Chronic limb-threatening ischemia

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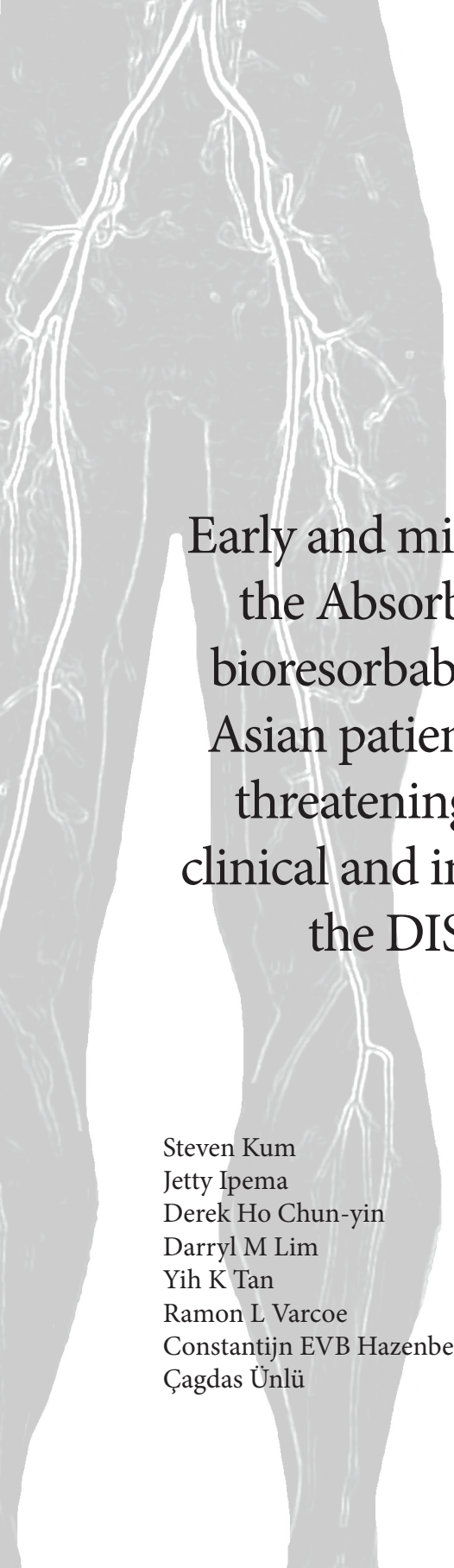

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Early and midterm experience with the Absorb everolimus-eluting bioresorbable vascular scaffold in Asian patients with chronic limb-threatening ischemia: one-year clinical and imaging outcomes from the DISAPEAR registry

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Abstract

Purpose: To report an experience with the Absorb bioresorbable vascular scaffold (BVS) in an Asian cohort with chronic limb-threatening ischemia (CLTI) from the DISAPEAR (Drug Impregnated Bioresorbable Stent in Asian Population Extremity Arterial Revascularization) registry.

Materials and methods: A retrospective analysis was conducted of 41 patients (median age 64 years; 23 men) with CLTI owing to >50% de novo infrapopliteal lesions (n = 53) treated with the Absorb BVS between August 2012 and June 2017. The majority of patients (37, 90%) had diabetes, 24 (59%) had ischemic heart disease, and 39 (95%) had Rutherford category 5/6 ischemia with tissue loss. The mean lesion length was 22.7 ± 17.2 mm; 10 (24%) lesions were severely calcified. Assessments included technical success, primary patency, freedom from clinically driven target lesion revascularization (CD-TLR), amputation-free survival, limb salvage, complete wound healing, resolution of rest pain, and resolution of CLTI without TLR at 6 and 12 months after the index intervention.

Results: Overall, 69 scaffolds were implanted in the 53 lesions, with 100% technical success. There were no deaths within 30 days of the index procedure. The primary patency rates at 6 and 12 months were 95% and 86%, respectively. The corresponding rates of freedom from CD-TLR were 98% and 93%, respectively. Freedom from major amputation was 98% at both time points, and amputation-free survival was 93% and 85% at 6 and 12 months after the index procedure. Wound healing occurred in 31 patients (79%) with Rutherford category 5/6 ischemia by the end of 12 months.

