EuroIntervention
2025;21:e102-e104
published online e-edition January 2025
DOI: 10.4244/EIJ-E-24-00062

DEBATE

Drug-coated balloon angioplasty for in-stent restenosis: pros and cons

Fernando Alfonso[1]*, MD, PhD; Robert A. Byrne[2], MB, BCh, PhD; Bruno Scheller[3], MD, PhD; Eric Van Belle[4], MD, PhD; Julinda Mehilli[5,6]**, MD, PhD

*Corresponding author: Department of Cardiology, Hospital Universitario de La Princesa, Universidad Autónoma de Madrid, Instituto de Investigación Sanitaria Princesa, IIS-IP, CIBERCV, Diego de León 62, 28006, Madrid, Spain. E-mail: falf@hotmail.com
**Corresponding author: LAKUMED Kliniken, Landshuter Kommunalunternehmen für medizinische, Versorgung AdöR, Achdorfer Weg 3, 84036, Landshut, Germany. E-mail: julinda.mehilli@lakumed.de

In-stent restenosis (ISR) is the leading cause of failure of percutaneous coronary intervention (PCI). Primarily based on neoatherosclerosis or neointimal hyperplasia, ISR has become less common with advancements in stent technology. Both drug-eluting stents (DES) and drug-coated balloons (DCB) have been shown to represent valid alternative options for the treatment of ISR, although they come with distinct benefits and limitations. More specifically, despite a substantial equipoise in the treatment of ISR of bare metal stents (BMS), DCB have been demonstrated to be less effective than repeat DES implantation in treating DES-ISR. As such, 2024 European guidelines on chronic coronary syndromes recommend DES over DCB for the treatment of DES-ISR, with a Class I recommendation. However, numerous anatomical and procedural factors (e.g., lesion complexity, small vessels, stent underexpansion, or prior multiple stent layers) may impact outcomes and could inform treatment modality selection. In light of the current evidence, whether PCI with DES implantation should be adopted as the standard treatment for ISR or whether the decision between DCB and DES should be based on a tailored approach remains controversial.

Pros

Fernando Alfonso, MD, PhD; Robert A. Byrne, MB, BCh, PhD; Bruno Scheller, MD, PhD

Treatment of ISR constitutes an unmet clinical need affecting a large number of patients[1]. Percutaneous treatment is usually technically straightforward but limited by a high recurrence rate. The previous 2018 European Society of Cardiology (ESC) clinical practice guidelines on myocardial revascularisation recommended the use of either repeat stenting with DES or angioplasty with DCB (both Class I, Level of Evidence [LoE] A recommendations) for treatment of ISR[1]. They also emphasised that a class effect should not be expected for DCB and that intracoronary imaging was of value in this anatomic scenario.

DES and DCB are widely available treatment strategies providing superior results to those obtained with other historical modalities in this setting. Initial randomised clinical trials (RCT) comparing new-generation DES with paclitaxel DCB for ISR demonstrated the safety and efficacy of both strategies[2,3]. However, compared with DCB, DES provided better acute and long-term angiographic results[2,3]. In the relatively favourable scenario of BMS-ISR, only a marginal benefit for target lesion revascularisation (TLR) was found with DES after a 3-year follow-up[2]. Alternatively, in the more complex scenario of DES-ISR (where antiproliferative drugs have already failed) the acute and late angiographic superiority of DES translated into reduced recurrence rates[3].

Importantly, the superiority of DES over DCB regarding repeat TLR in patients with DES-ISR and the equivalence of both strategies in patients with BMS-ISR were subsequently confirmed by a large, comprehensive patient-level meta-analysis (10 RCT, 1,976 patients)[4]. However, in this study concerns about an adverse safety signal were raised, in terms of a numerically higher rate of death or myocardial infarction (MI) in patients treated with first-generation DES[4]. Of note, no safety issues were found with new-generation DES. In addition, the importance of optimal lesion preparation before DCB was not emphasised in some of these RCTs. Recently, the 10-year follow-up of the ISAR-DESIRE 3 trial (comparing plain balloon, paclitaxel DCB and paclitaxel DES), provided the longest clinical follow-up available of patients with ISR[5]. The pairwise comparison between paclitaxel DCB and paclitaxel DES resulted in a non-significant difference in the primary endpoint (cardiac death, target vessel MI, target lesion thrombosis, or TLR) and the secondary endpoint (TLR). However, a landmark analysis found an excess of death and cardiac death within 5 years after repeat stenting with paclitaxel DES[5]. Taken together, these findings support

the practical approach taken by many operators to avoid the implantation of additional metal layers at least in a first presentation of ISR.

