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Editorial

Bare-metal coronary stents for patients at high bleeding risk?

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The widespread use of drug-eluting stents (DES) replacing bare-metal stents (BMS) in every day clinical practice has been able to significantly reduce clinical and angiographic rates of in-stent restenosis (ISR) [1–3]. This was especially clear in patients with complex clinical and angiographic characteristics [1–3]. However, whether BMS may be used in patients with a very low risk of restenosis was a matter of controversy for some years until it also became clear that even in highly favorable lesions (ie, short lesions in large vessels) DES provide superior long-term clinical and angiographic results compared with BMS [4]. Nevertheless, until very recently, BMS were considered to be safer than DES regarding the risk of stent thrombosis, a rare but dreadful complication [2,3]. Moreover, first-generation DES required long-term dual antiplatelet therapy (DAPT) (at least 1 year) to ensure a "safety net" capable of bridging the extended healing time required for complete endothelialization as compared with BMS [2,3]. Accordingly, BMS were considered especially suited for patients unable to maintain a prolonged DAPT regimen and in those with high bleeding risk. Actually, initial clinical practice guidelines assigned a class III recommendation for the use of first-generation DES in these patients. However, second-generation DES proved to be not only more effective but also safer than first generation DES [2]. Moreover, aggregate studies confirmed that current generation DES are indeed safer than BMS [5]. This paradigm shift, based in robust clinical evidence, was recently emphasized by the clinical practice guidelines on coronary revascularization that recommend the use of DES as a default strategy in all clinical and anatomic scenarios [3]. Of interest, this recommendation includes patients with high bleeding risk (including thrombosis diathesis, cancer, etc) clinical indication for oral anticoalgulation, planed staged non-cardiac surgeries requiring withdrawal of antiplatelet medications and patients with anticipated poor DAPT compliance [3]. If current DES are actually safer than BMS, patients fulfilling these untoward characteristics -a classical niche for BMS- would actually benefit from new-generation DES implantation. But, are we really convinced that this is always the case?

1. Current study

The ZEUS (Zotarolimus-eluting Endeavor sprint stent in Uncertain DES candidates) randomly assigned 1606 patients with stable or unstable symptoms with high risk of bleeding or thrombosis but also patients with low risk for ISR, to either a zotarolimus-eluting stent (ZES) with biocompatible polymer and fast drug-eluting characteristics or a thin-strut BMS [6]. Of note, this challenging patient population has been previously excluded from most randomized clinical trials. This ZES was intentionally selected because, although the rapid drug-release profile limits its ability to blunt the neointimal response, it might also lead to more rapid strut coverage. Unique to this trial was that DAPT duration was based on patient characteristics including personalized, tailored, abbreviated DAPT (allowing for only 1-month duration independent of stent type). Actually, the median DAPT duration was only 32 days. The primary end-point (a composite of death, myocardial infarction and target vessel revascularization) was significantly reduced by ZES (17.5 vs 22.1%, $p < 0.01$), mainly driven by a reduction in myocardial infarction and revascularization as compared with BMS. Moreover, the risk of definitive/probable stent thrombosis was halved in the ZES arm (2 vs 4.1%, $p = 0.019$). When clinical outcomes were evaluated according to indication (high bleeding risk, high thrombosis risk, low risk of restenosis) there was no signal of heterogeneity in safety or efficacy. Notably, the very short DAPT duration used in this study proved to be instrumental to disentangle the effects of the type of stent (DES vs BMS) from those related to the concomitant DAPT duration [6]. A subsequent report from the ZEUS trial specifically focused on the high-bleeding risk patient subset ($n = 828$) (advanced age, indication to oral anticoagulants or other pro-hemorrhagic medications, history of bleeding and known anemia) encompassing more than half of the total population [7]. In this high-bleeding risk cohort the primary end-point (22.6 vs 29%, $p = 0.03$) and the rates of stent thrombosis were also significantly reduced with ZES compared with BMS. Surprisingly, this study demonstrated that patients treated with BMS received longer

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cumulative DAPT duration compared with those assigned ZES. A detailed analysis of this unexpected finding unraveled that patients treated with BMS more frequently needed to "re-start" DAPT as a result of reinterventions for ISR or stent thrombosis [7].

