A Critical Appraisal of the Safety and Efficacy of Drug-Eluting Stents

G Maluenda[1], G Lemesle[1] and R Waksman[1]

Drug-eluting stents (DESs) have largely demonstrated their superiority to bare-metal stents (BMSs) with respect to in-stent restenosis. Since the US Food and Drug Administration (FDA) approved the first DES in 2003, there has been a significant increase in the use of these devices. They are used in 70–80% of all stent procedures worldwide. Nevertheless, safety concerns stemming from reports of increased risk of late stent thrombosis (ST) and myocardial infarction (MI) have tempered the enthusiasm that the advent of these stents originally generated. New-generation DESs with novel polymers, antiproliferative drugs, and improved platforms are now approved and available for use. In this review we provide a critical appraisal, based on published clinical data, of the safety and efficacy of various DESs.

Drug-eluting stents (DESs) have revolutionized the field of interventional cardiology. It has been nearly a decade since they were introduced in preclinical and phase I clinical trials in which, with single-digit target-lesion revascularization (TLR), they demonstrated outstanding results in regard to restenosis. Since their approval for marketing by the US Food and Drug Administration (FDA) in 2003, the pattern of their clinical use in the United States has been somewhat of a roller-coaster ride. Initially there was a rapid adoption, and within a few months the penetration of DES use in the United States accounted for nearly 90% of all coronary stent procedures. The enthusiasm subsided with accumulating reports of subacute and late stent thrombosis (ST) requiring prolonged dual antiplatelet therapy. In September 2006, at the European Society of Cardiology Congress in Barcelona, a meta-analysis of all available published studies on DESs suggested that sirolimus-eluting stents (SESs) are associated with increased mortality as compared with bare-metal stents (BMSs). This disturbing information, along with other reports on the incidence of very late ST (developing more than 1 year after implantation), decreased the use of DESs in the United States to <60%. An advisory panel of experts met with FDA officials in December 2006 in Rockville, MD. The panel concluded that the safety issues of DESs are comparable to those of BMSs, and that DESs have the advantage of inducing less revascularization when used for on-label indications. However, there is an increase in major adverse cardiac events when DESs are used off label. In addition, the FDA recommended dual antiplatelet therapy (aspirin and clopidogrel therapy) for ≥1 year and aspirin use to be continued indefinitely in patients who had received DESs. Over the past 2 years, more studies based on "real-world" registries have reported on the issue of safety and efficacy of DESs as compared with BMSs for off-label indications; few of them suggest that DESs save lives. Concurrently, reports surfaced regarding the lack of healing and the incidence of very late ST (with a constant hazard ratio (HR) of 0.6% per year) associated with the use of DESs. These reports are in addition to those dealing with chronic inflammation, impaired vasoreactivity of the DES-implanted blood vessel, and acquired stent malposition. In 2008, DES use in the United States was once again on the rise, and penetration of the use of these devices is estimated to reach 75% of all stent procedures by the first quarter of 2009. The purpose of this review is to critically appraise the safety profile of DESs using published data and to determine the magnitude of the risk/benefit ratio of DES use in clinical practice.

SAFETY OF DESs

Mortality

Despite the major benefit of DESs in regard to the reduction of restenosis rates and repeated revascularization, some studies have reported adverse outcomes, indicating a possible increase in mortality associated with DESs as compared with BMSs in long-term follow-up. The safety of DESs was questioned for the first time in September 2006 at the meeting of the European Society of Cardiology (World Congress of Cardiology in Barcelona), at which a meta-analysis reported a statistically significant increase in mortality at 2–3 years in patients who had received SESs. An analysis of the Swedish Coronary Angiography and Angioplasty Registry observational study published in 2007 also showed an increase in mortality associated with the use of

[1]Division of Cardiology, Washington Hospital Center, Washington, DC, USA. Correspondence: R Waksman (ron.waksman@medstar.net)

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DESs, one that became apparent 6 months after the procedure.[1] It is important to note that detailed data on the duration of dual antiplatelet therapy, a major point of concern related to the risk of ST, were not available in these reports.

