Bioresorbable Stents
The Next Revolution

John A. Bittl, MD

Usually elegant and sometimes ingenious, most innovations in interventional cardiology represent incremental advances. Quantum leaps are rare. A major transformation in practice occurred when bare metal stents (BMS) replaced balloon angioplasty, because stenting could scaffold intimal tears, reduce elastic recoil, and prevent negative remodeling. A negative consequence of drug-eluting stents has been a low incidence of late stent thrombosis caused by incomplete arterial healing and exposed metal struts left in contact with circulating blood. Because the need for vessel-wall support after coronary intervention may be temporary, bioresorbable coronary stents might represent a solution to prevent late stent thrombosis. Bioresorbable drug-eluting stents could provide temporary scaffolding when it is needed after coronary intervention, reduce the risk of restenosis, and completely disappear without leaving thrombogenic residua. If the devices are user-friendly and regulatory requirements are satisfied, bioresorbable stents could revolutionize the practice of interventional cardiology.

Bioresorbable stents were first implanted in animals in 1980. The first bioresorbable stent implanted in man was the Igaki-Tamai stent, a non-drug-eluting stent made of poly-L-lactide with a strut thickness of 170 m that required a combination thermal self-expansion and balloon expansion for deployment. In the initial study of 15 patients with 19 lesions, there were no cases of stent thrombosis. In the second cohort of 50 patients, however, there were 3 cases of stent thrombosis, with 1 subacute event occurring at 5 days, 1 late event occurring after 30 days, and 1 very late event occurring after 1 year. Despite the pioneering efforts, concerns arose about the use of heat to expand the stent and possible thermal injury to the arterial wall.

The bioresorbable vascular scaffold (BVS) under current investigation is a balloon-expandable, drug-eluting device with a backbone of poly-L-lactide coated with amorphous poly-D, L-lactide. During the manufacturing process, the poly-L-lactide backbone solidifies into a mixture of crystalline and amorphous phases and has a “strut thickness” of 150 m, as compared with 140 m for the Cypher stent and 81 m for the Xience V everolimus-eluting stent. On the surface of the BVS, the racemic mixture of poly-D,L-lactide prevents crystallization of the coating itself and slowly elutes the antiproliferative drug everolimus. During bioresorption, long chains of poly-L-lactide and poly-D,L-lactide are progressively shortened as the bonds between repeat units of lactide are de-esterified. Small particles less than 2 m in diameter are phagocytosed by macrophages. The final product, lactic acid, is metabolized via the Krebs cycle.

In the initial evaluation of the first-generation BVS (version 1.0), 30 patients were treated with a single 3.0×12 mm or 3.0×18 mm device. Procedural success was 100%. Matched pairs of measurements were made with quantitative coronary angiography, intravascular ultrasound, and optical coherence tomography at baseline and at 6 months. The BVS 1.0 showed greater acute recoil than conventional metallic stents. At 6 months, the scaffold area was reduced by 11.7%, and the minimal lumen area was decreased by 24.3%. Despite the discontinuation of thienopyridine drugs, no late or very late stent thrombosis occurred, and no additional clinical restenosis was evident by 2 years. Vasodilator and vasoconstrictor responses to methergine and acetylcholine in the stented segments suggested that physiological vasoreactivity had recovered.

In the current issue of Circulation, Serruys and colleagues report the experience in 45 patients treated with a new-generation bioresorbable stent. The BVS 1.1 was designed to provide better vascular support than the BVS 1.0 and to release everolimus more slowly from the coating so that 80% elutes by 30 days. Matched pairs of measurements for quantitative coronary angiography, intravascular ultrasound, and optical coherence tomography were made at baseline and at 6 months. Quantitative coronary angiography revealed a binary restenosis rate of 2.4%. As compared with a late loss for the BVS 1.0 of 0.44±0.35 m, the late loss for the BVS 1.1 was 0.19±0.18 mm. In comparison with the ultrasonic changes seen with the BVS 1.0 at 6 months, the backscattering of the BVS 1.1 struts did not decrease over time. At 6 months, the scaffold area of the BVS 1.1 was reduced by only 2.0%, and the minimal luminal area was decreased by only 5.4%. Optical coherence tomography showed that 96.9% of the struts were covered and that malapposition of at least 1 strut, which was observed in 12 stents at baseline, was detected in 3 stents at follow-up. Cumulative distribution curves showed almost metallic-like angiographic follow-up findings for the BVS 1.1. No cases of stent thrombosis were reported.
The Limitations of Current Therapy
Although the use of BMS or drug-eluting stents is superior to optimal medical therapy for relieving anginal symptoms, neither stent type has been shown to improve survival or reduce the risk of myocardial infarction (MI) in patients with stable coronary artery disease. In an early landmark study, the use of BMS was associated with a higher rate of summed end points for death and for Q-wave MI after 5 years than the use of balloon angioplasty (33 of 256 [12.9%] versus 17 of 256 [6.6%]; odds ratio 2.1; 95% confidence interval [CI] 1.1 to 3.8; P=0.01). Several meta-analyses have reported that the use of BMS (as compared with balloon angioplasty) and the use of drug-eluting stents (as compared with BMS) reduced the risk of restenosis but not the risk of death or MI.13–15

