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EDITORIAL COMMENT

Who Is Thrombogenic: The Scaffold or the Doctor? Back to the Future!*

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Twenty years ago, Drs. Patrick Serruys and Carlo Di Mario wrote an editorial in *Circulation* titled "Who Was Thrombogenic: The Stent or the Doctor?" (1), that discussed optimal stent implantation technique. They highlighted the critical roles played by both the use of intravascular ultrasound to optimize stent implantation and the administration of dual antiplatelet therapy (DAPT) to prevent metal stent thrombosis (ST) (2). These suggestions and considerations were particularly pertinent at the time, and although the designs of metallic stents have evolved to make the technology more forgiving, these factors are still valid and must be seriously revisited when considering the use of current early-generation bioresorbable scaffolds.

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In this issue of *JACC: Cardiovascular Interventions,* Lipinski et al. (3) present a systematic review and meta-analysis evaluating the risk of ST following implantation of the Absorb bioresorbable vascular scaffold (BVS) (Abbott Vascular, Santa Clara, California) when compared with implantation of second-generation drug-eluting stents (DES). The authors performed a study-level meta-analysis of 25 studies from 26 publications that included 10,510 patients with a mean follow-up of 6.4 ± 5.1 months. Absorb BVS was implanted in 8,351 patients with an average of 1.22 ± 0.16 treated lesion/patient, whereas 2,159 patients received metallic DES. In this study population, 59% of patients underwent percutaneous coronary intervention for acute coronary syndromes (ACS), including BVS use in more complex lesions, with only 16% of lesions being American Heart Association/American College of Cardiology class A, 37% of lesions in class B1, 28% in class B2, and 19% in class C.

Amongst 8,183 patients receiving a BVS, death occurred in 0.8% of patients, cardiovascular death in 0.6% of patients, major adverse cardiovascular events in 4.1% of patients, myocardial infarction in 2.1% of patients, target vessel revascularization in 2.7% of patients, target lesion revascularization in 2.0% of patients, and definite or probable ST in 1.2% of the overall study population. There were 9 studies evaluating outcomes of BVS versus DES comparing 1,948 patients who received a BVS with 2,150 patients who received a DES. No differences were found between groups with regard to cardiovascular death, major adverse cardiovascular events, target lesion revascularization, or target vessel revascularization. It is not very clear from this study what the actual incidence of ST in patients treated with DES was, but the reported 1.2% overall incidence of ST in BVS treated patients is far from being a bad result! However, a detailed statistical analysis showed that definite or probable ST was significantly increased following placement of a BVS compared with a DES (odds ratio [OR]: 2.06 [95% confidence interval (CI): 1.07 to 3.98], $I^2 = 0\%$; $p = 0.03$), with a trend toward an increase in definite scaffold thrombosis (OR: 1.91 [95% CI: 0.82 to 4.46]; $p = 0.13$) and ST at 1 month (OR: 2.02 [95% CI: 0.69 to 5.93]; $p = 0.20$).

These findings did not translate into an increase in cardiovascular or all-cause mortality; thus, although reassuring, the study should not temper our efforts to lower the rates of ST. This objective can be achieved

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because the doctor is in control of many of the aspects that predispose to ST (4).

The number 1 procedural characteristic that stands out from this study is the fact that post-dilation was performed in only 52% of lesions. Aware of the high compliance of the balloon on which the Absorb BVS is mounted, we are surprised that post-dilation was not performed in a greater number of lesions. The potential sequelae of this procedural omission is further multiplied in the absence of intravascular imaging guidance, with low reported usage rates in the larger published registries that were included in this meta-analysis (5,6). To achieve homogenous scaffold expansion and apposition, in the absence of routine intravascular ultrasound or optical coherence tomography evaluation, high-pressure noncompliant balloon post-dilation needs to be almost universally performed. The fact that there was no correlation between post-dilation and ST does not negate a role of post-dilation for the following reasons:

1. This was a study-level analysis, and lesion-specific details have not been analyzed (e.g., balloon/artery ratio, noncompliant balloon use, maximal pressure of balloon inflation); therefore, the general observations may be difficult to interpret.
2. By chance, post-dilation may have been performed in lesions that did not need post-dilation and not performed in lesions that needed post-dilation.
3. Considering that ST occurred more frequently in ACS (which represented the majority of the study population), we need specific patient-level data regarding post-dilation in this subset.

Along these lines, we are not surprised that second-generation DES performed well in comparison with BVS. Current DES are manufactured with thin struts in combination with drug-delivery systems promoting rapid endothelialization, and therefore, they are more forgiving toward procedural optimization. The fact that the authors reported a higher ST rate for Absorb BVS when compared with DES in patients with ACS highlights the need for specific improvement in this subset of patients. The specific features of current Absorb BVS with stent struts that are 157 um thicker and also wider when compared to DES (2.5- and 3.0-mm BVS: 190.5 μm; 3.5-mm BVS: 215.9 μm) results in greater protrusion (both length and height) of struts causing loss of laminar flow, with areas of oscillatory shear stress promoting platelet activation (7). A report (8) failing to demonstrate a relationship between strut thickness and ST does not negate the opposite findings collected over the past decades from both experimental (7) and clinical studies (9,10). These physical attributes demand the scaffold to be fully post-dilated, embedding the struts deeply in the wall of the vessel to avoid any malapposition and favoring rapid endothelization. Additionally, it is of the utmost importance that the largest possible lumen cross-sectional area is achieved. Many studies (with both metal stents and scaffolds) identify a small final lumen cross-sectional area as a predictor of ST (11).

DAPT following stent implantation is mandatory to reduce the risk of ST (12). The fact that ST occurred in 4 patients treated with BVS who stopped DAPT prematurely is not a surprise and is not a hallmark of increased dependency of these novel devices upon DAPT. Indeed, no metal stent has been immune to ST when DAPT has been stopped prematurely (11).

The recent Absorb Japan study (13) reported a similar 1.5% thrombosis rate with both Absorb and everolimus-eluting stents (EES). A small residual in-segment diameter was present in the 6 cases of ST (4 BVS and 2 EES). This ST rate was confirmed by the TROFI II (Comparison of the Absorb Everolimus Eluting Bioresorbable Vascular Scaffold System With a Drug-Eluting Metal Stent [Xience] in Acute ST-Elevation Myocardial Infarction) trial (14) that reported 1 ST event (1.1%) in the BVS group compared with 0 cases in the EES group. An important additional finding from the TROFI II study was that lesions treated with BVS demonstrated nearly complete arterial healing, comparable to that of EES at 6 months.

This debate highlights how the Virchow triad for thrombogenesis can be almost completely controlled by the operator. The doctor can optimize: 1) the lumen with appropriate pre- and post-dilation (with judicious use of rotational atherectomy or scoring balloons as required); and 2) the flow by selecting the appropriate vessel (with adequate run-off, supplying viable myocardium) to be stented. However, the third element of the triad—the optimal modulation of blood thrombogenicity with antiplatelet therapy—remains uncertain. Despite the recent findings of the ADAPT-DES (Platelet Reactivity and Clinical Outcomes After Coronary Artery Implantation of Drug-Eluting Stents) study (15) showing a relationship between ST and the degree of platelet inhibition, it is still unclear how best to individualize (regimen and duration) antiplatelet therapy.

The important final message we should take away from this study is: “Absorb BVS may have a higher

risk of ST, but this can be overcome by the operator who is in charge to ensure optimal implantation". Looking forward, there is no darkness or uncertainty in the tunnel of ST. We are in control and we can shed the light!

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