In contrast, important and robust evidence from randomized control trials and several meta-analyses have shown that DESs do not result in excess mortality after 4–5 years of follow-up.[2–5] Of these, Stettler *et al.*[2] have reported outcomes of 38 DES trials in more than 18,000 patients with >4 years of follow-up. They reported that mortality and risk of ST were similar for DESs and BMSs. Death due to acute myocardial infarction (AMI), congestive heart failure, and ST occurred only infrequently after DES implantation[2] (**Table 1**). Results from multicenter registries such as REAL (Registro Angoplastiche dell'Emilia Romagna)[6] and a recently published article by Shishehbor *et al.*,[7] both of which represent "real-world" practice, did not show any difference in terms of safety when DES and BMS were compared in patients with off-label indications for DESs. In addition, Shishehbor *et al.* have reported, with a study carried out in a large population (8,032 patients; 6,053 DESs and 1,983 BMSs), that all-cause mortality was significantly lower with DESs in unadjusted and adjusted Cox proportional models when compared with BMSs (HR: 0.62, 95% confidence interval (CI): 0.53–0.73; $P < 0.001$) at 4½-year follow-up and that this remained significant after propensity-score matching (HR: 0.54, 95% CI: 0.45–0.66; $P < 0.001$).

ST

Patients who develop ST have a poor prognosis. Ten to thirty percent of patients presenting with definite ST die in the hospital.[8,9] Moreover, ST can lead to unexplained sudden death. In the past, this was not often considered, but it is now included in the new Academic Research Consortium definition.[10] However, nonfatal AMI is the most frequent clinical presentation of ST (70–80%).[8,9]

Early ST. Early definite ST was a common complication following BMS implantation in the early 1990s.[11] With the advent of thienopyridine, combined antiplatelet therapy greatly decreased the incidence of ST to around 1%, according to the most recent studies and meta-analyses.[12,13] To date, no difference has been found between DESs and BMSs in relation to early ST.[1,3,4,12]

Table 1 Sensitivity analyses summary of 29 DES trials with 13,677 patients

	Hazard ratio (95% credibility interval)			
	Death overall	MI	Definite ST	TLR
SES vs. BMS	1.00 (0.82–1.25)	0.81 (0.66–0.97)*	1.00 (0.68–1.63)	0.30 (0.24–0.37)*
PES vs. BMS	1.03 (0.84–1.22)	1.00 (0.81–1.23)	1.38 (0.96–2.24)	0.42 (0.33–0.53)*
SES vs. PES	0.96 (0.83–1.24)	0.83 (0.71–0.99)*	0.71 (0.48–1.13)	0.70 (0.56–0.84)*

BMS, bare-metal stent; MI, myocardial infarction; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; ST, stent thrombosis; TLR, target-lesion revascularization.

*$P < 0.05$.

Late ST. Spaulding *et al.*,[4] in their meta-analysis of the four Cypher trials (RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS) that included 1,748 patients and used the Academic Research Consortium definition of ST, reported a cumulative rate of ST of 0.8% for BMSs vs. 1.8% for SESs ($P = 0.53$), at 1 year after the stent procedure. Using a per-protocol definition of ST, Stone *et al.*[3] reported, in a meta-analysis of nine trials (RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS, and TAXUS I–V) that included 3,513 patients, a cumulative rate of ST of 0.6% for BMSs vs. 1.2% for SESs ($P = 0.2$) and 0.9% for BMSs vs. 1.3% for paclitaxel-eluting stents (PESs) ($P = 0.3$). Using the Academic Research Consortium definition, however, Mauri *et al.*,[13] in their meta-analysis of the same nine trials, reported a cumulative rate of ST of 1.7% for BMSs vs. 1.5% for SESs ($P = 0.7$) and 1.4% for BMSs vs. 1.8% for PESs ($P = 0.52$). In the Stettler *et al.*[2] meta-analysis (38 DES trials) using the Academic Research Consortium definition, ST incidence rates of 1% for BMSs, 1.1% for PESs, and 1.1% for SESs, ($P = 0.62$) were reported. Based on the findings from these recent studies and meta-analyses, the incidence rates of late ST for DESs and BMSs seem to be similar. However, the duration of dual antiplatelet therapy was usually longer with DESs than with BMSs in these studies (3 or 6 months vs. 1 month), thereby making conclusions more difficult.

