

Aggressive predilatation seeking medial dissection: a prerequisite for a drug-coated balloon-only strategy in *de novo* coronary lesions?

Tom Adriaenssens*, MD, PhD; Johan Bennett, MD, PhD

The authors' affiliations can be found at the end of this article.

*Corresponding author: Department of Cardiovascular Medicine, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium

Drug-coated balloons (DCBs) are approved for the treatment of in-stent restenotic lesions, based on the results of several randomised controlled trials (RCTs)¹. In clinical practice, operators balance the undeniable advantages of DCBs (predominantly the avoidance of an extra layer of metal in the coronary artery) against the moderately reduced antirestenotic efficacy as compared to repeat drug-eluting stent (DES) treatment².

In recent years, the adoption of DCB technology in treating *de novo* coronary artery lesions has attracted important attention. The 'leave nothing behind' concept is certainly appealing. Apart from the restoration of physiological vasomotion, long-term adverse events associated with stent implantation can also be avoided. Nevertheless, important questions remain with respect to safety in the short term (risk of subacute vessel closure) and efficacy in the long term. Data from small RCTs comparing DCBs with DES in *de novo* small coronary arteries have shown encouraging results^{3,4}. When the vessel diameter is small, even moderate late lumen loss (LLL) after DES implantation can lead to an important reduction in the residual lumen area, leading to clinically relevant restenosis and an increase in target lesion failure (TLF).

In contrast, a phenomenon described as late lumen enlargement (LLE) has been identified – at least with the most commonly used paclitaxel-eluting DCBs – in a substantial proportion of patients⁵. The precise mechanisms underlying this phenomenon are incompletely understood. However, it is an important finding, as it adds support to a strategy where an acceptable, but not perfect, angiographic result after predilatation would still allow for a DCB strategy, anticipating further improvement in luminal diameters in time.

In the current issue of EuroIntervention, Lee et al describe the largest dataset to date on high-detail intracoronary imaging using optical coherence tomography (OCT) in this domain⁶. The authors conducted high-quality

OCT assessment, pre- and post-percutaneous coronary intervention (PCI), in 328 patients treated with DCBs for *de novo* narrowings in small coronary arteries (mean reference vessel diameter 2.49 mm) and identified haemodialysis, severely calcified lesions, and the absence of post-PCI medial dissection as predictors of TLF at a median follow-up of 460 days.

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This latter finding especially deserves further consideration, as it provides important insight into the relation between lesion preparation and efficacy of DCB treatment.

It is generally accepted that DCBs should be solely considered as a drug delivery device. As a rule, adequate lesion preparation with vessel recoil <30% and an absence of flow-limiting dissections on angiography have been proposed as the predominant requisites for a successful DCB strategy. More recently, however, the routine use of scoring or cutting balloons has been proposed, with the theoretical benefit of creating cracks and dissections in the vessel wall, thereby facilitating drug transfer and penetration into the vessel wall, potentially enhancing the antirestenotic efficacy of DCBs^{7,8}. As scoring and/or cutting balloons were used in >90% of patients in this study, even though only half of the patients were reported to have moderate or severe calcification on baseline angiography, we assume this more aggressive lesion preparation strategy was adopted. The availability of post-PCI OCT assessment and the excellent sensitivity of OCT for detecting vessel wall dissection sheds light on the relation between lesion preparation and medium-term TLF in DCB PCI. The strong association between the absence of medial dissection flaps on OCT post-PCI and TLF in the current study supports the theory that aggressive lesion preparation creating vessel wall dissections would facilitate antiproliferative drug uptake in the vessel wall and enhance DCB efficacy.

The results of the current study support earlier findings of Sogabe et al and Yamamoto et al that deep dissections after DCB therapy predict the occurrence of LLE^{9,10}.

However, a word of caution: even a strong association does not necessarily imply a causal relationship. The absence of medial dissections might be a sign of insufficient lesion preparation and an indication that in some lesions, even more intense lesion preparation – for example, with atherectomy – would have been needed. Confronted with severe and extensive superficial calcification, the application of cutting or scoring balloons is not always sufficient to break the calcium mass. In that regard, the absence of medial dissections on OCT might be an indicator of the most severe forms of vessel calcification. It would be no surprise that in such cases, with a DCB applied in a suboptimally prepared lesion and in contact with a calcified mass, the risk of TLF would be substantially increased compared to simpler lesions in the dataset.

Another interesting aspect of the study is the insight it delivers with respect to the degree of intracoronary dissection left at the end of the procedure and the subsequent risk of acute vessel closure.

Based on the post-PCI OCT data provided, a maximum dissection angle well above 1 quadrant, a longitudinal dissection length close to 10 mm, medial involvement of the dissection in more than half of the population, adventitial involvement in another 20%, and a post-PCI minimum lumen area of 3.25 mm² (compared to a mean reference vessel area just above 5 mm²) were observed at the end of the procedure in the overall study population. Based on currently accepted recommendations for OCT-guided PCI optimisation with respect to edge dissections after DES implantation, these degrees of dissection would qualify for additional stent implantation in the hands of most operators. But apparently (reflected by the negligible numbers of TLF in the first days after a procedure), even these relatively important grades of dissections did not translate into an substantial number of (sub)acute vessel closures. Of course, the retrospective design of this study should be acknowledged in this regard (5 cases where additional stent implantation was undertaken after a final post-DCB OCT analysis were not included in the current analysis). The risk of (sub)acute vessel closure is an important consideration with respect to the use of DCB in *de novo* lesions. Acute vessel closure due to flow-limiting dissection was the most feared complication in the first decade of PCI, when no bailout stenting was available. Compelling data on the safety of leaving a certain degree of intracoronary dissection untreated will be needed to convince many operators of changing this winning strategy for a potential – yet to be proven – advantage in the very long term.