Conclusion: The Absorb BVS demonstrated good 1-year patency and clinical outcomes in CLTI patients with complex infrapopliteal disease.

Introduction

Chronic limb-threatening ischemia (CLTI), an advanced stage of obstructive peripheral artery disease (PAD), is characterized by highly complex lesions, frequent infrapopliteal involvement, and poor prognosis.[1,2] Diabetes is one of the significant risk factors for CLTI.[3] The 2019 estimates from the International Diabetes Federation highlight a 2-fold increase in the number of individuals with diabetes globally by 2045,[4] which may plausibly contribute to an increase in the prevalence of CLTI worldwide.[5]

Although, endovascular treatment through percutaneous transluminal angioplasty (PTA) is a common treatment approach for CLTI, rates of procedural success and 1-year clinical outcomes with this modality are suboptimal.[2] The use of drug-eluting stents (DES) for the revascularization of infrapopliteal disease has played a promising role in optimizing CLTI outcomes, with better patency rates and favorable clinical outcomes compared to plain PTA and bare metal stent implantation.[6–10] Although effective in reducing restenosis in short lesions, a metallic implant may hinder future reinterventions or bypass surgery.

The Absorb everolimus-eluting bioresorbable vascular scaffold (BVS; Abbott Vascular, Santa Clara, CA, USA) was introduced in the cardiac field to overcome the limitations of DES in the coronary circulation, allowing restoration of physiological vasomotion and stabilization of lumen dimensions.[11] However, the BVS has been withdrawn due to inferior results and increased coronary events compared with DES.[12] Contrarily, early and midterm results of BVS implantation in infrapopliteal arteries were encouraging.[13–15]

The current report presents the early and midterm experience with the Absorb BVS in a cohort of patients with CLTI from the DISAPEAR (Drug Impregnated Bioresorbable Stent in Asian Population Extremity Arterial Revascularization) registry.

Materials and methods

Study design and patient sample

This was a single-center, retrospective study undertaken at Changi General Hospital, Singapore, encompassing 41 CLTI patients (median age 64 years; 23 men) treated between August 2012 and June 2017 for 53 de novo infrapopliteal lesions with >50% stenosis extending from the distal third of the popliteal artery to the crural arteries 8 cm above the ankle joint. Patients with lesions in the distal 8 cm of the tibial arteries were not included due to proximity to the ankle joint; patients with arterial thrombosis or restenotic lesions were also not included.

The baseline patient characteristics are shown in Table 4.1. The majority of patients (37, 90%) had diabetes, 24 (59%) had ischemic heart disease, and 39 (95%) had Rutherford category 5/6 ischemia with tissue loss. The mean lesion length was 22.7 ± 17.2 mm; 10 (24%) lesions were severely calcified (Table 4.2). The target vessels had a visually estimated angiographic reference vessel diameter (RVD) between 2.5 and 4.0 mm. The protocol was approved by the SingHealth Institutional Review Board (2013/539/C).

Table 4.1. Characteristics of the 41 patients treated in 41 limbs[a]

Characteristic	Total; patients n = 41, limbs n = 41
Age, years	64 (IQR 15)
Men	23 (56)
Comorbidities	
Ischemic heart disease	24 (59)
Diabetes mellitus	37 (90)
Hyperlipidemia	36 (88)
Hypertension	37 (90)
Chronic kidney disease	13 (32)
Dialysis-dependent renal failure	5 (12)
Smoking history	16 (48) (n = 33)[b]
Rutherford category	
4	2 (5)
5	24 (59)
6	15 (37)

[a]Continuous data are presented as the mean ± standard deviation or median (interquartile range, IQR); categorical data are given as the number (percentage).
[b]Smoking history data was available for 33 patients.

