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EDITORIAL COMMENT

# Late Vascular Response Following Drug-Eluting Stent Implantation*

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The therapeutic effect of drug-eluting stents (DES) as compared with bare-metal stents (BMS) is most pronounced during the first year as a result of the potent inhibition of neointimal hyperplasia in the presence of the antiproliferative drug. Whereas healing with BMS, and in parallel, neointimal proliferation, has been shown to be complete after 3 to 6 months (1), potentially followed by a late lumen enlargement beyond 1 year, a different pattern emerged with early generation DES, characterized by delayed healing with an ongoing neointimal growth beyond 6 months in both experimental and clinical studies (2,3). However, the long-term course of neointimal growth has not been well investigated in early generation DES, and it remains unclear whether newer generation DES show a similar response despite improvements in design.

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In this issue of *JACC: Cardiovascular Interventions*, Collet et al. (4) report long-term intravascular ultrasound (IVUS) data from patients included in the first-in-man evaluation of sirolimus-eluting stent (SES) slow-release cohort and the first-in-man evaluation of biolimus-eluting stent using a biodegradable polymer (BES). All patients underwent serial IVUS investigation post-procedure, between 6 and 12 months and at 4 to 5 years. Neointimal growth was not halted after the first follow-up at 6 (BES) and 12 months (SES), respectively, but continued to increase with a similar magnitude for both BES and SES during long-term follow-up. These results indicate that neointimal growth continues with durable (SES) as well as with biodegradable (BES) polymer-based DES beyond the time point, at which healing is complete with BMS.

The different time point at which the first follow-up was performed (6 months in BES vs. 12 months in SES) makes any comparison of the dynamics in neointimal response between the 2 stent types questionable. SES release 80% of the drug during the first 30 days, with nearly all drug eluted at 3 months, whereas BES is characterized by a bioabsorbable abluminal polymer, namely polylactide, which is predictably degraded by surface hydrolysis to lactide during a period of 6 to 12 months (5). It remains uncertain whether the increase in neointimal tissue from 6 months to 5 years observed with BES is solely related to the decrease of drug dose, or whether it reflects a true increase beyond 1 year as the result of impaired healing as has been described in early generation DES. Since the bioabsorption of the polymer has been correlated with a transient inflammatory response, it would be interesting to evaluate the intimal thickness after completion of biodegradation (12 to 18 months) and during long-term follow-up (4 to 5 years). Only this design would allow the investigation of whether BES is associated with an increasing neointimal proliferation during long-term follow-up after completion of the bioabsorption process.

## BMS Versus Early-Generation DES

In BMS, longitudinal angiographic and angioscopic follow-up series observed late improvements in lumen diameter, suggesting fibrotic maturation and regression of the neointima, and a similar pattern with absence of delayed late loss beyond 8 months was noted with a polymer-free DES (6–8). Caution, however, should be exercised because limited data are available with BMS beyond 3 years. An optical coherence tomography study reported on a transformation of the neointima into lipid-laden tissue, reflecting atherosclerotic progression (9) and very late erosion of the minimal lumen diameter between 4 and 10 years and beyond 10 years have been observed in a small angiographic study. In contrast to BMS, angiographic and IVUS studies of early generation DES documented a continued increase in neointimal formation. Recently, the 5-year angiographic follow-up results of the SIRTAX LATE (Sirolimus-Eluting versus Paclitaxel-Eluting Stents for Coronary Revascularization-Late) trial have shown a catch-up of 0.33 ± 0.66 in delayed late loss between 8 months and 5 years for both SES and paclitaxel-eluting stents (PES). The study of Collet et al. (4), not only is confirmatory, but further improves our understanding in terms of late stent vessel wall interactions using IVUS. A limitation of this study is that patients presenting for repeat revascularization of the target lesion did not undergo IVUS and are not part of the present analysis. This inherently leads to a much lower absolute

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increase in neointimal tissue growth than observed in reality.

## Mechanisms of Late Intimal Growth in Early-Generation DES

What are the mechanisms responsible for the ongoing growth of neointima, and how might these be mitigated, and perhaps most important, are these observations clinically relevant (Fig. 1)? As a first mechanism, the antiproliferative drug concentration diminishes over time according to the individual elution profile of the devices, and with decreasing dose, the inhibiting effect declines. As a second mechanism, the presence of fibrin—which has been described in the vicinity of stent struts in experimental and autopsy studies—is an initiator of smooth muscle cell migration and proliferation (10). Porcine coronary models have revealed an increasing amount of fibrin in the long-term course (90 days) following implantation of early generation DES, and in analogy to prolonged wound healing that may result in an exaggerated scar formation, delayed fibrinolysis is a stimulus to smooth muscle cell proliferation and excessive collagenous matrix formation (11). Third, chronic inflammation is a trigger for late neointimal growth, and histological animal studies suggest that the inflammatory response among different DES appears clearly distinct in terms of the proportion of giant cells, granulomas, eosinophils, lymphocytes, and fibrin deposition (11). Whereas SES may cause a granulomatous and eosinophilic reaction starting at 28 days that continues to increase over time, PES is characterized by lower levels of inflammation, but higher amounts of fibrin deposition (2). Information about newer generation DES, such as BES, is currently still lacking. Fourth, the formation of neoatherosclerosis, mainly characterized by in-stent thin-cap fibroatheroma-containing neointima and neocalcifications, may reflect a contributing factor that arises later in the time course and is not yet sufficiently described (12,13).

