Coronary and endovascular applications of the Absorb™ bioresorbable vascular scaffold

Atherosclerotic cardiovascular disease is the leading cause of death and disability in the world, accounting for nearly one-third of all human mortality. In the modern era, the mainstay of therapy for established occlusive lesions in the cardiovascular tree is percutaneous balloon angioplasty and stent implantation. The procedure is widely applied, with over 2 million procedures performed annually, and the acute results are favorable in >95% of patients. Significant problems with angioplasty and stenting remain, however, including the need for early reintervention for restenosis and/or thrombosis, and the requirement for continual antiplatelet therapy as the artery heals. Furthermore, although the remarkable progress in intravascular stent development is incontrovertible, stents still generate an alarming amount of long-term complications including fracture and late thrombosis. In order to circumvent the myriad problems associated with permanent intravascular implants, stents that slowly dissolve after deployment have long been imagined. So-called ‘bioresorbable vascular scaffolds’ potentially offer several key biologic and physiologic advantages including: effective scaffolding without the permanence of a metal implant; attenuation of inflammation and chronic foreign body reaction leading to reduced restenosis and enhanced long-term patency; assistance of adaptive vascular remodeling; restoration of vasoactive function in response to exogenous infusion; and facilitation of intravascular imaging and surveillance during follow-up. The purpose of this article is to describe the rationale and design of everolimus-eluting bioresorbable scaffolds and their use in completed and ongoing clinical trials.

KEYWORDS: absorbable stent  bioresorbable scaffold  coronary artery disease  everolimus  peripheral vascular disease

Over the past 50 years, magnificent strides have been made in the understanding and primary prevention of atherosclerosis. Nonetheless, as patients age and arteries become brittle, early atherosclerotic plaques inexorably progress to their occlusive end-stage and induce the clinical syndromes of angina pectoris, transient ischemic attack and claudication and, all too frequently, their sinister counterparts myocardial infarction, stroke and amputation.

In the current era, revascularization of end-stage atherosclerotic plaques is most commonly afforded through catheter-based balloon dilation with or without the implantation of permanent metal stents. Although successful recanalization can be achieved in almost all cases, the chronic presence of an indwelling foreign body forever creates the potential for ongoing neointimal hyperplasia and neatherosclerosis, culminating in ‘late catch-up’ restenosis. Indeed, a recent study of the long-term outcome following percutaneous coronary intervention (PCI) suggested that, during 5-year follow-up, a full 26% of patients sustain clinical events, including 10% mortality, 8.4% myocardial infarction and 17% repeat revascularization [1]. Symptomatic recurrence following percutaneous peripheral intervention is even more frequent. In the superficial femoral artery, for example, restenosis still complicates approximately 40% of all procedures in the first year [2–19]. Indwelling metal stents in the superficial femoral artery are particularly problematic, given their unsettling tendency toward fracture. Although only occasionally observed in the coronary [20,21], carotid [22,23], renal [24,25], iliac [26] and venous systems [27], stent fracture following femoropopliteal implantation is disturbingly common [28–36], as high as 65% in one clinical report [37].

Although bothersome and costly, fracture and restenosis are complications of stenting that are generally treatable. More disquieting is the ongoing risk of frank coronary thrombosis which, even using the most conservative estimates, can be expected to generate immediate mortality in 20% of cases [38]. The risk of stent thrombosis within the first year following PCI with drug-eluting stents (DES) is thankfully low, between 1 and 2% when using older generation devices and <1% with newer entrants [39]. However, stent thrombosis beyond the first year continues to be
observed. In fact, it’s estimated that so-called ‘very late stent thrombosis’ occurs at a persistent rate of about 0.6%/year [40,41] such that, after 10 years of treatment, the patient’s cumulative risk of stent thrombosis has accrued to an alarming 6%. Patients in certain subgroups are exposed to even higher risk – for example, patients undergoing PCI for acute myocardial infarction may sustain thrombosis in as many as 10% of cases [42].

Stent occlusion in the peripheral vasculature is less well-studied but no less important. In the setting of critical limb ischemia (CLI), failure to maintain patency in stented segments of ‘flow-dependent’ limbs will result in amputation. Also, because lesions tend to be longer and more complex, stent occlusion in the periphery tends to be more common than in the coronary arteries; incidences of up to 6–25% have been reported depending on the clinical scenario and the length and variability of follow-up [43–49].

