



Editorial



Drug-Coated Balloons for Unselected Real World Patients: Are We There Yet?

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Currently drug-eluting stents (DES) represent the default strategy during coronary interventions.¹⁾ Clinical practice guidelines on coronary revascularization recommend the use of new-generation DES in all clinical and anatomic subsets of patients with coronary artery disease.¹⁾ However, patients treated with DES still suffer from a very low but, nevertheless, persisting risk of DES-related adverse events during long-term clinical follow-up.¹⁾ Accordingly, drug-coated balloons (DCB), a “*leave nothing behind*” strategy, represents an attractive therapeutic strategy for selected patients requiring coronary revascularization.²⁾ Many observational registries, randomized clinical trials and meta-analyses, have demonstrated the safety and efficacy of DCB in patients presenting with in-stent restenosis (ISR) but also in patients with *de novo* lesions.³⁻⁶⁾ In clinical practice guidelines DCB received the highest level of recommendation (IA) for patients with either bare-metal stent (BMS) ISR or DES-ISR.¹⁾ Although there is also important evidence on the value of DCB in well-selected patients with *de novo lesions* (including lesions on small vessels or at bifurcation and patients presenting with an acute myocardial infarction or at high-bleeding risk), this indication is less robust and still is not embraced by clinical practice guidelines.¹⁾²⁾⁵⁾⁶⁾ Therefore, additional information on the value of DCB in unselected patients with coronary artery disease is always welcome.

Many factors could be implicated to explain why the use of DCB is still relatively marginal during coronary interventions. Most randomized clinical trials assessing the efficacy of DCB are relatively small and have focussed on surrogate angiographic endpoints but large randomized trials, powered for hard clinical endpoints, are not available yet.²⁾⁵⁾⁶⁾ This may explain why this technology has not been approved for clinical use in some countries so far. In addition, most of the available evidence in this field has been generated using a particular DCB eluting paclitaxel and, therefore, a “class effect” should not be assumed.¹⁾²⁾ Paclitaxel has been classically selected for DCB because its lipophilicity allows a rapid transit and retention at high concentrations from the tunica intima to the adventitia. Recent advances currently allow the use of limus-drugs in DCB, but clinical information on the safety and effectiveness of these novel DCB still remains limited compared with that available for paclitaxel. Whether novel limus-DCB will fulfil the emerging expectations and actually prove to be superior to the well-established and time-honoured clinical efficacy of paclitaxel-DCB, still remains unsettled.

Data Sharing Statement

The data generated in this study is available from the corresponding author upon reasonable request.

Author Contributions

Conceptualization: Fernando A, Cortese B; Investigation: Fernando A; Supervision: Fernando A; Validation: Fernando A; Visualization: Fernando A; Writing - original draft: Fernando A; Writing - review & editing: Fernando A, Cortese B.

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In this issue of the journal Lee et al.⁷⁾ present the results of a large-scale, multicenter, Korean registry on coronary revascularization using DCB. Real world patients with coronary artery disease and either *de novo* or ISR lesions were treated in 18 hospitals in Korea between January 2009 and December 2017. The primary outcome measure was target lesion failure (TLF) (a composite of cardiovascular death, target vessel myocardial infarction, and clinically-driven target lesion revascularization), at 1 year. A total of 2,509 patients with 2,666 lesions treated with DCB (1,688 [63.3%] ISR, 978 [36.7%] *de novo*), were included. At 1-year TLF occurred in 179 (6.7%), 151 (8.9%), 28 (2.9%) patients in the total, ISR, and *de novo* lesion populations, respectively. Interestingly, a history of hypertension, diabetes, acute coronary syndrome, previous coronary surgery, reduced left ventricular function, types B2/C and ISR lesions, emerged as independent predictors of TLF in the entire population.

Due to the important potential implications of this uniquely large registry on real world patients treated with DCB discussing some methodological issues may be of interest.

The study originates from the “Korean Stent Failure Research Group” initiative and currently represents the largest registry of patients treated with DCB and provides especially relevant insights on patients with *de novo* lesions. However, this remains a retrospective observational registry. Retrospective analyses suffer from inherent problems of selection biases, data quality (potentially missing relevant clinical, angiographic, or procedural-related information) and, more importantly, from the possibility of incomplete capture of adverse clinical events during follow-up. Under-reporting of events, might misleadingly suggest favorable clinical outcomes, leading to an overoptimistic interpretation of the safety and efficacy of these devices. Reassuringly, however, in this multicenter registry all events were carefully adjudicated by an independent and blinded clinical event committee.

A remarkably low event rate was found in all lesion subsets, but the results were particularly favorable in *de novo* lesions. This information is consistent with many previous studies suggesting that irrespective of the selected treatment modality the results of coronary interventions are significantly poorer in ISR as compared with *de novo* lesions.³⁾ In addition, previous real world DCB registries have demonstrated that this technology also achieves poorer clinical results in patients with ISR than in those with *de novo* lesions.⁸⁾ The present study provides robust data confirming these findings (target lesion revascularization (TLR) was three-fold higher for ISR than in *de novo* lesions) in a very large patient population.

