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New-generation drug-eluting stents in patients with complex coronary artery disease: still a "work in progress"?

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Treatment of complex obstructive coronary artery disease remains a challenge for physicians in practice around the globe. However, drug-eluting stent (DES) therapy represents an important breakthrough technology which has enabled cardiologists to offer percutaneous intervention to patients with complex disease patterns who were formerly precluded from such treatment due to a high rate of stent failure, mainly as a result of in-stent restenosis[1,2]. Nevertheless, rates of certain adverse clinical events after stenting remain higher in patients with complex disease and in those where the indication for stenting is deemed "off-label" in comparison to patients with more straightforward disease[3,4].

Early-generation DES were associated with some important limitations, including very late stent thrombosis and late catch-up restenosis. The basis for these problems seems to be systematic delayed healing of the stented arterial segment[5]. Although undoubtedly multifactorial in aetiology, persistent inflammatory response to the durable polymer coatings used on these stents plays a central role[6]. However, iterative development of newer-generation DES has resulted in improved healing after stent implantation[7] and has further improved patient outcomes with reduced rates of restenosis and stent thrombosis in comparison to early-generation DES[8,9].

The zotarolimus-eluting Resolute stent (Medtronic CardioVascular, Santa Rosa, CA, USA) is a newer-generation thin-strut durable polymer-based DES. The key difference in relation to its predecessor zotarolimus-eluting Endeavor stent (Medtronic CardioVascular) is its durable polymer coating, which facilitates more controlled drug elution. This has been shown in translational investigation to be the key factor in determining antirestenotic efficacy[10], and clinical trials have demonstrated that this iterative change results in improved clinical outcomes with the Resolute ZES in comparison with the Endeavor ZES[11,12]. Moreover, large-scale randomised trials with wide inclusion criteria have shown broadly comparable results between the Resolute ZES and the initial benchmark durable polymer everolimus-eluting XIENCE stent (Abbott Vascular, Santa Clara, CA, USA) in both industry-initiated and investigator-initiated studies[13-16].

In the current issue of AsiaIntervention, Zambahari and the RESOLUTE Asia Investigators report the results of a multicentre registry enrolling a total of 311 patients undergoing multivessel stenting or those with lesions requiring implantation of long stents (>38 mm)[17]. Patients were included across nine Asian countries and analysis of baseline characteristics of treated patients is notable for a young mean age (under 60 years) and a high prevalence of diagnosed diabetes mellitus (over 40%). The main finding of the investigators was that rates of target lesion failure, the composite of cardiac death, target vessel myocardial infarction or target lesion revascularisation, were low, around 5% at one year in both subgroups of patients. These excellent rates are in line with the results of randomised trials with new-generation durable polymer DES in recent years, many of which included patients with multivessel stenting **(Figure 1)**[13-16]. In addition, the results in patients treated with long stents are very encouraging: the acute performance is excellent with a high rate of device success, in line with what we have come to expect in terms of deliverability from current-generation DES. The advantages in treating long lesions with a single stent are obvious in view of the known unfavourable healing profile of overlapping DES layers[18].

However, the data must be interpreted in the light of some important limitations. Firstly, the impact of patient selection must be considered. With data from 25 centres and an enrolment period of 21 months it can be estimated that in crude terms fewer than one patient per month was recruited at each centre. This suggests that only selected patients were enrolled and impacts on the external validity of the findings. In addition, in terms of disease complexity, patients with interventions for chronic total occlusions and in-stent restenosis are not represented. Secondly, event rates in registry studies are very sensitive to the rigour and completeness of data acquisition and follow-up. In this respect, however, the high

