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EDITORIAL COMMENT

The DESIRE-Late Registry

What Is Left to Be Desired?*

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Drug-eluting stents (DES) were introduced into clinical practice after the pioneering work of Sousa et al. (1) in São Paulo, Brazil. The detailed first-in-man investigations of this renowned group supplemented by large-scale clinical trials established DES as a breakthrough technology due to their potent reduction of restenosis, the principal shortcoming compared with coronary artery bypass surgery and a nuisance in the quality of life of affected patients. Thus, first-generation DES with controlled release of sirolimus or paclitaxel from durable polymers has been consistently shown to reduce repeat revascularization procedures by 40% to 70% compared with bare-metal stents (BMS) (2). The benefit, albeit attenuated, prevailed in studies without protocol-mandated angiographic follow-up, was particularly pronounced in diabetic patients (3), and endured during long-term follow-up extending to 5 years.

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Although the efficacy of first-generation DES remained undisputed, safety concerns soon emerged after the widespread application of these devices in routine clinical practice with a wide range of on-label and off-label indications. Very late stent thrombosis, that is, thrombotic occlusion of the device more than 1 year after implantation, was recognized as a distinct entity complicating the use of first-generation DES with a continuous risk up to 4 years (4). Human autopsy studies and recent clinical investigations of thrombosed DES specimens implied delayed healing, incomplete endothelialization, and vessel remodeling due to chronic inflammation as potential mechanisms leading to this adverse event (5,6). Despite the somewhat increased risk of very late stent thrombosis, comprehensive review of the available evidence showed similar rates of death and myocardial infarction among patients treated with DES and BMS (2). It has been suggested that the slightly increased risk of very late stent thrombosis associated with DES is compensated by adverse events caused by the treatment of the more frequent recurrences with BMS.

It is against this background that the results of the DESIRE (Drug-Eluting Stents in the Real World)-Late registry (7) reported in this issue of *JACC: Cardiovascular Interventions* must be critically appraised. During a median follow-up time of 5 years of 1,010 patients treated with first-generation DES (sirolimus- and paclitaxel-eluting stents) between 2002 and 2005, the cumulative rate of cardiac death, target vessel revascularization, and major adverse cardiac events amounted to 5.6%, 6.6%, and 15.4%, respectively. The rate of definite and probable stent thrombosis was 1.7%, with more than one-half of events (0.9%) encountered beyond 1 year of stent implantation. The investigators should be applauded for obtaining complete follow-up information in more than 98% of patients. Moreover, there was no protocol-mandated angiographic follow-up, thereby avoiding the oculostenotic reflex and the associated inflation of repeat revascularization procedures.

Although these data are reassuring, event rates in the DESIRE-Late study are low compared with long-term follow-up data derived from meta-analyses and large-scale registries (Table 1) (2,8–11) and require careful scrutiny. First, not all patients undergoing percutaneous coronary intervention at this institution were treated with DES. Instead, BMS were used in more than 50% of patients in 2002 and still in 22% of patients in 2005. It would be of interest to compare event rates among DES and BMS because the selection of patients for a particular stent type may have influenced the favorable results (selection bias). Along the same line, registry studies without monitoring of all patients are susceptible to detection bias because not all events may have been captured, particularly during longer-term follow-up.

Second, patients included at a single center in the DESIRE-Late trial may not be representative of those encountered in routine clinical practice elsewhere. Although patient characteristics, including vessel size and lesion length, in the present study are comparable with published all-comer patient populations, the mean number of stents per patient (1.4) is rather low, suggesting that only 1 lesion was treated in the vast majority of patients (4). This is of importance because the number of treated lesions directly correlates with the risk of early and late ischemic and revascularization events as evidenced in the recent FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial (12). Moreover, the investigators paid particular attention to careful quantitative coronary analysis-guided stent

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Table 1. Clinical Long-Term Outcomes With First-Generation DES

Author (Ref. #)	n	Follow-Up Time (yrs)	DES Type	Death (%)	Cardiac Death (%)	MI (%)	TLR (%)	Per Protocol Stent Thrombosis
Stettler et al. (2)	6,771	4	SES	7.3	4.2	4.4	6.9	1.4
Stettler et al. (2)	6,331	4	PES	7.4	4.2	5.4	9.8	2.3
Stone et al. (8)	1,748	4	SES	6.7	3.5	6.4	7.8	1.2
Stone et al. (8)	3,513	4	PES	6.1	2.4	7.0	10.1	1.3
Daemen et al. (4)	8,146	3	DES	10.3	NA	4.1	11.7	2.9
Kimura et al. (9)	10,778	2	SES	7.2	3.7	1.5	10.2	0.8
Tu et al. (10)	3,751	2	DES	4.3	NA	5.7	7.4	NA
Mauri et al. (11)	5,549	2	DES	9.8	NA	8.3	11.0	NA

DES = drug-eluting stent(s); MI = myocardial infarction; NA = not applicable; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s); TLR = target lesion revascularization.

implantation, which may have been instrumental in the prevention of adverse events related to poor stent implantation technique.