In the current issue of the *Journal* Gargiulo et al. present a *post-hoc* analysis of the ZEUS trial that sought to assess the impact of coronary artery disease complexity and extension using the SYNTAX score, on ischemic and bleeding risks [8]. Patients were stratified according to tertiles of the SYNTAX score (mean 16.3 ± 13, median 12). Overall, this study found that the higher the SYNTAX score the higher the ischemic risk and bleeding risk. However, after careful adjustment for potential confounders, disease complexity remained associated with adverse ischemic events but no with bleeding events. This suggests that the adverse clinical and angiographic characteristics of patients with complex coronary artery disease explained the elevated bleeding risk. Of interest, the superiority of ZES over BMS regarding the primary endpoint was consistent across the SYNTAX tertiles, mainly as a result of a reduction in the rates of myocardial infarction (particularly type 1 and 4b) and target vessel revascularization. However, no interaction was noticed between the stent type and ischemic or bleeding complications. This new study suggests that, even for patients in the lower end of the spectrum of anatomic lesion complexity, DES should be preferred over DES [8].

Some methodological issues of this interesting study merit further discussion. First, each SYNTAX tertile remained well balanced across treatment regarding clinical and angiographic characteristics. However, as expected, patients with the highest SYNTAX scores were older had more coronary risk factors and had more complex disease requiring multiple stents. In this regard, the statistical adjustment performed by the ZEUS investigators was instrumental to support the finding that coronary artery disease complexity "per se" was not an independent predictor of bleeding risk in this population. Second, a single senior interventional cardiologists, blinded to clinical data and treatment allocation, evaluated the SYNTAX score. This is a strength of the study that circumvents the potential variability of this tool in the assessment of lesion complexity seen in every day clinical practice. Third, most patients showed a relatively low SYNTAX score, and the number of patients with relatively high anatomic complexity was rather limited (two-third of patients had a score < 23, the classical low cut-off used in clinical decisions for the selection of revascularization strategies). Fourth, the ZES selected has been blamed of lower efficacy compared with newer generation DES (the Endeavor Sprint was replaced time ago by the Resolute ZES and is no longer on the market). Fifth, bleeding events are closely related to access route and antithrombotic medication. Although the study was performed some years ago, the radial access was used in two-third of patients. However, the vast majority of patients were treated with clopidogrel rather than with the more effective agents (prasugrel or ticagrelor) currently available. Finally, the study was not fully powered to ascertain the influence of disease complexity on ischemic and bleeding risk and, therefore, should be considered as hypothesis generating [8].

2. Previous related studies

The NORSTENT (Norwegian Coronary Stent Trial) randomized ~9000 patients with stable or unstable coronary artery disease to DES (ZES or Everolimus-DES) or BMS [9]. The primary outcome was a composite of death and nonfatal spontaneous myocardial infarction at 5 years. In this all-comers study, the primary endpoint was similar in both arms but DES were associated, not only with a lower need of repeat revascularization (16.5 vs 19.8%, $p < 0.001$), but also with a lower rate of definite stent thrombosis (0.8 and 1.2%, $p < 0.05$) [9]. In a high bleeding risk patient population, the LEADERS-FREE (A Randomized Clinical Evaluation of the BioFreedom Stent) also suggested a better safety and efficacy of a polymer-free biolimus-DES compared with BMS [10]. In this trial ~2.500 patients receiving only 1-month course of DAPT were included. As expected, target-lesion revascularization was significantly reduced in the DES arm (5.1 vs 9.8%, $p < 0.001$). However, the primary safety end point (a composite of cardiac death, myocardial infarction, or stent thrombosis at 1 year) was also significantly reduced in the DES arm (9.4 vs 12.9%, $p = 0.005$) [10]. More recently, the SENIOR trial randomly allocated 1200 elderly patients (≥75 years) to DES or BMS [11]. By protocol, the intended duration of DAPT was 1 month for stable and 6 months for unstable patients, irrespective of the allocated stent type. The primary outcome measure (a composite of mortality, myocardial infarction, stroke and ischemia-driven target lesion revascularization at 1 year) was 12% in the DES group and 16% in the BMS group ($p < 0.05$). Bleeding complications (5%) and stent thrombosis rates (1%) were identical in both arms. This trial provided additional evidence reinforcing the value of a strategy of combining a DES (to reduce the risk of subsequent repeat revascularization) with a short BMS-like DAPT regimen (to reduce bleeding risk) as the best choice in elderly patients requiring revascularization [11].

