JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 8, NO. 1, 2015

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2014.11.010

EDITORIAL COMMENT

Bioresorbable Drug-Eluting Stents

An Immature Technology in Need of Mature Application*

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Bioresorbable coronary stents represent a breakthrough technology promising to enhance the outcomes of patients treated by percutaneous intervention (1). The benefits of bioresorbable stents are intuitive. Indeed, all else being equal, most physicians and patients would agree that a stent that disappears after its useful function is served would be a preferable device to a permanent metallic implant. Moreover, as suggested by recent findings, bioresorbable stents offer additional potential benefits deriving from both restoration of normal vasomotor tone over the entire stented segment and an increase in lumen caliber due to positive vessel remodeling associated with stent degradation (1). These latter benefits might translate into improvements in coronary physiology and a reduction in angina symptom burden.

To date, the medical device industry has pursued 2 principal strategies in the development of bioresorbable stents: 1 based on backbones comprised of lactic acid polymers, and another using magnesium-based scaffolds. At present, the former development track is more advanced, and 2 lactic acid-based devices have received CE (Conformité Européene) mark approval for use in Europe: the everolimus-eluting ABSORB stent (Abbott Vascular, Santa Clara, California) and the novolimus-eluting DESolve stent (Elixir Medical Corporation, Sunnyvale, California). Although neither device is currently approved for use in the United States, the ABSORB stent may receive approval from the U.S. Food and Drug Administration by the first quarter in 2016.

An important requirement for any new stent technology should be demonstration of noninferiority versus contemporary metallic stents in the initial phase after implantation (2). This is a sine qua non, an essential condition, for their adoption as well as for testing potential late benefit. Until recently, experience of clinical outcomes with these devices was limited to reports from single-arm studies enrolling relatively well-selected patients with comparatively straightforward lesion morphology (1). Accordingly, although the performance of these devices seemed encouraging, the external validity of these observations remained unclear.

Recent months have seen the publication of important additional data with these devices. First, an increasing body of data from patients treated outside of the setting of carefully-conducted clinical trials has become available. Although generally favorable overall clinical outcomes have been reported, in the 3 registries that enrolled more than 100 patients each, rates of stent thrombosis were higher than the rates we have become accustomed to after stenting with metallic drug-eluting stents (DES) (3–5). Second, preliminary results from the first randomized trial comparing bioresorbable stents with everolimus-eluting metallic DES have been reported (6). Although the trial was not powered to detect differences in clinical events, 12-month outcome data showed broadly comparable outcomes between the treatment groups. Moreover, although the overall rate of stent thrombosis was low, the 2 definite stent thrombosis events in the trial occurred in the bioresorbable stent arm.

Against this background, the report from Brugaletta et al. (7) in this issue of *JACC: Cardiovascular Interventions* represents a further important contribution

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

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to the growing debate about this technology. The investigators focused on the setting of stent implantation for ST-segment elevation myocardial infarction.

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This is a potentially attractive indication for bioresorbable stents, as lesions are often less calcified and more focal and patients are typically younger than for other treatment indications (8). However, stent sizing—a particularly important issue with bioresorbable stents due to restricted post-dilation capacity with certain devices—is more challenging in primary angioplasty. The study design is observational, combining data from 2 separate datasets and comparing clinical outcomes with everolimus-eluting bioresorbable stents against those with everolimus-eluting metallic stents and those with uncoated metallic stents. Propensity-score matching was used in an attempt to adjust for differences in baseline patient risk between the treatment groups. The main finding was that, in terms of target lesion failure, comparable results were found across the treatment groups. However, the rate of definite stent thrombosis was numerically higher with bioresorbable stents compared with DES at 12 months (1.7% vs. 0.7%), driven primarily by a higher rate of events in the first 30 days (1.4% vs. 0.3%).

In interpreting the data, a number of limitations must be considered. First, the presented comparison is nonrandomized, so observed outcome differences may be due to factors other than the type of stent received. In particular, the bioresorbable stent group comprised consecutive patients enrolled in a registry study; the control stent group was derived from a randomized clinical trial. No method of adjustment can fully account for the resultant differences in baseline risk. Second, the study is considerably underpowered for comparison in relation to clinical endpoints in general and rarely-occurring events such as stent thrombosis in particular. Third, although interesting, the inclusion of a comparison with bare-metal stents might be seen as superfluous, as these stents are no longer recommended for use in patients undergoing primary angioplasty (9). Finally, although propensity score matching by the investigators was generally well performed, the model used might have been more carefully constructed. Propensity score modeling is based on estimating the causal association of pre-treatment variables with interventions received, and only characteristics that might have influenced treatment selection should be entered (10). In particular, procedural characteristics (e.g., stent length and diameter) should not be used.