Third, the proportion of patients with ST-segment elevation myocardial infarction (12%) at the time of the index procedure as well as the incidence of thrombotic lesions (3%) is lower compared with that in previously published DES registries (4). Acute myocardial infarction has been identified as an independent predictor of very late stent thrombosis, results in an increased incidence of late acquired stent malapposition (13), and has been associated with more extensive inflammation and a higher proportion of uncovered struts compared with stable lesions after DES implantation (14). The lower proportion of patients with acute myocardial infarction in the DESIRE-Late trial therefore may have contributed to the low incidence of very late stent thrombosis.

Fourth, the low overall (1.7%) and very late (0.13% per year) rate of definite and probable stent thrombosis is reminiscent of recent results obtained in the Japanese Cypher registry, with a cumulative incidence of only 0.9% (9). Of note, these results were observed despite a relatively short duration of dual-antiplatelet therapy of 3 to 6 months. Ethnic differences may come into play as they relate to the propensity for the development of hypersensitivity reactions to DES or nonresponsiveness to the thienopyridine clopidogrel and render the results difficult to apply to other patient populations.

How do we apply the results of the DESIRE-Late study to clinical practice? It is certainly reassuring for patients as well as responsible physicians that first-generation DES are associated with an excellent long-term clinical outcome in appropriately selected patients, even in the presence of a short-duration regimen of dual-antiplatelet therapy. Notwithstanding, the results have been obtained with the first generation of sirolimus- and paclitaxel-eluting stents, which have been superseded by the advent of newer-generation DES. Excellent short- and long-term clinical outcome have been reported with newer-generation DES, as summarized in Table 2 (15–20). Although it is still premature to definitively conclude, available data suggest that newer-generation DES may put to rest previous concerns of very late stent thrombosis.

Table 2. Clinical Outcomes of Trials With Newer-Generation DES

Trial (Ref. #)	n	Indication	Clopidogrel Therapy (Months)	Follow-Up Time	DES Type	Cardiac Death (%)	MI (%)	TLR (%)	MACE (%)	Definition of MACE	Per Protocol Stent Thrombosis
SPIRIT II (15)	300	Selected patients	6	3 yrs	EES vs. PES	0.5 vs. 4.3 p = NS	3.6 vs. 7.2 p = NS	4.6 vs. 10.1 p = NS	7.2 vs. 15.9 p < 0.05	Cardiac death, MI, TLR	2.1 vs. 4.4 p = NS
SPIRIT III (16)	1,002	Selected patients	6	3 yrs	EES vs. PES	1.6 vs. 2.0 p = NS	3.8 vs. 6.6 p = 0.07	5.7 vs. 9.2 p = NS	9.7 vs. 16.4 p = 0.004	Cardiac death, MI, TLR	1.0 vs. 1.7 p = NS
SPIRIT IV (17)	3,690	Selected patients	12	12 months	EES vs. PES	0.4 vs. 0.4 p = NS	1.9 vs. 3.1 p = 0.02	2.5 vs. 4.6 p = 0.001	4.2 vs. 6.9 p = 0009	Cardiac death, MI, TLR	0.2 vs. 0.9 p = 0.004
ENDEAVOR II (18)	1,197	Selected patients	3	5 yrs	ZES vs. BMS	3.1 vs. 3.6 p = NS	3.8 vs. 4.8 p = NS	7.5 vs. 16.3 p < 0.001	15.4 vs. 24.6 p < 0.001	Death, MI, TLR	0.5 vs. 1.4 p = NS
ENDEAVOR III (19)	436	Selected patients	3	4 yrs	ZES vs. SES	0.3 vs. 1.8 p = NS	1.0 vs. 4.5 p < 0.05	7.8 vs. 6.4 p = NS	12.7 vs. 19.1 p = NS	Death, MI, TLR	0.0 vs. 0.0 p = NS
ENDEAVOR IV (20)	1,548	Selected patients	6	3 yrs	ZES vs. SES	1.6 vs. 2.3 p = NS	2.2 vs. 4.9 p = 0.007	6.5 vs. 6.0 p = NS	11.4 vs. 13.8 p = NS	Death, MI, TLR	1.0 vs. 1.0 p = NS

EES = everolimus-eluting stent(s); MACE = major adverse cardiovascular events; ZES = zotarolimus-eluting stent(s); other abbreviations in Table 1.

