

Do Improvements in Stent Technology Affect Stent Thrombosis?

A review of the literature on the safety of first- and second-generation drug-eluting stents.

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Drug-eluting stents (DES) have been shown to significantly reduce restenosis compared with bare-metal stents (BMS).^{1,2} Restenosis after BMS implantation is associated with a high rate (30% to 80%) of recurrence³ and carries a significant morbidity rate because it leads to frequent target lesion revascularization (TLR) and has been associated with acute myocardial infarction in approximately 10% of cases.⁴

The primary mechanism of restenosis after stenting is neointimal hyperplasia, which is likely due to exaggerated vascular smooth muscle cell proliferation in response to medial injury. DES were developed to reduce neointimal hyperplasia by delivering antiproliferative drugs to the angioplasty site. The three components of current DES are the stent struts (scaffolding that is usually made of a radiopaque metal with high radial strength), a biostable polymer that controls drug release and diffusion to the arterial wall, and the antiproliferative drug. Although frequently considered to be a single class, DES can be distinguished based on variations in these components (Table 1).

Since 2003, the US Food and Drug Administration (FDA) has approved four DES platforms: the earlier (frequently termed *first-generation*) DES include a sirolimus-eluting stent (SES) (Cypher, Cordis Corporation, Bridgewater, NJ) and a paclitaxel-eluting stent (PES) (Taxus, Boston Scientific Corporation, Natick, MA). Newer or second-generation DES include a zotarolimus-eluting stent (ZES) (Endeavor, Medtronic, Inc., Minneapolis, MN) and an everolimus-eluting stent (EES) (Xience, Abbott Vascular, Santa Clara, CA/Promus, Boston Scientific Corporation). This article reviews the early benefits of first-generation DES, sub-

sequent safety concerns related to late stent thrombosis with these devices, and notes potential advantages of newer designs that may have similar effectiveness with a lower risk for late stent thrombosis.

EFFECTIVENESS AND EARLY SAFETY OUTCOMES FOR FIRST-GENERATION DES

The pivotal clinical trials of the SES and PES versus their respective BMS counterparts demonstrated approximately 70% relative reduction in TLR at 1 year.^{5,6} Although such dramatic reductions in clinical restenosis were unprecedented, clinicians were further encouraged by the absence of any apparent increase in stent thrombosis during 1-year follow-up, with rates for DES and BMS at approximately 1% in these pivotal clinical trials, as well as in a subsequent meta-analysis that provided more precision for this estimate.⁷

After equally encouraging results in small registry studies of more complex lesions,^{8,9} there was widespread use of SES and PES, including in an array of lesion subsets that had not been included in the pivotal studies for FDA approval. By late 2005, DES were used in more than 90% of the stent procedures performed in the United States.

In the spring and summer of 2006, concerns were raised due to reported observations of increased death and myocardial infarction beyond the first year after DES implantation. The evidence included a post hoc analysis of the BASKET (Basel Stent Kosten Effektivitäts) study, which included 746 patients who survived free of major events and had a significantly higher risk for death or myocardial infarction (MI) between 6 and 18 months, possibly due to more stent thromboses.¹⁰ Meta-analyses of the DES clinical trials added to the

TABLE 1. DESIGN CHARACTERISTICS OF FDA-APPROVED DES

Stent	Drug (Dose [μg]/Stent Diameter X Length)	Platform and Material (Strut Thickness [μm])	Polymer (Thickness [μm])	Elution Characteristics
Cypher	Sirolimus (150/2.5–3 X 18 mm)	Bx Velocity stent (Cordis Corporation), 316L stainless steel (140)	PEVA/PBMA (12.6)	Rapid early diffusion, > 80% released over 30 days
Taxus	Paclitaxel (77–108 ^a / 2.5–3 X 16 mm)	Express 2 or Liberté stents (Boston Scientific Corporation), 316L stainless steel (97–132)	Translute (SIBBS) (Boston Scientific Corporation) (16)	Early-burst release, next 10 days slow release, next 30 days plateau, approximately 90% of drug remains bound
Xience V/ Promus	Everolimus (88/3 X 18 mm)	Multi-Link Vision stent (Abbott Vascular), cobalt chromium (81)	Fluorinated copolymer (7.6)	80% of drug released within 30 days, 100% of drug released within 120 days
Endeavor	Zotarolimus (180/2.5–3 X 18 mm)	Driver stent (Medtronic, Inc.), cobalt chromium (91)	Phosphorylcholine (5.3)	95% of drug released within 15 days

Abbreviations: PBMA, poly-n-butyl methacrylate; PEVA, polyethylene-co-vinyl acetate; SIBBS, styrene-*b*-isobutylene-*b* styrene.