What are the key messages from the study of Brugaletta et al. (7) for clinicians in practice? First, bioresorbable stents in patients undergoing intervention in the setting of ST-segment elevation myocardial infarction seem to be associated with similar clinical outcomes to standard-of-care metallic DES at 12 months. This is certainly encouraging and needs to be confirmed by data from ongoing randomized clinical trials, including those examining device use in the specific setting of myocardial infarction (TROFI-II [11] and ISAR-ABSORB MI [12]). At the same time, we must realize that we know very little of the late outcomes of patients treated with bioresorbable stents. Enthusiasts expect better outcomes due to favorable effects on vasomotion and positive remodeling of the treated vessel. Sceptics express concerns about the consequences of possible inflammatory reactions associated with bioresorption during a period when protection is no longer offered by drug elution. The reality can only be revealed by analysis of data from large-scale trials with long-term follow-up. Moreover, the implications of recently-reported trial data concerning the duration of dual

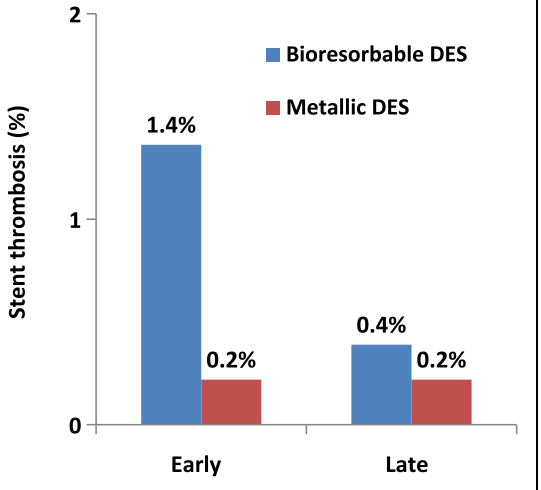

FIGURE 1 Rates of Stent Thrombosis After Implantation of Bioresorbable and Metallic DES

Rates refer to pooled data analysis on adjudicated definite stent thrombosis (of 23 stent thrombosis patients included from 1 registry, 3 patients with probable stent thrombosis were also included [3]) from published registries with more than 100 treated patients, the ABSORB-II (A bioresorbable everolimus-eluting scaffold versus a metallic everolimus-eluting stent for ischemic heart disease caused by de-novo native coronary artery lesions) randomized trial, and the BVS-EXAMINATION (A Clinical Evaluation of Everolimus Eluting Coronary Stents in the Treatment of Patients With ST-segment Elevation Myocardial Infarction) study (3–7).

antiplatelet therapy for patients treated with bioresorbable stents remains unclear (13,14).

Second, the possible higher incidence of stent thrombosis after bioresorbable stent implantation is consistent with other reports (3–6). The majority of these events occur within the first 30 days (**Figure 1**). This means that their occurrence is most likely related to the acute procedural results per se rather than the specific chemical or pharmacological properties of the stent itself. This distinction is important, as procedural outcomes can be influenced by the expertise of the operator. Specifically, careful selection of patients and lesions is critical, with reassessment of the stent strategy after thorough lesion preparation. Moreover, meticulous attention to procedural detail is vital, including a low threshold to use intravascular imaging for optimization of stent deployment. Finally, device iteration from industry—with improved backbones and optimized radial strength—will likely have a favorable effect on rates of early stent failure.

At this time, on the basis of our experiences as well as the available published data, it is our belief that we can well serve a proportion of our patients by treatment with bioresorbable stents. The key element in the use of this immature technology is the maturity of application, both in relation to the selection of patients and the optimization of the procedural results. In the coming years, the real progress in this field will be measured by growth in the proportion of patients to whom we can offer this promising treatment.

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KEY WORDS bioresorable stent, myocardial infarction, stent thrombosis