Table 4.2. Lesion and scaffold characteristics in the 41 limbs[a]

Parameter	Total; patients n = 41, limbs, n = 41
Total lesions treated	53
Target lesion location[b]	
Tibioperoneal trunk	17
Anterior tibial artery	17
Posterior tibial artery	11
Peroneal artery	6
Popliteal artery	5
Target lesion length, mm	22.7 ± 17.2
Degree of stenosis, %	80 (50–100)
Total occlusions	4 (8)
Reference vessel diameter, mm	3 (2.5–3.5)
Calcification (PARC classification)	
Non	1 (2)
Focal	19 (46)
Mild	4 (10)
Moderate	7 (17)
Severe	10 (24)
TASC classification	
A	25 (61)
B	14 (34)
C	0 (0)
D	2 (5)
Total scaffolds deployed	69
Scaffold per lesion	1.3 ± 0.6
Scaffolds per limb	1.7 ± 0.9

[a]Continuous data are presented as the mean ± standard deviation or median (range); categorical data are given as the number (percentage).
[b]A lesion could involve more than one vessel.
PARC = Peripheral Academic Research Consortium; TASC = Trans-Atlantic Inter-Society Consensus.

Study device

The Absorb BVS is a balloon-expandable, everolimus-eluting scaffold with a poly-l-lactic acid backbone coated with a polymer [poly(d,l-lactide)] that elutes the antiproliferative drug everolimus. The scaffold is radiolucent but has two radiopaque platinum markers at each end to facilitate visualization. The Absorb BVS is fully bioresorbable, with complete resorption occurring within 3 years.[12] The scaffold was available in diameters of 2.5, 3.0, and 3.5 mm and lengths of 18 and 28 mm during the study period.

Procedure overview

All patients received antiplatelet therapy with 100 mg/d of aspirin at least 3 days prior to the procedure. If the patient was not on clopidogrel before stent implantation, the patient was loaded with 300 mg within 1 hour of the procedure. Diagnostic angiography was performed via antegrade or crossover access. Two orthogonal magnified angiographic projections of the target lesion were obtained prior to the intervention. After angiography, systemic heparinization was initiated with a 3000-unit bolus of intra-arterial heparin, followed by 1000 units of heparin hourly per the institutional protocol. Any inflow lesions in the superficial femoral artery or proximal/mid popliteal artery were treated to improve inflow prior to the below-the-knee (BTK) intervention.

A 0.014-inch guidewire was passed through the target lesion, which was then predilated with a balloon sized to within ± 0.25 mm of the RVD and shorter than the intended BVS length to avoid geographic miss. Lesions were adequately predilated with a residual stenosis <30%. The BVS, which was sized on a 1:1 basis with the lesion, was deployed through slow incremental inflation of 2 atmospheres every 5 seconds until the desired pressure and related diameter were reached. Maximum inflation was maintained for 30 to 60 seconds to facilitate complete scaffold expansion.

There was no restriction on the numbers of target vessels treated or the scaffolds used. If more than one scaffold was required, the distal lesions were treated first followed by the more proximal lesions. Consecutive scaffolds were abutted or overlapped by not more than 1 mm. Total lesion coverage was mandatory as shown in Figure 4.1. Scaffolding across the main branch in a

bifurcation was performed, but side branch stenting or kissing balloon dilation was not done. A similar deployment technique has been described in earlier studies to achieve optimal outcomes.[13] (Pre- and postdilation were not mandatory in the early experience but became routine in more recent cases.)

Concomitant treatment of other crural vessels was performed if deemed necessary. Simultaneous debridement of the foot wound or minor amputation was done at the end of the procedure. Dual antiplatelet therapy (aspirin 100 mg/d and clopidogrel 75 mg/d) was continued for at least 6 months, followed by aspirin for life.

Patients were examined at least monthly until complete wound healing occurred. More frequent follow-up (weekly or twice weekly) were done as needed for wound care. Duplex ultrasound was performed at 6 and 12 months; angiography was done only on suspicion of clinically relevant restenosis.