Critical limb ischemia

CLI represents the end-stage of chronic peripheral arterial disease. It arises when lower-extremity blood flow and oxygen delivery have decreased to such an extent as to be inadequate to maintain tissue viability, giving rise to ischemic rest pain, ulceration, and/or gangrene. Without prompt intervention, CLI will result in limb loss.

Endovascular revascularization is an attractive therapeutic option for patients with CLI given its minimally invasive nature and the potential for recanalization of multiple affected arteries. Successful endovascular recanalization can now be achieved in the majority of cases, even in tibial arteries with complex disease. However, arterial patency following endovascular recanalization tends to be short-lived, as sluggish blood flow in the long and diminutive conduits generates elastic recoil, neointimal hyperplasia, restenosis and therapeutic failure. In general, only approximately 50% of tibial lesions treated with percutaneous transluminal angioplasty (PTA) will remain patent and free from restenosis after the first year [50–53]. The use of intravascular stents following tibial angioplasty certainly enhances acute results, but whether primary bare metal stenting improves long-term patency remains controversial [53–55].

In the coronary arteries, the risk of restenosis has been profoundly attenuated by DES, and some have theorized that coronary DES might also be useful in the similarly sized infrapopliteal arteries. Several nonrandomized clinical registries support such a notion [53,56–62], and to date, three randomized trials addressing the hypothesis that DES would enhance tibial artery patency have been conducted: YUKON BTK [63], DESTINY [64] and ACHILLES [65].

The purpose of the prospective, randomized, multicenter, double-blind YUKON BTK trial was to compare a polymer-free sirolimus-eluting stent (Yukon®; Translumina, Hechingen, Germany) with a placebo-coated bare metal stent in patients with either intermittent claudication or CLI with a de novo occlusive lesion in an infrapopliteal artery [63]. The main study end point was 1-year primary patency defined as freedom from in-stent-restenosis (luminal narrowing of ≥50%) detected with duplex ultrasound or angiography. 161 patients with a mean lesion length of 31 ± 9 mm were included in the trial (25 patients died during follow-up, leaving 125 for analysis). After 1-year, the primary patency rate was significantly higher in the sirolimus-eluting stent group (80.6%) than in the bare-metal stent group (55.6%; p = 0.004) and, clinically, the median (interquartile range) change in Rutherford–Becker classification was -2 (-3 to -1) in the sirolimus-eluting stent group compared with only -1 (-2 to 0) in the bare-metal stent group (p = 0.004).

The purpose of the prospective, randomized, controlled DESTINY trial was to test the hypothesis that treatment of infrapopliteal arterial occlusive lesions with an everolimus-eluting stent (Xience V®; Abbott Laboratories, Abbott Park, IL, USA) would provide superior patency to treatment with a bare metal stent (Multi-Link Select Plus; Cordis [64]). The primary end point was arterial patency at 12 months defined as the absence of ≥50% restenosis based on quantitative analysis of contrast angiography. Between March of 2008 and September of 2009, 74 patients were treated with Xience V and 66 patients were treated with Vision. After 12 months, the primary patency rate following treatment with Xience V was 85% compared with 54% after treatment with Vision (p = 0.0001; Figure 1). Treatment with Xience V significantly reduced mean in-stent diameter stenosis (21 ± 21% vs 47 ± 27%; p < 0.0001) and mean in-stent late lumen loss (0.78 ± 0.63 mm vs 1.41 ± 0.89 mm; p = 0.001), and the use of the Xience V stent significantly reduced the need for repeat intervention (freedom from target lesion revascularization 95% for Xience V vs 65% for Vision; p = 0.005).

