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EDITORIAL

Drug-Coated Balloons in In-Stent Restenosis, a New Standard of Care or Yesterday's News?

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Despite the successes of percutaneous coronary intervention (PCI) with contemporary drug-eluting stents (DESs) in reducing rates of in-stent restenosis (ISR) compared with bare-metal stents and plain old balloon angioplasty (POBA), the initial vascular injury and consequent neointimal proliferation caused by DES implantation still lead to a long-term risk of ISR and late-stent thrombosis.[1,2] It therefore easy to see how the idea of angioplasty without leaving a residual scaffold, especially in high-risk disease, remains appealing to the interventional cardiology community.[3]

See Article by von Koch et al.

The evidence for a drug-coated balloon (DCB) strategy for ISR in preference to POBA or even DES has emerged predominantly over the past decade. ISAR-DESIRE 3 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis: 3 Treatment Approaches) demonstrated the noninferiority of paclitaxel-eluting balloons to paclitaxel-eluting stents in patients with DES-ISR and demonstrated clear superiority over POBA, with a primary outcome of diameter stenosis at follow-up angiography at 6 to 8 months,[4] although this trial was not powered to detect differences in clinical end points. Importantly, the recently published 10-year follow-up data from ISAR-DESIRE 3 found no significant difference in all-cause or cardiovascular mortality endpoints for paclitaxel-eluting balloons compared with paclitaxel-eluting stents.[5] Further studies supported the DCB strategy, with PEPCAD-DES (Treatment of Drug-Eluting Stent In-Stent Restenosis With Sequent Please Paclitaxel Eluting Percutaneous Transluminal Coronary Angioplasty Catheter) demonstrating the superiority of paclitaxel-coated balloons to POBA in ISR up to 36 months, for both major adverse cardiovascular events and target lesion revascularization (TLR).[6]

Nevertheless, many of the previous trials have limitations, such as limited follow-up of 3 years, inclusion of platforms not used in contemporary practice such as bare metal stents or first-generation DESs or have focused on only 1 type of DCB. In this issue of the *Journal of the American Heart Association* (*JAHA*), von Koch et al.[7] have used the SCAAR (Swedish Coronary Angiography and Angioplasty registry), which includes data from all patients in Sweden undergoing coronary angiography or intervention in any of the 29 PCI centers providing acute cardiac care to study the long-term outcomes of ISR treated by DCB, DES, or POBA. The primary outcome was TLR at 5-year follow-up and secondary outcomes included all-cause mortality,

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cardiovascular mortality, myocardial infarction, and any PCI.

Patients included had a mean age of just under 70, were predominantly male (78%), and had a range of indications for their PCI, including stable coronary artery disease, unstable angina, non–ST-segment–elevation myocardial infarction, and ST-segment–elevation myocardial infarction. This was the first large-scale national study of DCB angioplasty that included a range of different DCBs, with previous DCB trials having predominantly focused on paclitaxel-coated balloons. Importantly, this study compared DCBs to both POBA and the current standard of care, DES.

The finding of DCB superiority to POBA for the primary outcome of TLR (risk ratio [RR], 0.69 [95% CI, 0.57–0.82]) and all-cause mortality (RR, 0.72 [95% CI, 0.59–0.88]), after adjusting for a range of important demographic features, comorbidities, indication, and type of ISR is not surprising, and is in keeping with contemporary trials. However, it is the comparison to the contemporary DES platforms that will generate the most interest, as this is the most clinically important question for interventional cardiologists worldwide who are presented with patients with ISR. The primary outcome of TLR was higher in the group with DCBs when compared with DESs (adjusted hazard ratio [aHR], 1.20 [95% CI, 1.06–1.37], *P*=0.005); however, no significant differences in all-cause mortality, cardiovascular mortality, or myocardial infarction were demonstrated in these clinically important secondary outcomes.

Additionally, von Koch et al. suggest from their subgroup analysis of TLR that there is a group of patients, aged >80 years old, for whom the DCB strategy is advantageous compared with DES (aHR, 0.57 [95% CI, 0.36–0.89])(with a *P* value of interaction =0.001), which could be an important, clinically significant finding worthy of future investigation, given our aging population and greater numbers of patients receiving DESs, who will no doubt encounter ISR in the future.

This was an important trial for a range of reasons. First, this was a large, national study from a comprehensive registry, with a total study population of 10 561 ISR lesions, from a total of 9062 patients, with 5 years of mortality follow-up available for all patients included in the study. This significant population size importantly enabled the trial to be powered for secondary outcomes such as all-cause mortality and cardiovascular mortality, rather than solely TLR, unlike many other contemporary trials of DCB angioplasty.