Before a DCB-only strategy can be widely adopted, including in larger vessels and going beyond the indications where DES implantation is considered less ideal (small vessels, ostial side branch lesions, long and diffuse disease, etc.), a confirmation of the safety and efficacy of such a strategy will need to be achieved in larger-size RCTs. In such studies, the suitability of both DCB and DES would need to be confirmed upfront, and in an ideal scenario, the adequacy of lesion preparation and presence of medial dissection confirmed with intracoronary imaging, and crossover from a DCB to a DES arm decided according to a clearly defined protocol. The size of such

a study would need to be large enough to capture the relatively rare, but devastating, events of acute vessel closure, and the follow-up would need to be long enough to allow for the beneficial (very) long-term effects of this stentless strategy to become apparent whilst eliminating any concerns regarding long-term effects of paclitaxel on the vessel wall.

Like all interesting studies, the current report from Lee et al answers some questions but raises even more.

Authors' affiliations

Department of Cardiovascular Medicine, University Hospitals Leuven, Leuven, Belgium and Department of Cardiovascular Sciences, Katholieke Universiteit Leuven, Leuven, Belgium

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Juni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferovic PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87-165.
2. Giacoppo D, Alfonso F, Xu B, Claessen BEPM, Adriaenssens T, Jensen C, Pérez-Vizcayno MJ, Kang DY, Degenhardt R, Pleva L, Baan J, Cuesta J, Park DW, Schunkert H, Collieran R, Kukla P, Jiménez-Quevedo P, Unverdorben M, Gao R, Naber CK, Park SJ, Henriques JPS, Kastrati A, Byrne RA. Paclitaxel-coated balloon angioplasty vs. drug-eluting stenting for the treatment of coronary in-stent restenosis: a comprehensive, collaborative, individual patient data meta-analysis of 10 randomized clinical trials (DAEDALUS study). *Eur Heart J*. 2020;41:3715-28.
3. Jeger RV, Farah A, Ohlow MA, Mangner N, Möbius-Winkler S, Leibundgut G, Weilenmann D, Wöhrle J, Richter S, Schreiber M, Mahfoud F, Linke A, Stephan FP, Mueller C, Rickenbacher P, Coslovsky M, Gilgen N, Osswald S, Kaiser C, Scheller B; BASKET-SMALL 2 Investigators. Drug-coated balloons for small coronary artery disease (BASKET-SMALL 2): an open-label randomised non-inferiority trial. *Lancet*. 2018;392:849-56.
4. Cortese B, Di Palma G, Guimaraes MG, Piraino D, Orrego PS, Buccheri D, Rivero F, Perotto A, Zambelli G, Alfonso F. Drug-Coated Balloon Versus Drug-Eluting Stent for Small Coronary Vessel Disease: PICCOLETO II Randomized Clinical Trial. *JACC Cardiovasc Interv*. 2020;13:2840-9.
5. Kleber FX, Schulz A, Wäliszewski M, Hauschild T, Böhm M, Dietz U, Cremers B, Scheller B, Clever YP. Local paclitaxel induces late lumen enlargement in coronary arteries after balloon angioplasty. *Clin Res Cardiol*. 2015;104:217-25.
6. Lee T, Ashikaga T, Nozato T, Nagata Y, Kaneko M, Miyazaki R, Misawa T, Taomoto Y, Okata S, Nagase M, Horie T, Terui M, Kachi D, Odanaka Y, Matsuda K, Naito M, Koido A, Yonetsu T, Sasano T. Predictors of target lesion failure after percutaneous coronary intervention with a drug-coated balloon for *de novo* lesions. *EuroIntervention*. 2024;20:e818-25.
7. Scheller B, Gemeinhardt O, Kleber FX. Late lumen enlargement after treatment of *de-novo* lesions with drug coated balloon catheters - Glagov effect or plaque regression? *Int J Cardiol*. 2021;329:79-81.
8. Yamamoto T, Sawada T, Uzu K, Takaya T, Kawai H, Yasaka Y. Possible mechanism of late lumen enlargement after treatment for *de novo* coronary lesions with drug-coated balloon. *Int J Cardiol*. 2020;321:30-37.
9. Sogabe K, Koide M, Fukui K, Kato Y, Kitajima H, Akabame S, Zen K, Nakamura T, Matoba S. Optical coherence tomography analysis of late lumen enlargement after paclitaxel-coated balloon angioplasty for *de-novo* coronary artery disease. *Catheter Cardiovasc Interv*. 2021;98:E35-42.
10. Yamamoto M, Hara H, Kubota S, Hiroi Y. Predictors of late lumen enlargement after drug-coated balloon angioplasty for *de novo* coronary lesions. *EuroIntervention*. 2024;20:602-12.