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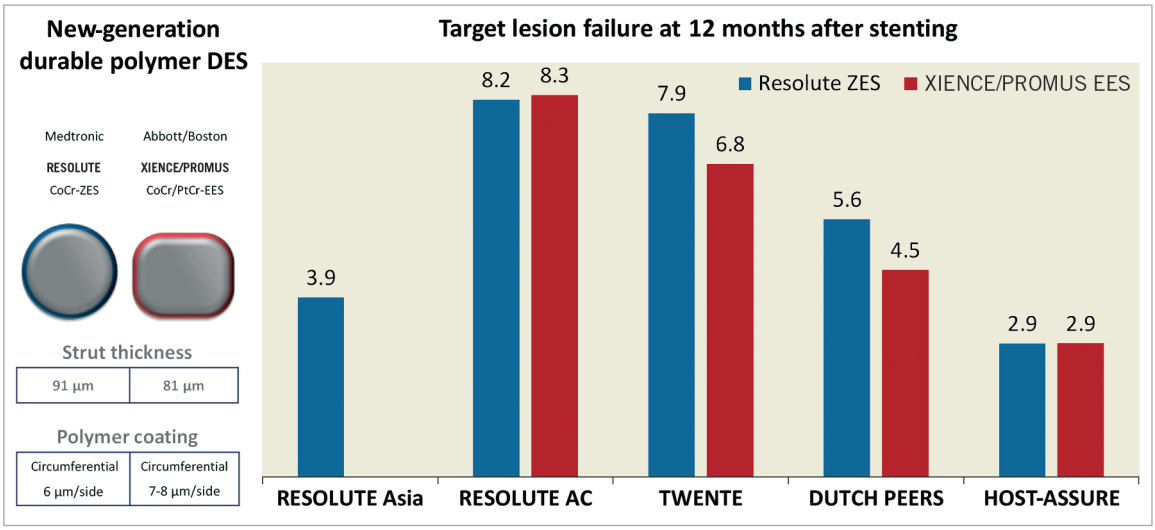

Figure 1. *Key features of current durable polymer drug-eluting stents and rates of target lesion failure at 12 months after implantation from the RESOLUTE Asia registry and selected large-scale randomised clinical trials with primary comparison of outcomes between durable polymer DES. CoCr: cobalt chromium; EES: everolimus-eluting stent; PtCr: platinum chromium; RESOLUTE AC: Resolute All Comers; ZES: zotarolimus-eluting stent*

rate of monitoring and the use of an independent events adjudication committee and angiographic core lab are reassuring. Thirdly, in general terms, the impact of publication bias must always be considered: registry studies are perhaps more susceptible to this than randomised clinical trials. Finally and importantly, the follow-up in this present report is limited to two years. Longer-term surveillance of these patients up to five years should be undertaken.

Overall, the data reported by Zambahari and colleagues with this current-generation durable polymer DES are encouraging and consistent with recent registry and randomised clinical trial reports in showing excellent patient outcomes even with relatively complex disease patterns and lesion subsets at short to medium-term follow-up[13-16]. At the same time, we need to remember that unmet needs continue to exist, particularly with regard to late adverse events after DES implantation, which continue to accrue with time even with newer-generation platforms[19]. In addition, recent autopsy reports suggest that hypersensitivity reactions to durable polymer coatings, a problem well described with the first-generation durable polymer sirolimus-eluting stent (Cypher; Cordis, Miami Lakes, FL, USA), continue to be observed with newer-generation durable polymer DES[20]. Indeed, this is not entirely unexpected, as current-generation durable polymer stents also include methacrylate components, which may well be the trigger for such reactive processes[21]. Moreover, preliminary reports suggest that the rates of neoatherosclerosis, an important, and perhaps the dominant, cause of late stent failure, seem to be similar between early and newer-generation durable polymer DES[20]. For these and other reasons, it is our belief that novel stent solutions, including biodegradable polymer and polymer-free as well as fully bioresorbable DES[22], present attractive alternatives to durable polymer devices and should continue to be pursued. While recently reported initial long-term data comparing biodegradable polymer DES with newer-generation durable polymer DES at five years are encouraging[23], further results from long-term comparative efficacy data are awaited with great interest. With this in mind, in spite of ever improving patient outcomes, we contend that DES technology remains very much a "work in progress".

Conflict of interest statement

R. Byrne reports receiving lecture fees from B. Braun Melsungen AG, Biotronik and Boston Scientific. A. Kastrati reports patent applications related to drug-eluting stent coatings.

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