$), TLF (EES = 4.4% vs PES = 7.9%, $P = 0.03$), TLR (EES = 2.4% vs PES = 5.5%, $P = 0.02$), and stent thrombosis (EES = 0.2% vs PES = 1.2%, $P = 0.04$) in the EES group compared with the PES group. Relative benefits of EES over PES were comparable in small and larger vessels (P interaction > 0.05) although the absolute benefits were greater in patients with small coronary arteries disease[34] (Table 2).

There are also few data on the use of second-generation EES in small vessels; however, the currently available outcomes support the safety and efficacy of EES in small size coronary arteries. The 2 studies discussed above that compared EES with first-generation DES showed that EES was superior to PES but not to SES for the treatment of small coronary arteries.

Saphenous vein graft. Kitabata et al[35] compared the safety and efficacy between EES (88 patients) and first-generation DES (243 patients) in saphenous vein grafts. At the 2-year follow-up, MACE was significantly lower in patients who underwent EES deployment than first-generation DES (EES = 18.2% vs first-generation DES = 35.0%, $P = 0.003$), mainly driven by significant lower TVR (EES = 6.8% vs first-generation DES = 24.5%, $P < 0.001$) and TLR rates (EES = 1.1% vs first-generation DES = 11.6%, $P = 0.005$). Stent thrombosis was low and similar between the 2 groups composed of different DES generations (EES = 0% vs first-generation DES = 0.8%, $P = 1.0$). On multivariate analysis, the type of DES implanted and the graft age were the only independent predictors of MACE[35] (Table 2).

The superiority of EES over first-generation DES shown in the treatment of de novo lesions in native coronary arteries was also demonstrated in saphenous vein grafts by the study discussed above; however, more data from randomized trials are required to consider EES as first choice for the saphenous vein graft disease setting.

Chronic total occlusion. Chronic total occlusions are a challenge indication for stent deployment because of the difficulty crossing the occlusion segment, the usually long stented coronary artery segment, and the threat of restenosis.

A comparison between EES and PES in 258 patients with long (≥ 40 mm) total chronic occlusions showed lower binary restenosis rates for EES in comparison with PES (EES = 11.8% vs PES = 31.4%, $P = 0.001$), with overall patency rate of 98% for EES and 85% for PES at 9 months ($P = 0.003$). The EES also promoted lower rates of MACE (EES = 8.9% vs PES = 22.6%, $P = 0.003$) and definite or probable stent thrombosis (EES = 0% vs PES = 3.4%, $P = 0.048$) at 9 months. In the multivariate analysis, EES was the only variable independently related to the risk of binary angiographic restenosis with an odds ratio of 0.29 (95% CI = 0.14–0.62; $P = 0.002$).[36]

A randomized trial compared EES with SES in 207 patients with coronary total occlusions and estimated time since occlusion > 2 weeks. The primary end point of in-stent late loss at the 9-month angiographic follow-up was 0.29 ± 0.60 mm for SES and 0.13 ± 0.69 mm for EES. The observed difference in in-stent late loss between both groups was −0.16 mm (95% CI = 0.04 to −0.36 mm; P for noninferiority < 0.01). The rate of binary angiographic restenosis was 10.8% for SES and 9.1% for EES ($P = 0.709$), whereas the rate of vessel reocclusion was 3.2% for SES and 1.1% for EES ($P = 0.339$). There was also no significant difference in MACE (SES = 15.9% vs EES = 11.1%, $P = 0.335$) and probable or definitive stent thrombosis (SES = 3.0% vs EES = 0%, $P = 0.075$) between both DES groups at 12-month clinical follow-up.[37] (Table 2).

Chronic total occlusions are an independent risk factor for restenosis and PCI with bare metal stents results in high rates of restenosis.[38] Thus, DES is mandatory for this setting if there is no contraindication. The studies of chronic total occlusions discussed above showed clear superiority of EES over PES with even decreased risk of stent thrombosis; however, no significant advantage was demonstrated of EES over SES.

In-stent restenosis. DES emerged as first choice for the treatment of bare metal stent restenosis after showing better results when compared with other techniques such as balloon angioplasty, cutting-balloon, brachytherapy, and another bare metal stent inside in-stent restenotic lesion.[39–43]

EES was compared with PES for the treatment of bare metal stent restenosis in 174 patients. The MACE rates at 1-year follow-up were 4.5% for EES and 13.6% for PES ($P = 0.066$). The TLR rates were higher in the PES group at 1-year follow-up compared with the EES group (EES = 1% vs PES = 11.5%, $P = 0.02$). There was no significant difference in the rates of death (EES = 3% vs PES = 2.1%, $P = 0.68$), AMI (EES = 0% vs PES = 4.2%, $P = 0.098$), and definite stent thrombosis (EES = 0% vs PES = 2.1%, $P = 0.2$) at the 1-year follow-up in both groups. The use of PES for treatment

of in-stent restenosis was the only independent predictor of recurrent TLR at the 1-year follow-up (odds ratio [OR] = 1.11, 95% CI = 1.05–1.18; $P = 0.02$). During the complete follow-up period (PES = 42.2 ± 22.2 and EES = 18.3 ± 8.2 months), the rates of TLR, AMI, death, MACE, and definite stent thrombosis were not different between the 2 treatment groups. The authors concluded that EES resulted in reduced rates of TLR at 1 year of follow-up compared to PES when used for treatment of bare metal in-stent restenosis; however, at long-term follow-up, the event rates between EES and PES were comparable.[44]