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REFERENCES

1. Sousa JE, Costa MA, Abizaid A, et al. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: a quantitative coronary angiography and three-dimensional intravascular ultrasound study. Circulation 2001;103:192–5.
2. Stettler C, Wandel S, Allemann S, et al. Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. Lancet 2007;370:937–48.
3. Stettler C, Allemann S, Wandel S, et al. Drug eluting and bare metal stents in people with and without diabetes: collaborative network meta-analysis. BMJ 2008;337:a1331.
4. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667–78.
5. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202.
6. Cook S, Ladich E, Nakazawa G, et al. Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. Circulation 2009;120:391–9.
7. Costa JR Jr., Sousa A, Moreira AC, et al. Incidence and predictors of very late (≥4 years) major cardiac adverse events in the DESIRE (Drug-Eluting Stents in the Real World)-Late registry. J Am Coll Cardiol Intv 2010;3:12–8.
8. Stone GW, Moses JW, Ellis SG, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med 2007;356:998–1008.
9. Kimura T, Morimoto T, Nakagawa Y, et al. Antiplatelet therapy and stent thrombosis after sirolimus-eluting stent implantation. Circulation 2009;119:987–95.
10. Tu JV, Bowen J, Chiu M, et al. Effectiveness and safety of drug-eluting stents in Ontario. N Engl J Med 2007;357:1393–402.
11. Mauri L, Silbaugh TS, Wolf RE, et al. Long-term clinical outcomes after drug-eluting and bare-metal stenting in Massachusetts. Circulation 2008;118:1817–27.
12. Tonino PA, De Bruyne B, Pijls NH, et al. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 2009;360:213–24.
13. van der Hoeven BL, Liem SS, Jukema JW, et al. Sirolimus-eluting stents versus bare-metal stents in patients with ST-segment elevation myocardial infarction: 9-month angiographic and intravascular ultrasound results and 12-month clinical outcome results from the MISSION! Intervention Study. J Am Coll Cardiol 2008;51:618–26.
14. Nakazawa G, Finn AV, Joner M, et al. Delayed arterial healing and increased late stent thrombosis at culprit sites after drug-eluting stent placement for acute myocardial infarction patients: an autopsy study. Circulation 2008;118:1138–45.
15. Garg S, Serruys P, Onuma Y, et al., on behalf of the SPIRIT II Investigators. 3-year clinical follow-up of the XIENCE V everolimus-eluting coronary stent system in the treatment of patients with de novo coronary artery lesions: the SPIRIT II trial (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients with de novo Native Coronary Artery Lesions). J Am Coll Cardiol Intv 2009;2:1190–8.
16. Stone GW. SPIRIT III—3 Year Clinical Follow Up Results. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA.
17. Stone GW. A Large-Scale Randomized Comparison of Everolimus-Eluting and Paclitaxel-Eluting Stents: One-Year Clinical Outcomes From the SPIRIT IV Trial. Presented at: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA.
18. Eisenstein EL, Wijns W, Fajadet J, et al. Long-term clinical and economic analysis of the Endeavor drug-eluting stent versus the Driver bare-metal stent: 4-year results from the ENDEAVOR II trial (Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver Coronary Stent in De Novo Native Coronary Artery Lesions). J Am Coll Cardiol Intv 2009;2:1178–87.
19. Eisenstein EL, Leon MB, Kandzari DE, et al., on behalf of the ENDEAVOR III Investigators. Long-term clinical and economic analysis of the Endeavor zotarolimus-eluting stent versus the Cypher sirolimus-eluting stent: 3-year results from the ENDEAVOR III trial (Randomized Controlled Trial of the Medtronic Endeavor Drug [ABT-578] Eluting Coronary Stent System Versus the Cypher Sirolimus-Eluting Coronary Stent System in De Novo Native Coronary Artery Lesions). J Am Coll Cardiol Intv 2009;2:1199–207.
20. Leon MB. Late Safety and Efficacy of a Zotarolimus-Eluting Stent Compared With a Paclitaxel-Eluting Stent in Patients With De Novo Coronary Lesions: Three-year Follow-Up From the ENDEAVOR IV Trial. Paper presented at: Transcatheter Cardiovascular Therapeutics; September 21, 2009; San Francisco, CA.

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