Outcomes

Technical success was defined as the ability to successfully cross the target lesion and deploy the BVS without signs of immediate thrombosis or >30% residual stenosis. The main outcome was primary patency per scaffold at 6 and 12 months after the index intervention based on duplex ultrasound examination with a sensitive peak systolic velocity ratio 50%.

Secondary outcomes were freedom from clinically driven target lesion revascularization (CD-TLR), freedom from major amputation, amputation-free survival, complete wound healing (defined as full epithelialization of the wound), resolution of rest pain, and resolution of CLTI (defined as complete wound healing/resolution of rest pain) without TLR. The composite outcome of freedom from imaging-defined occlusion and CD-TLR was also analyzed. All-cause mortality and any related adverse events within 30 days of the index procedure were also evaluated.

Statistical analysis

Baseline characteristics and procedural information were analyzed in univariable analysis. Continuous variables are presented as mean ± standard deviation or median and interquartile range (IQR). Categorical variables are presented as

frequency and percentages. The Kaplan-Meier method was used to estimate primary patency, freedom from CD-TLR, freedom from major amputation, and amputation-free survival; estimates are provided with the 95% confidence intervals (CI). Statistical significance was defined as $p < 0.05$. Statistical analysis was performed using IBM SPSS software (version 26; IBM Corporation, Armonk, NY, USA).

Results

Vessel preparation was done in 40 of 53 lesions (76%) with different types of semi- and noncompliant balloons (scoring balloons and atherectomy devices were not utilized for vessel preparation). Overall, 69 scaffolds (mean 1.3 ± 0.6) were implanted in the 53 lesions; 41 (78%) of patients received BVS in vessels contributing significantly to the perfusion of the foot. In all except one of the patients, the number of vessels with runoff to the foot after the procedure was increased compared with baseline. Technical success was achieved in all implantations. There were no procedure-related complications or deaths in the first 30 days.

The median radiological follow-up was 23 months (IQR 36). The primary patency estimates per scaffold at 6 and 12 months were 95% (95% CI: 90% to 100%) and 86% (95% CI: 77% to 96%), respectively (Figure 4.2A). Binary restenosis was detected in 8 scaffolds in 6 limbs within a 12-month period after the index procedure. An example of an Absorb BVS after 4-year follow-up is shown in Figure 4.1.

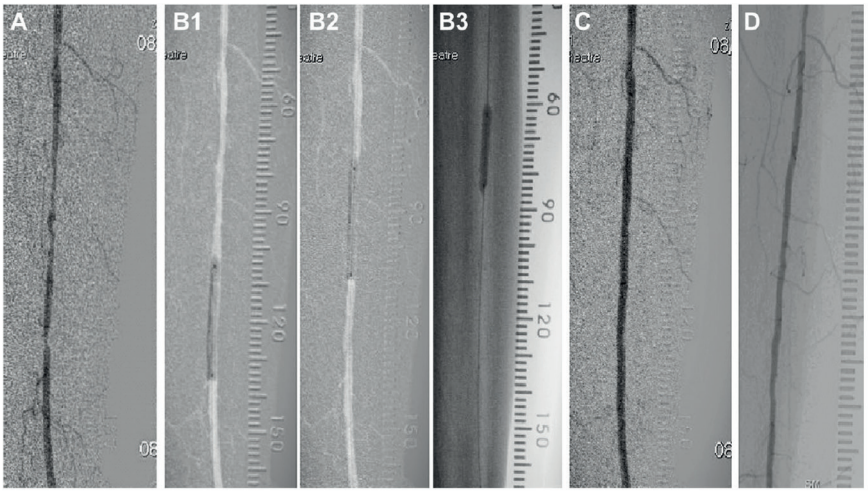

Figure 4.1. (A) High-grade stenosis in the anterior tibial artery. (B) Implantation of 3 bioresorbable vascular scaffolds after predilation: 3.0×28 mm (B1), 3.0×28 mm (B2), and 3.0×18 mm (B3). Angiograms (C) after implantation of the scaffolds and (D) at 4 years.

