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EDITORIAL COMMENT

The Magic of Disappearing Stents*

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In this issue of the *Journal* (1), we are presented with 1-year outcomes of a fourth-generation drug-eluting stent (DES): an everolimus-eluting bioresorbable vascular scaffold (E-BVS). Made of thick strut poly-L-lactide, with another lactide acting as a controlled release polymer coating, the stent elutes everolimus to prevent smooth muscle cell proliferation: the new and improved (less recoil compared with a prior version) E-BVS releases everolimus over 30 days, and the stent degrades into lactic acid over a 2-year period (2–4). To understand the potential for enhanced late loss and recoil with a bioresorbable scaffold, the authors investigated the 12-month outcomes of a 56-patient registry of low-risk patients receiving the E-BVS. The authors demonstrate, despite the potential for recoil or variable drug delivery (5), an E-BVS late loss of <0.3 mm with a corresponding 3.5% restenosis rate. These results are confirmed by intravascular ultrasound and optical coherence tomography (OCT) substudies demonstrating that >95% of stent struts are covered at 12-month follow-up.

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Developing the DES family tree. Development of more biocompatible polymers as well as thinner stent struts and polymer coatings (6) is improving efficacy and safety of second-generation DES compared with the early taxol-eluting stents (7). Given the link between certain polymers and chronic inflammatory responses to DES, it is a natural next step to develop either a third-generation bioresorbable polymer/durable platform or a fourth-generation of bioresorbable polymer/bioresorbable platform (3,8,9).

The first version of the E-BVS (late loss of 0.44 mm) made the fourth-generation platform at higher risk of restenosis (10) as was seen with a magnesium alloy bioresorbable stent platform (5). The stronger E-BVS 1.1 (Abbott Vascular, Santa Clara, California) now being studied allays the risk considerably: late loss of 0.27 mm is consistent with current metallic scaffold second-generation DES (11). Although one might initially conclude that there is evidence of ongoing recoil of the E-BVS by comparing the previously reported 6-month late loss of 0.19 mm with current 12-month results, this would be an overstatement: the 6- and 12-month cohorts are entirely different groups of patients, and comparisons can only state that there is a general consistency of hyperplasia suppression seen throughout the first year.

The positive findings of minimal intimal hyperplasia, lack of late incomplete scaffold apposition, and return of vasomotion in some patients should not be overstated from this relatively small low-risk registry. Caution is found in an early ischemic failure for a patient with a myocardial bridge—could there be other situations where coronary motion stress or architectural demands (ostial lesions, overlapping stents, bifurcation stenting) might crack or compromise E-BVS stents? Furthermore, the BVS 1.1 (Abbott Vascular) is a thick strut stent (150 μm), and the patients presented in this report (median lesion length <10.0 mm) would not challenge issues of deliverability generally coexisting with thick stents. Before declaring BVS 1.1 (Abbott Vascular) the workhorse stent of our future, the daily challenges of more complex coronary anatomy will need to be investigated.

In addition to the potential for anatomic challenges, clinical scenarios might impact the healing properties of E-BVS. In an analysis of 51 patients from the CVPath registry, stable patients (similar to those studied in the E-BVS registry) were compared with patients with myocardial infarction: DES placement in the setting of myocardial infarction was associated with a 5-fold increase in uncovered struts and a 2-fold increase in fibrin deposition and inflammation (12). The interaction between higher-risk plaque morphology with the drug-eluting nonpermanent scaffold/polymer requires much more investigation. The authors plan for a noninferiority trial to compare this novel disappearing DES with current second-generation DES. The design of this trial is critical to the future of fourth-generation DES adoption and development.

Of magic and soft endpoints. Assuming that the fourth-generation DES can meet the delivery and healing challenges of higher-risk patients, how will we define the clinical advantages of this exciting new technology? A 50% reduction in clinical events with a $p < 0.05$ is feasible with a 1,000-patient trial comparing DES with bare-metal stents. Event rates >6% with the taxol-eluting stents allowed favorable superiority comparisons with the second-generation everolimus-eluting stents (7). But, the bar has been set much higher as we move toward proving the superiority of E-BVS over current comparators (Fig. 1). We have 12-month target vessel event rates with second-generation DES that are <5% in the context of recent

