Commentary

Contemporary drug-eluting stents and companion polymers: durable is not synonymous with harm

Salvatore Cassese[1], Sebastian Kufner[1], Adnan Kastrati[1,2]

[1]German Heart Center Munich, Technical University Munich, (SC, SK, AK), Munich, Germany; [2]German Centre for Cardiovascular Research, Partner Site Munich Heart Alliance (AK), Munich, Germany

Correspondence to: Salvatore Cassese, MD, PhD. German Heart Center Munich, Technical University Munich, Lazarettstrasse 36, Munich, Germany. Email: cassese@dhm.mhn.de.

Submitted Aug 25, 2016. Accepted for publication Sep 27, 2016.
doi: 10.21037/jtd.2016.10.70
View this article at: http://dx.doi.org/10.21037/jtd.2016.10.70

On September 3, 2006 during the annual European Society of Cardiology meeting in Barcelona, two independent meta-analyses revealed for the first time that the superior efficacy of early-generation drug-eluting stents (DESs) as compared with bare metal stents (BMSs) came at the expense of increased mortality due to very late stent thrombosis (ST) (1). Subsequently, the main DESs components (supportive backbones, polymer coatings or carriers and antiproliferative drugs) underwent a systematic investigation to rule-out the underlying reasons of early-generation DESs failure. Preclinical and necropsy studies showed that, among other factors, the methacrylate-based polymers, responsible for drug-release modulation in a large part of early-generation DESs, persisted in the implanted vessel wall long after their function was duly served (2). This kind of durable carriers caused chronic inflammatory response and delayed arterial healing at the stented site, which have been associated with neoatherosclerosis, restenosis and ST over the long term (3).

Ten years later, contemporary DESs have definitely proved to be safer than preceding coronary prostheses. This achievement arises from the iterations to which DES technology has been subject during this interval (4). In this scenario, the development of coronary implants with transient components (either polymers or backbones) has attracted considerable interest. Currently, biodegradable-polymer DESs and fully bioresorbable DESs are promoted as valuable alternative to durable-polymer metallic DESs.

The peculiarity of biodegradable-polymer DESs is that once the antirestenotic drug is eluted and the carrier completely degraded, the stent platform left behind is comparable to that of a BMS. By virtue of the temporary nature of the carrier, these modern devices should reduce the thrombotic risk and the need for long-term antiplatelet therapy, two intrinsic disadvantages of early-generation DESs (5). Although previous investigations displayed that stents eluting antirestenotic drugs from a biodegradable polymer have superior safety in comparison with early-generation DESs (6,7), the utility of these platforms against contemporary biocompatible durable-polymer DESs is not so easily discounted. At the opposite, biodegradable-polymer DESs showed a higher risk for ST out to 1 year as compared to the benchmark everolimus-eluting stent (EES) with a fluorinated durable-polymer coating (Xience; Abbott Vascular, Santa Clara, California, USA) (8). This latter platform appears the safest among contemporary DESs, notwithstanding the durable nature of both carrier and metallic frame (9).

Fully bioresorbable DESs aim at providing a temporary scaffold for the vessel until the elution process is completed and then self-degrade into inert breakdown products after about 3 years (10). In consideration of initial positive reports in highly selected patients populations, the everolimus-eluting bioresorbable vascular scaffold (Absorb/BVS, Abbott Vascular, Santa Clara, CA, USA) has been the first of such devices deserving CE-mark approval. Preclinical and imaging-based clinical studies reported a favorable behavior of this platform in terms of healing, vasomotricity and late remodeling of the treated segment. However, recent investigations suggest a between 2- and 3-fold higher risk of ST out to 1-year follow-up with BVSs compared to the benchmark metallic EES with a durable fluoropolymer (11).

Notably, in the fall of 2015, the first DES with a bioresorbable polymer has received US Food and Drug

Administration (FDA) approval for use in the United States. Similarly, the BVS represents the only fully bioresorbable DES approved for clinical use from FDA since July 2016. Nonetheless, the creeping skepticism surrounding these two new technologies depends on whether the temporary nature of either polymers or backbones contributes to improve their safety against contemporary DESs with biocompatible durable coatings and thinner metallic frames. Intuitively, the plethora of randomized studies comparing different platforms results largely underpowered to investigate rare outcomes, as in the case of ST. In this respect, an interesting report, which was published in *JACC Cardiovasc Interv* in 2016 has to be highlighted (12).

