EDITORIALS

Bioresorbable Vascular Scaffolds — Will Promise Become Reality?

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All other things being equal, most of us would agree that a coronary-artery stent that disappears after its useful function has been served would be preferable to a permanently indwelling device. Late stent failure occurs at a low but steady rate with the passage of time,[1] and an increasing body of evidence implicates an accelerated form of atherosclerosis inside the stent as a common underlying cause.[2] Moreover, the presence of a rigid metal scaffold in the vessel wall permanently abolishes physiologic vasomotion in the stented area.

With this in mind, researchers have sought to develop self-degrading coronary stents with enough strength to produce a good short-term result and a degradation profile that results in gradual breakdown in a safe manner.[3] Thus far, most success in the field has been with polylactic acid stent technology. Two such devices have received CE-mark approval, which is a prerequisite for clinical use in Europe: the everolimus-eluting Absorb bioresorbable vascular scaffold system (Abbott Vascular) in 2011 and the novolimus-eluting DESolve bioresorbable coronary scaffold system (Elixir Medical) in 2013.

Ellis and colleagues now report in the *Journal* the results of a clinical trial designed to generate data that could lead to device approval for the Absorb scaffold in the United States.[4] To do this, the investigators randomly assigned patients with stable or unstable angina to treatment with the Absorb scaffold or with the conventional metallic everolimus-eluting stent (Xience, Abbott Vascular). The primary outcome was the rate of target-lesion failure (consisting of cardiac death, target-vessel myocardial infarction, or target-lesion revascularization) at 1 year. In the intention-to-treat analysis, the authors report a rate of the primary outcome of 7.8% in the Absorb group versus 6.1% in the Xience group, for a difference of 1.7 percentage points (95% confidence interval, −0.5 to 3.9; P=0.007 for noninferiority). Accordingly, the investigators concluded that the Absorb scaffold was noninferior under the circumstances tested. However, although the conduct of the trial was held to high standards and the investigators should be congratulated for executing an important clinical trial in a timely manner, there are a number of issues that need to be considered when interpreting the findings.

First, intention-to-treat analysis is the conventional standard for trials testing superiority, since such analyses tend to provide a more conservative estimate of differences between comparator devices. For noninferiority trials, most experts prefer an as-treated analysis, which tends to be less biased.[5] The current study is a nice example: because of unbalanced crossover, the differences were slightly more pronounced in the as-treated analysis, with rates of target-lesion failure of 8.0% in the Absorb group and 6.0% in the Xience group. Although statistical noninferiority is still proved, the trend toward higher event rates with the Absorb scaffold is noteworthy. Moreover, the point estimates for each of the primary outcome components all favor the conventional metallic stent.

Second, although the trial was designed in consultation with regulatory authorities, the absolute risk difference between the devices that is considered to be clinically unimportant — the

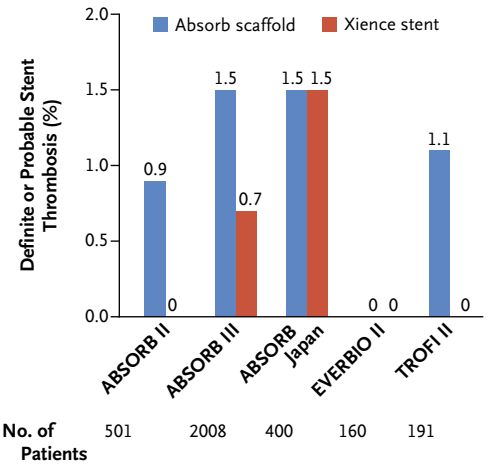

Figure 1. Stent Thrombosis after Implantation of Bioresorbable Vascular Scaffolds versus Metallic Stents.

Shown are rates of stent thrombosis in randomized trials with published data comparing the outcomes, at 9 to 12 months, in patients treated with the everolimus-eluting Absorb bioresorbable vascular scaffold versus everolimus-eluting metallic stents, including Xience. The total number of patients who were enrolled in each trial is displayed beneath the trial name. EVERBIO denotes Comparison of Everolimus- and Biolimus-Eluting Stents with Everolimus-Eluting Bioresorbable Vascular Scaffold Stents.

noninferiority margin — is large at 4.5 percentage points against a background rate of the primary outcome of 6.0% with the metallic stent. Most clinicians in everyday practice would not accept this degree of difference between two stents in their catheterization laboratories. This means that the clinical relevance of the finding of statistical noninferiority is open to question.

