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Drug-coated balloons for acute myocardial infarction. Ready for prime time?

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Drug-coated balloons (DCB) represent a very attractive therapeutic alternative for percutaneous coronary interventions (PCI)[1]. The value of DCB in patients presenting with in-stent restenosis (ISR) has been well established[1-5].

Actually, this was the first ever clinical indication for this emerging treatment modality, as demonstrated in a pivotal study more than a decade ago[2]. In this unique scenario many randomised clinical trials (RCT) have demonstrated that DCB are superior to other strategies, including conventional balloon angioplasty and bare metal stents (BMS) and at least equivalent to first-generation drug-eluting stents (DES)[1-3]. Only new-generation DES appear to be superior to DCB in these patients[3-5]. However, the superiority of second-generation DES over DCB on late angiographic findings only translates into a modest reduction in clinical events, mainly driven by a reduction in target lesion revascularisation (TLR)[3,4]. These results stem mainly from the superiority of new-generation DES over DCB in patients with DES-ISR (a particularly challenging anatomic substrate), whereas the differences are not so clinically meaningful in patients with BMS-ISR[3-5]. In fact, many interventional cardiologists are still reluctant to implant a second metal layer ("stent sandwich") for patients presenting with a "first" episode of ISR and prefer selecting DCB over new-generation DES[3]. The rationale behind this decision would be to reserve the implantation of a new-generation DES for patients with "recurrent" ISR. DCB are also usually preferred over DES in patients with ISR encompassing a large side branch (to avoid a double metal "jailing") or in those with multiple previous metal layers in the vessel wall. In addition, DCB are attractive in patients with ISR at high bleeding risk, where a drastic reduction in the duration of the dual antiplatelet regimen is clinically appealing[3]. Recent revascularisation guidelines recommend the use of DCB or DES (both with the same level of evidence: IA) for patients presenting with either BMS-ISR or DES-ISR[1].

On the other hand, there is also a large body of evidence supporting the value of DCB for *de novo* lesions. However, this indication is still not endorsed by current guidelines which, in principle, consider that new-generation DES represent the default treatment strategy for virtually all lesions[1]. Nevertheless, often in real-world

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clinical practice implantation of a metallic stent may not be very attractive[6]. Results of stents are suboptimal in *de novo* lesions located in small vessels, in segments with diffuse or distal disease and in those involving a true bifurcation with a relevant side branch. The use of a DCB in a side branch that eventually requires treatment after a provisional stenting strategy is very appealing[7]. In addition, although new-generation DES are currently considered very safe in patients with a high bleeding risk, DCB still represent a valid alternative for these challenging patients[8]. Recently the DEBUT RCT demonstrated that, in patients at a high bleeding risk, DCB are superior to BMS (selected to avoid the need for a prolonged antithrombotic regimen)[8]. Finally, small vessel disease remains the most classic niche for DCB in *de novo* lesions[9]. However, only very recently, BASKET-SMALL 2, the first RCT powered for clinical events (n=758 patients), confirmed the non-inferiority of DCB versus new-generation DES for a composite of cardiac death, MI, and target vessel revascularisation (7.5 vs 7.3%) at 12 months[9]. Likewise, the PICCOLETO II RCT (n=232) recently confirmed that in small vessels the late lumen loss at late follow-up (primary endpoint) was significantly reduced (0.04±0.28 vs 0.17±0.39 mm, p=0.03) with contemporary DCB versus new-generation DES (Cortese B. PICCOLETO II: 6-Month Clinical and Angiographic Findings From a Randomized Trial of Drug-Coated Balloons vs. Drug-Eluting Stents for Treatment of Small Vessel Coronary Artery Disease. Presented at the Transcatheter Cardiovascular Therapeutics meeting, San Francisco, CA, USA, 27 September 2019) **(Figure 1)**.

All of the above indicates that DCB could play an important role for selected patients with *de novo* coronary lesions, but what about patients suffering an acute myocardial infarction (MI)? May DCB also play a relevant role in this adverse scenario?