Lastly, the purpose of the prospective, randomized, multicenter ACHILLES trial was to compare PTA to sirolimus-eluting stent implantation (Cypher® Select Plus; Cordi
 Corporation, Miami Lakes, FL, USA) for the treatment of infrapopliteal arterial disease. As of the time of writing, the results of ACHILLES have not been formally published, although the data have been presented publicly [68]. The study enrolled 99 patients that received the sirolimus-eluting (Cypher) stent, and 101 that were treated with PTA alone. Mean lesion lengths were 26.9 ± 20.9 mm and 26.8 ± 21.3 mm in the Cypher and PTA groups, respectively. After 1 year, the use of the Cypher stent resulted in a highly statistically significant decrease in binary restenosis (45.5 vs 21.3%; p = 0.004), as well as a significant improvement in clinical status (change in Rutherford–Becker Clinical Category -2.2 ± 1.6 vs -1.6 ± 1.8; p = 0.044). Unfortunately, although the results were strongly positive, the Cypher device has been removed from the market by the manufacturer. Nonetheless, these three clinical trials suggest that DES implantation in the tibial arteries yields superior patency to either PTA or bare metal stenting, and form the basis of the rationale for the use of drug-eluting bioresorbable vascular scaffolds (BVS) for the treatment of CLI.

Bioresorbable vascular scaffolds

Stack and colleagues, from Duke University (NC, USA), are generally credited with the first descriptions of intravascular bioresorbable scaffolds [66]. In 1990, a technique was described wherein monofilaments of poly(l-lactic acid) (PLLA) were braided into an open tubular mesh and implanted in dogs for up to 12 weeks [67]. The stented arteries maintained patency without significant inflammation or thrombosis. More extensive preclinical studies of bioresorbable scaffolds were conducted by Keiji Igaki and Hideo Tamai in the mid- and late-1990s. They fashioned balloon-expandable knitted stents from polyglycolic acid or PLLA filaments and implanted the devices in both canine and porcine models [68,69]. Although significant diameter reductions were observed in the early postprocedure period, the devices were well-tolerated without evidence for thrombosis or undue neointimal reaction. Interestingly, this same group more recently explored the feasibility of coating the device with a tyrosine kinase inhibitor, which had the effect of attenuating experimental neointimal hyperplasia [70].

The first bioresorbable vascular scaffold developed for clinical use was the Igaki-Tamai® device. The nondrug-coated scaffold was designed as a coil made of PLLA monofilament with a zigzag helical pattern [69–71]. Deployment of the device was facilitated with a balloon-expandable covered sheath system and included two radiopaque gold markers to confirm placement. Due to the thermal properties of the scaffold, balloon inflation was performed with a heated dye at 80°C to ensure adequate expansion. Following deployment, it was designed to fully resorb within 6–12 months.

The Igaki-Tamai coronary scaffold was first clinically tested in 1998 at the Shiga Medical Center for Adults in Shiga (Japan) [72]. A total of 25 scaffolds were successfully implanted in 19 lesions. After 6 months, both the restenosis and target lesion revascularization rates were only 10.5%, representing a major advance in the field at that time. The authors of this initial clinical experience suggested that the device was “feasible, safe and effective in humans”. 1-year clinical and angiographic results from a larger cohort were subsequently reported by Tsuji et al. in 2001 in abstract form [73]. Serial quantitative angiography at 3, 6 and 12 months demonstrated somewhat disappointing percent diameter stenoses of 12 ± 8%, 38 ± 23% and 33 ± 23%, respectively, including ≥50% binary restenosis in 21% of patients at 6 months. Given the superior results of drug-eluting stents, further development of these nondrug scaffolds was halted. Nonetheless, the original cohort of patients treated with the Igaki-Tamai device were continuously followed, and their 4-year results were reported in abstract form in 2004 [74]. In total, 50 patients had been followed for
40–61 months, with 4-year overall survival and MACE-free survival rates of 98% and 82%, respectively. More recently, the long-term results (>10 years) of this 50-patient original cohort have been published [75]. There was only a single cardiac death, six noncardiac deaths and four myocardial infarctions. The cumulative rates of target lesion revascularization were 16% at 1 year, 18% at 5 years and 28% at 10 years, with only two definite scaffold thromboses reported (one subacute and one very late). Although these rates of target lesion revascularization are probably unacceptable in the current era of coronary drug-eluting stents, the long-term experience using the Igaki-Tamai device demonstrates the safety and feasibility of resorbable coronary scaffolds.

The Absorb™ bioresorbable vascular scaffold

The Absorb™ Bioresorbable Vascular Scaffold (Abbott Laboratories) is the first resorbable device to incorporate antiproliferative drug elution into its design [76]. It is composed of three basic components: a PLLA polymer scaffold, a poly-D,L-lactide coating and the antiproliferative drug everolimus [77,78].

