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Will LEADERS-FREE change my practice? A randomised double-blind comparison of the BioFreedom™ drug-coated stent vs. the Gazelle™ bare metal stent in patients at high bleeding risk using a short (1 month) course of dual antiplatelet therapy

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Introduction to the session

The aim of the article is to capture the session at EuroPCR 2016, communicate the analysis of the trialist, and report the views expressed in the interactive discussion. The article does not constitute an independent review of the topic by the authors. The session focused on whether the LEADERS-FREE randomised trial will change clinical practice[1].

Background: what was known before LEADERS-FREE

A large body of evidence consistently proved superiority of drug-eluting stents (DES) over bare metal stents (BMS) in terms of antirestenotic effectiveness[2]. In 2006, early-generation DES were associated with an increased risk of very late stent thrombosis (ST) occurring beyond cessation of dual antiplatelet therapy (i.e., >1 year after stent implantation). Long-term DAPT was, therefore, implemented to prevent very late ST after early-generation DES implantation. Extended DAPT duration is associated with an increased bleeding risk, which in turn has been shown to affect prognosis negatively[3]. During the last decade, the introduction of new-generation DES has eliminated the exacerbated risk of very late ST observed with earlier devices[2]. Recent lines of evidence support early DAPT cessation among patients treated with new-generation DES. Notwithstanding – before the LEADERS-FREE trial – limited evidence was available on patients at high bleeding risk (HBR) undergoing DES implantation, since these patients were not included in pivotal DES trials due to the recommended duration of DAPT. The ZEUS trial has been the only trial including a pre-specified subgroup of HBR patients treated with 30-day DAPT after stent implantation. It showed superiority of Endeavor® zotarolimus-eluting stents (Medtronic, Minneapolis, MN, USA) as compared with BMS in terms of the primary endpoint – a composite of all-cause death, myocardial infarction (MI), and target vessel revascularisation[4]. Based on available evidence, 2014 European

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guidelines on myocardial revascularisation recommend considering short DAPT duration (<6 months) after DES implantation in HBR patients (class IIb, level of evidence A). However, a recent survey indicates that HBR remains the most frequent reason for BMS implantation in current clinical practice[5].

Trial analysis: summary of the trialist's critical review

The LEADERS-FREE is a randomised trial directly comparing the BioFreedom™ polymer-free biolimus-eluting stent (PF-BES; Biosensors, Morges, Switzerland) with BMS in HBR patients treated with one-month DAPT. The trial had two hypotheses: non-inferiority for safety (composite of cardiac death, MI and definite/probable ST) and superiority for efficacy (clinically indicated target lesion revascularisation), tested sequentially to avoid splitting the alpha error. Inclusion criteria were quite broad for an HBR population. Beyond patients with known risk factors for bleeding, the trial also included patients with planned major surgery and anticipated poor compliance to DAPT. The result was a study population combining pure HBR patients as well as patients who did not want or could not adhere to extended DAPT. Such a patient population represents almost 40% of patients treated in routine clinical practice. A total of 2,466 patients were randomised in the trial. Unfortunately, a screening log was not recorded and therefore it is unknown how many patients fulfilling the inclusion criteria were not randomised. Considering an average recruitment of 36 patients/site over 18 months, it is likely that many HBR patients were not randomised. Looking at clinical indication to PCI, it is notable that over 57% of patients had stable coronary artery disease, 15% had unstable angina, 23% had non-ST-segment elevation MI, and only less than 5% had ST-segment elevation MI (STEMI) at baseline. This distribution suggests that a selection bias might have negatively affected the inclusion of STEMI patients.

The primary findings of the trial demonstrated superiority of PF-BES over BMS for both the primary safety endpoint (9.4% vs. 12.9%, p non-inferiority <0.0001, p superiority=0.005) and the primary efficacy endpoint (5.1% vs. 9.8%, p<0.0001). The event rate was higher than expected as it relates to the primary safety endpoint (predicted 8%, observed 12.9%) – an uncommon scenario in contemporary trials that provided additional power to the LEADERS-FREE trial. The individual components of the primary safety endpoint were all three numerically lower in PF-BES as compared to BMS-treated patients. However, only MI occurred significantly less frequently with PF-BES than BMS (6.1% vs. 8.9%, p=0.01), while cardiac death (4.2% vs. 5.3%, p=0.19) and definite/probable ST (2.0% vs. 2.2%, p=0.70) did not differ significantly between groups. Stratified analyses of the primary safety and efficacy endpoints showed consistent findings across major pre-specified subgroups. With respect to safety, a significant interaction between treatment effect and acute coronary syndromes (ACS) at presentation was observed. Patients with ACS appeared to benefit most from treatment with PF-BES as compared to patients without ACS at baseline (p for interaction=0.04). Conversely, as it relates to efficacy, stratified analyses showed some paradoxical findings with significant interactions between treatment effects and absence of renal failure (p interaction=0.02), CRUSADE score <35 (p interaction=0.02), and no history of anaemia/transfusion/bleeding leading to hospitalisation (p interaction=0.03). These paradoxical findings might be explained by competing risks with respect to mortality. This could be clarified by analysing mortality rates in these subgroups, as a markedly higher risk of mortality may explain a lower risk of target lesion revascularisation.

Overall, the LEADERS-FREE provides clear answers on the tested hypotheses. However, it remains unanswered whether one-month DAPT represents the optimal DAPT duration in this selected patient population. Moreover, it is unknown whether LEADERS-FREE findings are applicable to other new-generation DES.

Discussion and audience interaction

The discussion focused on the two key issues.

First, the mechanistic explanation for the safety benefit associated with PF-BES. The degree of benefit was largely driven by MI rather than ST. This may be explained by the marked antirestenotic effectiveness of PF-BES compared with BMS. In-stent restenosis is known to present with acute coronary syndromes in a significant proportion of patients. Notably, a sensitivity analysis of LEADERS-FREE showed that type 4c MI (i.e., related to in-stent restenosis) differed significantly between stent types.

Second, it was largely debated whether one-month DAPT in HBR patients is a strategy applicable only after PF-BES implantation or whether it is translatable to other new-generation polymer-coated DES. In this respect, it was also a matter of debate whether short DAPT duration is favoured by the absence of polymer coatings or by drug-release kinetics (i.e., fast elution with PF-BES coupled with high lipophilicity of biolimus). Many cardiologists attending the session apply a similar strategy with other contemporary DES in their routine clinical practice. However, there was general consensus that the interpretation of LEADERS-FREE should be fair and evidence-based. As cardiologists we do have the experience with pharmaceutical trials (e.g., statins, ACE inhibitors, etc.) and are used to interpreting findings of these studies as compound-specific. Similarly, we should interpret the LEADERS-FREE findings as device-specific.

The Chairperson's conclusion: where do we stand now?

Now, given all this, will LEADERS-FREE change my practice? Yes, this pivotal randomised trial is an extinction event for BMS. Based on the convincing findings of LEADERS-FREE, it would be surprising if BMS will still be used two years from now.

Conflict of interest statement

G. Stefanini has received speaker/consultant fees from B. Braun and Boston Scientific. M. Behan has received travel grants from Biosensors and consultancy fees from Medtronic. M. Valgimigli has received a research grant from Medtronic for the ZEUS trial

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