Kang and colleagues combined in the form of network meta-analysis direct and indirect evidence concerning the safety of early- and new-generation DESs, as well as of BMSs. The primary objective was to investigate the risk of definite/probable ST across a wide spectrum of DESs and BMSs out to 1-year follow-up. With a total of 110 randomized controlled trials and 111,088 patients available for risk estimation of primary outcome, the final messages of this study were as follows: at 1-year follow-up (I) contemporary DESs have a lower risk for ST as compared to earlier stent platforms (both DESs and BMSs); (II) among contemporary metallic DES platforms, the safety of those with a fluorinated coating is superior to that of DESs with biodegradable-polymer and thicker strut design and similar to that of biodegradable-polymer DESs with thinner metallic frames; (III) fully bioresorbable DESs have inferior safety as compared to fluoropolymer-based DESs and biodegradable-polymer DESs with thinner metallic frames. These results deserve an in-depth discussion.

First, the findings of a network meta-analysis should not be over-interpreted. Those who are familiar with this statistical method are aware that a low degree of inter-study variability and balanced nodes (each one reflecting the actual number of patients available for a certain comparison) are prerequisite for a credible estimation of treatment effects. These premises were not rigorously fulfilled in this report, especially in those comparisons involving biodegradable-polymer DESs with thinner metallic frames.

Second, the meta-analysis of Kang and co-workers remarks that the restraint of DES platforms and coatings within approximate categories (durable, biodegradable, bioresorbable etc.) appears more manufacturers-guided than scientifically-based. Indeed, the safety of contemporary durable-polymer DESs with fluorinated coatings cannot be assimilated to that of early durable-polymer DESs with metacrylate-based coatings. Similarly, the performance of biodegradable-polymer DESs cannot be handled as a "class effect". For example, the complete degradation of the polymer coating of the Nobori stent (Terumo, Tokyo, Japan), one of the first biodegradable-polymer DESs receiving CE-mark approval, occurs in 6 to 9 months and its metallic frame is based on a thicker-strut design (150 μm). In contrast, a recently marketed stent eluting sirolimus from a biodegradable coating (Orsiro; Biotronik, Bülach, Switzerland) has complete degradation of the carrier after 12 to 24 months and a thinner-strut design (60 μm). These two biodegradable-polymer DES platforms subtend a different thrombotic risk, as highlighted in the report from Kang and co-workers and in a recent randomized head-to-head comparison (13).

Third, Kang and co-workers reinforce the common concern that the thrombotic risk within 1 year after BVS implantation is higher than we have accustomed to with contemporary metallic DESs (14). The fact that the performance of current BVSs does not reflect initial enthusiastic expectations should not preclude further investigations of this technology. Researchers should define procedural protocols for proper selection and implantation specific to these devices, including a more liberal use of intracoronary imaging. Manufacturers should profit from the awareness of intrinsic limitations of this immature technology to pursue meaningful ameliorations, replicating the virtuous process, which guided the transition from early- to new-generation DESs.

Finally, although the study of Kang and co-workers focused on ST at 1-year follow-up, long-term data is needed to properly address the relative safety of different DESs. This aspect is of paramount importance for DES technologies with transient components for which the main benefit is expected to accrue time after implantation. For example, the direct comparison of biodegradable-polymer DES with thicker-strut design and fluoropolymer-based EESs revealed a similar safety out to 5-year follow-up (15). This may suggest a negligible impact of contemporary biocompatible durable coatings on long-term outcomes. In contrast, long-term safety data from large-scale clinical trials investigating fully bioresorbable DESs are not expected before 2020 or 2021, leaving a sense of uncertainty regarding the possible late benefits of this technology.