In this study all ISR treated were DES-ISR with no patient treated for BMS-ISR. This is of interest because results of treatment of DES-ISR are significantly poorer than those seen in patients presenting with BMS-ISR, irrespective of the selected treatment modality.³⁾⁴⁾ DES-ISR indeed represent a challenging patient subset with a high rate of recurrences. Patients presenting with DES-ISR already experienced a failure of the antiproliferative drug and the culprit underlying substrate frequently consist of neoatherosclerosis rather than neointimal hyperplasia.³⁾ In this regard, the excellent mid-term clinical results found in this study in patients with DES-ISR are highly reassuring.

Notably, the left anterior descending coronary artery was more frequently the target vessel in the subgroup of patients with ISR than in those with *de novo* lesions. This may suggest that this technology was less frequently selected for the treatment of *de novo* lesions in this prognostically important vessel at the time of enrollment (2009–2017). Likewise, in most series of patients undergoing coronary interventions the reference vessel of lesions with ISR

is smaller than that seen in *de novo* lesions.^{3,4)} However, the opposite pattern was actually found in the present study (vessels treated for ISR were significantly larger) suggesting that the use of DCB in *de novo* lesions was preferentially selected in patients with small vessels.

No independent predictors of adverse events could be identified in patients with *de novo* lesions treated with DCB. This is unfortunate as information in this regard is scarce and would have been valuable to identify the subset of *de novo* lesions experiencing less favorable clinical outcomes after DCB treatment. However, this appears to be simply a result of the extremely low rate of adverse events found during follow-up in *de novo* lesions treated with DCB.

In most patients the classical paclitaxel-DCB (using contrast agent as a drug-carrier) was used whereas a different paclitaxel-DCB was only used in 5% of cases. Of note, novel limus-DCB were not used in this registry. Results were comparable with the 2 devices although the small number of patients treated with one of the DCB prevents a reliable assessment in this regard. This issue is of interest because not all DCB are created equal and not all of them are supported by the same degree of scientific evidence. This is emphasized by current guidelines on coronary revascularization and also by expert consensus documents.^{1,2)} Some first generation DCB were abandoned due to limited efficacy. In a previous nation-wide Swedish registry the classical paclitaxel-DCB, using contrast agent as the drug carrier, was found to be superior to other DCB in patients with ISR with regards to clinical outcomes.⁹⁾ However, in another large Swedish registry of patients with *de novo* lesions, the results obtained with 3 different commercially available DCB, were comparable.¹⁰⁾ Importantly, however, observational studies suffer from selection biases and also by unmeasured confounders impossible to adjust for. Moreover, comparison with historical data tends to prove unreliable. Adjunctive medical treatment of coronary artery disease has significantly evolved over time, favoring the clinical results obtained in most recent studies. Only properly designed, randomized head-to-head studies, powered for surrogated angiographic outcome measures or, ideally, for major clinical endpoints, will be able to address this burning question.

It is also important to keep in mind that only selected patients were considered for DCB treatment. Therefore, the possibility of selection bias is not negligible and should be considered to properly interpret the study results. Accordingly, data on % DCB use, with regard to the total number of coronary interventions performed in the participating centers during the study period, would have provided the required perspective. Likewise, recent expert consensus documents on DCB highlight the importance of careful lesion preparation in order to obtain optimal results.²⁾ Therefore, it would have been important to clarify the number of patients initially considered for possible DCB treatment but that, eventually, required immediate DES implantation after suffering a significant dissection or suboptimal residual stenosis after lesion predilation. A bailout stenting rate of only 0.6% is surprisingly lower than expected according to previous studies.

Unfortunately, no angiographic data (either before, immediately after the procedure, or at latest follow-up) were available in this study. This is typical of real world studies but prevents any mechanistic analysis on the effectiveness of these interventions. However, the excellent clinical results obtained in this registry are indisputable. Furthermore, both vessel size and lesion length play a major role in the long-term fate of any coronary intervention. Reassuringly, however, in this study authors used the device diameter and length (as a surrogate for vessel size and lesion length), to be able to adjust the results obtained with DCB for these important anatomic characteristics.

An important limitation of the current analysis is the relatively short follow-up time, considering the very large period of enrollment. Some of the potential advantages of DCB are exerted on the long term, differently from DES, which suffer catch-up events yearly. A hypothetical flattening of the events in a Kaplan-Meier curve could be expected in DCB-treated patients, but long-term data as still scarce.

Finally, authors nicely address the possibility that ethnic differences should be considered when these results are compared with those previously obtained with the use of DCB in European patients. Overall, as discussed, Asian populations with coronary artery disease appear to have some distinct characteristics, including genetic polymorphisms, coronary plaque features, inflammatory biomarkers, response to antiplatelet agents and lipid-lowering drugs and rates of ischemic and bleeding events.⁷⁾ However, further studies are needed to confirm these observations emerging from the comparison of large observational studies or subgroups analyses by ethnicity from large clinical trials. Many potential confounding factors, including body mass index, should be also considered. In any case, although the clinical results obtained in this study are excellent, most previous studies suggested that the results of DCB are largely similar in patients from different continents.

Lee et al.⁷⁾ should be commended for conducting this interesting, updated, and uniquely large registry on coronary revascularization using DCB. The excellent results obtained both in *de novo* and ISR lesions clearly invigorate the field with important data supporting a wider application of this technology in routine clinical practice. Whether novel DCB will further improve the clinical results obtained with this therapeutic modality requires further investigation.

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