Another study evaluated the outcomes of EES (n = 91) and PES (n = 107) for the treatment of restenosis in both bare metal and DES. Dual antiplatelet therapy was given to all patients for 6 months. The outcomes were evaluated by angiographic control at 6 months and clinical follow-up at 24 months. There was no significant difference in the rates of MACE (EES = 18.7% vs PES = 15.0%, $P = 0.48$) and TLR (EES = 13.2% vs PES = 9.3%, $P = 0.39$) at 24 months. In-stent late loss (EES = 0.20 ± 0.39 mm vs PES = 0.18 ± 0.31 mm, $P = 0.34$) and binary restenosis (EES = 18.0% vs PES = 16.7%, $P = 0.85$) at 6 months were also similar in both groups. In the multivariable analysis stented length ($P = 0.014$), minimal lumen diameter post-stenting ($P < 0.01$) and repeat restenosis ($P < 0.001$) were found as predictors of higher late lumen loss but not type of DES or presence of diabetes mellitus. This study showed similar clinical and angiographic outcomes between EES and PES; however, all the identified predictors of higher late lumen loss as well as higher rates of DES restenosis (EES = 44.8% vs PES = 30.7%, $P = 0.04$) were more present as lesion characteristics or procedural data in the EES group, which could have led to biased results in favor of PES[45] (Table 2).

First-generation DES are clearly superior to balloon catheter, cutting-balloon, brachytherapy, and other bare metal stents to treat bare metal in-stent restenosis. The 2 studies discussed above present conflicting results since one study showed that EES was superior to PES due to a significant lowering of TLR in 1 year of follow-up but not at long-term follow-up, while the other one revealed similar clinical and angiographic outcomes between EES and PES with potentially biased results in favor of PES.

Safety

The safety of a DES is evaluated through the clinical end points of cardiac death and AMI, as well as stent thrombosis.

The articles discussed above showed no difference in cardiac death between EES and first-generation DES. As for AMI, EES showed to be more effective than PES in reducing AMI according to the SPIRIT IV and COMPARE trials, which enrolled patients with de novo coronary lesions; however, no benefits were found in other studies of de novo lesions or specific settings. Also, no benefits from EES over SES or other second-generation DES related to AMI were shown by the studies discussed above. These results are supported by a meta-analysis of 11 randomized trials that compared EES with SES and showed no significant differences in the risk of cardiac death or AMI between both DES.[46] Therefore, there is no clear evidence that EES is superior to first-generation or other second-generation DES in relation to the clinical safety end points comprising cardiac death and AMI; nevertheless, EES seems to decrease AMI in patients with de novo lesions when compared to PES.

According to the Academic Research Consortium (ARC), definite stent thrombosis is described in coronary angiography as the presence of a thrombus that originates in the stent or in the segment 5 mm proximal or distal to the stent with the presence of at least 1 of the following criteria within a 48-hour time window: acute onset of ischemic symptoms at rest, new ischemic ECG changes that suggest acute ischemia, typical rise and fall in cardiac biomarkers, nonocclusive thrombus, or occlusive thrombus. Pathological description of stent thrombosis is characterized as evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy. Definite stent thrombosis is confirmed by either angiographic or pathological findings. The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered definite stent thrombosis (silent occlusion). Probable stent thrombosis is defined as presence of any unexplained death within the first 30 days after the index procedure or any AMI in the territory of the implanted stent without angiographic confirmation of stent thrombosis. Stent thrombosis timing categories are defined as follows: acute stent thrombosis within 0 to 24 hours after stent implantation, subacute stent thrombosis from 24 hours to 30 days after stent implantation, late stent thrombosis from 30 days to 1 year after stent implantation, and very late stent thrombosis more than 1 year after stent implantation.[47]

EES showed reduced stent thrombosis when compared with PES in the SPIRIT IV and COMPARE trials, as well as in the SPIRIT III trial, which enrolled patients with de novo and bifurcation lesions, respectively. EES also presented lower stent thrombosis rates when compared with SES in the SORT OUT IV trial; however, similar stent thrombosis rates were found when compared with SES in the EXCELLENT trial. In the RESOLUTE All Comers trial, the initial reduced stent thrombosis rate of EES over ZES at the 1-year follow-up was not confirmed at the 2-year follow-up. Thus, there is important evidence that EES reduce stent thrombosis when compared with PES, some evidence that EES decrease stent thrombosis when compared with SES, and no evidence of EES benefits over other second-generation DES regarding stent thrombosis.

The suggested reduced rates of stent thrombosis from EES over first-generation DES were the mainstay for a meta-analysis of 11 comparative randomized controlled trials with 16,775 patients that aimed to evaluate the risk of 2-year definite

stent thrombosis between EES and other DES. From the 11 randomized controlled trials, 5 trials compared EES with PES, 5 trials compared EES with SES, and 1 trial (RESOLUTE All Comers) compared EES with ZES. By 2 years, definite stent thrombosis with EES compared with pooled DES occurred in 0.5% versus 1.3% patients, respectively (relative risk [RR] = 0.38, 95% CI = 0.240.59, $P < 0.0001$). Similar results were observed when the broader definition of definite/probable stent thrombosis was considered (RR = 0.46, 95% CI = 0.33–0.66, $P < 0.0001$). EES compared with other DES reduced the risk of early (within 30 days), late (31 days to 1 year), cumulative 1-year, and very late (1 to 2 years) stent thrombosis, being the significant reduction of definite stent thrombosis an effect that appears early and increases in magnitude through at least 2 years.[48]