Current study

In this issue of EuroIntervention, Scheller et al present the PEPCAD NSTEMI study, a multicentre RCT focusing on patients with non-ST-segment elevation MI (NSTEMI)[10].

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Patients with an identifiable culprit lesion without angiographic evidence of large thrombus were eligible. A total of 210 patients with NSTEMI were randomly allocated to iopromide-based paclitaxel DCB (n=104) or primary stent treatment (n=106). In the stent group, 56% of patients received BMS and 44% new-generation DES. Alternatively, in the DCB group, 85% of patients were treated with DCB alone, whereas 15% eventually required additional stent implantation. Using a non-inferiority design the selected primary endpoint for the intention-to-treat analysis was target lesion failure (TLF) (cardiac/unknown death, MI, and TLR at nine months). At late follow-up (9.2±0.7 months), DCB treatment was non-inferior to stent treatment (TLF 3.8% vs 6.6%, p=0.53). In the stent arm, no differences were found between BMS and new-generation DES. Likewise, although in the DCB group results were better when a DCB-only strategy could be used, the differences with patients eventually requiring additional stent implantation were not statistically significant. Finally, the rate of major adverse cardiovascular events (MACE) (death, MI, stroke, or any revascularisation) was 6.7% in the DCB group and 14.2% in the stent group (p=0.11). Interestingly, in the per protocol analysis there was a non-significant trend favouring DCB for MACE (5.9% vs 14.4%, p=0.056)[10].

The results of this study are important and indeed provocative. Accordingly, some issues deserve further consideration.

First, as the authors nicely acknowledge, the study is underpowered for its primary endpoint. In this emergent clinical scenario,

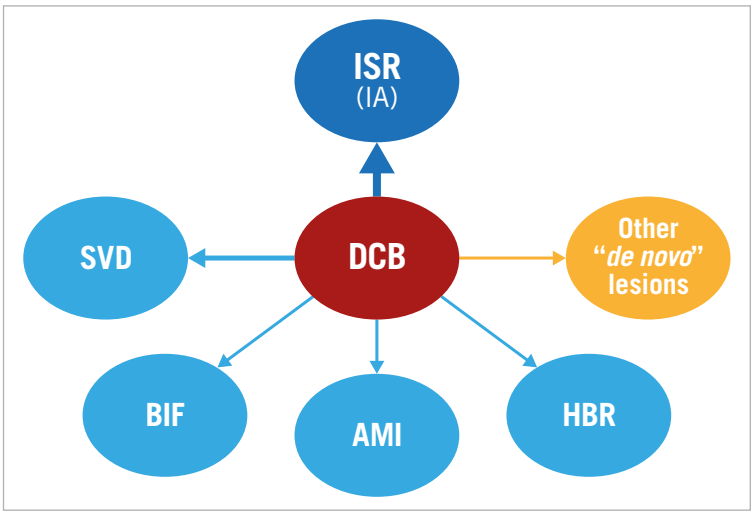

Figure 1. *Clinical use of drug-coated balloons (DCB) in the coronary territory. In blue, indications supported by randomised clinical trials (RCT) with either surrogate angiographic or clinical endpoints. Only the use in in-stent restenosis (ISR) is approved by current revascularisation guidelines with a IA level of recommendation. In gold, other potential indications including any de novo lesion with a good result after predilation. AMI: acute myocardial infarction; BIF: bifurcation; HBR: high bleeding risk patients; SVD: small vessel disease*

selecting candidates for the trial was not easy: the investigators from many centres needed four years to achieve a sample size of 210 patients. The selected non-inferiority margin was relatively large. This is important because absence of statistically significant difference should not be erroneously interpreted as equivalence. Moreover, the long recruitment period suggests that selection bias could have played a role, potentially limiting the generalisability of the study findings.

