

EDITORIAL COMMENT

# Long-Term Results of Drug-Coated Balloons for Drug-Eluting In-Stent Restenosis

## Gaining Perspective\*

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Compared with the use of bare-metal stents (BMS), the introduction of drug-eluting stents (DES) drastically reduced the occurrence of both clinical and angiographic in-stent restenosis (ISR) (1,2). Recent reports also suggest that new-generation DES could provide a safety edge by reducing the risk of stent thrombosis. The widespread use of DES enabled the expansion of coronary interventions to increasingly complex patients (1). However, ISR still develops in patients treated with DES, especially when these devices are used in challenging clinical and anatomic scenarios (2). The underlying substrate of DES-ISR appears to be particularly complex (2). This problem has major clinical implications as the results of reinterventions for DES-ISR are poorer than those seen in BMS-ISR (2). Recent guidelines suggest that both DES and paclitaxel-eluting balloons (PEB) are very effective and, therefore, may be equally used (recommendation/evidence IA) in patients presenting with ISR (3). Nevertheless, the therapy of choice for patients presenting with DES-ISR still remains unsettled. Therefore, additional studies are warranted to unravel potential outcome differences between these 2 therapeutic modalities to inform clinical decisions (3). From a clinical perspective, a critical appraisal of the long-term efficacy and safety of these competing therapies would provide uniquely valuable information.

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### PRESENT STUDY

In this issue of *JACC: Cardiovascular Interventions*, Kufner et al. (4) present the long-term results of the ISAR-DESIRE 3 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stent In-Stent Restenosis: 3 Treatment Approaches) clinical trial (5). In this study, 402 patients (500 lesions) presenting with limus-DES-ISR were randomly allocated to PEB (n = 137/172 lesions), paclitaxel-eluting stents (PES) (n = 131/168 lesions), or conventional balloon angioplasty (BA) alone (n = 134/160 lesions). Regarding the

SEE PAGE 877

primary endpoint (percentage of diameter stenosis at 6- to 8-month angiographic follow-up), PEB were noninferior to PES, whereas both pharmacologic arms were significantly superior to BA. These angiographic results translated into clear long-term clinical benefits mainly driven by significant reduction in target-lesion revascularization (TLR) compared with the BA arm. The risk of TLR was similar with PEB versus PES but significantly lower with PEB versus BA (hazard ratio [HR]: 0.51, 95% confidence interval [CI]: 0.34 to 0.74). As compared with PES, the risk of death/myocardial infarction (MI) also tended to be lower with PEB, whereas the risk of death was significantly reduced with PEB (HR: 0.38, 95% CI: 0.17 to 0.87). Conversely, the risk of death/MI was identical with PEB and BA. The investigators suggest that the sustained efficacy of PEB, without any trade-off in safety, supports the role of PEB as an attractive therapeutic option for patients with DES-ISR.

Kufner et al. (4) should be commended for this elegant study that compared 3 therapeutic

alternatives (including 2 pharmacoactive strategies that used the same drug) in this challenging anatomical scenario. This systematic long-term analysis provides robust clinical evidence further supporting the maintained safety and efficacy of PEB in patients with DES-ISR. Due to the clinical relevance of the current findings, discussing some methodological aspects would be of major interest.

First, the generalizability of the findings appears promising as exclusion criteria were very limited in this trial (5). Second, the possibility of bias appears to be extremely low although some imprecision cannot be ruled out due to the sample size. Due to the study design, treatment allocation was not concealed but blinded outcome assessors were used. There is a possibility, however, that the indication for reinterventions at follow-up would have been influenced by their perceived risk benefit. Treating recurrent ISR in patients with a double metal layer or in those previously treated with PEB might be considered as less attractive than treating ISR after BA failure (2). However, the magnitude of the outcome differences in favor of the 2 pharmacoactive arms dispels any potential concern in this regard (4).

Third, as these findings do not come from the primary analysis of the trial, they should be considered exploratory in nature. Results, however, were consistent among several pre-specified clinical and angiographic subsets of interest that showed wide confidence estimates but no interaction between PEB and PES.