Another meta-analysis of 117,762 patient-years from 76 randomized trials of de novo coronary lesions showed no increase in the risk of stent thrombosis with DES when using appropriate concomitant antiplatelet theraphy and a reduction in the risk of stent thrombosis with EES compared with BMS in the short term (≤ 1 year) and long term (> 1 year). The results were consistent even when > 6-month trials with clopidogrel in the DES arm were separately analyzed. The reduced risk of stent thrombosis with EES compared with BMS is difficult to explain but could result from extended dual-antiplatelet therapy with DES. EES also showed lower definite and combined definite or probable stent thrombosis rates in comparison with SES and PES, confirming that EES were safer compared with first-generation DES as found in the previously discussed trials[49] (Fig. 1).

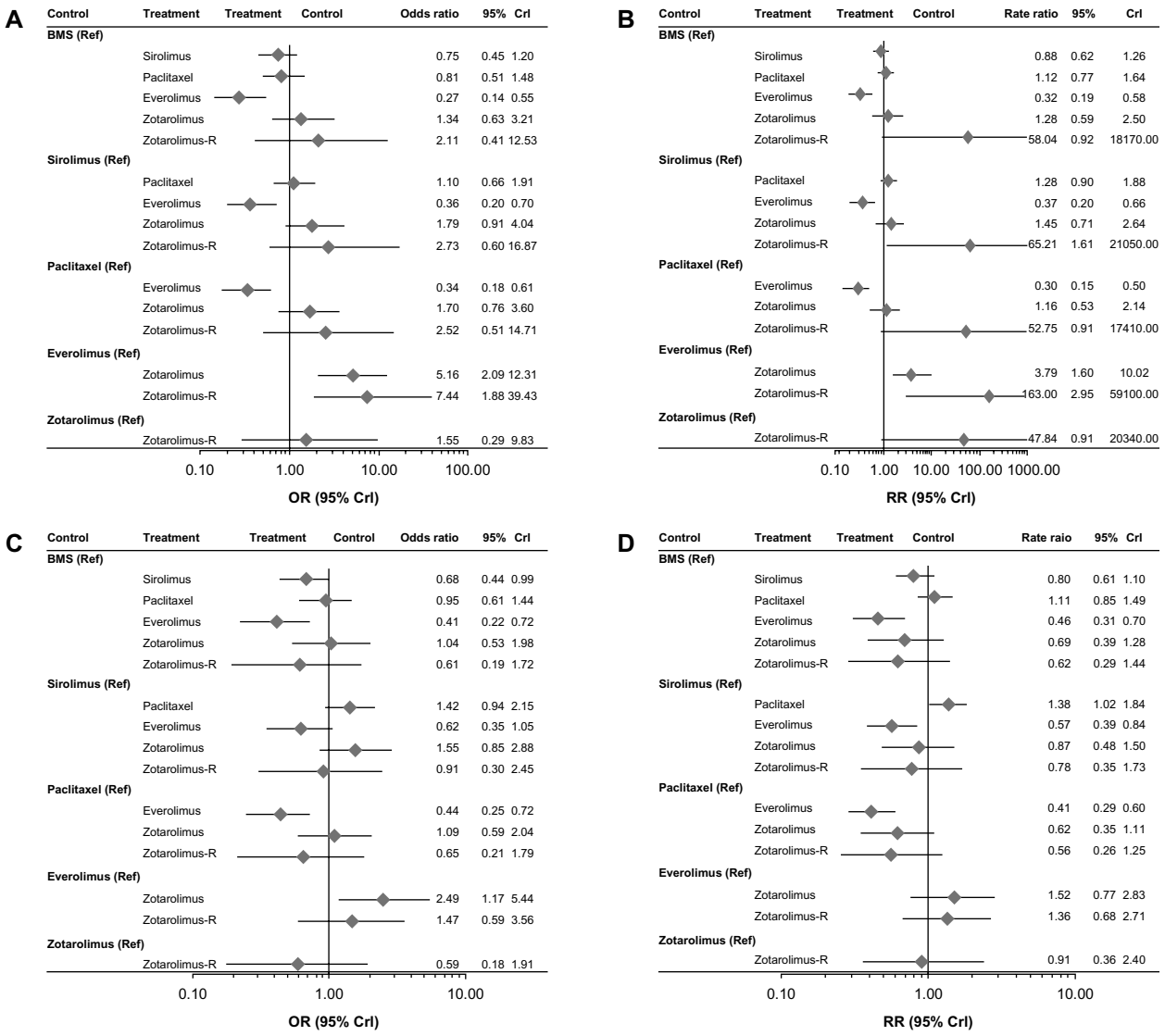

Figure 1. Stent type and risk of stent thrombosis. (**A**) Stent type and short-term risk of definite stent thrombosis. (**B**) Stent type and long-term risk of definite stent thrombosis. (**C**) Stent type and short-term risk of definite or probable stent thrombosis. (**D**) Stent type and long-term risk of definite or probable stent thrombosis. (Adapted from Bangalore et al. *Circulation.* 2012;125:1873–91).

Efficacy

The efficacy of a DES is evaluated mainly through the TLR or TVR end points, which assess the capacity of a DES to sustain the mid- and long-term angiographic result. As in-stent restenosis is the main cause of stent failure and usually occurs in the first 6 months, mid-term evaluation is important to identify this stent obstructive phenomenon. Long-term assessment is also important due to in-stent late restenosis as well as to the recent concept of in-stent neoatherosclerosis.