Very late ST. The real incidence of very late ST is a poorly described, controversial topic, with little consensus on the potential increased risk of very late ST after DES implantation. Several authors have reported an incidence of very late ST of 0.4–0.6% per year after DES implantation.[4,14] Gruberg *et al.*, at the Transcatheter Cardiovascular Therapeutics conference in 2006 (Washington, DC), suggested that the incidence of very late ST seems to be higher in relation to the use of DESs than BMSs (0.6% vs. 0.2% per year). Additionally, Stettler *et al.*,[2] in their meta-analysis, reported similar rates of death for BMSs, SESs, and PESs, but with a significantly higher rate of very late ST in the PES group. Consequently, according to these meta-analyses, it would appear that the use of DESs increases the risk of very late ST moderately but significantly.

Endothelial dysfunction

Endothelial nitric oxide–dependent vasodilatation is the normal coronary response to exercise or acetylcholine infusion. Endothelial dysfunction, occurring during the early stages of atherosclerosis, can be demonstrated when paradoxical vasoconstriction occurs in the presence of stimuli that normally trigger vasodilatation. Endothelial function after DES deployment has been studied in two series of patients; the SES group had a higher rate of dysfunctional response as compared with the BMS group.[15,16] Another study also suggests that PESs and SESs induce similar patterns of abnormal distal vasoconstriction responses after acetylcholine infusion as compared with BMSs.[17]

Mechanisms for endothelial dysfunction after stent implantation may be directly associated with the severity of arterial injury.[18] Furthermore, incomplete endothelialization after DES

deployment may also contribute to more severe endothelial dysfunction.[19] Finally, it has been postulated that direct toxic effects of sirolimus and a lack of release of nitric oxide or other vasodilator from the endothelium within the stented segment could prevent downstream vasodilatation.[20] The newer generation of DESs has shown better endothelium-dependent coronary vasomotor response than SESs, but it is still unknown whether this finding is related to stent polymer or to drug class effect.[21]

Late-acquired incomplete stent apposition

Incomplete stent apposition (ISA) is defined as the clear separation of stent struts from the vessel wall as detected by intravascular ultrasound, with evidence of blood speckle behind the struts. Late-acquired ISA refers to ISA that is discovered at follow-up even though there had been complete apposition at the time of the stent implantation. This seems to be related to positive vessel remodeling after stent deployment.[22] Late-acquired ISA has been reported in 5.4 % of patients after BMS implantation at 6-month follow-up, but this figure did not affect the long-term incidence of cardiovascular events.[23] Higher rates of late-acquired ISA have been reported after DES implantation as compared with those after BMS implantation, with the former ranging from 8 to 12% at 6-month follow-up. But once again, no difference in mortality rates has been demonstrated.[24,25] Using intravascular ultrasound, Siqueira *et al.*[26] examined 195 DES patients at the time of stent implantation and 6 months later. Among these patients, 5.1% had evidence of late-acquired ISA. At 29 ± 15 months, no patient without ISA had presented with very late ST, whereas two of the patients with late-acquired ISA (20%) did. A possible association between the two phenomena must be investigated with a larger and longer intravascular ultrasound follow-up.

Hypersensitivity reactions associated with DESs

Although rare, several hypersensitivity-related adverse reaction symptoms associated with DESs have been reported. Nebeker *et al.*,[27] extracting cases from three databases, reported 17 cases (14 SESs and 3 PESs) of probable or certain DES-induced hypersensitivity syndromes. Clinical manifestations included nonurticarial rash ($n = 8$), hives ($n = 5$), dyspnea ($n = 6$), myalgia/arthralgia ($n = 3$), itching ($n = 2$), and blisters ($n = 1$). All urticarial eruptions began within 10 days of the implantation. Laboratory findings included hypereosinophilia and elevated IgE titers more than five times the normal value. According to this report, intrastent eosinophilic infiltrates and poor intimal healing as long as 18 months after stent implantation were observed in four patients who died of late ST.