Six patients underwent CD-TLR involving eleven scaffolds during the study period, with three patients undergoing TLR within one year of the index intervention. Freedom from CD-TLR estimates were 98% (95% CI: 95% to 100%) after 6 months and 93% (95% CI: 86% to 100%) after 12 months (Figure 4.2B). Freedom from imaging-defined occlusion and CD-TLR estimates at 6 and 12 months were 98% (95% CI: 95% to 100%) and 93% (95% CI: 86% to 100%), respectively.

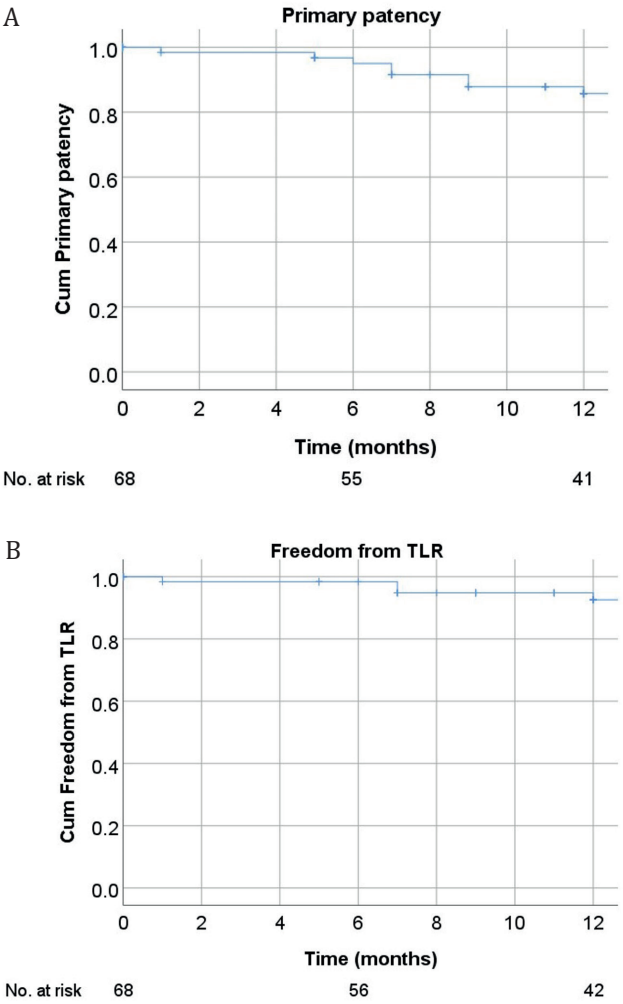

Figure 4.2. Kaplan-Meier curves for (A) primary patency per scaffold and (B) freedom from target lesion revascularization (TLR).

There was one major amputation within 30 days of the index procedure due to infected wet gangrene of the heel after successful revascularization. This was not deemed to be procedure related. Freedom from major amputation was 98% (95% CI: 93% to 100%) at 6 months and 1 year after the index procedure. Amputation-free survival was estimated at 93% (95% CI: 85% to 100%) at 6 months and 85% (95% CI: 74% to 97%) at 1 year after the index procedure. Five (12%) deaths occurred within 1 year of the index procedure due to cardiovascular causes (n = 2), pneumonia (n = 2), and sepsis (n = 1).

Wound healing was achieved in 24 (62%) of the 39 Rutherford category 5/6 patients at 6 months and in 31 patients (79%) at 12 months. Median time to wound healing was 4 months (IQR 6). Rest pain was resolved in all patients. Resolution of CLTI without TLR was noted in 26 of 41 patients (63%) at 6 months and in 33 (81%) by 12 months.

Discussion

This is the first study to report the safety and effectiveness of the Absorb BVS for the treatment of infrapopliteal disease in Asian patients with CLTI. Good clinical and patency outcomes were achieved in this cohort of patients with multiple comorbidities.