Reasonably straightforward to implant, metallic stents are widely used in interventional cardiology. The magnitude of use—combined with the failure to lower the risk of death or MI in elective settings—has raised the concerns of a prominent consumer organization, which has announced that coronary stenting is 1 of the 10 most overused treatments in medicine.16 After insertion of drug-eluting stents, the mandatory requirement for dual antiplatelet therapy remains unpopular with patients, general surgeons, and gastroenterologists, who frequently face therapeutic dilemmas involving noncardiac surgery or gastrointestinal bleeding. There is a need to identify safer devices and treatments for patients with chronic coronary artery disease who require coronary intervention.

The study of bioresorbable stents tests the hypothesis that re-endothelialization of the treated arterial segment will occur after the stent disappears. If correct, the hypothesis has several practical and clinical consequences. The use of bioresorbable stents may prevent permanent obstruction of side branches, eliminate the consequences of a “full-metal jacket” for diffuse coronary artery disease, and improve the accuracy of imaging techniques like MRI or computerized tomography. After stent resorption, adaptive remodeling of the treated segment may improve coronary flow reserve and reduce the likelihood of anginal symptoms under conditions of high myocardial oxygen demand. Importantly, complete resorption of the stent could eliminate an uncommon but potentially fatal complication: late or very late stent thrombosis.

Remaining Challenges
Before bioresorbable stents become widely accepted, they must meet several requirements. Ease of use is a desirable feature, but the insertion of bioresorbable stents will probably be more difficult and require more attention to detail than the insertion of metallic stents. The BVS has 37-μm platinum markers at each end for angiographic visualization, but the scaffold itself is radiolucent. The rigid crystalline backbone of the BVS will be less tolerant of plastic deformation than metallic stents and will require more accurate vessel sizing to avoid overexpansion, scaffold fracture, and an increased risk of thrombosis. Correct sizing will require quantitative coronary angiography in every case, and optimal stent deployment will likely require either intravascular ultrasound or optical coherence tomography as well.

Bioresorbable stents should be proved in randomized trials to be at least noninferior to metallic stents for several end points and for several indications. A multicenter single-arm evaluation, the ABSORB EXTEND study, is currently enrolling patients in preparation for a pivotal noninferiority trial, but further investigation should determine whether bioresorbable stents are suitable for patients with more complex coronary artery disease than those treated in the early-phase studies reviewed here.7,8,10 The use of bioresorbable stents should be investigated in patients with acute coronary syndromes who have the highest risk of late and very late stent thrombosis.3 To remain competitive with the popular Xience V everolimus-eluting stent, bioresorbable stents should produce rates for very late stent thrombosis of less than 0.5% per year.17 Because of possible limitations in radial support, bioresorbable stents may be unsuitable for calcified vessels, ostial stenoses, complex bifurcations stenoses, or resistant lesions.

Bioresorbable stents will need to be compared with evolving metallic-stent technology. A recent study investigated a novel drug-eluting stent coated with a biodegradable poly lactacid polymer.18 In a randomized trial, a stent eluting biolimus from a biodegradable polymer was compared with a stent eluting sirolimus from a durable polymer.18 The rates of the primary end point of cardiac death, MI, or target vessel revascularization (9% versus 11%, rate ratio 0.88 [95% CI 0.64 to 1.19], P=0.39) and definite stent thrombosis within 9 months were similar for the 2 stent types (1.9% versus 2.0%, RR=0.93 [95% CI, 0.47 to 1.85], P=0.84). These important findings suggest that getting rid of the polymer is an incremental advance but the promising initial investigations of the BVS, as evaluated by Serruys and colleagues using multimodality imaging studies and long-term follow-up,7,8,10 suggest that getting rid of the stent would be better. While current evidence suggests that no single stent design or polymer type is optimal for all lesions or patients, the availability for selected patients of a bioresorbable stent with negligible restenosis and no risk of stent thrombosis would be ideal.

Disclosures
None.

References


**Key Words:** Editorials | biodegradable polymers | drug eluting stent | percutaneous coronary intervention | stent optimization | stent thrombosis