^aLower value for Taxus Liberté and higher value for Taxus Express.

controversy by reporting increased all-cause death or Q-wave MI for SES versus BMS¹¹ in the SES trials at 3 years and increased noncardiac mortality after 1 year for SES but not PES compared with BMS.¹² Finally, an incomplete report of 3-year follow-up data from the large, nonrandomized Swedish registry showing increased late mortality for DES compared with BMS fueled the firestorm.¹³ Much of the concern regarding increased mortality was later tempered by findings of no increase in death or MI for DES compared with BMS in patient-level analyses of 4-year follow-up data of the SES and PES pooled clinical trials.¹⁴ There was also a report of more complete 5-year follow-up of the Swedish registry that no longer showed an increase in mortality for DES compared with BMS at any time point.¹⁵ The importance of a possible increased risk for late stent thrombosis and the possible relationship to timing of dual-antiplatelet therapy discontinuation had been highlighted as major concerns for ongoing and subsequent clinical trials.

LATE AND VERY LATE STENT THROMBOSIS FOR FIRST-GENERATION DES VERSUS BMS

At the time of the controversy regarding possible increased late mortality after DES, post hoc analyses of SES and PES clinical trials showed a small but signifi-

cant increase in stent thrombosis events occurring after 1 year.¹⁴ However, it became evident that the definitions of *stent thrombosis* used in the various clinical trials were nonuniform and had perhaps biased the analysis in favor of BMS by excluding any stent thrombosis that occurred after TLR. A consortium of academic researchers, FDA, and industry was formed to develop standardized clinical trial definitions for endpoints, including stent thrombosis (Table 2).¹⁶ The Academic Research Consortium (ARC) has recommended the definite plus probable classification for reporting stent thrombosis events. When this definition was applied across the pooled SES and PES clinical trials, there was no difference during 4-year follow-up for either DES compared with the BMS counterpart.¹⁷ Although there were numerically more events in the DES groups beyond 1 year (very late stent thrombosis [VLST]), the difference was no longer significant, and it was observed that events continued to accrue after both DES and BMS implantation. Of note, in the BMS arms, stent thrombosis was associated with prior TLR, with eight of 11 incidences of VLST occurring in patients with intervening TLR. Furthermore, seven of these eight patients had also undergone intracoronary brachytherapy at the time of at least one TLR before the stent thrombosis event. With 5-year follow-up now reported,

TABLE 2. ARC STANDARDIZED DEFINITION FOR STENT THROMBOSIS^a

Level of Certainty	Timing (Postprocedure)
Definite · Acute coronary syndrome plus · Angiographic (thrombus/occlusion) or pathologic confirmation	Early · Acute (0–24 hours) · Subacute (> 24 hours–30 days)
Probable · Unexplained sudden death within 30 days or · Target vessel territory MI without confirmation of stent patency and no other culprit identified	Late · > 30 days–1 year
Possible · Unexplained death beyond 30 days	Very Late · > 1 year

^aAdapted from Cutlip DE et al. *Circulation*. 2007;115:2344–2351.¹⁶

TABLE 3. STENT THROMBOSIS RATES FROM INDIVIDUAL CLINICAL TRIALS OF FDA-APPROVED DRUG-ELUTING STENTS BY ARC CLASSIFICATION

Stent Thrombosis Definite or Probable	First-Generation DES Randomized Trials ¹⁷						Second-Generation Randomized Trials ^{18,19}					
	SES	BMS	P Value	PES	BMS	P Value	EES	PES	P Value	ZES	PES	P Value
Overall	1.5%	1.7%	.7	1.8%	1.4%	.52	1.3%	1.7%	.77	1.1%	0.9%	.99
Early	0.5%	0.3%		0.5%	0.5%		0.4%	0%		0.4%	0.1%	
Late	0.1%	1%		0.4%	0.3%		0.5%	0.6%		0.5%	0%	
Very late	0.9%	0.4%		0.9%	0.6%		0.3%	1%	.07	0.1%	1.5%	.006

the frequency of VLST in the SIRIUS (Sirolimus-Eluting Stent for Native Coronary Lesion) trial is almost identical for SES versus BMS (0.8% vs 0.7%),²⁰ whereas in the TAXUS IV trial, the frequency for PES versus BMS is similar (1.4% vs 1%).²¹