Second, in the comparator arm both BMS and contemporary DES were used, apparently with similar results. However, due to the small sample size subgroup analyses may be misleading. When the study was designed, BMS were still selected for patients with acute MI considering the complex inflammatory and thrombogenic milieu. However, several studies have demonstrated that, in patients with acute MI, new-generation DES are not only more effective in preventing recurrences but also safer, reducing thrombotic events[1]. Accordingly, new-generation DES are currently considered the therapy of choice for patients with acute MI[1]. Therefore, a large RCT comparing DCB with new-generation DES in patients with NSTEMI, powered for angiographic and clinical endpoints, is warranted to confirm the non-inferiority of DCB over new-generation DES in this challenging scenario.

Third, careful lesion predilation was mandated, as recommended by consensus documents on optimal DCB use[6]. This was performed by investigators experienced in the use of DCB and may help to explain the excellent results obtained in this arm.

Fourth, in RCT with an open design the risk of ascertainment bias should be mitigated by a blind, centralised adjudication of events, by an independent clinical events committee. Unfortunately, this was not done in the present study. Notwithstanding the care taken by the local investigators to adjudicate events following predefined criteria, this methodological issue remains a study limitation.

Finally, systematic angiographic surveillance was not obtained in this trial. Late angiographic findings are powerful surrogate outcome measures to ascertain the relative efficacy of competing interventions. They provide important pathophysiological insights with a smaller number of patients than that required to compare clinical outcomes. This mechanistic information is particularly relevant when therapeutic devices are used in new or off-label indications.

Notwithstanding the above issues, the present study provides important novel findings and constitutes the best information currently available on the value of DCB in patients with NSTEMI.

Previous studies of DCB in acute myocardial infarction

Results of stents in patients with acute MI are classically considered suboptimal and associated with a relatively high restenosis and thrombosis rate. Suboptimal sizing, expansion and apposition of the stents in this complex anatomic substrate characterised by a large thrombus burden appear implicated in the unfavourable results. Accordingly, DCB have been considered an interesting alternative to stents in these patients. The DEB-AMI single-arm registry (n=40) sought to assess the value of DCB in ST-segment elevation MI (STEMI) patients[11]. Angiographic late lumen loss was 0.51 mm and the one-year MACE rate was 17.5%[11]. In the DEB-AMI RCT (n=150), the use of DCB followed by BMS implantation failed to demonstrate angiographic or clinical superiority over BMS alone[12]. Another small RCT (n=85) compared DCB followed by BMS with BMS alone in patients with either NSTEMI or unstable angina[13]. In this study, angiographic late lumen loss was significantly lower (0.22 vs 0.68 mm, p=0.002) with the combined strategy although clinical events were similar in both groups. In these trials different DCB were used following thrombus aspiration, but before BMS implantation, in an attempt to increase the effect of the drug. However, geographical miss phenomena could have played a role in the suboptimal results. In STEMI patients, the PEBSI RCT compared a combined strategy of BMS followed by DCB (n=111) versus BMS alone (n=112)[14]. The BMS+DCB group had a lower late lumen loss (primary endpoint: 0.31 vs 0.8 mm, p<0.0001) and binary restenosis rate (2.2 vs 29.8%, p<0.0001) and, importantly, a reduced rate of MACE at one year (3.6 vs 12.5%, p=0.016)[14]. More recently, the REVELATION single-centre RCT compared the use of DCB alone with new-generation DES in 120 STEMI patients[15]. In this study, only patients with acceptable results after lesion predilation (residual stenosis <50%) were randomised. The fractional flow reserve at nine months (primary endpoint) was similar (0.92±0.05 vs 0.91±0.06) in both groups[15].

Final remarks

Scheller et al should be commended for designing and executing this important yet challenging study that opens up new avenues in the management of selected patients with NSTEMI[10]. Results should be considered as hypothesis-generating and should pave the way for future research to establish definitively the value of DCB in selected patients with *de novo* lesions. Avoiding the need for a permanent implant in the coronary wall – with its inherent potential long-term risks – remains a sound rationale for all "leave nothing behind" strategies where, currently, DCB are enthroned with an undisputed role in clinical practice.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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