Fourth, regarding efficacy, TLR at 3 years occurred in 33.3% of cases treated with PEB and in 24.2% of those treated with PES. Although this numeric difference was not statistically significant, the trend ( $p = 0.11$ ) in favor of PES may be a cause for concern. Whether this represents a chance finding or rather a real signal of reduced relative efficacy remains to be determined. "Late" TLR (after the first year) was similar and low (<15%) for PEB, PES, and BA. As expected, the landmark analyses revealed a clear step-down in the TLR-free survival curves at the time of scheduled angiography with all therapies. Interestingly, at this precise time interval, TLR rates were identical for PEB and PES, but then they slightly diverged in favor of PES up to the first year and subsequently run parallel. Further studies with longer clinical follow-up are required to confirm and assess the implications—if any—of these subtle efficacy signals.

Fifth, the safety differences in favor of PEB are also of major interest. After the first year, curves tended to diverge with rates of death/MI being 2-fold with PES compared with PEB (12.3% vs. 6.3%,  $p = 0.12$ ). Moreover, unexpectedly, PEB showed a significantly lower risk of death at 3 years than did PES. Likewise,

target-lesion thrombosis rates were numerically lower with PEB than with PES (0.8% vs 1.6%) (4). The investigators clearly acknowledged that these safety differences between PEB and PES may well represent a chance finding due to the post-hoc nature of the analysis and the limited sample size. However, similar findings on mortality have been recently reported in the 2-year follow-up of the PEPCAD-China-ISR (Prospective, Multicenter, Randomized Trial of Paclitaxel-Coated Balloon versus Paclitaxel-Eluting Stent for the Treatment of DES In-Stent Restenosis) trial (6) that compared PEB with PES in patients with DES-ISR. Similarly, data on compliance or actual duration of the prescribed dual antiplatelet therapy (the protocol just recommended to maintain it for 6 months) would have been of major interest, but were not available. One might speculate that it is likely that patients treated with PES would have received more frequently this therapy for up to 1 year and, if this was the case, the safety edge in favor of PEB would be reinforced. Notably, the potential value of long-term dual antiplatelet therapy in patients with ISR treated with DES was suggested in a subanalysis of the PRODIGY trial (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia) (7). In that study, the use of 24-month dual antiplatelet therapy proved to be safer (reducing the rate of death/MI) compared with a shorter duration (6 months), without any difference in bleeding (7).

A close scrutiny of the study results as discussed above may help to disclose some hypothesis-generating findings but may also be misleading. In this regard, the cautious and balanced interpretations reached by Kufner et al. (4) certainly remain the best scientific approach. Notwithstanding that the trial was unpowered to detect safety differences, death in particular, these long-term results are rather provocative and should pave the way for future studies.

Finally, we should keep in mind that in ISAR-DESIRE-3 the comparator stent was an early generation DES. Recent studies consistently demonstrate that in "de novo" lesions results of novel-generation DES are clearly superior to those of early generation DES.

#### PREVIOUS STUDIES ON LONG-TERM RESULTS OF PEB

Scheller et al. (8) reported the very long-term outcomes of the pivotal study comparing PEB and BA in patients with BMS-ISR. In that study, PEB maintained a superior clinical efficacy out to 5 years of follow-up. Interestingly, although dual antiplatelet therapy was maintained only for 4 weeks, no single case of stent thrombosis was detected. Moreover, no signal of a late

“catch-up” phenomenon was seen and “late” TLR (from 2 to 5 years) was only 3.7% and 5.6%, in the BA and PEB arms, respectively. More recently, the 3-year results of the PEPCAD-DES (Treatment of DES-In-Stent Restenosis With SeQuent Please Paclitaxel Eluting PTCA Catheter) randomized trial (9) comparing PEB with BA in patients with DES-ISR have been reported. Again, the superior efficacy of PEB was confirmed with no signs of a late “catch-up” phenomenon on TLR at follow-up (9). The current analysis by Kufner et al. (4) constitutes the first report on the long-term outcomes of PEB compared with DES in patients with DES-ISR. All together, these studies provide robust evidence supporting the maintained efficacy and safety of PEB in these patients.

