JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 11, NO. 3, 2018

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

What Treatment Should We Dare in Patients With In-Stent Restenosis?*

Adnan Kastrati, MD,[a,b] Michael Joner, MD,[a,b] Sebastian Kufner, MD[a]

Forty years after the first balloon angioplasty (BA) in a coronary artery, contemporary percutaneous interventional techniques have reached very high antirestenotic efficacy. Nevertheless, a substantial number of patients who undergo percutaneous coronary intervention continue to present with restenosis in an implanted stent. Although various factors may considerably influence the risk for restenosis (1), it often remains unpredictable and carries an important prognostic role (2). Successive procedural iterations, from plain BA to bare-metal stents (BMS) to first- and second-generation drug-eluting stents (DES), have led to a progressive decline in the rate of this complication; yet, treatment of in-stent restenosis (ISR) continues to be a challenging issue in clinical practice (3). Several effective treatment options have been used in patients presenting with ISR, including BA with provisional BMS (4), first-generation DES (5), drug-coated balloons (DCBs) (6), and second-generation DES (7,8). A recent meta-analysis indicated that both second-generation DES and DCBs are very effective in patients with ISR, with DES having the advantage of better angiographic and clinical outcomes and DCBs having the advantage of avoiding a new stent layer (9).

SEE PAGE 275

In this issue of *JACC: Cardiovascular Interventions*, Baan et al. (10) present the results of the randomized DARE (Drug Eluting Balloon for In Stent Restenosis) trial, which compared a second-generation DES, the everolimus-eluting stent (EES), with DCBs in patients with ISR. In this study, a total of 278 patients with ISR within BMS (44%) or DES (56%) were randomly assigned to treatment with DCBs or EES. Regarding the primary endpoint (in-segment minimal luminal diameter on 6-month angiography), DCBs were noninferior to EES. The 12-month incidence of target vessel revascularization and other clinical events was also comparable between the 2 treatment arms. In view of this, the investigators conclude that DCBs are an attractive treatment option for ISR by obviating the need for additional stent implantation (10). The most apparent strength of the DARE trial is its broad inclusion criteria. The investigators chose to include all patients with ISR, irrespective of whether it was located in a native vessel or a venous graft, in the left main coronary artery or more distal, and in BMS or DES. In contrast, the broad inclusion criteria might preclude insights into particular subgroups of patients on account of limited patient numbers, as was the case in the DARE trial. There is a lack of sufficient detail in the present study regarding baseline characteristics and 12-month outcomes of patients with BMS versus DES ISR according to the treatment arm, DCBs or EES. Thus, it is difficult to draw conclusions on whether there is an interaction between treatment effect of DCBs or EES and the type of stent (BMS vs. DES) underlying ISR.

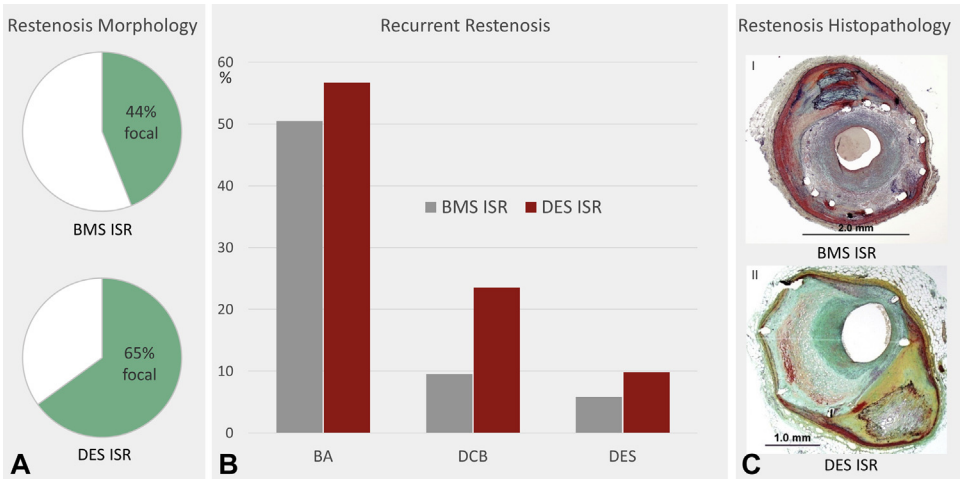
There are differences regarding the angiographic morphology of ISR between BMS and DES, with DES presenting more often with focal ISR compared with BMS (11). Earlier studies in the BMS era showed that repeat treatment of focal ISR is associated with a lower risk for recurrence (12). Thus, treatment of ISR of DES with predominant focal morphology is expected to be more effective than treatment of ISR of BMS with predominant nonfocal morphology. However, the reality does not seem to be in line with these expectations. Indeed, when combining 1,392 lesions from the randomized trials that compared different treatment strategies (BA, DCBs, or second-generation DES) for

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the [a]Deutsches Herzzentrum München, Technische Universität München, Munich, Germany; and the [b]DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany. Dr. Kastrati is a patent holder regarding DES technology, outside the submitted work. Dr. Joner has received consultant fees from Orbus Neich and Biotronik outside the submitted work; and speaker fees from Orbus Neich, Biotronik, and AstraZeneca, outside the submitted work. Dr. Kufner has reported that he has no relationships relevant to the contents of this paper to disclose.