The studies discussed above in this article showed that EES is more effective than PES in de novo lesions (SPIRIT IV and COMPARE), multivessel disease (pooled analysis of SPIRIT III and IV and COMPARE), total chronic occlusions (Valenti et al[36]), small vessels (pooled analysis of SPIRIT III and IV), and saphenous vein graft disease (Kitabata et al[35]). EES superiority over SES is not as clear as it is over PES since only 1 of the previously discussed studies demonstrated lower rates of TLR and MACE (EXCELLENT—LMCA disease: statistically significant only after adjustment) for EES in comparison with SES while most of the other studies showed similar results (EXCELLENT—de novo lesions, PRECOMBAT-2—LMCA disease, Kitabata et al[33]—small vessels, and Moreno et al[37]—chronic total occlusions); however, no study showed SES superiority over EES. In order to clarify the possible superiority of EES in comparison with SES, a systematic review and meta-analysis of 11 randomized trials comparing EES and SES was performed and a significant reduction in the risk of repeat revascularization in the EES arm was found (OR = 0.85, 95% CI = 0.71–1.00, $P = 0.047$).[46]

Regarding second-generation DES, there are few studies comparing EES with other second-generation DES. The robust RESOLUTE All Comers randomized trial showed comparable TLR and TLF between EES and ZES in de novo lesions at 1- and 2-year follow-up. Conversely, a small study (Herrador et al[31]) showed lower TLR for EES in comparison with ZES in bifurcation lesions at 12-month follow-up, while a subanalysis of the TWENTE trial in bifurcation lesions demonstrated similar TLF rates.

A meta-analysis of 117,762 patient-years from 76 randomized trials of de novo coronary lesions showed that DES (including EES) are highly efficacious in reducing short- and long-term TVR and TLR in comparison with BMS. Furthermore, the results demonstrated significant differences among DES types, showing lower rates of TVR and TLR for EES compared with PES and ZES-Endeavor Sprint (Medtronic, Fridley, Minnesota), but similar rates of TVR and TLR for EES in comparison to SES and ZES-Endeavor Resolute (Medtronic) in the short and long term[49] (Fig. 2).

Several studies compared first-generation DES with CABG for the treatment of LMCA disease and evidenced that CABG was superior to first-generation DES driven by lower rates of TVR, especially among high SYNTAX score patients. EES was also compared with CABG for the treatment of LMCA in the PRECOMBAT-2 study that demonstrated higher TVR rates for patients who underwent EES. The ongoing robust and randomized EXCEL trial comparing EES with CABG for the treatment of LMCA disease will probably define the role of PCI with EES for this setting in patients with low and intermediate SYNTAX scores.

Specific Group of Patients

EES were evaluated not only in different anatomical settings, but also in different profile of patients such as diabetics and women as well as under a special and threatening clinical condition—AMI.

Diabetes. The use of DES is of particular interest for restenosis in high-risk patients such as diabetic patients, diabetes being one of the most important predictors of in-stent restenosis. Diabetic patients respond less favorably to revascularization and have more than twice the risk of coronary artery disease. The first-generation DES dramatically reduced the in-stent restenosis in comparison with BMS; however, PCI in diabetic patients are still challenging in the DES era because of the more extensive and aggressive coronary artery disease as well as the presence of comorbidities.

The ESSENCE-DIABETES trial was a prospective, multicenter, and randomized study that compared EES (n = 149) with SES (n = 151) in diabetic patients with de novo lesions. EES were noninferior to SES for 8-month in-segment late loss (EES = 0.23 ± 0.27 mm vs SES = 0.37 ± 0.52 mm, 95% CI = −0.25 to −0.02, upper 1-sided 95% CI = −0.04, $P < 0.001$ for noninferiority). EES promoted reductions in in-stent restenosis (EES = 0% vs SES = 4.7%, $P = 0.029$) and in-segment restenosis (EES = 0.9% vs SES = 6.5%, $P = 0.035$) rates at 8 months; however, in-stent late loss (EES = 0.11 ± 0.26 mm vs SES = 0.20 ± 0.49 mm, $P = 0.114$) was not statistically different between the 2 groups. The clinical events at 12 months, ischemia-driven TLR (EES = 0.7% vs SES = 2.6%, $P = 0.317$), death (EES = 1.3% vs SES = 3.3%, $P = 0.448$), AMI (EES = 0% vs SES = 1.3%, $P = 0.498$), and MACE (EES = 2.0% vs SES = 5.3%, $P = 0.218$) were not statistically different between the 2 groups. Therefore, this trial showed that EES were noninferior to SES in reducing in-segment late loss, EES reduced angiographic restenosis at 8 months, and EES promoted no safety or efficacy clinical benefits over SES in diabetic patients.[50]

The SCAAR (Swedish Coronary Angiography and Angioplasty Registry) analyzed 4751 all-comer diabetic patients treated with 8134 DES (EES = 3928, PES = 2836, and SES = 1370). The results showed that EES presented less stent thrombosis (SES vs EES HR = 2.87, 95% CI = 1.08–7.61, and PES vs EES HR = 1.74, 95% CI = 0.82–3.71) and mortality (SES vs EES HR = 2.02, 95% CI = 1.03–3.98, and PES vs EES HR = 1.69, 95% CI = 1.06–2.72) in comparison with SES and PES. Hence, these results suggest better safety rather than efficacy with EES when compared with SES or PES, since the restenosis rates were similar between EES and first-generation