The 2024 ESC clinical practice guideline on chronic coronary syndromes provides a nicely balanced discussion on the relative values of these distinct alternatives for patients with ISR[6]. However, the final recommendation issued was, in our opinion, too rigid: "DES is recommended over DCB for treatment of in-DES restenosis", with Class I, LoE A[6]. Unfortunately, this could be misinterpreted as if DES were the only evidence-based treatment for these patients and, accordingly, should always be selected. In fact, the data supporting the value of angioplasty with DCB in this scenario are robust[7], and the common sense of endeavouring to avoid additional stent layers is compelling for ISR, particularly in patients with ISR and multiple previous stent layers, resistant stent underexpansion, ISR on small vessels or with diffuse lesions or in ISR involving major bifurcations, where further side branch jailing may have untoward clinical consequences[7]. Besides, reducing the intensity and duration of the antiplatelet regimen may be appealing in high bleeding risk patients. Finally, we should keep in mind that, even with the latest-generation DES, the rate of very late stent failure (beyond 1 year) may be as high as 2% per year – without a plateau – and a "leave nothing behind" strategy might be of potential value in this regard.

In summary, in patients with ISR, while trial evidence shows that repeat stenting with DES provides a significant reduction in TLR compared with angioplasty with DCB, the marginal efficacy gains must be carefully weighed against the potential adverse safety risk of multiple stents over time. Ultimately, these two strategies are complementary rather than competitive and, when carefully selected in individual patients according to their clinical and anatomical characteristics, both technologies will continue to be of major value to improve clinical outcomes in patients with ISR in day-to-day practice.

Conflict of interest statement

R.A. Byrne does not accept direct or personal payments from medical device or pharmaceutical industry; he reports research funding to the institution from Abbott, Biosensors, Boston Scientific and Translumina without impact on personal remuneration. B. Scheller reports payments or honoraria from Medtronic and B. Braun; and stock or stock options with InnoRa GmbH. F. Alfonso has no conflicts of interest to declare.

Cons

JULINDA MEHILLI, MD, PHD; ERIC VAN BELLE, MD, PHD

First, the biological pattern of contemporary ISR. Due to adequate lesion preparation using scoring/cutting/high- and ultrahigh-pressure balloons, rotablation, lithoplasty and radiological stent enhancement, mechanical factors are now less frequently observed as a cause for ISR. It is neoatherosclerosis (NA) – lipid-rich or calcified – that is the most frequent cause of ISR that we treat nowadays. NA has a time-dependent incidence – circa 70% of very late ISR after BMS implantation and 60-75% of late and very late ISR after DES implantation, particularly with older-generation DES[8]. Although BMS and older-generation sirolimus- and paclitaxel-eluting stents (PES) are not available on the market, we still treat their long-term failures in the form of NA-ISR.