As long as biodegradable-polymer DESs and fully bioresorbable DESs will undergo continuous technological improvements, comparative studies and long-term follow-up data are fundamental to disclose possible advantages

of these technologies in comparison with contemporary high-performance metallic DESs. Until further data will be available, the fluoropolymer-based EES with its durable components represents an appropriate comparator for studies investigating the relative safety of different DES platforms for patients undergoing percutaneous revascularization because of obstructive disease of coronary arteries.

Acknowledgements

None.

Footnote

Provenance: This is an invited Commentary commissioned by the Section Editor Yue Liu (Associate Professor, Department of Cardiology, the First Affiliated Hospital of Harbin Medical University, Harbin, China).
Conflicts of Interest: A Kastrati has submitted patents in relation to DES technologies. The other authors have no conflicts of interest to declare.

Comment on: Kang SH, Chae IH, Park JJ, *et al*. Stent Thrombosis With Drug-Eluting Stents and Bioresorbable Scaffolds: Evidence From a Network Meta-Analysis of 147 Trials. JACC Cardiovasc Interv 2016;9:1203-12.

References

1. Cook S, Meier B. Have we been misled by the ESC DES firestorm? EuroIntervention 2008;3:535-7.
2. Joner M, Finn AV, Farb A, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193-202.
3. Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Grüntzig Lecture ESC 2014. Eur Heart J 2015;36:3320-31.
4. Mennuni MG, Pagnotta PA, Stefanini GG. Coronary Stents: The Impact of Technological Advances on Clinical Outcomes. Ann Biomed Eng 2016;44:488-96.
5. Byrne RA, Kastrati A. No country for old stents? Improving long-term patient outcomes with biodegradable polymer drug-eluting stents. Expert Rev Cardiovasc Ther 2012;10:429-32.
6. Stefanini GG, Byrne RA, Serruys PW, et al. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. Eur Heart J 2012;33:1214-22.
7. Cassese S, Fusaro M, Byrne RA, et al. Clinical outcomes of patients treated with Nobori biolimus-eluting stent: Meta-analysis of randomized trials. Int J Cardiol 2014;175:484-91.
8. 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.
9. Stefanini GG, Holmes DR Jr. Drug-eluting coronary-artery stents. N Engl J Med 2013;368:254-65.
10. Kereiakes DJ, Onuma Y, Serruys PW, et al. Bioresorbable Vascular Scaffolds for Coronary Revascularization. Circulation 2016;134:168-82.
11. Cassese S, Byrne RA, Ndrepepa G, et al. Everolimus-eluting bioresorbable vascular scaffolds versus everolimus-eluting metallic stents: a meta-analysis of randomised controlled trials. Lancet 2016;387:537-44.
12. Kang SH, Chae IH, Park JJ, et al. Stent Thrombosis With Drug-Eluting Stents and Bioresorbable Scaffolds: Evidence From a Network Meta-Analysis of 147 Trials. JACC Cardiovasc Interv 2016;9:1203-12.
13. Jensen LO, Thayssen P, Maeng M, et al. Randomized Comparison of a Biodegradable Polymer Ultrathin Strut Sirolimus-Eluting Stent With a Biodegradable Polymer Biolimus-Eluting Stent in Patients Treated With Percutaneous Coronary Intervention: The SORT OUT VII Trial. Circ Cardiovasc Interv 2016;9. pii: e003610.
14. Cassese S, Kastrati A. Bioresorbable Vascular Scaffold Technology Benefits From Healthy Skepticism. J Am Coll Cardiol 2016;67:932-5.
15. PCR online. The final five-year results from the COMPARE II trial: the first real long-term results between biodegradable polymer biolimus-eluting stent and durable polymer everolimus-eluting stent. Available online: http://www.pcronline.com/Lectures/2016/The-final-five-year-results-from-the-COMPARE-II-trial-the-first-real-long-term-results-between-biodegradable-polymer-biolimus-eluting-stent-and-durable-polymer-everolimus-eluting-stent

Cite this article as: Cassese S, Kufner S, Kastrati A. Contemporary drug-eluting stents and companion polymers: durable is not synonymous with harm. J Thorac Dis 2016;8(10):E1413-E1415. doi: 10.21037/jtd.2016.10.70