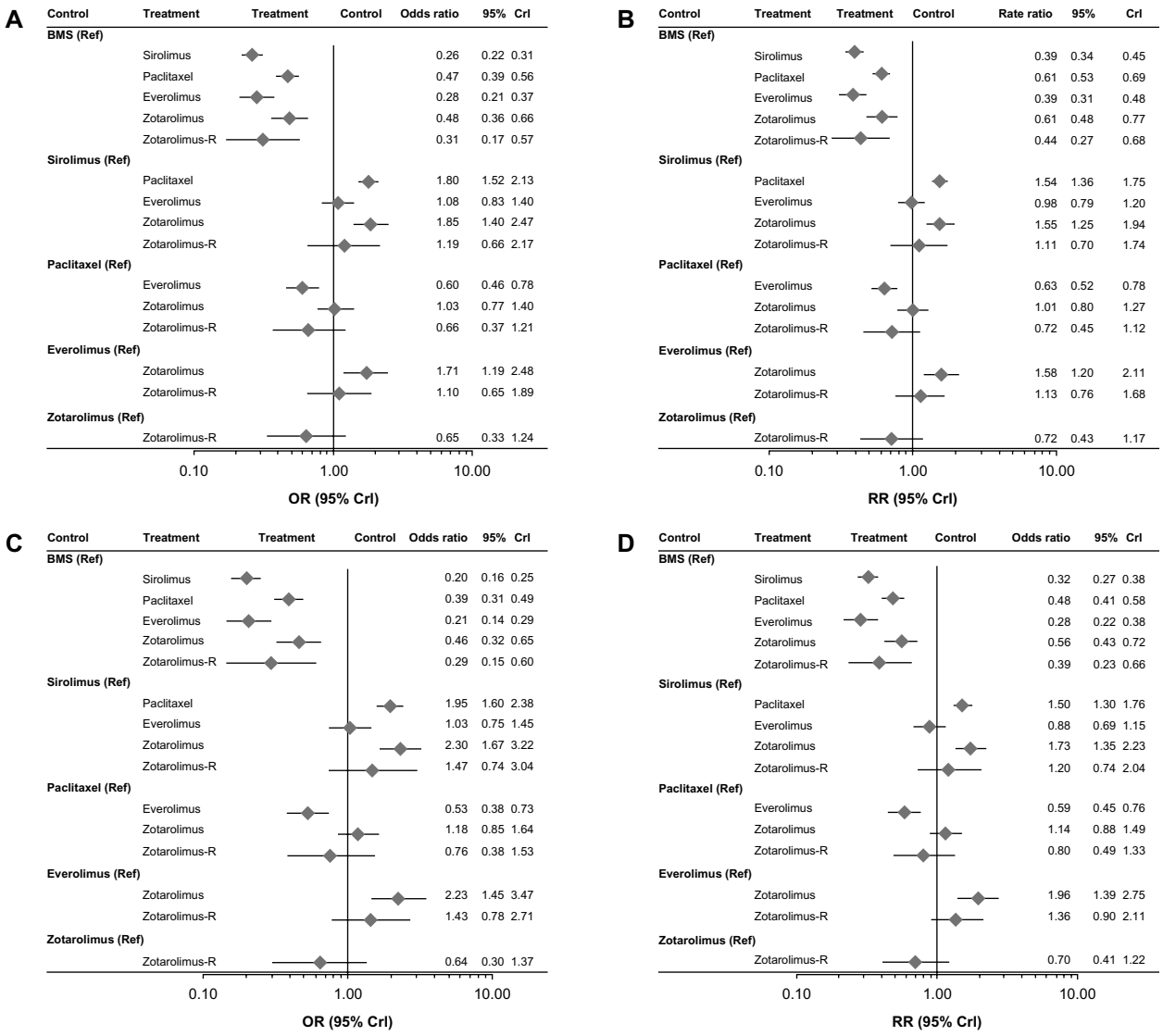

Figure 2. Stent type and risk of TVR and TLR. (**A**) Stent type and short-term risk of TVR. (**B**) Stent type and long-term risk of TVR. (**C**) Stent type and sort-term risk of TLR. (**D**) Stent type and long-term risk of TLR. (Adapted from Bangalore et al. *Circulation*. 2012;125:1873–91).

DES (SES vs EES HR = 1.26, 95% CI = 0.77–2.08, and PES vs EES HR = 1.05, 95% CI = 0.71–1.55).[51]

The absence of efficacy superiority of EES over PES in diabetic patients was also observed in the SPIRIT IV trial (diabetic = 1185 patients and nondiabetic = 2498 patients). EES compared with PES reduced TLF in nondiabetic patients (EES = 3.1% vs PES = 6.7%, $P < 0.001$) with significant reductions in AMI, stent thrombosis, and target lesion revascularization. However, no significant difference in TLF (EES = 6.4% vs PES = 6.9%, respectively, $P = 0.80$) or any of its components was shown among diabetic patients.[52]

The pooled analysis from SPIRIT II, III IV and COMPARE trials that included a total of 6780 patients, of these 1869 (27.6%), who were diabetic patients, also demonstrated no significant difference between EES and PES stent types in any evaluated safety or efficacy outcomes in diabetic patients.[53]

The SPIRIT V Diabetic Study randomized 324 diabetic (insulin and non-insulin dependent) patients for EES or PES. The primary end point was sequential noninferiority and superiority of EES for in-stent late loss at 9 months. Secondary clinical end points included stent thrombosis, death, AMI, and repeat revascularization rates up to 1 year. The results evidenced lower in-stent late loss at 9 months for EES compared with PES (EES = 0.19 mm vs PES = 0.39 mm, $P = 0.0001$). The composite of death, AMI, and TVR rates were similar in both groups at 1 year (EES = 16.3% vs PES = 16.4%). There was no thrombosis through 1 year with EES compared with 2% with PES ($P = 0.11$). The authors concluded that EES compared with PES resulted in significantly better neointimal hyperplasia inhibition but comparable safety outcomes[54] (Table 3).