An autopsy series reported five cases of late ST in SES patients secondary to hypersensitivity reaction. All of them were associated with positive vessel remodeling with extensive diffuse intimal, medial, and adventitial inflammation.[28] Hypersensitivity reactions seem to be a late phenomenon involving the entire stented segment, and they appear to be associated with the presence of eosinophil and T-lymphocyte infiltrates. It has been hypothesized that the Cypher nonerodible polymer, consisting of poly(ethylene co-vinyl acetate) and poly(n-butyl methacrylate), is the underlying cause of hypersensitivity reactions. Indeed, both components have been associated with allergic and toxic reactions in other territories.[29]

EFFICACY OF DESs

Restenosis

The main advantage of DESs over BMSs is the lower rate of restenosis (**Figure 1**).[2,3] Long-term follow-ups from the SIRIUS (sirolimus-eluting stent in coronary lesions)[30,31] and TAXUS IV[32] trials show yearly rates of angiographic restenosis

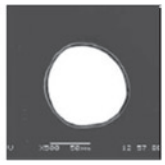
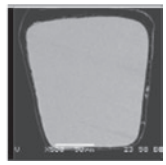
	Xience V	Endeavor	Taxus Express	Cypher
Picture of strut cross-section (×500)				
Strut thickness	81 μm	91 μm	132 μm	140 μm
Polymer thickness	7 μm	6 μm	16 μm	14 μm
Stent material	Co-Chr	Co-Chr	Stainless steel	Stainless steel
Chemical nature of the polymer	Biocompatible fluoropolymer	Hydrophilic phosphorylcholine	Hydrocarbon-based elastomer	PEVA and PBMA
Angiographic late loss (mm)	0.12 ± 0.29 mm	0.61 ± 0.46 mm	0.41 ± 0.54 mm	0.14 ± 0.42 mm
Binary restenosis	1.3%	9.4%	10.1%	2.6%

Figure 1 Comparison of strut cross-section thicknesses (microphotography at similar ×500 magnification levels), stent platforms, polymer characteristics, and efficacies of the different types of DESs. Co-Chr, cobalt–chromium alloy; PEVA, poly(ethylene co-vinyl acetate); PBMA, poly(n-butyl methacrylate).

of 6.8–7.9% for DESs. It is already known, from the pre-DES era, that more complex lesions such as long lesions, smaller-diameter lesions, saphenous vein grafts, bifurcations, and ostial locations predict the occurrence of restenosis. The presence of diabetes has also been strongly associated with restenosis.[33] It is therefore accepted that the use of DESs in these settings improves clinical outcomes as compared with the use of BMSs. Unfortunately, DESs have not been tested in most of these lesion types in randomized controlled trials (RCTs) against BMSs. Consequently, their use currently remains off label for these indications. Another hot topic in which significant controversies persist is the continued use of BMSs in the treatment of AMI, even though the first RCT Horizon AMI trial (Transcatheter Cardiovascular Therapeutics conference, Washington, DC, 2008) showed that it is beneficial to use DESs in this setting.

First-generation PES

Currently, nearly 5 million PESs (Boston Scientific, Natick, MA) have been implanted in patients worldwide. The platforms for both the first-generation Express stent and the second-generation Liberté stent consist of a polymer-based stent. The Liberté platform has smaller, more uniform open cells and thinner struts, thereby conferring more flexibility and navigability. Both stent platforms contain paclitaxel, an antiproliferative agent that stabilizes microtubules and blocks intracellular signaling, inhibiting smooth-muscle-cell migration and trophism.[34]

The Taxus stent is made with poly(styrene-b-isobutylene-b-styrene) (TransLute), which is a hydrocarbon-based elastomer with paclitaxel embedded in it. This diffusion-based controlled-release matrix system allows a slow and very specific delivery of the drug.[35] Data from the TAXUS IV, V, and VI RCTs[32,36,37] and a meta-analysis of the TAXUS RCT[3] showed that the Taxus Express stent significantly reduced the rates of TLR and binary restenosis as compared with the BMS Express stent, with no significant difference in death and MI rates in patients at standard risk.