Second, DCB are safer than PES, but not safer than other DES types. A wealth of research has proven paclitaxel-coated balloons (PCB) and DES to be more effective than plain balloon angioplasty to treat restenosis after BMS or DES implantation[5,6]. In one of the largest studies, the ISAR-DESIRE 3 trial, DCB were shown to be safer than PES, albeit losing their efficacy to reduce the need for TLR compared to DES over time. Not surprisingly, at 10-year follow-up there was an excess of death (20.9% vs 9.3%; p=0.028) and cardiac death (13.6% vs 5.8%; p=0.047) associated with PES compared with DCB[5]. Three-year follow-up of the modern RIBS IV trial proved both the greater efficacy and safety of everolimus-eluting stent over DCB to treat ISR – death 7.1% versus 7.8% (hazard ratio [HR] 0.91, 95% confidence interval [CI]: 0.40-2.06) and thrombosis 1.3% versus 2.3% (HR 0.50, 95% CI: 0.09-2.71)[9]. The DAEDALUS study, an individual patient meta-analysis including 10 randomised clinical trials comparing DCB angioplasty with DES implantation for treatment of ISR, revealed a significant interaction between treatment effect and the generation of DES used for the treatment of ISR. PCB led to a lower incidence of the composite of death, myocardial infarction and target lesion thrombosis compared with PES (HR 0.53, 95% CI: 0.32-0.87; p=0.012) and to a similar incidence when compared with second-generation DES (HR 1.06, 95% CI: 0.71-1.60; p=0.764)[10]. Unsurprisingly, the inferior performance of PES compared to other old and new generations of DES in all types of coronary lesions has been shown in virtually all randomised trials and their meta-analyses.

Third, DCB are inferior to DES and lose their initial efficacy over time. In the ISAR-DESIRE 3 trial, DCB and PES were comparable in terms of 6-8-month percentage diameter stenosis, while at 1 year, a higher incidence of TLR was observed with DCB (22.1% vs 13.5%; p=0.09)[5]. In the RIBS IV trial, the everolimus-eluting stent was associated with TLR at 3-year follow-up compared to DCB (7.1% vs 15.6%, HR 0.43, 95% CI: 0.21-0.87; p=0.015)[9]. The DAEDALUS study showed a risk increase in TLR at 3-year follow-up with DCB (adjusted HR 1.38, 95% CI: 1.05-1.82; p=0.020) compared to DES. The increased risk associated with DCB was more pronounced in patients who had DES-ISR (HR 1.60, 95% CI: 1.19-2.14; p=0.002)[10]. Thus, the theoretical advantage of avoiding an additional metallic layer with DCB does not lead to higher long-term safety or efficacy compared to modern DES. Current European guidelines on the management of chronic coronary syndromes recommend the use of DES over DCB for the treatment of coronary ISR (Class of recommendation I, LoE A)[6].

Lastly, there is no "one size fits all" in medicine. Intracoronary imaging – particularly optical coherence tomography – enables a virtual histological evaluation of restenotic lesions, which might support an individualised treatment of ISR by using DES or DCB according to its biological pattern. Randomised evidence in this regard is still missing.

Conflict of interest statement

J. Mehilli declares having received speaker fees from Daiichi Sankyo Europe GmbH, AstraZeneca, Pfizer, Bayer Vital GmbH, and Biotronik; and institutional research grants from Boston Scientific. E. van Belle has no conflicts of interest to declare.

Authors' affiliations

1. Department of Cardiology, Hospital Universitario de La Princesa, CIBERCV, IIS-IP, Universidad Autónoma de Madrid, Madrid, Spain; 2. Department of Cardiology, Cardiovascular Research Institute Dublin, Mater Private Network, and School of Pharmacy and Biomolecular Sciences, RCSI University of Medicine and Health Sciences, Dublin, Ireland; 3. Clinical and Experimental Interventional Cardiology, Saarland University, Homburg, Germany; 4. Department of Cardiology, Department of Interventional Cardiology for Coronary, Valves and Structural Heart Disease, CHU Lille, Institut Coeur Poumon, Inserm U1011, Institut Pasteur de Lille, EGID, Universite de Lille, Lille, France; 5. LAKUMED Hospital Landshut-Achdorf, Medizinische Kinik I, Landshut, Germany; 6. Ludwig-Maximilians University Clinic, Munich, Germany

References

1. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet JP, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferović PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO. 2018 ESC/EACTS Guidelines on myocardial revascularization. *EuroIntervention.* 2019;14:1435-534.