Diabetes is one of the most important predictors of in-stent restenosis for BMS. The first-generation DES dramatically reduced in-stent restenosis rates in diabetic patients in comparison with bare metal stents; nevertheless, the expected superiority of the second-generation EES over

the first-generation DES was not confirmed by the safety and efficacy outcomes of the main trials in diabetic patients (ESSENCE-DIABETES; SPIRIT IV; pool of SPIRIT II, III, and IV + COMPARE; and SPIRIT V).

Women. Women are underrepresented in coronary clinical research, and few data are available from randomized head-to-head comparisons of EES with other DES in female patients.

The SPIRIT Women was the first interventional cardiology trial dedicated exclusively to women, focusing on symptoms at presentation and referral time to coronary intervention, as well as safety and efficacy of the EES in 1573 women. The 1- and 2-year composite end point of all death, AMI, and TVR was 12% and 15%, respectively. At the 1- and 2-year follow-ups, the TLR rates were 2.4% and 3.6%, respectively. Definite or probable stent thrombosis occurred in 0.59% of women at 1 year and 0.73% at 2 years. The total referral time for coronary intervention was 4 days longer in women than in men according to the SPIRIT V study. The authors concluded that EES is safe and effective for women, with low TLR and stent thrombosis rates.[55]

A retrospective study with 1649 women evaluated the safety and efficacy of second-generation EES in comparison with first-generation SES. Baseline clinical characteristics were similar between stent types although more peripheral vascular disease and family history of coronary artery disease were seen in the SES group, while more unstable angina pectoris at initial diagnosis was more prevalent in the EES group. The EES group also had more type C and distal lesions. The SES group presented higher rates of TVR and MACE (EES = 10.8% vs SES = 14.7%, $P = 0.04$) at 1 year. Stent thrombosis tended to be higher in the SES group (EES = 0.4% vs SES = 1.5%, $P = 0.06$) at 12 months. After adjustment, multivariate analysis indicated that the EES group was less likely to have TVR and MACE (HR = 0.67, 95% CI = 0.47–0.95, $P = 0.024$) and had lower rates of stent thrombosis (HR = 0.09, 95% CI = 0.01–0.70, $P = 0.022$) at 1 year. Therefore, this trial showed that EES in women is associated with improvement in efficacy and safety profiles compared with SES.[56]

In the TWENTE trial, 382 women (27.5% of total patients) were randomized to EES or ZES. The predefined end point was TVF at 1 year. Patient-oriented composite end point was a prespecified secondary end point that comprised all-cause mortality, any myocardial infarction, and any repeat revascularization. Baseline and procedural characteristics were similar for females in both study arms except for smaller vessel and stent diameters in ZES-treated lesions. The 1-year follow-up showed similar rates of TVF (EES = 8.4% vs ZES = 8.9%, $P = 0.91$) and patient-oriented composite end point (EES = 12.1% vs ZES = 13.0%, $P = 0.79$) for women in both DES arms. Compared with men, women were older ($P < 0.01$) and had higher rates of diabetes mellitus (female = 26.4% vs male = 19.8%, $P = 0.01$) and hypertension (female = 63.6% vs male = 52.5%, $P < 0.01$); however, there was no significant gender difference in TVF (adjusted OR = 1.18, 95% CI = 0.73 to 1.92, $P = 0.50$). This gender-stratified TWENTE trial analysis revealed no significant difference in safety and efficacy clinical outcomes between second-generation EES and ZES in women[57] (Table 3).

The 3 gender studies focusing on PCI with second-generation DES in women showed that EES are equally safe and effective for women. The importance of these female gender studies is based on the usual lower number of female patients in comparison with male ones in most interventional cardiology studies. Another interesting finding was the longer total referral time for coronary intervention in women when compared with that in men, which suggests that chest pain is underestimated in women. Finally, 1 of these studies showed that second-generation EES were superior to first-generation SES in women, while another showed no significant difference in safety and efficacy clinical outcomes between the 2 second-generation EES and ZES in women.

Acute myocardial infarction. The use of DES in AMI still remains controversial due to concerns related to increased stent thrombosis and its lower efficacy in this specific setting. The safety concerns of increased stent thrombosis are theoretically based on the presence of thrombogenic stent polymer in a thrombogenic clinical setting as well as on the DES delayed reendothelialization, while efficacy concerns are theoretically

Table 3. Studies comparing EES with other DES in different profile of patients and in AMI.