Higher-risk populations have been studied in other trials. In the TAXUS Express meta-analysis, the use of PESs was associated with a reduction in restenosis rates without affecting safety in diabetic patients.[38] And in the TAXUS ATLAS trial, patients with smaller-diameter (<2.5 mm) vessel lesions treated with Taxus Liberté implantation presented a decrease in the rates of TLR and late loss up to the 9-month follow-up.[39]

The expected results of the Horizon AMI trial, which tested the safety and efficacy of PESs in the setting of AMI, were presented by Stone *et al.* at the 2008 Transcatheter Cardiovascular Therapeutics conference (Washington, DC). This trial showed that, at 1 year after the stent implantation procedure, the duration of ischemia-driven TLR was significantly shorter with Express Taxus (7.5%, $n = 2,257$) than with Express BMS (4.5%, $n = 746$) ($P = 0.002$). Angiographic follow-up was available for 1,204 patients, and the finding was that the incidence of binary restenosis was significantly lower in the Taxus group than in the Express BMS group (10.0% vs. 22.9%; $P < 0.0001$).

The recently published ARRIVE-1 Registry[40] consists of a detailed 2-year follow-up of 2,487 patients representing "real world" Taxus performance. Of these, the on-label group (35%) presented similar rates of death and MI as compared with the pooled data from the four TAXUS RCTs (death 3.5% vs. 3.4%, $P = 0.78$; MI 0.7% vs. 0.9%, $P = 0.72$) but lower rates of target vessel revascularization (TVR) (5.8% vs. 13.4%, $P < 0.0001$). The "expanded-use" group (65%), consisting of patients with conditions associated with greater risk and more complications, showed higher rates of death (7.4% vs. 3.5%, $P = 0.0003$) and TLR (9.4% vs. 5.8%, $P = 0.0031$) as compared with the on-label group.

First-generation SES

The Cypher stent is made with poly(ethylene co-vinyl acetate) and poly(n-butyl methacrylate) and has a stainless steel platform. It contains sirolimus, an antiproliferative drug that inhibits the G1 phase of the cell cycle. Most of the drug is released in ~3 weeks; thereafter, the concentration in the base coat decreases, resulting in decreased release rates.[35] Approved in April 2003 by the FDA, the Cypher stent has been the most widely used DES in the world and is considered to be the standard of comparison for all DESs. Indeed, the Cypher stent is currently the most extensively evaluated DES, tested in various trial designs and in diverse populations, and it has been studied for follow-up periods that are longer that those for other DESs.

Several multicenter RCTs have evaluated the safety and efficacy of SESs as compared with BMSs. In an analysis of pooled data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS trials ($n = 1,748$), at 5-year follow-up the SES group had a rate of death similar to that of the BMS group (8.9% for SES vs. 8.2% for BMS, $P = 0.57$) and an incidence of MI similar to that of the BMS group (7.9% for SES vs. 6.8% for BMS, $P = 0.44$). However, like for PESs, a sustained and significant reduction in the TLR rate was observed (9.8% for SES vs. 23.9% for BMS, $P < 0.0001$).[4]

In addition, the safety and efficacy of SESs have been demonstrated for off-label indications in higher-risk patients. In a systematic analysis of 14 RCTs comparing SES with BMS, the overall risk of death (HR: 1.03, 95% CI: 0.80–1.30) and the combined risk of death or MI (HR: 0.97, 95% CI: 0.81–1.16) were not significantly different between the groups.[12] There was a significantly lower combined outcome of death-MI-TVR (HR: 0.43, 95% CI: 0.34–0.54) associated with the use of SESs. This benefit was driven by a reduction in the TVR rate.