### PATHOPHYSIOLOGY OF ACUTE AND LATE HEALING AFTER PEB

The mechanisms of lumen enlargement after BA and repeat stent implantation in patients with ISR are well established (2). With both strategies, tackling any residual stent underexpansion with high-pressure non-compliant balloon dilations remains of paramount importance (2). Recent studies using combined imaging modalities suggest that in patients with DES-ISR, BA enlarges the lumen by a combination of tissue extrusion and additional stent expansion (10). However, multiple intrastent residual neointimal dissections are systematically detected in spite of excellent angiographic results. In this scenario, repeat DES implantation further increases the lumen by additional tissue extrusion and stent expansion and virtually eliminates the presence of intrastent dissections, providing not only a larger but also a smoother lumen (10).

The analysis of healing patterns after PEB has also generated major interest. Preliminary reports suggested that PEB could induce a favorable healing response with “neointimal remodeling,” progressive reduction in tissue volume and disappearance of residual dissections (11). Agostoni et al. (12) performed detailed combined morphometric and physiologic analyses in 25 patients with ISR treated with PEB. At 6-month follow-up, they found a decrease in neointimal volume associated with an increase in lumen volume compared with post-intervention results. Finally, the SEDUCE (Safety and Efficacy of a Drug Eluting Balloon in Coronary Artery Restenosis) randomized trial (13) compared healing characteristics of PEB versus everolimus DES in patients with BMS-ISR. At 9-month follow-up, the percentage of uncovered struts on optical coherence tomography (primary endpoint) was significantly reduced with PEB versus DES, neointimal hyperplasia tended to be larger after PEB, whereas the

percentage of malapposed struts was very low and similar in both groups. This controlled mechanistic study suggested that PEB was associated with better healing characteristics although it tended to be less effective than new generation DES (13).

Finally, it has been suggested that “preparing” the underlying tissue before PEB therapy could enhance the local effects of the drug. In this regard, the ISAR-DESIRE-4 (Intracoronary Stenting and Angiographic Results: Optimizing Treatment of Drug Eluting Stent In-Stent Restenosis 4) trial will determine the potential value of cutting balloon angioplasty before PEB therapy.

### FINAL REMARKS

ISR remains a significant clinical problem (2). Patients with ISR represent a high-risk cohort with increased risk of adverse events in comparison with patients who remain restenosis free. Recent data suggest that the occurrence of angiographic ISR has prognostic value even in asymptomatic patients (14). A large study, also from the Munich group, (including ~10,000 patients with ~15,000 treated lesions) suggested that the presence of ISR during late angiographic surveillance was an independent predictor of 4-year mortality after adjusting for classical clinical and angiographic factors (14).

Treatment of DES-ISR remains particularly challenging (2). In these patients, PEB certainly provide encouraging results. The current study by Kufner et al. (4) confirms the safety and durable antirestenotic efficacy of this therapeutic modality in patients with DES-ISR with results comparable to those seen with first-generation DES. Very recently, however, the results of RIBS-V (Restenosis Intra-Stent of Bare Metal Stents: Paclitaxel-Eluting Balloon vs. Everolimus-Eluting Stent) (in patients with BMS-ISR) (15) and RIBS IV (Restenosis Intra-Stent of Drug-Eluting Stents: Paclitaxel-Eluting Balloon vs. Everolimus-Eluting Stent) (in patients with DES-ISR) (16) randomized trials demonstrated that everolimus-DES offer a superior angiographic efficacy compared with that of PEB. Moreover, in patients with DES-ISR, a superior clinical efficacy of everolimus-DES was also demonstrated (16). The currently ongoing analyses of the long-term results of these 2 studies will help to gain perspective on the role of PEB in the era of new-generation DES.