SETTING	STUDY	N	FU	STENT TYPE	TLF/ MACE (%)	TLR/ TVR (%)	ST (%)
Diabetes	ESSENCE DIABETES	300	1 year	EES SES	2.0 5.3	0.7 2.6	0.7 0.7
	SPIRIT IV	1,185	1 year	EES PES	6.4 6.9	4.2 4.7	0.8 1.3
	SPIRIT V	324	1 year	EES PES	16.3 16.4	12.1 7.7	0 1.9
Women	SPIRIT Women	1,573	1 year 2 years	EES	12.0 15.0	2.4 3.6	0.59 0.73
	Badr	1,649	1 year	EES SES	10.8* 14.7*	5.8 5.0	0.4 1.5
	TWENTE	382	1 year	EES ZES	12.1 13.0	– –	– –
AMI	XIENCE USA	673	1 year	EES	9.1	4.1	1.08
	EXAMINATION	1498	1 year	EES BMS	11.9 14.2	2.1* 5.0*	0.9* 2.5*
	KAMIR	2,646	1 year	EES ZES	6.5* 8.7*	1.2 2.2	0.3* 1.6*
	XAMI	625	1 year	EES SES	4.0* 7.7*	1.2 0.9	1.2 2.7

Note: *$P < 0.05$.
Abbreviations: N, number of patients; FU, follow-up; TLF, target lesion failure; MACE, major adverse cardiac events; TLR, target lesion revascularization; TVR, target vessel revascularization; ST, stent thrombosis; AMI, acute myocardial infarction.

supported by the partial or total antiproliferative drug delivery inside a thrombus instead of the coronary wall.

Most of the trials of first-generation DES and second-generation EES (such as SPIRIT II, III, and IV trials) excluded patients presenting AMI, probably because of the higher mortality and the safety and efficacy concerns discussed above. Hence, AMI dedicated trials are the most appropriate way to study safety and efficacy of EES in this complex setting.

The XIENCE V USA was a large, prospective, multicenter, and real-world single-arm postmarket surveillance trial that aimed to compare clinical outcomes in 673 patients presenting AMI (ST elevation AMI [STEMI], n = 125) with patients without AMI (n = 3528) at 1 year. Defined stent thrombosis rates were 1.08% in AMI and 0.85% in the non-AMI group ($P = 0.49$) at 1 year. The late stent thrombosis (30 days to 1 year) rates were 0.31% in AMI and 0.47% in the non-AMI ($P = 0.75$). There was no significant difference in the rates of TLR (AMI = 4.1% vs non-AMI = 4.6%, $P = 0.61$) and TLF (AMI = 9.1% vs non-AMI = 8.5%, $P = 0.59$) at 1 year. Improvements in quality of life, angina frequency, angina stability, and physical limitations occurred at 6 months (each $P < 0.001$) and were sustained at 1 year in both groups. There was also no significant difference in clinical outcomes between STEMI and non-STEMI patients. Therefore, EES for patients with AMI promoted low rates of stent thrombosis, TLR, and TLF, similar to non-AMI patients.[58]

The EXAMINATION was a multicenter, prospective, and randomized trial, in which 1498 patients with STEMI within 48 hours after the onset of symptoms requiring emergent PCI were randomized (1:1) to PCI with EES or BMS. The primary end point defined as composite of all-cause death, any recurrent myocardial infarction, and any revascularization was similar in both groups (EES = 11.9% vs BMS = 14.2%, 95% CI = –5.75 to 1.07, $P = 0.19$) at 1 year. TLR (EES = 2.1% vs BMS = 5.0%, $P = 0.003$) and TVR (EES = 3.7% vs BMS = 6.8%, $P = 0.0077$) were significantly lower in the EES group. Definite stent thrombosis and combined definite or probable stent thrombosis rates were also significantly lower in the EES arm (EES = 0.5% vs BMS = 1.9% and EES = 0.9% vs BMS = 2.5%, respectively, both $P = 0.019$). Bleeding rates did not differ between groups. This trial showed that EES were not able to reduce MACE when compared with BMS in the setting of STEMI; however, EES reduced TLR and were associated with a lower incidence of stent thrombosis in comparison with BMS.[59]

A propensity score-matched analysis of 2646 patients from the registry KAMIR (Korea Acute Myocardial Infarction Registry) sought to compare EES (n = 1343) with ZES (n = 1343) in patients with AMI. The results showed significantly lower rates of TLF (EES = 6.5% vs ZES = 8.7%, $P = 0.029$) and probable or definite stent thrombosis (EES = 0.3% vs ZES = 1.6%, $P < 0.001$) for EES in comparison with ZES at 1-year. Furthermore, EES promoted lower rate of TLR (EES = 1.2% vs ZES = 2.2%, $P = 0.051$) than ZES. The incidence of recurrent nonfatal myocardial infarction and in-hospital or 1-year mortality was similar in both DES groups. This study corroborated the satisfactory results of EES in patients presenting AMI and showed that EES were superior to ZES in this setting through reduced rates of TLR and probable or definite stent thrombosis; however, it should be pointed out that the ZES used was the old-fashioned Endeavor Sprint (Medtronic) and not the newest and superior Endeavor Resolute or Resolute Integrity (Medtronic).[60]

The XAMI was an all-comer, randomized, and multicenter trial that compared the efficacy and safety of second-generation EES with first-generation SES in primary PCI for patients presenting AMI. A total of 625 patients with AMI were randomized (2:1) to receive EES or SES and primary end point was MACE at 1 year consisting of cardiac death, nonfatal AMI, or any TVR. The study was powered for noninferiority of EES. The MACE rates at 1 year were 4.0% for EES and 7.7% for SES (absolute difference = –3.7%, 95% CI = –8.28 to –0.03, $P = 0.048$) with relative risk of 0.52 (95% CI = 0.27–1.00). No significant difference between both DES from different generations was found for cardiac mortality (EES = 1.5% vs SES = 2.7%, $P = 0.36$) or definite and/or probable stent thrombosis (EES = 1.2% vs SES = 2.7%, $P = 0.21$) at 1 year. This trial showed that second-generation EES were noninferior to SES, and superiority for MACE was suggested[61] (Table 3).