Furthermore, a recent analysis (which implemented risk adjustment and propensity-score matching) of data from 76,525 Medicare beneficiaries treated with implantation of Cypher or BMS showed that the use of SESs was associated with a significant reduction in both mortality and repeat revascularization.[41]

Second-generation everolimus-eluting stents (Xience V, Promus)

The platform is the Multi-Link Vision stent (Abbott Vascular, Markham, Ontario, Canada), which is made of a cobalt–chromium alloy and has very thin struts (81 μm). The open cells and a nonlinear design make the stent quite flexible. This stent is assembled on a semi-compliant balloon with short tapers that are intended to minimize injury outside the stent area. The drug, everolimus, has a high potency and high lipophilicity and

is an antiproliferative agent that inhibits the G1 phase of the cell cycle.[42] The everolimus-eluting stent (EES) has a nonadhesive, durable, and biocompatible fluoropolymer composed of an outer layer (poly(n-butyl methacrylate)) and a drug-reservoir layer (poly(vinylidene fluoride co-hexaflu-oropropylene)) that releases the drug slowly. This DES system releases ~80% of the drug in the first month and nearly 100% of it by 4 months.

The first pivotal RCT was SPIRIT I,[43] which demonstrated the safety and accuracy of EES as compared with BMS (Multi-Link Vision). The SPIRIT II trial,[44] conducted in Europe, had 300 subjects; 223 of these were randomized to receive EESs and 77 to receive PESs (3:1 EES:PES randomization). The primary end point—late loss at 6 months—was lower for EES (0.11 mm for EES vs. 0.36 mm for PES, 69% relative risk, $P < 0.0001$). Also, lower rates of ischemia-driven TLR (2.7% vs. 6.5%) and protocol-defined late ST (0.5% vs. 1.3%) were observed for EES as compared with PES (**Figure 1**).

The SPIRIT III RCT,[45] aimed at evaluating noninferiority of EESs in comparison with PESs, was carried out in 65 sites in the United States, had 1,002 subjects (2:1 EES:PES randomization). In-segment late loss at 240 days was significantly lower in EESs than in PESs (mean 0.14 mm vs. 0.28 mm; $P < 0.004$). At the 9-month follow-up, EESs were noninferior to PESs with respect to the major secondary end point, ischemia-driven target vessel failure (TVF) (7.2% vs. 9.0%; risk ratio: 0.79, $P <0.001$ for noninferiority); this held true at the 1-year follow-up as well (6.0% vs. 10.3%; risk ratio: 0.58, $P = 0.02$ for noninferiority). On the basis of these results, the FDA approved the use of this new DES in 2008. However, the long-term safety of EESs is a pending issue and the assessment of patient-reported outcomes in real-world settings should be followed for longer durations.

Second-generation zotarolimus-eluting stent (Endeavor)

The Endeavor zotarolimus-eluting stent (ZES) system (Medtronic CardioVascular, Minneapolis, MN) uses a cobalt-based alloy stent (Driver) coated with the sirolimus analogue zotarolimus, delivered via a phosphorylcholine polymer-based coating. The hydrophilic phosphorylcholine polymer of the ZES was designed to be biocompatible. The release kinetics of zotarolimus enables nearly complete drug delivery within the first month after stent placement.

The ENDEAVOR I[46] study was a single-arm, prospective, multicenter, first-in-human trial evaluating the performance and safety of the ZES in 100 patients with symptomatic coronary artery disease. At 12 months, in-stent late lumen loss was 0.61 ± 0.44 mm (corresponding to a percentage volume obstruction of $9.7 \pm 8.5\%$ as determined using intravascular ultrasound). The cumulative incidence of major adverse cardiac events (death, MI, emergent cardiac surgery, and repeat revascularization of the index lesion), was 1% at 30 days and 2% at 12 months.

The ENDEAVOR II[47] RCT was designed to examine the efficacy and safety of the ZES as compared with the Medtronic Driver BMS. A total of 1,197 patients with a single coronary artery stenosis were enrolled and randomly assigned to receive the ZES ($n = 598$) or the BMS ($n = 599$). At the 9-month follow-up, the primary end point, TVF, was lower in the Endeavor group (7.9%) as compared with the BMS group (15.1%) ($P = 0.0001$). The rate of occurrence of major adverse cardiac events decreased from 14.4% with the BMS to 7.3% with the ZES ($P = 0.0001$). The rate of ST was 0.5% with the ZES, which was not significantly different from the value of 1.2% associated with the BMS. In the 531 patients who submitted themselves to the angiographic follow-up, in-stent late loss had reduced from 1.03 ± 0.58 to 0.61 ± 0.46 ($P < 0.001$) (**Figure 1**). At 4 years, the ZES maintained an advantage over the BMS with respect to rate of TVF (13.6% for ZES vs. 22.6% for BMS; $P < 0.001$), primarily through a persistent reduction in TVR (9.8% vs. 18.8%; $P < 0.001$), as presented by Fajadet *et al.* at the EuroPCR Meeting (May 2008).

