Letter to the Editor

Treatment for in-stent restenosis: patient-specific decision rather than universal recommendation

Joo Myung Lee[1], Jonghanne Park[2], Tae-Min Rhee[2], Hyo-Soo Kim[2,3]

[1]Division of Cardiology, Department of Internal Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Seoul, Korea; [2]Department of Internal Medicine and Cardiovascular Center, [3]Molecular Medicine & Biopharmaceutical Science, Graduate School of Convergence Science & Technology, Seoul National University, Seoul, Korea

Correspondence to: Hyo-Soo Kim, MD, PhD. Professor, Department of Internal Medicine, Cardiovascular Center, Seoul National University Hospital, 101 Daehak-ro, Jongro-gu, Seoul 110-744, Korea. Email: usahyosoo@gmail.com or hyosoo@snu.ac.kr.

Submitted Jun 07, 2016. Accepted for publication Jun 17, 2016.
doi: 10.21037/jtd.2016.07.57
View this article at: http://dx.doi.org/10.21037/jtd.2016.07.57

The development of the drug-eluting stent (DES) created a milestone in the field of percutaneous coronary intervention (PCI) by markedly reducing the rates of in-stent restenosis (ISR) compared to the bare metal stent (BMS). The development of a thinner strut and biocompatible or bioresorbable polymer coating in newer generation DES has enhanced the efficacy and safety of DES. However, along with the widespread use of this newer generation DES in most clinical conditions, including high-risk patients with more complicated lesion profiles, ISR has continued to be a major concern, even in the era of newer generation DES (1). The incidence of ISR ranges from 3% up to 20% of patients (1). The clinical importance of ISR should be further emphasized, since more than half of ISR patients present with acute coronary syndromes (ACS) such as unstable angina or acute myocardial infarction (1), and patients who have been treated for ISR consistently show higher rates of future adverse cardiovascular events compared to those without ISR (2). In this regards, decision regarding optimal treatment option for ISR lesion should be considered even in contemporary era of PCI using newer generation DES. In order to address this issue, our group recently published the first network meta-analysis which compared clinical and angiographic outcomes among DES, DEB, and plain old balloon angioplasty (POBA). As specifically discussed in the previous editorials (3-6), our group firstly presented the superior efficacy and safety of DEB and DES, compared with POBA, and comparable efficacy and safety between DEB and DES to treat BMS or DES ISR lesion. Although DEB and DES showed similar risk of MI, DEB tended to show lower risk of MI during follow-up period, compared with DES. Although the network meta-analysis by our group comprehensively summarized previous evidences from 11 randomized controlled trials (RCTs) with 2,059 patients with BMS or DES ISR, some unsolved issues are worth to be discussed.

First, it should be considered that there has been relatively scarce evidence which evaluated newer generation DES as treatment option for ISR. Current European Society of Cardiology/European Association for Cardiothoracic Surgery (ESC/EACTS) guidelines recommend drug-eluting balloon (DEB) and DES as class IA recommendations for the treatment of BMS or DES-ISR (7). However, most previous studies, which evaluated DEB as a treatment option for ISR, compared its safety and efficacy to first generation DES, which is no longer used in daily clinical practice (1,8-12). Our network meta-analysis also shared the common limitation. Among the included trials, 6 out of 7 RCTs which had a DES arm to treat ISR in the previous network meta-analysis, actually used old-fashioned 1st generation DES such as sirolimus-eluting or paclitaxel-eluting stents. Among the included RCTs, only the RIBS-V trial used 2nd generation everolimus-eluting stent (Xience Prime, EES) which has been proved to be superior to 1st generation DES (13). In the RIBS-V trial, DES was comparable to DEB both in the rates of MI and TLR for BMS ISR (14).

After publication of our meta-analysis, RIBS IV trial (15), which randomly compared DEB versus EES in DES-ISR patients, firstly demonstrated the superior efficacy of EES group in terms of MACE (18.0% *vs.* 10.0%, HR

0.58, 95% CI, 0.35–0.98, P=0.042) and TVR (16.2% *vs.* 8.4%, HR 0.33, 95% CI, 0.14–0.79, P=0.035). The pooled analysis using RIBS V and RIBS IV trial population further strengthen the superior efficacy and safety of newer generation EES for treatment of BMS or DES ISR patients, compared with DEB (16). Furthermore, more recent network meta-analysis by Siontis *et al.* consistently showed that EES was the most effective treatment, compared with DEB, sirolimus-eluting stent, paclitaxel-coated stent, vascular brachytherapy, BMS, rotablation, or POBA (17). However, it should be noted that all these previous evidences which favored EES as best treatment option were derived from the only 2 RCTs (RIBS IV and V). Except EES, other types of newer generation DES, for example, bioresorbable polymer coated DES or drug-coated polymer free DES have never been tested in this clinical setting.

