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Scaffold thrombosis: what is to blame?

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Bioresorbable scaffolds (BRS) were originally designed on the premise that the absence of a permanent metallic cage would mitigate late adverse events such as late stent thrombosis and restenosis, and would fully restore vasomotor and endothelial function of the vessel, inducing luminal gain and atherosclerotic plaque passivation[1]. Meanwhile, drug-eluting-stent (DES) technology continued to improve the short- and long-term outcomes of percutaneous coronary intervention (PCI) and challenged the merits of BRS. Absorb (Abbott Laboratories, Inc.), a first-generation poly-L-lactic acid (PLLA)-based BRS, was approved for marketing and taken to trials against the best-in-class DES. Whilst the initial results at one-year follow-up of BRS against second-generation metallic everolimus-eluting stents (EES) were comparable, with a large non-inferiority margin[2], the enthusiasm for BRS was lessened when the three-year outcomes of the ABSORB II trial demonstrated an increased incidence of scaffold thrombosis (ST), with two thirds occurring after one year[3]. Furthermore, a meta-analysis of four randomised trials showed higher rates of target lesion failure (TLF) and ST with BRS through three years of follow-up when compared to EES[4]. Consequently, the U.S. Food and Drug Administration (FDA) issued a warning and the European Society of Cardiology (ESC) downgraded BRS to Class III recommendations and limited their use outside of clinical studies[5]. Eventually, because of low commercial sales, Abbott pulled Absorb off the market in September 2017, and other ongoing BRS programmes ceased or slowed their activities in the field. One can argue that a second chance should have been given to the field with a second generation of BRS technology similar to the evolution of DES. But perhaps the lack of clarity for the cause of failure, manufacturing challenges, and doubts for the need of such technology weighed against pursuing a second generation of the BRS. Perhaps the main concern was the occurrence of late and very late ST. The question is whether blame should be attributed to the device, the operator, or selection of patients with low adherence to dual antiplatelet therapy (DAPT).

Mechanistically, thicker struts, limited expansion and apposition of the scaffold to the vessel wall, and incomplete resorption leading to "scaffold dismantling" were among the various factors attributed to higher hazards of early and late ST[6]. Thus, foreseeing delayed healing inherent to the design, the question of longer

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DAPT duration to be prescribed remains unknown, with recommendations to extend DAPT to at least three years. Therefore, we value the contribution of Azzalini et al in providing insight on the importance of DAPT duration in patients receiving BRS published in this issue of EuroIntervention[7]. The study presents an individual patient data pooled analysis from four ABSORB randomised trials and one prospective ABSORB EXTEND registry, assessing optimal DAPT duration following BRS implantation.

Article, see page 981

The authors found that DAPT interruption was indeed associated with higher adjusted risks of myocardial infarction (MI) and ST during the first year of BRS implantation. Intriguingly, DAPT use did not impact on the hard clinical endpoints between one and three years. Of note, the incidence of permanent DAPT discontinuation increased from 2.5% within the first six months to 16.5% between 6 and 12 months after the index procedure; however, the reason for the interruption was not documented, and it could be within the natural compliance of DAPT in patients who receive DES. Furthermore, there was a drastic drop in DAPT usage, from 91.6% at one year to 47.3%, at three years. Interestingly, DAPT use did not significantly alter all-cause death and bleeding events, which requires further explanation with regards to the quality of the adjudication of the events in some of the registries that contributed to the analysis. Moreover, spline analysis showed that the protective effect of DAPT to mitigate the risk of MI and ST was limited to the first 4-5 months following device implantation.

Undoubtedly, the major setback for BRS was the augmented risk of late and very late ST. Although numerous factors have been implicated for suboptimal clinical performance, the utmost question remains: what is to blame? Is it the strut thickness (≈156 μm), procedural techniques, lack of systematic intravascular imaging guidance, leaving underexpanded scaffold, device design (i.e., polymer biocompatibility, slower-than-intended polymer degradation), or suboptimal DAPT duration? All these factors can impact on early and late ST. While optimal scaffold deployment using imaging and high-pressure balloon could mitigate early ST (<30 days), very late ST (>1 year) is more troubling because it is not clear whether it could be reduced by altering the deployment technique. The device-associated factors such as scaffold discontinuity, followed by malapposition and dismantling of the polymer in the vessel wall, and chronic inflammation leading to neoatherosclerosis, were the foremost mechanisms for very late ST depicted by a registry study using optical coherence tomography (OCT)[8]. Azzalini et al advance our knowledge in regard to the use of DAPT, which did not seem to impact on ST beyond one year[7]. Further, occurrence of ST even in the first year despite DAPT solidifies the reasoning for the role of additional device-associated factors. Although aggressive lesion preparation and implantation technique (predilatation, vessel sizing and selection, and post-dilatation) were independently associated with freedom from TLF and ST[9], they are unlikely to be the fundamental saviour of BRS. Nevertheless, even with excellent stent deployment, the core device design appears to be at fault for late events.