3. Final remarks

Results of this novel study from the ZEUS trial by Gargiulo et al. [8] support current clinical practice guidelines recommendation to select DES as the default strategy in all patients requiring coronary interventions [3]. These include patients with a low risk of restenosis as a result of very favorable anatomy but also patients with very high ischemic and bleeding risk. Current generation DES are continuously evolving to offer even better efficacy yet improving their safety profile. The debate on the best antiplatelet therapy regimen and its optimal duration continues. In the meantime, new scales and tools open new venues to escape from "*one-side fits all*" strategies on DAPT, shifting to a new paradigm of "*personalized medicine*" able to select the optimal concomitant antithrombotic therapy in the individual patient [12].

Conflict of interest

There are no conflicts of interest to be disclosed in relation to this work.

References

[1] A.B. Cid Álvarez, O. Rodríguez Leor, R. Moreno, A. Pérez de Prado, Spanish Cardiac Catheterization and Coronary Intervention Registry. 27th Official Report of the Spanish Society of Cardiology Working Group on Cardiac Catheterization and Interventional Cardiology 1990–2017, Rev Esp Cardiol (Engl Ed) 71 (12) (2018 Dec) 1036–1046.

[2] F. Alfonso, C. Fernandez, Second-generation drug-eluting stents, Moving the field forward. J Am Coll Cardiol. 58 (1) (2011 Jun 28) 26–29.

[3] F.J. Neumann, M. Sousa-Uva, A. Ahlsson, F. Alfonso, A.P. Banning, U. Benedetto, R.A. Byrne, J.P. Collet, V. Falk, S.J. Head, P. Jüni, A. Kastrati, A. Koller, S.D. Kristensen, J. Niebauer, D.J. Richter, P.M. Seferovic, D. Sibbing, G.G. Stefanini, S. Windecker, R. Yadav, M.O. Zembala, ESC Scientific Document Group, ESC/EACTS Guidelines on myocardial revascularization, Eur. Heart J. (2018 Aug 25) (2018), https://doi.org/10.1093/eurheartj/ehy394 (Epub ahead of print).

[4] C. Kaiser, S. Galatius, P. Erne, F. Eberli, H. Alber, H. Rickli, G. Pedrazzini, B. Hornig, O. Bertel, P. Bonetti, S. De Servi, H.P. Brunner-La Rocca, I. Ricard, M. Pfisterer, BASKET–PROVE study group. Drug-eluting versus bare-metal stents in large coronary arteries, N. Engl. J. Med. 363 (24) (2010 Dec 9) 2310–2319.

[5] T. Palmerini, G. Biondi-Zoccai, D. Della Riva, C. Stettler, D. Sangiorgi, F. D'Ascenzo, T. Kimura, C. Briguori, M. Sabatè, H.S. Kim, A. De Waha, E. Kedhi, P.C. Smits, C. Kaiser, G. Sardella, A. Marullo, A.J. Kirtane, M.B. Leon, G.W. Stone, Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis, Lancet 379 (9824) (2012 Apr 14) 1393–1402.