ENDEAVOR III[48] was a prospective, randomized, single-blinded multicenter angiographic trial designed to show the noninferiority of the ZES as compared with the SES. In this study, 436 patients with *de novo* native coronary lesions were randomized in a 3:1 ratio for treatment with the ZES ($n = 323$) or the SES ($n = 113$). At 8 months, the rate of in-segment late loss was higher with the ZES as compared with the SES (0.34 vs. 0.13; $P < 0.001$ for superiority of SES; $P = 0.65$ for noninferiority). However, at the 9-month follow-up, there were no significant differences between the ZES and the SES with respect to the occurrence of major adverse cardiac events (7.6% vs. 7.1%) and TVF (12.0% vs. 11.5%).

Unpublished data of the ENDEAVOR IV study, which was a randomized, single-blind, prospective, multicenter trial, were presented by Leon *et al.* at the Transcatheter Cardiovascular Therapeutics conference (Washington, DC, 2007). This trial randomized patients with single *de novo* native artery lesions for implantation of the ZES ($n = 774$) or the PES ($n = 775$). The rate of TVF, the primary study end point, was similar in both arms at 9 months (6.6% vs. 7.2%; $P = 0.685$ for superiority; $P < 0.001$ for noninferiority). In summary, the ZES appears to be safe and effective in treating single *de novo* coronary artery lesions. Despite the association of the ZES with a higher rate of late loss as determined by coronary angiogram, the clinically assessed outcomes of TVR and TLR with the ZES are similar to those with the SES and the PES. The issues that remain to be clarified with the Endeavor ZES relate to its efficacy and safety in more diverse patient populations with longer follow-up terms.

Comments regarding off-label use of DESs

According to several registries, off-label use occurred in nearly 60% of patients undergoing DES implantation procedures. These patients are a high-risk population with numerous comorbidities, unfavorable lesion morphology, and unstable clinical presentations, and they are expected to have higher rates of adverse clinical outcomes.[49]

Although randomized trials of off-label use of the DES as compared with the BMS have not yet been reported, numerous registries and randomized trials suggest that DESs are safe and effective under such circumstances.[6,7,50] The original Swedish Coronary Angiography and Angioplasty Registry publication suggested that there is a higher rate of late events in DES-treated

patients,[1] but a later, more comprehensive, unpublished report presented by James *et al.* at the European Society of Cardiology Congress (Vienna, Austria, 2007) showed that restenosis is 50% less frequent with DES use than with BMS use and that long-term mortality rates (at 4-year follow-up) were comparable in the two procedures. In the meta-analysis of 38 trials (18,023 patients) conducted by Stettler *et al.*[2], which included trials of primary percutaneous coronary intervention and off-label indications, mortality and the risk of ST were similar for DESs and BMSs at 4-year follow-up. Interestingly, SESs were associated with a significant reduction in the risk of MI (HR: 0.81, 95% CI: 0.66–0.91, $P = 0.03$) as compared with BMSs. Although additional trials are needed, it appears that DESs are safe and effective both for FDA-approved indications and for several off-label indications. However, physicians must use their clinical judgment in order to select the best device, keeping in mind the risk of restenosis and ST and the expected level of compliance with dual antiplatelet therapy.

Conclusion

In 2008, the consensus was that there is an ongoing risk associated with DESs; the main challenge with the next generation of DESs is to ensure safety with less dependence on prolonged dual antiplatelet therapy. New scientific approaches such as using biocompatible or bioabsorbable polymers or no polymer at all, lowering the dose of the drug, and promoting healing with progenitor cells are intriguing but do not necessarily guarantee translation into improved clinical outcome. The motivation in the first 30 years of interventional cardiology was to reduce restenosis; it is now time to focus on improving the safety performance of DESs in a wider range of patient populations.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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