## Clinical Significance of Late Catch-Up

The most relevant question emerging from the observation by Collet et al. (4) is whether the late "catch up" translates into a clinically meaningful need for target lesion revascularization (TLR) during long-term follow-up, reducing the early efficacy benefit of DES. Long-term results from randomized controlled trials of early and newer generation DES consistently show a yearly TLR rate of <2% beyond 1 year without any differences as compared with BMS (Table 1). After subtraction of stent thrombosis–related TLRs (as they are often not restenosis related), the annual TLR rate is as low as 1% to 1.5%. Against this background, it is reasonable

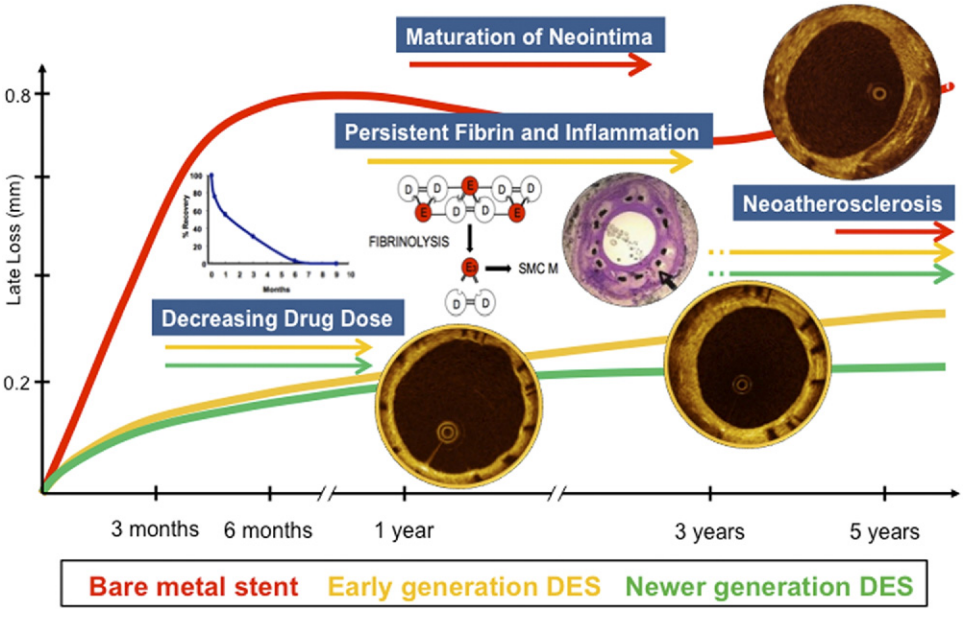


**Figure 1. The Different Time Course of the Neointimal Growth (Indicated by Late Loss) for BMS and for Early- and Newer-Generation DES Is Shown Throughout 5 Years**

Different mechanisms contributing to the late neointimal growth in drug-eluting stents (DES) are presented. SMC M = smooth muscle cell migration into neointima. D and E = D and E domains of fibrinogen. Schematic drawing of fibrinogen is referring to Naito et al. (10). **Arrow** in histological cross section depicts peristrut inflammatory cell infiltrates. In addition, a case example of a sirolimus-eluting stent showing delayed neointimal growth is depicted (kindly provided by Juan Luis Gutiérrez Chico, MD, Vigo, Spain).