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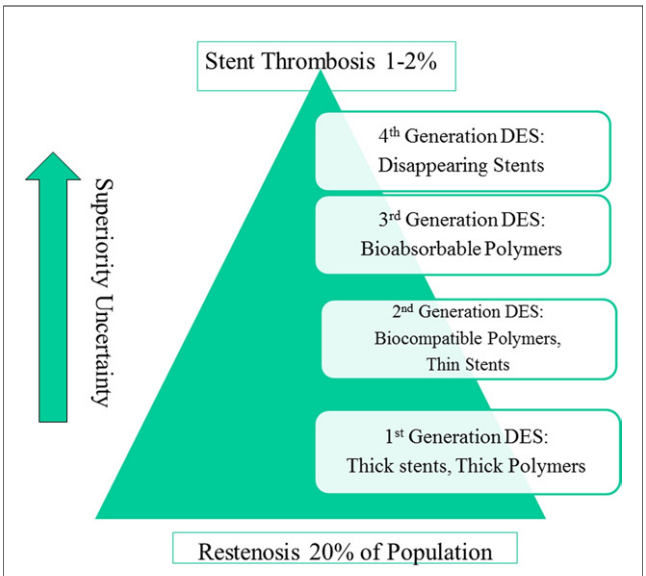

Figure 1 The Development Pyramid for 4 Generations of DES

As the stent generations progress, the rate of adverse events decreases. This leads to increasing superiority uncertainty for each new generation of stent. Novel soft endpoints might be needed to compare efficacy of newer-generation drug-eluting stents (DES).

clinical trials. Although a noninferiority trial design will likely allow fourth-generation DES to become a clinical reality (showing similar restenosis, target vessel revascularization, and stent thrombosis rates), how will the trial data be used to inform choice of ever less-expensive second-generation DES versus more costly third- or fourth-generation DES in actual practice?

A clinical trial of E-BVS compared with second-generation DES could require over 20,000 patients to answer the question of relative superiority of disappearing stents with respect to late stent thrombosis (13). Given the realities of clinical trials, such an investigation is unlikely; we need to live with the ascending event uncertainty that comes with our successful development pyramid (Fig. 1). Although the approval process might continue to focus exclusively on hard events, one can imagine soft competitive advantages for E-BVS: what if a fourth-generation E-BVS allows earlier discontinuation of dual antiplatelet therapy (DAPT) and thus prevents late bleeding complications among high-risk groups (potentially justifying higher up-front costs for a fourth-generation DES) (14)? One can see 2 scenarios for conducting an E-BVS trial with DAPT duration as a soft but real variable: 1) mandate 24 months of DAPT for the second-generation DES (as is common in current U.S. practice) versus 12 months of DAPT for fourth-generation E-BVS with a 2-year primary endpoint to include both bleeding and ischemic events; or 2) use the guideline-recommended 12 months of DAPT for the second-generation DES and compare with a 6-month duration of DAPT for the E-BVS and thus return us to an era where 12 months of DAPT was an option but not a requirement.

The results demonstrated in this current E-BVS registry might give pause to the appealing notion that disappearing stents will not require a full 12 months of DAPT. Magic would be a DES that removes the clinical correlates of late stent thrombosis seen with the earlier generation of DES—uncovered stent struts beyond 6 months, localized inflammation, and endothelial dysfunction (12,15,16). Although the lactide stent integrity might be lost by 12 months, the response to acetylcholine injection at the prior stent site is variable—of 19 patients studied, 10 showed vasoconstriction, 8 showed vasodilatation, and 1 showed no response. In its worst light, this is consistent with only 42% of patients demonstrating a healthy endothelial response at 1-year follow-up. In its best light, we can imagine a substudy of the planned Phase 3 trial where second-generation DES show enhanced levels of endothelial dysfunction compared with fourth-generation bioresorbable scaffolds and thus provide a rationale for choosing the E-BVS in patients unlikely to complete 12 months of DAPT. Because the second-generation DES comparator will not show any vasoconstriction at the scaffold site (due to the permanent metallic implant), the investigators might wish to compare the downstream impact on vasoconstriction. This comparison has been one soft method for demonstrating differences between second- and first-generation DES (16).

Optical coherence tomography and virtual histology intravascular ultrasound offer us 2 other magical methods to demonstrate superiority of E-BVS. Examination of plaque components associated with adverse 3-year outcomes by virtual histology (17) or extent of strut coverage by OCT might demonstrate differential behavior that is statistically significant between the E-BVS and the second-generation DES. A shotgun approach to the magical endpoints in the pivotal trial is not warranted or safe: as noted by the authors of this registry with respect to 1 patient: "the diagnostic procedure was unduly prolonged by IVUS and OCT examinations," leading to coronary thrombosis. The investigators will need to choose among the many softer possibilities (variable DAPT duration, OCT healing, stable plaque by virtual histology, or more rapid return of normal endothelial function) for demonstrating the magic of disappearing stents. Although none of these approaches will prove that the fourth-generation drug-eluting bioresorbable scaffolds can remove the risk of late stent thrombosis from the clinical arena, good magic might be better than absolute uncertainty in guiding future clinical choices.

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