Previous studies of the Absorb BVS in the infrapopliteal arteries included 68% to 90% of patients with CLTI, 65% to 71% of patients with Rutherford category 5 or 6 ischemia, 33% to 61% of patients with diabetes, and 2.9% with dialysis-dependent renal failure.[14–16] Our study cohort, however, included patients with more complex comorbidities and clinical presentation. All our patients had CLTI, with 95% Rutherford category 5 or 6 ischemia. There were also high proportions of patients with diabetes (90%) and chronic kidney disease (32%; 5 dialysis-dependent), thus making our patient cohort the most complex group of patients treated with BVS to date. The lesion characteristics in our study were broadly similar to previous studies.[14–16] The majority of the treated lesions were short, which was unavoidable due to the limited available lengths of the scaffold. A quarter of the lesions had severe calcification.

Despite the greater complexity of our patient cohort in terms of comorbidities, clinical presentation, and lesion characteristics, the early and midterm outcomes in our study were respectable compared with the other published series of infrapopliteal BVS and metallic DES.[14–17] Our 86% 12-month patency rate was somewhat inferior to patency rates noted in the existing BVS studies (92%–96%),[14–16] which could be explained by a more complex group of patients in the current study. The presence of diabetes, calcification, and associated lesion complexity is known to adversely affect the outcomes in patients with PAD[18,19] and could have been contributing factors. Furthermore, vessel preparation was not mandatory in our early experience nor was it mandatory in the early use of BVS in the coronary arteries. Standardized vessel preparation has been shown to be essential in obtaining a good angiographic and clinical result in coronary artery disease and PAD.[13,20] Despite these limitations, our patients experienced patency rates in the range reported for metallic DES (80%–86%).[17,21]

The lower 12-month patency rate in our study did not translate to a significant

need for CD-TLR. Freedom from CD-TLR at 12 months in our study was 93% vs 96% in a previous study on Absorb BVS with a relatively high 96% 12-month patency rate.[14]

Despite the high patient and lesion complexity and comparatively modest patency rates, complete wound healing was noted in a high proportion of Rutherford category 5 or 6 patients at 6 months and 1 year in our study (62% and 79%, respectively), with a similar trend seen in other BVS studies (64% at 1 year).[15]

There are very few published studies in the literature evaluating the use of bioresorbable scaffolds for the treatment of BTK disease; early studies were not promising. In the AMS INSIGHT study (Bioabsorbable Metal Stent Investigation in Chronic Limb Ischemia Treatment), 117 CLTI patients (Rutherford category 4 or 5) with 149 lesions were randomized to receive implantation of an absorbable metal (magnesium-alloy) stent (AMS; Biotronik AG, Berlin, Germany) (60 patients, 74 lesions) or PTA (57 patients, 75 lesions). The primary outcome of 6-month angiographic patency was significantly lower for lesions treated with AMS vs PTA (32% vs 58%, p = 0.013). The limb salvage rates were also numerically lower in the AMS vs PTA groups (87.6% vs 92.4%, respectively; p = 0.434).[22] On the contrary, the findings from our study and others[14–16] collectively suggest that the Absorb BVS may be an effective and safe option for the treatment of infrapopliteal disease, even in high-risk CLTI patients.

Limitations

First, as this was a retrospective, observational study, no direct comparison could be made with other treatment modalities. Second, not all patients had the same follow-up schedule. This resulted in different timing of radiologically-determined restenosis. Third, this was a single-center study, which may be a source of bias. Finally, duplex ultrasound was used to assess patency, which has not been universally validated for angiographic follow-up and is operator dependent.

Conclusion

The current study showed good clinical and radiological results with the Absorb BVS for the treatment of infrapopliteal arterial disease in a predominately diabetic

cohort of Asian patients with CLTI. Further research is needed to understand the long-term benefits with Absorb BVS in these patients and determine any influence of the high-risk phenotype of these patients (diabetes, cardiac disease, and complex PAD) on the treatment outcomes. Studies may also be needed in the future to establish the efficacy and safety of Absorb BVS in long BTK lesions.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Steven Kum and Ramon Varcoe are consultants to Abbott Vascular. Constantijn Hazenberg is a consultant at Boston Scientific and Philips Healthcare.

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