Third, definite or probable stent thrombosis at 1 year was about twice as likely in patients who received the Absorb scaffold as in those who received the Xience stent. Similar trends are observed in most of the other published randomized trials of this technology (Fig. 1).[4,6-9] These observations probably mandate the conduct of new trials in an attempt to define the most effective duration and intensity of dual antiplatelet therapy in patients receiving these devices.

Finally, both patient selection and implantation technique are more challenging with the Absorb scaffold than with standard stents.[10] Therefore, in applying the results of this trial to clinical practice, we must remember the lessons from the recent past, when concern about adverse events with early-generation drug-eluting stent technology first became apparent with broader clinical use. For this reason, it is important that clinicians who are operating outside of clinical trials respect the implantation protocols and patient-selection criteria used in this study. Evidence from Europe suggests higher rates of adverse events with this technology in registries than in clinical trials.[11]

Although the concept of self-degrading stents is intuitively attractive, promise alone is not enough to make us unconditionally embrace this technology. For the moment, the trends toward higher event rates with the Absorb scaffold and the additional challenges associated with implantation must be considered. Against this background, the advantages of the Absorb scaffold must be evident and tangible; otherwise, acceptance of these limitations will not be broad. Ultimately, long-term follow-up data from ongoing trials enrolling even larger numbers of patients and testing whether hypothesized late benefits are detectable (e.g., in the ABSORB IV trial; ClinicalTrials.gov number, NCT02173379) will go a long way toward determining whether this promise will become a reality.

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A suPAR Biomarker for Chronic Kidney Disease

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The worldwide epidemic of chronic kidney disease — an insidious illness that manifests with asymptomatic reductions in the estimated glomerular filtration rate (eGFR) to less than 60 ml per minute per 1.73 m^2 of body-surface area, excessive urinary excretion of protein, or both — afflicts an estimated 600 million people.[1] Many will have progression to end-stage kidney disease and require dialysis or kidney transplantation for survival or succumb to related cardiovascular complications, even while taking antihypertensive agents and medications to lower blood glucose levels.[2,3] Chronic kidney disease shortens survival, reduces the quality of life remaining to these patients, and constitutes a "death sentence" in regions of the world where renal-replacement therapies are not available. Unfortunately, albuminuria and decreased renal function are detected only after substantial kidney injury has already occurred. Thus, there is an urgent need to identify new biomarkers that can accurately determine the risk of impending chronic kidney disease while renal function is still well preserved and there is a higher likelihood that medical interventions can slow or prevent progression.[4]

The rationale for considering the plasma concentration of soluble urokinase-type plasminogen activator receptor (suPAR) as a candidate biomarker for incipient chronic kidney disease is based on reports that elevated levels of this receptor could act as a circulating permeability factor that may be involved in initiating focal segmental glomerulosclerosis, an important cause of chronic kidney disease.[5] In this scenario, elevated levels of circulating suPAR increase glomerular permeability, leading to a cascade of events that result in focal segmental glomerulosclerosis. As they now report in the *Journal*, Hayek et al.[6] have extended that initial observation by evaluating suPAR as a new biomarker for chronic kidney disease. The research on suPAR is controversial, because several studies, using a variety of suPAR assays and involving patients with different causes of kidney disease, did not confirm an association of an elevated suPAR level with nephropathy.[7] In addition, as stated by Hayek et al., the precise mechanisms of the suPAR effect remain unknown.

The current report evaluated two disparate patient cohorts with data on progression to chronic kidney disease: the Emory Cardiovascular Biobank cohort and the Women's Interagency HIV Study cohort. Cross-sectional associations were detected between plasma suPAR concentration and baseline eGFR in the Emory cohort, along with longitudinal associations of baseline suPAR level with a decline in the eGFR and with incident chronic kidney disease in both cohorts. Importantly, effects were strongest in participants with an initially preserved eGFR, in whom plasma suPAR concentrations improved risk discrimination for subsequent chronic kidney disease as compared with conventional predictors.

Several aspects of the study warrant discussion. The study design was relatively complex; association testing was performed in the full Emory cohort, followed by repeat analyses in