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EDITORIAL

Very late outcomes of drug-eluting stents: the 'catch-down' phenomenon

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This editorial refers to 'Ten-year clinical outcomes of first-generation drug-eluting stents: the Sirolimus-Eluting vs. Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) VERY LATE Trial'†, by K. Yamaji *et al.*, on page 3386.

Based on the current paradigm, drug-eluting stents (DES) are not only more effective, but also safer than bare metal stents (BMS).[1] Certainly, it was not always so: in spite of their lower risk of restenosis and target lesion revascularization (TLR) compared with BMS, first-generation DES have been blamed for years due to concerns of a 'catch-up' in late and very late ischaemic events that pathological and *in vivo* studies attribute to delayed arterial healing, polymer hypersensitivity reactions, continuous neointimal growth, late-acquired malapposition, and neoatherosclerosis.[2,3] Second-generation DES with biocompatible polymers, biodegradable polymers, or polymer-free—along with improved platform design, thinner struts, and novel antiproliferative drugs—have now addressed many of these limitations, translating into better clinical outcomes. In a network meta-analysis of > 52 000 patients summarizing data from a total of 51 stent trials at a median follow-up of 4 years, second-generation DES were found to outperform BMS and first-generation DES significantly with respect to both safety and efficacy.[4]

These improvements notwithstanding, very late stent failure owing to permanent caging of the vessel remains a matter of concern, which has been the impetus for the introduction of fully bioresorbable DES, also known as bioresorbable scaffolds. There is evidence from intracoronary imaging studies that these devices are no longer present in the coronary arteries at 5 years from implantation.[5] Therefore, the benefits of liberating the vessels from the metallic frame of DES, if any, are expected to accrue not immediately, but in the very long term. But what do we really know about the very late outcomes of DES (i.e. >5 years)? Are the concerns of an unceasing catch-up in clinical events justified? Indeed, capturing clinical endpoints beyond 5 years does not typically reflect the data collection plan of DES trials due to cost considerations, methodological issues, and the general belief that stent-related complications peak earlier in time.

In this issue of the journal, Yamaji *et al.* report on the 10-year follow up of SIRTAX, a randomized study comparing first-generation sirolimus-eluting stents (SES) ($n = 503$) and paclitaxel-eluting stents (PES) ($n = 509$).[6] The 5-year results of this study were published previously, showing no significant differences in clinical and angiographic outcomes between SES and PES.[7] In this update, the authors describe a significant decline in the annual rate of adverse clinical events between 5 and 10 years compared with 1–5 years with respect to both TLR (from 1.8% to 0.7% per year) and stent thrombosis (from 0.7% to 0.2% per year). Not surprisingly, due to the ageing of the population, the annual risk of cardiac death increased from 1.0% to 2.0%, while the annual risk of myocardial infarction was low (<1%) and tended to reduce over time. In aggregate, these figures resulted in similarly constant increases in the composite of cardiac death, myocardial infarction, and TLR between 1–5 and 5–10 years (2.8% and 3.3% per year, respectively). Interestingly, SES and PES behaved similarly, although a time to treatment interaction was previously noted in the 5-year report, with a progressive decrease of the initial 9-month advantage of SES over PES, which is compatible with the distinctive release kinetics of sirolimus compared with paclitaxel.[7]

The authors should be congratulated for an elegantly executed analysis, that adds meaningfully to our understanding of the natural history of first-generation DES. In particular, retrieving follow-up information for 88.4% of patients at 10 years is a respectable endeavour for a trial that did not pre-specify outcomes collection beyond 5 years. One may argue that with ~12% of patients missing at follow-up we are not sufficiently reassured on the lack of very late fatal and non-fatal events in a higher proportion of patients than that reported in the study. However, there were no differences in baseline characteristics between patients with and without 10-year follow-up, which minimizes this theoretical bias if we assume a similar risk of adverse

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events in patients with missing information. As expected in studies reporting on very long-term outcomes, death might have exerted some degree of selection on the study population, with healthier patients more likely to reach the 5–10 years part of the follow-up. The authors performed multiple sensitivity analyses accounting for the competitive risk of death on the non-fatal outcomes and stratified analyses based on age, which showed consistent results with the main analysis, thus making the authors' conclusions more credible and robust.

The key message of the study from Yamaji *et al.* is that DES-related events might not accrue at a constant rate over time, with the annual risk of TLR and stent thrombosis declining significantly after 5 years. Although first-generation DES are no longer on the market, the 10-year results of SIRTAX are reassuring for patients that have had SES and PES implanted in their coronary arteries. Unstable features of neoatherosclerosis arising from endothelial dysfunction have been described more frequently in autopsy cases of first-generation DES compared with BMS, and at a shorter time from implantation (1–2 years vs. 5–6 years).[8] Indeed, among 88 patients from SIRTAX who underwent optical coherence tomography assessment at 5 years, neoatherosclerosis was identified in ~16%.[9] The prevalence and consequences of in-DES neoatherosclerosis beyond 5 years remain uncertain, but the flattening of the cumulative event curves for TLR and stent thrombosis in SIRTAX, along with the low annual rates of myocardial infarction, make it tempting to speculate that the toll to pay to this pathological mechanism might be not as onerous as initially feared, at least within 10 years.