The backbone structure of the Absorb scaffold is shown in Figure 2 [77]. Absorb is made of PLLA, a semicrystalline polymer with a microstructure that can be tuned by varying the mechanical and thermal conditions of processing. In this application, a polymer scaffold was created, having similar radial force as a balloon-expandable metal stent, as shown by standard in vitro force measurements in comparison with multiple approved bare-metal and drug-eluting stents [76,77]. The Absorb scaffold is coated with a 1:1 mixture of poly-D,L-lactide to incorporate and elute everolimus. The equimolar mixture of polylactide D- and L-stereoisomers is fully amorphous, making it ideal as a drug carrier. The scaffold’s strut thickness of 158 µm [76,79,80] is similar to traditional sirolimus-eluting stainless steel stents (Cypher, 154 µm) [81] but somewhat larger than newer generation everolimus-eluting cobalt–chromium stents (Xience, 81 µm) [82].

The antiproliferative drug, everolimus (40-O-[2-hydroxyethyl]-rapamycin), is a macrolide immunosuppressant that, in conjunction with cyclosporine, has been shown to prevent chronic rejection episodes of solid organ transplants [83–85] and, more recently, has been suggested as an oncologic adjuvant in patients with certain solid malignant tumors [86–89]. In vascular tissue, everolimus effectively inhibits neointimal hyperplasia, enhances remodeling [90–93], and has been shown to be safe and effective as the drug component of coronary and peripheral drug-eluting stents [94–99]. Similar to the Xience everolimus-eluting cobalt chromium stent, everolimus is loaded onto the Absorb device at a dose of 100 µg everolimus per cm² device area. Via a nonenzymatic hydrolytic conversion to lactic acid, the Absorb PLA scaffold resorbs after approximately 24 months, after which the structure of the device cannot be readily discerned radiographically or histologically [100].

Clinical experience in percutaneous coronary intervention: the ABSORB trials

Clinical and morphological outcomes of patients treated with Absorb during PCI have been documented in the ABSORB serial of trials. Two different devices have been tested: the BVS 1.0 device tested in the ABSORB COHORT A trial and the BVS 1.1 device tested in the COHORT B trial. Early experience with BVS 1.0 in the COHORT A trial informed several important alterations in the evolution of the device, and also allows for examination of its noteworthy effects in the long-term.

The ABSORB COHORT A trial, begun in 2006, was initially reported in Lancet in 2008 [101]. In this prospective open-label study,
30 patients having either stable, unstable, or silent coronary ischemia from a single de novo occlusive lesion were treated with either a 3 × 12 mm or 3 × 18 mm Absorb scaffold. Procedural success was 100%, and the only subacute complication was a non-Q-wave myocardial infarction in a patient that required nonischemia-driven target lesion revascularization 46 days after the index procedure. After 6 months, mean in-scaffold late lumen loss was 0.44 ± 0.35 mm, mean in-scaffold percent diameter stenosis was 27% ± 14% and ≥50% binary restenosis was observed in only three of 26 evaluable lesions (12%) [102]. After 5 years of follow-up, all patients were well, without further episodes of myocardial infarction or target lesion revascularization [103–105].

Careful review of the imaging results of the ABSORB COHORT A study suggested that the scaffolding properties of the device required enhancement. The device was therefore redesigned with a more uniform strut distribution and reduced maximum circular unsupported scaffold area (Figure 3), which theoretically enhances radial strength, reduces recoil and provides more even support to the arterial wall [78,106]. The new device, called BVS 1.1 or, simply, Absorb, employs the same materials, markers, drug and elution rate as the original device.