**Table 1. Target Lesion and Stent Thrombosis Rates Beyond 1 Year in BMS and in Early- and Newer-Generation DES**

| Trial Acronym | Stent Type (n) | Clinical Setting | Follow-Up Period (yrs) | TLR Up to Maximal Follow-Up (%) | TLR Between 1 Yr and Maximal Follow-Up (%) | Annual Late TLR Rate (Beyond 1 Yr) (%) | ARC Definite VLST Between 1 Yr and Maximal Follow-Up (%) | Annual VLST Rate (%) |
|---|---|---|---|---|---|---|---|---|
| Early-generation DES (RCTs with 5-yr follow-up) | | | | | | | | |
| RAVEL | SES (n = 120) vs. BMS (n = 118) | Stable CAD | 5 | 10.3 vs. 26.0, p < 0.001 | 10.3 vs. 1.7*† | 2.6 vs. 0.4* | 0.8 vs. 0.8, p = 1.0 | 0.2 vs. 0.2* |
| SIRIUS | SES (n = 533) vs. BMS (n = 525) | Stable CAD | 5 | 9.4 vs. 24.2, p < 0.001 | 4.5 vs. 4.0, p = 0.76 | 1.1 vs. 1.0* | 0.8 vs. 0.4, p = 0.56 | 0.2 vs. 0.1* |
| TAXUS IV–SR | PES (n = 651) vs. BMS (n = 643) | Stable and unstable CAD | 5 | 16.4 vs. 4.3, p < 0.001 | 6.0 vs. 8.0* | 1.5 vs. 2.0, p = 0.26 | 0.8 vs. 0.4* | 0.2 vs. 0.1, p = 0.49 |
| SIRTAX LATE | SES (n = 503) vs. PES (n = 509) | All comers | 5 | 13.1 vs. 15.1, p = 0.29 | 7.4 vs. 4.9, p = 0.16 | 2.0 vs. 1.4, p = 0.17 | 2.6 vs. 2.4, p = 0.83 | 0.7 vs. 0.6, p = 0.85 |
| Newer-generation DES (RCTs with at least 3 yrs of follow-up) | | | | | | | | |
| LEADERS | BES (n = 857) vs. SES (n = 850) | All comers | 3 | 7.6 vs. 8.8, p = 0.38 | 2.7 vs. 3.4, p = 0.41 | 1.3 vs. 1.7, p = 0.56 | 0.3 vs. 0.9, p = 0.09 | 0.1 vs. 0.4, p = 0.12 |
| ENDEAVOR pooled program | ZES (n = 2,132) | Stable and unstable CAD | 3 | 6.7 | 1.3 | 0.65* | 0.8*‡ | 0.4‡ |
| SPIRIT II, III pooled | EES (n = 892) vs. PES (n = 410) | Stable and unstable CAD | 3 | 5.4 vs. 9.1 | 2.5 vs. 3.7, p = 0.27 | 1.3 vs. 1.9* | 0.2 vs. 0.5, p = 0.59 | 0.1 vs. 0.3* |

TLR is ischemia-driven, if available. *Unpublished data that were calculated using outcomes at 1 year and at the timepoint of the maximal available follow-up, therefore no p values are available. †TLR between 9 months and 5 years. ‡ARC definite or probable stent thrombosis,

ARC = Academic Research Consortium; BES = biolimus-eluting stent(s); BMS = bare-metal stent(s); CAD = coronary artery disease; ENDEAVOR = Randomized Controlled Trials of the Medtronic Endeavor Drug-Eluting Coronary Stent System; LEADERS = Limus Eluted From a Durable versus Erodible Stent Coating; PES = paclitaxel-eluting stent(s); RAVEL = A Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coaronary Revascularization; RCT = randomized controlled trial; SES = sirolimus-eluting stent(s); SIRIUS = Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions; SIRTAX LATE = Sirolimus versus Paclitaxel-Eluting Stents for Coronary Revascularization LATE trial; SPIRIT = A Clinical Evaluation of the XIENCE V Everolimus-Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions; TAXUS IV-SR = Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Slow Release Stent; TLR = target lesion revascularization; VLST = very late stent thrombosis; ZES = zotarolimus-eluting stent(s).

to conclude that early generation DES delay intimal formation and healing during the long-term course, yet without significantly compromising the early benefit in efficacy. Prolonged neointimal proliferation, however, may be a useful marker to assess the delay in healing. Of note, delayed healing has been characterized histologically by lack of endothelialization and persistent fibrin deposition, and both were identified as the principal pathological finding in an autopsy study distinguishing late thrombosed from patent early generation DES.

## Glimpse Into the Future

Newer generation DES were designed to overcome the limitations of early generation DES. The biocompatibility of the durable polymers was improved, and the concept of completely bioabsorbable polymers was introduced. The strut thickness was further reduced, the drug dose was adapted, and the release kinetics optimized. Animal studies revealed a lower rate of uncoverage (marker of healing), and similar observations were observed using optical coherence tomography in vivo with both BES and everolimus-eluting stents as compared with SES (14,15). As these findings were paralleled by improved clinical outcomes (16), it is tempting to hypothesize that newer generation DES will translate into a less pronounced neointimal growth beyond 1 year as a result of less fibrin deposition and less inflammation in nonrandomized studies, and, therefore, may result in less very late stent thrombosis during long-term follow-up. A common limitation of both early and newer generation DES is the presence of a permanent metallic scaffold that serves as the nidus for late adverse stent vessel wall interactions. Recently, the use of fully bioabsorbable everolimus-eluting scaffolds have demonstrated their potential ability to treat coronary artery stenoses, and other fully absorbable technologies are currently under investigation (17). Whether these "new kids on the block" will overcome the aforementioned limitations of conventional metallic DES has yet to be shown.

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**Key Words:** drug-eluting stent(s) ■ intravascular ultrasound ■ late restenosis ■ long-term clinical outcome.