Importantly, these results were obtained on a background of antiatherosclerotic drug therapy in the majority of patients. The authors speculate that this may contribute to explain the observed reduction in coronary events beyond 5 years, which comes at variance with another smaller study of SES-treated patients with 10-year follow-up suggesting TLR to represent a long-term hazard with no attenuation.[10] Indeed, statins are expected to counteract the progression of atherosclerosis both inside and outside the stent. In this regard—adding to the numerous device-oriented endpoints scrutinized by the authors—it would have been valuable to obtain insights into some more patient-oriented clinical endpoints that unfortunately have not been reported, such as myocardial infarction and revascularization in non-target vessels. This information would help to unravel whether in SIRTAX there was a global deceleration of plaque progression and related consequences (i.e. as the long-term effect of medical therapies instituted at the time of the index hospital stay) or whether plaque progression diminished at the stent site but continued in non-stented vessels, as shown in another study with very long-term follow-up,[11] carrying its burden of clinical consequences.

Acronym	PES	SES	E-ZES	R-ZES	CoCr-EES	PtCr-EES	BP-BES	BP-EES	O-SES	Dual DES	BVS
											
Name	TAXUS						BIOMATRIX				
Manufacturer	Boston Scientific						Biosensors				
											
Name	TAXUS LIBERTÉ	CYPHER	ENDEAVOR	RESOLUTE	XIENCE	PROMUS	NOBORI	SYNERGY	ORSIRO	YUKON PF	ABSORB
Manufacturer	Boston Scientific	Cordis	Medtronic	Medtronic	Abbott Vascular	Boston Scientific	Terumo	Boston Scientific	Biotronik	Translumina	Abbott Vascular
Material	Stainless steel	Stainless steel	Cobalt chromium	Cobalt nickel	Cobalt chromium	Platinum chromium	Stainless steel	Platinum chromium	Cobalt chromium	Stainless steel	PLLA
Strut thickness	132 (T) 96 (TL)	140	91	91	81	81	120 (B) 125 (N)	74	60	87	150
Polymer	SIBS	PEVA and PBMA	PC	PBMA, PHMA, PVP, and PVA	PBMA and PVDF-HFP	PBMA and PVDF-HFP	PDLLA	PLGA	PDLLA	-	PDLLA
Polymer type	Durable	Durable	Durable	Durable	Durable	Durable	Bio-degradable	Bio-degradable	Bio-degradable	Polymer-free	Bio-degradable
Polymer coating	Conformal	Conformal	Conformal	Conformal	Conformal	Conformal	Abluminal	Abluminal	Conformal	-	Conformal
Drug	Paclitaxel	Sirolimus	Zotarolimus	Zotarolimus	Everolimus	Everolimus	Biolimus A9	Everolimus	Sirolimus	Sirolimus Probucol	Everolimus

Figure 1 Key features of most investigated drug-eluting stents and bioresorbable scaffolds. Strut thickness is expressed in microns. B, Biomatrix; BP-BES, biodegradable-polymer biolimus-eluting stent; BP-EES, biodegradable-polymer everolimus-eluting stent; BVS, bioresorbable vascular scaffold; CoCr-EES, cobalt–chromium everolimus-eluting stent; DES, drug-eluting stent; E-ZES, Endeavor zotarolimus-eluting stent; N, Nobori; O-SES, Orsiro sirolimus-eluting stent; PBMA, poly n-butyl methacrylate; PC, phosphorylcholine; PDLLA, poly(D,L)-lactic acid; PES, paclitaxel-eluting stent; PEVA, polyethylene-co-vinyl acetate; PlCr-EES, platinum–chromium everolimus-eluting stent; PLGA, poly-lactide-co-glycide; PLLA, poly-L-lactic acid; PVA, polyvinyl acetate; PVDF-HFP, poly(vinylidene fluoride-cohexafluoropropylene); R-ZES, Resolute zotarolimus-eluting stent; SES, sirolimus-eluting stent; SIBS, poly(styrene-b-isobutylene-b-styrene; T, Taxus; TL, Taxus Liberté.

From a regulatory perspective, the 10-year results of SIRTAX support the recent recommendation from a European Task Force that follow-up of coronary stent trials should be performed up to 5 years only.[12] Indeed, this study is consistent with the hypothesis that stent-induced complications peak during this time frame and then diminish, making further assessment unnecessary in a cost containment perspective. Nonetheless, similar to what the SIRTAX investigators have laudably put in place, it would be highly informative for the community to get the 10-year outcomes of other landmark DES trials, such as those of first-generation DES vs. BMS or second-generation vs. first-generation DES. These extended follow-up collections would enable a more comprehensive picture of the comparative safety and effectiveness of different coronary devices over the course of life.

Because SIRTAX did not show clinical events to be zeroed after 5 years, its results should not detract from the quest to achieve better outcomes through technological advancements and better medical therapies. Several ameliorations in DES technologies have occurred over the course of the past decade (*Figure 1*) that would make it surprising if the 5- to 10-year results of second-generation DES are not 'at least' as good as those of first-generation DES. Along this line, the bar has been set very high by the study of Yamaji *et al.*, which represents a relevant benchmark for all new technologies whose follow-up beyond 5 years is still unavailable, and particularly for bioresorbable scaffolds. In fact, if the annual rate of TLR and thrombosis at >5 years from implantation of the 'imperfect' first-generation DES is as low as suggested by SIRTAX, and if second-generation DES can replicate these findings or do even better, then the need for a bioresorbable device might be less urgent than what we have largely assumed so far. This is important in view of the higher risk of 1-year thrombosis recently reported for bioresorbable scaffolds compared with newer-generation DES in a network meta-analysis.[13] The trade-off between early and long-term safety may be favourable to bioresorbable scaffolds only in the presence of substantial and marked reductions in long-term TLR and thrombosis compared with the current standard of care, which is not an easy achievement if the risk of very late events of DES at 10 years from implantation is consistent with the hypothesis of a 'catch-down', rather than a 'catch-up' phenomenon.

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