The limitations of this study are well acknowledged by the authors, sharing the standard pitfalls of observational studies of this type. First, as treatment was not randomized, there will be an element of selection bias, with the patients with the most multiple morbidities and frailty being more likely to be treated by POBA, and despite efforts to correct for this as part of the multivariate analysis, there will still be an element of residual confounding. Second, it is unclear how optimal the DCB results were in this analysis or what minimal lumen area was achieved, which would have an impact on future restenosis rates and the experience of the operators in using DCBs. Third, "hybrid" procedures involving both DCBs and DESs were included in the DES arm although it is not clear whether these were intentioned as hybrid from the start or were bailout procedures following suboptimal results from a DCB, which would be considered a DCB procedure in an intention-to-treat analysis from a randomized trial. Finally and importantly, the patterns of ISR are not captured by the database, and it is unclear whether there are differences between the groups studied in relation to (1) focal (≤10 mm length), (2) diffuse (ISR >10 mm within the stent), (3) proliferative (ISR >10 mm extending outside the stent), and (4) occlusive ISR, which are known to have an impact on longer term outcomes, particularly on the risk for future revascularization.

The superiority of DCBs compared with POBA for ISR is well established, but how DCBs compare with the current standard of care, DESs, is less clear. There are good data to suggest the long-term safety of paclitaxel DCBs compared with DESs, Scheller et al. demonstrating in their meta-analysis of 26 randomized controlled trials that paclitaxel-coated balloons do not exhibit increased mortality compared with control treatments (DESs, bare-metal stents, or POBA) for both ISR and de novo lesions, and that there is a trend toward lower mortality up to 1 year.[8]

However, despite the demonstration of safety, and several trials suggesting noninferiority of DCBs compared with DESs, should this change practice? First, the noninferiority of DCBs compared with DESs is not a consistent finding. The DAEDALUS (Difference in Anti-Restenotic Effectiveness of Drug-Eluting Stent and Drug-Coated Balloon Angioplasty for the Occurrence of Coronary In-Stent Restenosis) study showed in a population with ISR that although results were comparable in the case of bare-metal stents-ISR, DES was more effective than paclitaxel-coated balloons at preventing TLR at 3 years in DES-ISR, although all-cause death and myocardial infarction incidence was similar between arms.[9,10] Partly due to the results of this trial, the European Society of Cardiology's most recent (2024) guidelines for the management of chronic coronary syndromes now recommend DESs over DCBs in the treatment of in-DES restenosis as a class 1A recommendation.[11] Furthermore, there is a question about the longevity of the benefits of a DCB strategy compared with DES for ISR, with a meta-analysis by Elgendy et al. suggesting that although the risk of target vessel revascularization at 1 year is broadly similar between both arms, the risk of target vessel revascularization

and TLR was higher in patients treated with DCBs compared with patients treated with DESs at 3 years.[12] One of the main problems of interpreting these trials is that repeat revascularization is not a spontaneous outcome; it must be ordered by a physician (and agreed to by a patient) and is prone to confounding. The threshold for repeat revascularization may be much lower for patients treated with DCBs than in patients treated with DESs who may have multiple layers of stents and may be more likely to be treated medically.

One important point regarding the interpretation of DCB trials is the range of different drug-coatings used, which is why von Koch et al.'s study inclusive of a range of different DCB coatings is so timely and significant. SORT OUT IV (Scandinavian Organization for Randomized Trials With Clinical Outcome IV) showed a significantly lower 5-year major adverse cardiovascular event rate with PCI with everolimus-eluting stents compared with sirolimus-eluting stents in a mixture of patients with chronic coronary syndrome and acute coronary syndrome.[13] This raises the question as to whether there could be clinically significant differences between the different DCB coatings and indeed the different loading systems. At present, the majority of DCB evidence is based on paclitaxel-coated balloons, although evidence is emerging of encouraging results, at least with regard to angiographic outcomes with newer generation sirolimus-coated balloons,[14] and further studies are ongoing worldwide assessing this further.

So where does this leave us? Overall, the evidence suggests that DCB is a safe alternative to DES in the context of ISR and may well have a particularly important role in older patients with more comorbidities and may have an important role in patients in whom shorter dual antiplatelet therapy is necessary such as those with high bleeding risk. There is still need for clarity around whether the efficacy of DCBs (in comparison with DESs) vary by the type of ISR treated or whether the efficacy is similar across different platforms/drugs used. Although DCBs represent a good treatment option for many patients presenting with DCBs, current evidence still suggests that DES should remain the standard of care for ISR DES for the time being.

ARTICLE INFORMATION

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