The newly designed scaffold was tested clinically in the ABSORB COHORT B trial which was designed to angiographically examine scaffolded arteries at multiple time points ranging from 6 months to 3 years. The trial was designed to enroll 101 patients with de novo occlusive coronary lesions and either stable angina, unstable angina or silent ischemia. Lesions were required to have a diameter range of 2.5–3.3 mm, length ≤14 mm, percent diameter stenosis ≥50% and <100%, and thrombolysis in myocardial infarction flow grade ≥1 [78,107]. Implanting physicians were advised to utilize quantitative coronary angiography to carefully size target arteries, as overdilatation of the polymer device was not allowed and ill-advised [108–110]. In order to avoid multiple serial radiographic examinations in the same patient, two distinct patient groups were enrolled: the first group of 45 patients was subjected to repeat angiographic examinations at 6 months and 2 years, while the second group of 56 patients was subjected to repeat examinations at 1 and 3 years. The currently available 2-year results show that in-scaffold late lumen loss was significantly improved over the first-generation device, and remained consistently low over time (6 months: 0.19 ± 0.18 mm; 1 year: 0.27 ± 0.32 mm; 2 years: 0.27 ± 0.19 mm) [78,107,111,112]. The binary restenosis rate remained low as well, <4% throughout the 2-year study (6 months: 2.4%; 1 year: 3.5%; 2 years: 0%). The average 2-year in-scaffold late lumen loss of only 0.27 ± 0.19 mm is particularly noteworthy, being the lowest reported amount of lost lumen in any trial of PCI [113–115].

The ABSORB series of trials also generated several additional observations that were unexpected and heretofore unimagined in the field of vascular intervention. Included among these novel findings were:

- That the Absorb device, although made of PLLA polymer, maintains its overall circular shape and area within the artery for at least 1 year [78,107];
- That dissolution of the device can be followed qualitatively using standard imaging techniques [76,100,116];
- That, compared with metal platforms, the resorbable device causes significantly less straightening of tortuous arterial segments [117], reducing untoward mechanical phenomena such as over-stretch, hinging and edge deformation;
- That many scaffolded arteries regain their ability to respond to exogenous vasoactive agents over time [103,107];
- That orifices of side branches that are ‘jailed’ by the device return to full patency after dissolution [118,119].

![Figure 3. Strut pattern design of BVS 1.0 and BVS 1.1 (Absorb™). Note the change in maximum circular (circles) and unsupported scaffold areas (contours) in the second-generation device. Data taken from [78].](image-url)
Without question, however, the most intriguing observation from the ABSORB series of trials is the finding that some coronary arteries, unencumbered by a permanent metal cage, can actually adapt and increase their lumen size over time. For instance, in the ABSORB COHORT A study, Intravascular ultrasound (IVUS)-measured mean lumen area, which decreased from 6.04 ± 1.12 mm² postprocedure to 5.19 ± 1.33 mm² after 6 months, had subsequently rebounded to 5.47 ± 2.11 mm² in the ensuing 18 months [107]. Although focal angiographic assessment suggested a slight decrease in minimum lumen diameter during this same interval (from 1.89 ± 0.31 mm to 1.76 ± 0.35 mm), the IVUS results suggested an overall increase in total lumen area and volume over time. Even more impressive was that this same observation was repeated in the ABSORB COHORT B trial although the second-generation device produced little in the way of initial neointima. The 2-year value for IVUS-measured mean lumen area of 6.85 ± 1.78 mm² was statistically significantly greater than the result at 6 months (6.36 ± 1.18 mm²; p = 0.01), and remarkably similar to the original postprocedure result (6.53 ± 1.24 mm²) [112]. Although the mechanism is speculative, late luminal enlargement after intervention with Absorb could conceivably arise from:

- The slow maturation, solidification and fibroelastic remodeling of neointimal hyperplasia as extracellular matrix is absorbed [120–126];
- Continued adaptation to the new environment of physiologically normal mean and oscillatory shear stress as the scaffold slowly dissolves;
- Physical reduction in lesion volume as the scaffold is resorbed;

### Executive summary

#### Critical limb ischemia
- Critical limb ischemia is the most severe form of peripheral arterial disease.
- Only 50% of patients remain alive and free from major amputation 1 year after the diagnosis of critical limb ischemia is made.
- The YUKON BTK trial showed significantly higher patency in tibial arteries treated with sirolimus-eluting stents (81%) compared with bare-metal stents (56%; p = 0.004).
- The DESTINY trial showed significantly higher patency in tibial arteries treated with everolimus-eluting stents (85%) compared with bare-metal stents (54%; p = 0.00014).
- The ACHILLES trial showed significantly decreased incidence of restenosis in tibial arteries treated with sirolimus-eluting stents (21%) compared with balloon angioplasty (46%; p = 0.004).