A recent meta-analysis of 22 trials including 12,453 patients compared the safety and efficacy profile of different stent types in patients with STEMI undergoing primary PCI. EES were associated with significantly lower rates of cardiac death or AMI, AMI, TVR, definite stent thrombosis, and combined definite or probable stent thrombosis than BMS. The reduced rates of cardiac death or AMI and stent thrombosis for EES compared with BMS were apparent as early as 30 days and were maintained up to the 2-year follow-up. EES were also associated with significantly lower rates of 1-year definite and combined definite or probable stent thrombosis as well as significantly lower rates of cardiac death or AMI up to the 2-year follow-up than PES. No significant differences regarding cardiac death or AMI, AMI, stent thrombosis, and TVR were found between EES and SES or ZES at the 1-year follow-up. The authors concluded that the most important finding of this study was the significantly lower risk of 1-year cardiac death or AMI, AMI, and stent thrombosis for EES in comparison with BMS, a finding not previously reported for any DES in the setting of STEMI.[62]

The safety and efficacy of DES in patients with AMI have been questioned by some authors. The safety concerns are related to either the increased risk of acute or subacute stent thrombosis in a clinical situation of coronary artery thrombosis, or late or very late stent thrombosis caused by DES delayed reendothelialization. Meanwhile, efficacy concerns are associated with partial or total antiproliferative

drug delivery inside a thrombus instead of inside the coronary wall. The XIENCE V USA trial demonstrated the safety and efficacy of EES in patients presenting AMI with low rates of stent thrombosis, TLR, and TLF, similar to non-AMI patients. The EXAMINATION trial showed that EES reduced TLR and was associated with a lower incidence of stent thrombosis in comparison with BMS. A propensity score-matched analysis of the KAMIR registry and the XAMI trial corroborated the satisfactory results of EES in patients presenting AMI, the first study having shown the EES superiority over the old-fashioned ZES platform through reduced rates of TLR and combined definite or probable stent thrombosis, and the second one suggesting the EES superiority for MACE over the first-generation SES. Finally, a recent meta-analysis showed a significantly lower risk of 1-year cardiac death or AMI, AMI, TVR, and stent thrombosis for EES in comparison with BMS. The analyzed trials allow us to conclude that EES are safe and effective in the STEMI setting through the expected reduced rates of TLR/TVR and the revealed lower rates of stent thrombosis in comparison with BMS.

Place in Therapy

According to the trials discussed herein, EES were proven to be safe and efficient for the treatment of coronary artery disease in a wide range of anatomic settings. There is strong evidence-based support for the use of EES in de novo lesions in which EES promote low rates of safety and efficacy clinical end points and are superior to first-generation DES. EES is also safe and efficient for the treatment of bifurcations, small vessels, multivessel disease, chronic occlusions, and saphenous vein grafts due to the low rates of safety and efficacy clinical end points, especially when compared with first-generation PES. EES promote satisfactory safety and efficacy outcomes respecting in-stent restenosis, but no clear superiority of EES over first-generation DES was shown by the few available head-to-head studies. As for LMCA, EES also promote satisfactory results; however, no clear superiority of EES over first-generation DES was even demonstrated. The ongoing EXCEL trial will clarify not only the safety and efficacy of EES in comparison with CABG, but also the role of DES in the treatment of low- and intermediate-risk subjects with LMCA disease.

In specific profile of subjects such as diabetic patients, women, and patients presenting AMI, EES were also proven to be safe and efficient with low rates of safety and efficacy clinical events. In diabetic patients, the expected superiority of the second-generation EES over the first-generation PES and SES has not been confirmed, but EES have promoted satisfactory results. Regarding the female gender, EES showed to be equally safe and effective for women as for the general population of patients enrolled in PCI trials, which were comprised mostly of male subjects. In patients presenting AMI, EES promote similar safety and efficacy outcomes to non-AMI patients, and significantly lower rates of stent thrombosis for EES in comparison with BMS are demonstrated.

It should be pointed out that none of the discussed studies showed that EES were inferior to first-generation or other second-generation DES in any anatomic or clinical situation which, taken together with the overall low rates of EES safety and efficacy clinical outcomes, turns EES into a universal DES for use in a wide range of clinical and anatomic settings.

Other data from randomized trials that should be pointed out are the greater number of patient-related than stent-related events in patients with complex clinical and lesion characteristics, which emphasizes that optimization of secondary prevention during long-term follow-up is at least as important as the decision of which DES to implant in a specific lesion.

Conclusion

Second-generation EES are safe and efficient for treatment of coronary artery disease in a wide range of anatomic and clinical settings.

Author Contributions

Conceived the concept: ACZ. Analyzed the data: ACZ, AMK, BSM. Wrote the first draft of the manuscript: ACZ, AMK, BSM. Contributed to the writing of the manuscript: ACZ, AMK, BSM. Agree with manuscript results and conclusions: ACZ, AMK, BSM. Jointly developed the structure and arguments for the paper: ACZ, AMK, BSM. Made critical revisions and approved final version: ACZ, AMK, BSM. All authors reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

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