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High bleeding risk patients: one size does not fit all

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In the past, patients deemed to have a high bleeding risk (HBR) were treated with bare metal stent (BMS) implantation and a short duration of dual antiplatelet therapy (DAPT) to lower the risk of stent thrombosis. Drug-coated stents (DCS) with a short duration of DAPT were introduced to maintain safety and improve efficacy, with less restenosis and fewer cardiovascular events when compared to BMS. The BioFreedom™ (Biosensors International, Singapore), a polymer-free stent with the abluminal Biolimus A9™ drug, was among the first DCS to be tested against BMS in HBR patients who received DAPT for only 30 days. LEADERS FREE (LF) was the pivotal randomised clinical trial (RCT) of DCS versus BMS, followed by the LEADERS FREE II (LF II) confirmatory US registry[1,2]. In this issue of EuroIntervention, Marquis-Gravel et al pooled the data from these two studies comparing DCS and BMS in the subgroup of patients satisfying the Academic Research Consortium (ARC)-HBR criteria utilising propensity-score modelling[3].

Article, see page 240

Their analysis showed that the primary safety endpoint, a composite of cardiac death, myocardial infarction (MI), or stent thrombosis at one year, met non-inferiority of the DCS to BMS. Further, superiority of DCS over BMS was demonstrated for the primary effectiveness endpoint of target lesion revascularisation (TLR).

DCS offer the possibility of eliminating the drawbacks of polymers such as inflammation and delayed healing. Preclinical studies have shown a reduction of intimal proliferation compared to BMS[4]. Do the results of the LF and LF II studies demonstrating net superiority of DCS over BMS make the BMS obsolete and the DCS the default stent for HBR patients? The Gazelle™ BMS (Biosensors), which was used as a control in the LF RCT, a first-generation BMS with thicker strut thickness, may be considered a weak comparator when compared to second-generation BMS. Would the superiority of the DCS in the LF study remain if the comparator were a second-generation BMS with thinner struts and improved stent design or a BMS with passive coating? While DCS may be more effective than BMS, their lack of polymer and control of drug elution may result in inferior efficacy when compared to second-generation DES. The BioFreedom USA study reported angiographic late lumen loss of 0.32±0.53 mm with the

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BioFreedom DCS at nine months, which is more than two times higher than that of second-generation DES[5]. In the first head-to-head study of DCS versus DES in HBR patients, the Resolute Onyx™ zotarolimus-eluting stent (Medtronic, Minneapolis, MN, USA) was non-inferior for the primary clinical endpoint at one year and with significantly better angiographic outcomes/success[6]. Onyx ONE Clear extends the findings of the Onyx ONE Global RCT to HBR patients treated with one month of DAPT in the USA and Japan[7]. Although not powered for superiority in patients with acute coronary syndrome (ACS), there was a lower rate of MI in the DES group than in the DCS group. When DCS were compared with the ultrathin-strut, biodegradable polymer sirolimus-eluting Orsiro stent (Biotronik, Bülach, Switzerland), DCS did not meet the criteria for non-inferiority because of higher TLR rates in the DCS arm in a non-HBR population[8]. Recently, several DES with durable and biodegradable polymers with a short duration of DAPT were proven to be safe and effective in HBR patients[9].

Of note, the BioFreedom stent is still awaiting approval for marketing in the USA, while DES with both durable and biodegradable polymers have received labelling for the HBR population. Of interest is the question of whether there is a preferred DES or a class effect for all second-generation DES for HBR patients. Unfortunately, with the lack of powered head-to-head RCTs with the same DAPT regimen and HBR criteria, along with the shift towards study designs with more objective performance goals, this question cannot be answered. Another intriguing device for the HBR population is the drug-coated balloon (DCB), with the premise of leaving nothing behind and eliminating prolonged DAPT for prevention of stent thrombosis. Studies comparing DES and DCB for HBR populations are being designed and can also benefit from uniform HBR criteria.

Since the initiation of the LF studies there has been a plethora of risk-score definitions, with over 27 variations, the majority of which focus on bleeding risk, along with some on ischaemic risk. The myriad of HBR criteria in clinical trials spanned from one (older age) to over 13, and the number of criteria per patient also varies across the HBR studies. As a result, the number of Bleeding Academic Research Consortium 3 or 5 bleeding events in these studies ranges from 7.2% in the LF study to 2.2% to 4.6% in the other DES HBR studies. Of note, none of the studies examining DES in HBR patients adopted the ARC-HBR criteria published in 2019. In the present study, the authors take pride in validating the ARC-HBR criteria using retrospective data from the patient cohorts from LF and LF II. Although the validity of the methodology of using randomised and registry data could be challenged, the investigators performed sensitivity analysis to mitigate this limitation. Updated, unified ARC-HBR criteria are imperative for the interpretation of the HBR studies, but they may come too late, as many of the HBR studies have already been launched.

The quest for optimal patients with HBR is ongoing with many remaining questions: what drug should be dropped, aspirin or $P2Y_{12}$ inhibitor? What is the optimal duration of DAPT for HBR patients? How long should the patients in these trials be followed? Can the risk score accurately detect late events? How should patients with atrial fibrillation and ACS be treated, and how do we account for the risk of ischaemic events? The HBR studies so far have taught us that the patients enrolled into these studies had significant ischaemic events not related to bleeding. In the LF studies and other HBR studies, patients meeting ARC-HBR criteria also had a significantly higher risk of ischaemic events such as cardiac death, MI, and stent thrombosis than patients not meeting those criteria. Although ARC-HBR criteria are now validated, they are incapable of differentiating between bleeding and ischaemic risk. Future risk scores should focus on stratifying ischaemic and bleeding risk, which will help to identify subsets of patients who would benefit from $P2Y_{12}$ inhibitor monotherapy after a short DAPT period. Balancing both risks is of prime importance after percutaneous coronary intervention. It is time to acknowledge that risk scores and trials can give us only limited guidance as one size will not fit all. There is a need to focus on individualisation of the DAPT duration and the stent choice for the HBR patient population.

Conflict of interest statement

R. Waksman – advisory board: Abbott Vascular, Amgen, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips, Pi-Cardia Ltd; consultant: Abbott Vascular, Amgen, Biotronik, Boston Scientific, Cardioset, Cardiovascular Systems Inc., Medtronic, Philips, Pi-Cardia Ltd, Transmural Systems; grant support: AstraZeneca, Biotronik, Boston Scientific, Chiesi; speakers bureau: AstraZeneca, Chiesi; investor: MedAlliance, and Transmural Systems. The other author has no conflicts of interest to declare.

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Corrigendum

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Corrigendum to: Highlights from the 2020 ACC/AHA guidelines on valvular heart disease

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Figure 1 – 29 April 2021

Information on the figure has been corrected and is available online.