#### Biodesorbable vascular scaffolds
- The first biodesorbable scaffold that was tested clinically was the Igaki-Tamai™ PLA (nondrug) coronary device.
- The cumulative rates of coronary target lesion revascularization in the original Igaki-Tamai cohort were 16% at 1 year, 18% at 5 years and 28% at 10 years.

#### The Absorb™ biodesorbable vascular scaffold
- Absorb™ is the first resorbable device to incorporate antiproliferative drug elution into its design.
- Absorb is composed of three basic components: a poly-L-lactide polymer scaffold, a poly-D,L-lactide coating and the antiproliferative drug everolimus.

#### Clinical experience in percutaneous coronary intervention: the ABSORB trials
- The ABSORB COHORT B trial has shown the lowest 2-year late loss of any trial of percutaneous coronary intervention to date (6 months 0.19 ± 0.18 mm, 1 year 0.27 ± 0.32 mm, 2 years 0.27 ± 0.19 mm).
- The binary restenosis rate in the 2-year cohort was 0%.
- The Absorb device maintains its overall circular shape and area within the artery for at least 1 year.
- Dissolution of the Absorb device occurs within 24 months and can be followed qualitatively using standard imaging techniques.
- Compared with metal platforms, the Absorb device causes significantly less straightening of tortuous arterial segments.
- Many scaffolded arteries regain their ability to respond to exogenous vasoactive agents over time.
- Some scaffolded coronary arteries, unencumbered by a permanent metal cage, can adapt and increase their lumen size over time.

#### The ABSORB BTK clinical trial
- The rationale for the ABSORB BTK trial is based upon:
  - Favorable clinical results in coronary arteries treated with the redesigned Absorb scaffold;
  - Favorable histologic findings in experimental peripheral arteries treated with Absorb;
  - The recent observation that everolimus-eluting metal stents significantly enhance patency in recalcitrant tibial artery occlusive disease.
- The purpose of the ABSORB BTK trial is to evaluate the safety and efficacy of the Absorb device for the treatment of subjects with critical limb ischemia from occlusive vascular disease of the tibial arteries.
- The primary end point of the ABSORB BTK trial is freedom from major adverse limb events occurring within 1 year or peri-procedural death occurring within 30 days.
And/or a pharmacological effect of everolimus which has been shown to favorably affect human coronary artery remodeling even in the absence of a stent [84].

The ABSORB BTK clinical trial

Given the success of the Absorb everolimus-eluting bioresorbable scaffold in the coronary arteries, some have suggested that this approach might also be feasible for the peripheral arteries [127]. Such rationale is based upon: the favorable clinical results of the redesigned Absorb scaffold outlined above; the favorable histologic findings in experimental peripheral arteries treated with Absorb [128]; and the recent observation that everolimus-eluting metal stents significantly enhance patency in recalcitrant tibial artery occlusive disease [99].

The purpose of the ABSORB BTK Clinical Investigation is to evaluate the safety and efficacy of the Abbott Vascular Bioresorbable Vascular Scaffold System for the treatment of subjects with CLI from occlusive vascular disease of the tibial arteries. The trial is a prospective, single-arm, open-labeled, multicenter clinical investigation that will enroll approximately 90 patients in Europe and Australasia. The primary end point of the trial, as suggested by the Society for Vascular Surgery, is freedom from major adverse limb events occurring within 1 year or peri-procedural death occurring within 30 days [129].

Future perspective

The future of intravascular intervention is bright. From its humble beginnings of battlefield amputations and digitalis leaves, has emerged a field wherein most occluded arteries in humans can be reopened without surgical incision. Percutaneous intervention has progressed rapidly from rudimentary balloon dilatation to streamlined, small-caliber instrumentation that maintains patency via the world’s first true application of localized intracorporeal drug delivery.

Despite these advances, the majority of patients with occlusive arterial syndromes are still treated by insertion of rigid metal stents within their fragile intravascular systems. It is hoped that the development of transient, resorbable, drug-eluting scaffolds will usher in a new interventional era wherein vascular disease can be treated organically and enduringly without the need for permanent metal implants.

References