ISSN 1936-8798/$36.00
https://doi.org/10.1016/j.jcin.2017.11.024

FIGURE 1 Differences in Angiographic Morphology, Efficacy of Repeat Treatment, and Histopathology, Between Restenosis After Bare-Metal and Drug-Eluting Stent Implantation



(**A**) Displays angiographic morphology of in-stent restenosis (ISR): percentage of restenosis with focal morphology **(green)** in bare-metal stents (BMS) and drug-eluting stents (DES) in the ISAR DESIRE (Intracoronary Stenting and Angiographic Results: Optimizing Treatment of Drug Eluting Stent In-Stent Restenosis) 1-4 trials and the RIBS (Restenosis Intra-Stent of Bare Metal Stents) II, IV and V trials. (**B**) Displays recurrent restenosis rates in DES **(red)** and BMS **(grey)** after treatment with BA (balloon angioplasty), DCB (drug coated balloon) angioplasty or DES implantation in the ISAR DESIRE 1-4 trials and the RIBS II, IV and V trials. (**C**) Shows low power magnification of a Multilink bare-metal stent (***I***) with severe in-stent restenosis with neointimal hyperplasia with a predominance of smooth muscle cells with neovascularization. Low power magnification of a Movat Pentachrome stained section of a zotarolimus-eluting stent (***II***) showing in-stent restenosis with lipid pool and cholesterol clefts and proteoglycan-rich neointimal tissue with predominance of extracellular matrix, with relative absence of smooth muscle cells. BA = balloon angioplasty; BMS = bare-metal stent(s); DCB = drug-coated balloon; DES = drug-eluting stent(s); ISR = in-stent restenosis.

ISR of BMS and DES (5-8,13,14), the proportion of lesions with focal ISR was higher if the underlying stent was a DES (**Figure 1A**). Nonetheless, all 3 treatment strategies—BA, DCBs, or second-generation DES—were less effective for DES ISR than for BMS ISR (**Figure 1B**). Apparently, angiographic morphology of restenosis is not sufficient to explain the observed relative effectiveness of treatment options. In fact, the differences observed between BMS ISR and DES ISR are not only confined to angiographic morphology. As shown in **Figure 1C**, the main difference is that restenosis after BMS placement is typically characterized by neointimal hyperplasia consisting of a high proportion of vascular smooth muscle cells; in contrast, restenosis after DES placement is typically characterized by a proteoglycan-rich neointimal hyperplasia with relatively few smooth muscle cells (11). However, the therapeutic implications of the differences in ISR between BMS and DES are losing relevance because of the drastic decrease in use of the former.

A recently described histologic feature of the restenotic tissue, in-stent neoatherosclerosis, is the focus of intensive research. Neoatherosclerosis is observed months to years after implantation of both BMS and DES, though there is an ongoing debate on differences in its timing and frequency between DES and BMS (15). Interestingly, recent pathological studies have identified an important association between the formation of in-stent neoatherosclerosis and the development of restenosis. Because compensatory luminal enlargement cannot occur in stented vascular segments, ISR occurs as a consequence of progressive necrotic core formation, intraplaque hemorrhage, and smooth-muscle cell proliferation (16). It is not known whether the presence and extent of neoatherosclerosis significantly influences the results of treatment of ISR. Remarkable progress has been achieved in the validation of intravascular imaging for in vivo characterization of restenotic tissue. In an atherosclerotic rabbit model of DES implantation, data derived from histology and optical coherence tomographic imaging showed excellent correlation (17). Optical coherence tomography has shed considerable light on mechanisms of stent thrombosis (18). In addition, optical coherence tomographic tissue characteristics of ISR seem to correlate with the results achieved by repeat treatment (19). However, much more evidence is needed before we can use optical coherence tomographic tissue characterization to guide selection of the optimal treatment strategy for ISR.

The DARE trial provides additional confirmation of the efficacy of DCBs in patients with ISR. Is it possible

to further improve on the results achieved with this technology? Recent evidence shows that neointimal modification by scoring balloon pre-dilatation enhances the effectiveness of DCBs in ISR (14). The proof of this concept in the ISAR-DESIRE 4 (Intracoronary Stenting and Angiographic Results: Optimizing Treatment of Drug Eluting Stent In-Stent Restenosis 4) trial (14) may justify the use of an "all-in-one" scoring-DCB device similar to that used in the PATENT-C (Paclitaxel-Coated or Uncoated Angio-Sculpt Scoring Balloon Catheter) trial (20). The DCB used in the DARE trial, as in all previous randomized trials in patients with ISR, was a paclitaxel-coated balloon. Paclitaxel proved less efficacious than the limus family of drugs when used as an antiproliferative drug in DES technology. However, development of a limus-based DCB has proved challenging. Recently, the single arm, first-in-human SABRE (Sirolimus Angioplasty Balloon for Coronary In-Stent Restenosis) trial showed promising results in patients with ISR treated with a sirolimus-based DCB (21).