2. Alfonso F, Pérez-Vizcayno MJ, García Del Blanco B, Otaegui I, Masotti M, Zueco J, Veláquez M, Sanchís J, García-Touchard A, Lázaro-García R, Moreu J, Bethencourt A, Cuesta J, Rivero F, Cárdenas A, Gonzalo N, Jiménez-Quevedo P, Fernández C; RIBS V Study Investigators. Long-Term Results of Everolimus-Eluting Stents Versus Drug-Eluting Balloons in Patients With Bare-Metal In-Stent Restenosis: 3-Year Follow-Up of the RIBS V Clinical Trial. *JACC Cardiovasc Interv.* 2016;9:1246-55.

3. Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, García del Blanco B, García-Touchard A, López-Mingué JR, Benedicto A, Masotti M, Zueco J, Iñiguez A, Velázquez M, Moreno R, Mainar V, Domínguez A, Pomar F, Melgares R, Rivero F, Jiménez-Quevedo P, Gonzalo N, Fernández C, Macaya C; RIBS IV Study Investigators (under auspices of Interventional Cardiology Working Group of Spanish Society of Cardiology). A Prospective Randomized Trial of Drug-Eluting Balloons Versus Everolimus-Eluting Stents in Patients With In-Stent Restenosis of Drug-Eluting Stents: The RIBS IV Randomized Clinical Trial. *J Am Coll Cardiol.* 2015;66:23-33.

4. 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, Kukla P, Jiménez-Quevedo P, Unverdorben M, Gao R, Naber CK, Park SJ, Henriques JPS, Kastrati A, Byrne RA. Drug-Coated Balloon Angioplasty Versus Drug-Eluting Stent Implantation in Patients With Coronary Stent Restenosis. *J Am Coll Cardiol.* 2020;75:2664-78.

5. Giacoppo D, Alvarez-Covarrubias HA, Koch T, Cassese S, Xhepa E, Kessler T, Wiebe J, Joner M, Hochholzer W, Laugwitz KL, Schunkert H, Kastrati A, Kufner S. Coronary artery restenosis treatment with plain balloon, drug-coated balloon, or drug-eluting stent: 10-year outcomes of the ISAR-DESIRE 3 trial. *Eur Heart J.* 2023;44:1343-57.

6. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, Banning AP, Budaj A, Buechel RR, Chiariello GA, Chieffo A, Christodorescu RM, Deaton C, Doenst T, Jones HW, Kunadian V, Mehilli J, Milojevic M, Piek JJ, Pugliese F, Rubboli A, Semb AG, Senior R, Ten Berg JM, Van Belle E, Van Craenenbroeck EM, Vidal-Perez R, Winther S; ESC Scientific Document Group. 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J.* 2024;45:3415-537.

7. Alfonso F, Coughlan JJ, Giacoppo D, Kastrati A, Byrne RA. Management of in-stent restenosis. *EuroIntervention.* 2022;18:e103-23.

8. Deng C, Liu Z, Zhang W, Deng Y, Liu H, Bai Z, Rong J, Deng W, Gu N, Shen Y, Hu X, Zhao Y, Zhao R, Shi B. Comparison of Neoatherosclerosis and Neovascularization of Restenosis after Drug-Eluting Stent Implantation: An Optical Coherence Tomography Study. *Rev Cardiovasc Med.* 2023;24:341.

9. Alfonso F, Pérez-Vizcayno MJ, Cuesta J, García Del Blanco B, García-Touchard A, López-Mínguez JR, Masotti M, Zueco J, Cequier A, Velázquez M, Moreno R, Mainar V, Domínguez A, Moris C, Molina E, Rivero F, Jiménez-Quevedo P, Gonzalo N, Fernández-Pérez C; RIBS IV Study Investigators (Under the Auspices of the Interventional Cardiology Working Group of the Spanish Society of Cardiology). 3-Year Clinical Follow-Up of the RIBS IV Clinical Trial: A Prospective Randomized Study of Drug-Eluting Balloons Versus Everolimus-Eluting Stents in Patients With In-Stent Restenosis in Coronary Arteries Previously Treated With Drug-Eluting Stents. *JACC Cardiovasc Interv.* 2018;11:981-91.

10. 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, Colleran 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.