[6] M. Valgimigli, A. Patialiakas, A. Thury, E. McFadden, S. Colangelo, G. Campo, M. Tebaldi, I. Ungi, S. Tondi, M. Roffi, A. Menozzi, N. de Cesare, R. Garbo, E. Meliga, L. Testa, H.M. Gabriel, F. Airoldi, M. Ferlini, F. Liistro, A. Dellavalle, P. Vranckx, C. Briguori, ZEUS Investigators, Zotarolimus-eluting versus bare-metal stents in uncertain drug-eluting stent candidates, J. Am. Coll. Cardiol. 65 (8) (2015 Mar 3) 805–815.

[7] S. Ariotti, M. Adamo, F. Costa, A. Patialiakas, C. Briguori, A. Thury, S. Colangelo, G. Campo, M. Tebaldi, I. Ungi, S. Tondi, M. Roffi, A. Menozzi, N. de Cesare, R. Garbo, E. Meliga, L. Testa, H.M. Gabriel, M. Ferlini, P. Vranckx, M. Valgimigli, ZEUS Investigators, Is bare-metal stent implantation still justifiable in high bleeding risk patients undergoing percutaneous coronary intervention? A Pre-Specified Analysis From the ZEUS Trial. JACC Cardiovasc Interv. 9 (5) (2016 Mar 14) 426–436.

[8] Gargiulo G, Patialiakas A, Piccolo R, Thury A, Colangelo S, Campo G, Tebaldi M, Ungi I, Tondi S, Roffi M, Menozzi A, de Cesare N, Garbo R, Meliga E, Testa L, Gabriel HM, Ferlini

M, Liistro F, Dellavalle A, Vranckx P, Briguori C, Windecker S, Valgimigli M. Impact of angiographic coronary artery disease complexity on ischemic and bleeding risks and on the comparative effectiveness of zotarolimus-eluting vs. bare-metal stents in uncertain drug-eluting stent candidates. Int. J. Cardiol. 2018 Oct 2. pii: S0167–5273(18)34840-X. https://doi.org/10.1016/j.ijcard.2018.09.120. [Epub ahead of print]. Cross-reference.

[9] K.H. Bønaa, J. Mannsverk, R. Wiseth, L. Aaberge, Y. Myreng, O. Nygård, D.W. Nilsen, N.E. Kløw, M. Uchto, T. Trovik, B. Bendz, S. Stavnes, R. Bjørnerheim, A.I. Larsen, M. Slette, T. Steigen, O.J. Jakobsen, Ø. Bleie, E. Fossum, T.A. Hanssen, Ø. Dahl-Eriksen, I. Njølstad, K. Rasmussen, T. Wilsgaard, J.E. Nordrehaug, NORSTENT Investigators, Drug-eluting or bare-metal stents for coronary artery disease, N. Engl. J. Med. 375 (13) (2016 Sep 29) 1242–1252.

[10] P. Urban, I.T. Meredith, A. Abizaid, et al., Polymer-free drug-coated coronary stents in patients at high bleeding risk, N. Engl. J. Med. 373 (2015) 2038–2047.

[11] O. Varenne, S. Cook, G. Sideris, S. Kedev, T. Cuisset, D. Carrié, T. Hovasse, P. Garot, R. El Mahmoud, C. Spaulding, G. Helft, J.F. Diaz Fernandez, S. Brugaletta, E. Pinar-Bermudez, J. Mauri Ferre, P. Commeau, E. Teiger, K. Bogaerts, M. Sabate, M.C. Morice, P.R. Sinnaeve, SENIOR Investigators, Drug-eluting stents in elderly patients with coronary artery disease (SENIOR): a randomised single-blind trial, Lancet 391 (10115) (2018) 41–50.

[12] F. Alfonso, L.J. Jiménez-Borreguero, Optimizing dual antiplatelet therapy duration after myocardial infarction: evidence-based, precision, or personalized medicine? Eur. Heart J. 38 (14) (2017 Apr 7) 1056–1059.