With increased use of intravascular imaging and better understanding of the therapeutic implications of the information it provides, we will see further refinement of the treatment of ISR in the years to come. In the interim, we can be satisfied that we have 2 effective treatment options for patients with ISR: DCBs and DES. DCBs might be preferred in smaller coronary vessels, bifurcations, and restenotic lesions with multiple stent layers. DES might be preferred in large vessels, in the presence of fractures of previously implanted stent(s), in restenotic lesions with marked device recoil, or if edge dissections are observed after balloon dilatation of the ISR lesion. In all other situations, a strategy that alternates between DCBs and repeat DES may be used for treatment of ISR and its recurrences.

ADDRESS FOR CORRESPONDENCE: Dr. Adnan Kastrati, Deutsches Herzzentrum München, Technische Universität München, Lazarettstrasse 36, 80636 Munich, Germany. E-mail: kastrati@dhm.mhn.de.

REFERENCES

1. Cassese S, Byrne RA, Tada T, et al. Incidence and predictors of restenosis after coronary stenting in 10 004 patients with surveillance angiography. Heart 2014;100:153–9.

2. 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.

3. Alfonso F, Byrne RA, Rivero F, Kastrati A. Current treatment of in-stent restenosis. J Am Coll Cardiol 2014;63:2659–73.

4. Elezi S, Kastrati A, Hadamitzky M, Dirschinger J, Neumann FJ, Schomig A. Clinical and angiographic follow-up after balloon angioplasty with provisional stenting for coronary in-stent restenosis. Catheter Cardiovasc Interv 1999;48:151–6.

5. Kastrati A, Mehilli J, von Beckerath N, et al. Sirolimus-eluting stent or paclitaxel-eluting stent vs balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: a randomized controlled trial. JAMA 2005;293:165–71.

6. Byrne RA, Neumann FJ, Mehilli J, et al. 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.

7. Alfonso F, Perez-Vizcayno MJ, Cardenas A, et al. 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.

8. Alfonso F, Perez-Vizcayno MJ, Cardenas A, et al. 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.

9. Siontis GC, Stefanini GG, Mavridis D, et al. Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis. Lancet 2015;386:655–64.

10. Baan J Jr., Claessen BE, Boerlage-van Dijk K, et al. A randomized comparison of paclitaxel-eluting balloon versus everolimus-eluting stent for the treatment of any in-stent restenosis: the DARE trial. J Am Coll Cardiol Intv 2018;11:275–83.

11. Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Gruntzig Lecture ESC 2014. Eur Heart J 2015;36:3320–31.

12. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. Circulation 1999;100:1872–8.

13. Alfonso F, Perez-Vizcayno MJ, Hernandez R, et al. A randomized comparison of sirolimus-eluting stent with balloon angioplasty in patients with in-stent restenosis: results of the Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting (RIBS-II) trial. J Am Coll Cardiol 2006;47:2152–60.

14. Kufner S, Joner M, Schneider S, et al. Neointimal modification with scoring balloon and efficacy of drug-coated balloon therapy in patients with restenosis in drug-eluting coronary stents: a randomized controlled trial. J Am Coll Cardiol Intv 2017;10:1332–40.

15. Nakazawa G, Otsuka F, Nakano M, et al. The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. J Am Coll Cardiol 2011;57:1314–22.

16. Otsuka F, Byrne RA, Yahagi K, et al. Neoatherosclerosis: overview of histopathologic findings and implications for intravascular imaging assessment. Eur Heart J 2015;36:2147–59.

17. Malle C, Tada T, Steigerwald K, et al. Tissue characterization after drug-eluting stent implantation using optical coherence tomography. Arterioscler Thromb Vasc Biol 2013;33:1376–83.

18. Adriaenssens T, Joner M, Godschalk TC, et al. Optical coherence tomography findings in patients with coronary stent thrombosis: a report of the PRESTIGE Consortium (Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort). Circulation 2017;136:1007–21.

19. Tada T, Kadota K, Hosogi S, et al. Association between tissue characteristics evaluated with optical coherence tomography and mid-term results after paclitaxel-coated balloon dilatation for in-stent restenosis lesions: a comparison with plain old balloon angioplasty. Eur Heart J Cardiovasc Imaging 2014;15:307–15.

20. Scheller B, Fontaine T, Mangner N, et al. A novel drug-coated scoring balloon for the treatment of coronary in-stent restenosis: results from the multi-center randomized controlled PATENT-C first in human trial. Catheter Cardiovasc Interv 2016;88:51–9.

21. Verheye S, Vrolix M, Kumsars I, et al. The SABRE trial (Sirolimus Angioplasty Balloon for Coronary In-Stent Restenosis): angiographic results and 1-year clinical outcomes. J Am Coll Cardiol Intv 2017;10:2029–37.

KEY WORDS bare-metal stent(s), drug-eluting balloon, drug-eluting stent(s), restenosis