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## REFERENCES

- García del Blanco B, Hernández Hernández F, Rumoroso Cuevas JR, Trillo Nouche R. Spanish Cardiac Catheterization and Coronary Intervention Registry: 23rd official report of the Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology (1990-2013). *Rev Esp Cardiol* 2014;67:1013-23.
- Alfonso F, Byrne RA, Rivero F, Kastrati A. Current treatment of in-stent restenosis. *J Am Coll Cardiol* 2014;63:2659-73.
- Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014;35:2541-619.
- Kufner S, Cassese S, Valensini M, et al., for the ISAR-DESIRE 3 Investigators. Long-term efficacy and safety of paclitaxel-eluting balloon for the treatment of drug-eluting stent restenosis: 3-year results of a randomized controlled trial. *J Am Coll Cardiol Intv* 2015;8:877-84.
- Byrne RA, Neumann FJ, Mehilli J, et al., for the ISAR-DESIRE 3 Investigators. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. *Lancet* 2013;381:461-7.
- Zhao Y, Xu B, Ge J, et al. Lower mortality of paclitaxel-coated balloon compared with paclitaxel-eluting stent for the treatment of DES in-stent restenosis: two-year follow-up of the PEPCAD China ISR Trial (abstr). *J Am Coll Cardiol* 2014;64 Suppl 11:B78.
- Campo G, Tebaldi M, Vranckx P, et al. Short-versus long-term duration of dual antiplatelet therapy in patients treated for in-stent restenosis: a PRODIGY trial substudy (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia). *J Am Coll Cardiol* 2014;63:506-12.
- Scheller B, Clever YP, Kelsch B, et al. Long-term follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *J Am Coll Cardiol Intv* 2012;5:323-30.
- Rittger H, Waliszewski M, Schlundt C, Achenbach S, Brachmann J, Wöhrle J. PEPCAD-DES: A randomized, multicenter, single blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis - 3-year results (abstr). *J Am Coll Cardiol* 2014;64 Suppl 11:B77.
- Alfonso F, Sandoval J, Pérez-Vizcayno MJ, et al. Mechanisms of balloon angioplasty and repeat stenting in patients with drug-eluting in-stent restenosis. *Int J Cardiol* 2015;178:213-20.
- Sandoval J, Medina M, Alfonso F. Neointimal tissue healing patterns after paclitaxel-eluting balloon treatment of in-stent restenosis: optical coherence tomography and intravascular ultrasound insights. *J Invasive Cardiol* 2012;24:E215-8.
- Agostoni P, Belkacemi A, Voskuil M, Nathoe HM, Doevendans PA, Stella PR. Serial morphological and functional assessment of drug-eluting balloon for in-stent restenotic lesions: mechanisms of action evaluated with angiography, optical coherence tomography, and fractional flow reserve. *J Am Coll Cardiol Intv* 2013;6:569-76.
- Adriaenssens T, Dens J, Ughi G, et al. Optical coherence tomography study of healing characteristics of paclitaxel-eluting balloons vs. everolimus-eluting stents for in-stent restenosis: the SEDUCE (Safety and Efficacy of a Drug eluting balloon in Coronary artery rEstenosis) randomised clinical trial. *EuroIntervention* 2014;10:439-48.
- Cassese S, Byrne RA, Schulz S, et al. Prognostic role of restenosis in 10 004 patients undergoing routine control angiography after coronary stenting. *Eur Heart J* 2015;36:94-9.
- Alfonso F, Pérez-Vizcayno MJ, Cárdenas A, et al., for the RIBS V Study Investigators. A randomized comparison of drug-eluting balloon versus everolimus-eluting stent in patients with bare-metal stent-in-stent restenosis: the RIBS V Clinical Trial (Restenosis Intra-stent of Bare Metal Stents: paclitaxel-eluting balloon vs. everolimus-eluting stent). *J Am Coll Cardiol* 2014;63:1378-86.
- Alfonso F. RIBS IV: A prospective, randomized trial of paclitaxel-eluting balloons versus everolimus-eluting stents in patients with coronary in-stent restenosis of drug-eluting stents. Paper presented at: 26th Transcatheter Cardiovascular Therapeutics Congress; September 13, 2014; Washington, DC.

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