STENT THROMBOSIS AND SECOND-GENERATION DES

Clinical trials using the second-generation EES and ZES have suggested possibly lower rates of VLST (Table 3). At 3 years, in the SPIRIT III (Clinical Evaluation of the Xience V Everolimus-Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions) trial, VLST occurred in 0.3% of EES versus 1% of PES ($P = .34$).¹⁸ Interestingly, lower rates of ST at 2 years were also noted in EES patients who discontinued thienopyridine after 6 months of stent implantation compared to their counterpart in the PES arm (0.4% vs 2.6%; $P = .10$).²² In SPIRIT III, rates of early and late stent thrombosis were similar after EES or PES, and the observed differences in VLST were not statistically significant. Whether longer-term follow-up

and larger numbers of patients will confirm these findings or demonstrate significance of the VLST differences requires further study. The differences may also be more significant when more complex lesions are treated. In the SPIRIT IV trial of real-world lesions, a 74% reduction in stent thrombosis was seen even at 1 year for EES compared with PES (0.29% vs 1.1%; $P = .004$).²³

The ZES Endeavor stent system also had less VLST compared with the PES control in the ENDEAVOR IV trial. At 3 years, this difference was highly significant (0.1% vs 1.5%; $P = .006$), with only one VLST in the ZES group and 11 in the PES group. Interestingly, five of 11 VLST in the PES group occurred during continued dual-antiplatelet therapy (4/11 were taking aspirin alone), whereas the patient who had VLST in the Endeavor group was not taking dual-antiplatelet therapy.¹⁹ Furthermore, pooled studies including more than 2,100 ZES patients (with 5-year follow-up of 1,199 patients) have demonstrated similarly low rates of VLST for ZES compared with the BMS counterpart (0.2% vs 0.3%), representing only two VLST events in the ZES group (Figure 1).²⁴

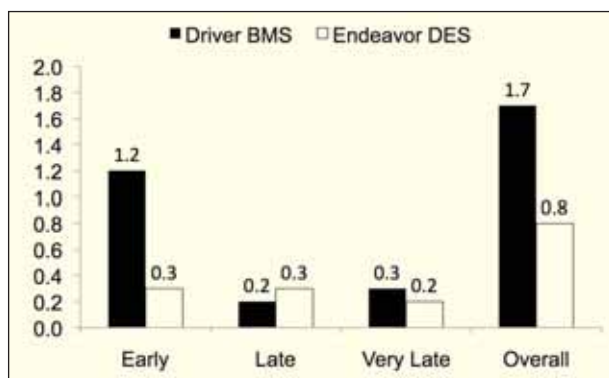


Figure 1. Rates of stent thrombosis according to Academic Research Consortium classification for the Endeavor DES and the Driver BMS (Medtronic, Inc.) counterpart. The groups are pooled from Endeavor clinical trials and do not represent randomized comparisons or concurrent treatment. Adapted from Kanzari DE et al. *J Am Coll Cardiol*. 2010;55A:1805.²⁴

MECHANISMS FOR STENT THROMBOSIS AND POTENTIAL EFFECTS OF NEW STENT DESIGNS

Early (0–30 days) and late (31 days–1 year) stent thrombosis occurs with nearly equal frequency after BMS and each of the four approved DES types. The predictors of stent thrombosis are also similar within the early and late time intervals and across stent types and include various patient, lesion, and procedural characteristics.^{25–27} The most important of these factors for early or late stent thrombosis are stent length, residual dissection, diabetes, stent underexpansion, bifurcation lesion, and premature discontinuation of dual-antiplatelet therapy. Although easier delivery and possible lower inflammatory scores related to thinner struts may result in reduced risk for early or late stent thrombosis for the second-generation devices, it is more likely that the technical facets of the procedure and the particularly critical role of dual-antiplatelet therapy in this time period make stent design a less important contributor.

However, VLST after DES is almost entirely related to delayed healing.^{28–32} Although the effect may be greater with certain lesion types, such as bifurcation and ST-elevation MI culprit lesions, the impact of procedural or technical factors appears to be less, and the biological response to individual DES seems to be a more critical factor. Other factors, such as persistent fibrin and increase in inflammatory cells, are associated with impaired healing response and may lead to late malapposition, which is more frequent in patients with VLST.³³

There are several design features that may affect healing. First, flow disturbances caused by increased strut thickness may be a deterrent of endothelial coverage.³⁴ The effect of drug concentration and potential local toxicity may also increase inflammation and interfere with healing.^{29,32}

Nonabsorbable polymers used in first-generation DES have been recognized as an important contributor to VLST, with observed inflammatory reactions due to hypersensitivity or late polymer breakdown.^{28,31}

As a three-component system, newer designs can improve healing and reduce the risk of stent thrombosis by improvement in any of these areas. As noted in Table 1, the EES and ZES have thinner struts, while the EES also has a substantially lower total dose. Both newer devices also have markedly thinner polymers, with other unique polymer characteristics that may increase biocompatibility and reduce inflammatory response.

CONCLUSION

Future improvements in DES technology may provide even safer DES with further reductions in stent thrombosis. Such technological improvements include a next-generation DES with bioabsorbable polymers or a polymer-free DES, and the eventual availability of a totally bioabsorbable stent. ■

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