Second, although EES showed clear benefit over DEB in the previous 2 RCTs (RIBS IV and V) (14-16), and recent network meta-analysis incorporating these two RCTs (17), it should be noted that these two RCTs excluded several high-risk patients and lesion subsets such as acute MI, small vessel lesions (≤2.0 mm in diameter), long lesions (>30 mm in length), or ISR with thrombotic total occlusion. Therefore, there has been no further evidence for safety and efficacy of newer generation DES or DEB in patients with high-risk patients or lesional characteristics. Our group currently preparing the patient-level pooled analysis comparing the clinical outcomes between newer generation DES (including bioresorbable polymer coated DES) and DEB in all-comers ISR population. This study will more clarify the clinical outcomes after DES or DEB treatment in high-risk population with ISR.

Third, all the previous RCTs have never compared the incidence of bleeding and the impact of duration of dual antiplatelet therapy (DAPT). The optimal duration of DAPT to maximize clinical outcome after DEB angioplasty remains uncertain. Further RCTs might be warranted regarding this subject.

Since the DEB possesses a fundamental difference from DES implantation in ISR lesions, the treatment strategy for ISR should be individualized with careful assessment of the balance between the benefits and risks of additional DES implantation including the risk which inevitably following the maintenance of long-term DAPT, especially after DES implantation. Considering insufficient evidences and heterogeneous results across all the previous studies warranted "individualized approach" in deciding the treatment option for ISR lesion, rather than universal recommendation of DES or DEB for all the ISR patients.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Response to: Yang J, Mamuti W, Zhang F. Optimal interventional strategy for the treatment of coronary in-stent restenosis. J Thorac Dis 2015;7:1669-71.
Akin I, Nienaber CA. Treatment of coronary in-stent restenosis—evidence for universal recommendation? J Thorac Dis 2015;7:1672-5.
Alfonso F, Rivero F. Network meta-analyses on in-stent restenosis treatment: dealing with complexity to clarify efficacy and safety. J Thorac Dis 2015;7:1678-83.
Yudi MB, Waksman R, Ajani AE. In-stent restenosis: local drug delivery with a stent or balloon? J Thorac Dis 2015;7:1691-2.

References

1. Alfonso F, Byrne RA, Rivero F, et al. Current treatment of in-stent restenosis. J Am Coll Cardiol 2014;63:2659-73.
2. Lee JM, Park J, Kang J, et al. Comparison among drug-eluting balloon, drug-eluting stent, and plain balloon angioplasty for the treatment of in-stent restenosis: a network meta-analysis of 11 randomized, controlled trials. JACC Cardiovasc Interv 2015;8:382-94.
3. Akin I, Nienaber CA. Treatment of coronary in-stent restenosis-evidence for universal recommendation? J Thorac Dis 2015;7:1672-5.
4. Alfonso F, Rivero F. Network meta-analyses on in-stent restenosis treatment: dealing with complexity to clarify efficacy and safety. J Thorac Dis 2015;7:1678-83.
5. Kilic ID, Konstantinidis N, Pighi M, et al. Stop adding metal layers: Will bioabsorbable scaffolds become the gold standard for late in-stent restenosis and neo-atherosclerosis? Cardiovasc Revasc Med 2015;16:124-6.
6. Yudi MB, Waksman R, Ajani AE. In-stent restenosis: local drug delivery with a stent or balloon? J Thorac Dis 2015;7:1691-2.
7. Wöhrle J, Zadura M, Möbius-Winkler S, et al. SeQuentPlease World Wide Registry: clinical results of

SeQuent please paclitaxel-coated balloon angioplasty in a large-scale, prospective registry study. J Am Coll Cardiol 2012;60:1733-8.
8. Unverdorben M, Vallbracht C, Cremers B, et al. Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. Circulation 2009;119:2986-94.
9. Rittger H, Brachmann J, Sinha AM, et al. A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEPCAD-DES study. J Am Coll Cardiol 2012;59:1377-82.
10. 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. JACC Cardiovasc Interv 2012;5:323-30.
11. 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.
12. Steinberg DH, Gaglia MA Jr, Pinto Slottow TL, et al. Outcome differences with the use of drug-eluting stents for the treatment of in-stent restenosis of bare-metal stents versus drug-eluting stents. Am J Cardiol 2009;103:491-5.
13. Kang SH, Park KW, Kang DY, et al. Biodegradable-polymer drug-eluting stents vs. bare metal stents vs. durable-polymer drug-eluting stents: a systematic review and Bayesian approach network meta-analysis. Eur Heart J 2014;35:1147-58.
14. Alfonso F, Pérez-Vizcayno MJ, Cárdenas 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.
15. Alfonso F, Pérez-Vizcayno MJ, Cárdenas 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.
16. Alfonso F, Pérez-Vizcayno MJ, García Del Blanco B, et al. Comparison of the Efficacy of Everolimus-Eluting Stents Versus Drug-Eluting Balloons in Patients With In-Stent Restenosis (from the RIBS IV and V Randomized Clinical Trials). Am J Cardiol 2016;117:546-54.
17. 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.

Cite this article as: Lee JM, Park J, Rhee TM, Kim HS. Treatment for in-stent restenosis: patient-specific decision rather than universal recommendation. J Thorac Dis 2016;8(8):E847-E849. doi: 10.21037/jtd.2016.07.57