In addition to downgrading routine use of BRS to Class III, the ESC recommended a minimum of three years of DAPT for all the patients who underwent BRS implantation. While we agree with these recommendations for the PLLA-based BRS, generalising them to all BRS platforms irrespective of the polymer composition, scaffold design, and strut thickness should be reconsidered. For example, a study of more than 1,000 patients who received the Magmaris (Biotronik AG) magnesium resorbable scaffold (MRS) and were followed up to two years in the BIOSOLVE IV registry, showed early or late thrombosis rates similar to the best-in-class DES with only one year of DAPT (Torzewski J, Safety and performance of Magmaris at 24-month follow-up of BIOSOLVE-IV. Poster presented at virtual EuroPCR, May 18, 2021). Further, the MRS system completely resorbed within 12 months, so there is no justification for three years of DAPT for this system. Likewise, the Absorb Esprit BVS System (Abbott), a PLLA-based scaffold, showed adequate safety and efficacy for the below-the-knee intervention in a prospective, non-randomised pilot study of 55 patients with critical limb ischaemia, where BRS deployment was 100% successful, with a 90.7% freedom from target lesion revascularisation rate at 60 months[10]. The MOTIV bioresorbable scaffold (REVA Medical), which uses a thinner 95 μm Tyrocore-based platform, is currently under clinical investigation[11]. Further studies with the latest-generation BRS are eagerly awaited.

Preliminary studies from China support that second-generation PLLA-based scaffolds are non-inferior to DES, but these data need to be corroborated in larger, definitive studies such as ABSORB III. The problem with such studies is that DES technology has also improved, and short DAPT durations support the safety of these second and third generations of DES, posing an even larger challenge for the upcoming second-generation BRS technology. Confidence in BRS would only be regained in a head-to-head trial with an adequate non-inferiority margin against the best-in-class DES, with similar DAPT duration and without excess risk of ST or any significant trade-off between the devices. While the advancement in technology is still ongoing, looking back, we acknowledge the initial apprehensions for ST related to early-generation DES. If DES had been abandoned in the first place, we would not have reached the current "standard of care" second-generation DES. Similarly, a more insightful preclinical investigation of newer scaffold technology may allow better refinement and overcome the drawbacks with a greater chance of success. What we should look for is the second generation of the BRS technology, specifically the thinner strut of the new magnesium alloy, which is current being tested in clinical feasibility studies, and thinner-strut Poly-d-l-lactic acid (PDLLA)-based BRS technology that is being developed in China and India. Finally, the utility of BRS technology in 2022 and beyond remains in question. Restoration of vessel vasoreactivity may not be enough to justify the efforts in developing new BRS platforms. The burden is on the industry that promotes the technology to deliver not only equivalence to DES, but superiority, with respect to reduction of major

adverse cardiac events over time. This would resurrect the interest and enthusiasm for BRS technology.

Conflict of interest statement

R. Waksman is a member of the Advisory Boards of Abbott Vascular, Boston Scientific, Medtronic, Philips IGT, and Pi-Cardia Ltd.; he is a consultant to Abbott Vascular, Biotronik, Boston Scientific, Cordis, Medtronic, Philips IGT, Pi-Cardia Ltd., Swiss Interventional Systems/SIS Medical AG, Transmural Systems Inc., and Venous MedTech. He received grant support from AstraZeneca, Biotronik, Boston Scientific, Chiesi, Medtronic, Philips IGT; is part of the Speakers' Bureau of AstraZeneca; and is an investor in MedAlliance and Transmural Systems Inc. The other author has no conflicts of interest to declare.

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