A systematic review and meta-analysis of bioresorbable vascular scaffolds for below-the-knee arterial disease

Ipema, Jetty; Kum, Steven; Huizing, Eline; Schreve, Michiel A; Varcoe, Ramon L; Hazenberg, Constantijn E; DE Vries, Jean-Paul; ÜnlÜ, Çağdaş

Published in:
International angiology

DOI:
10.23736/S0392-9590.20.04462-4

Publication date:
2021

Online version at http://www.minervamedica.it

International Angiology 2021 February;40(1):42-51
DOI: 10.23736/S0392-9590.20.04462-4

REVIEW

PERIPHERAL ARTERIAL DISEASE

EDITOR'S CHOICE

A systematic review and meta-analysis of bioresorbable vascular scaffolds for below-the-knee arterial disease

Jetty IPEMA [1] *, Steven KUM [2], Eline HUIZING [1], Michiel A. SCHREVE [1], Ramon L. VARCOE [3, 4, 5], Constantijn E. HAZENBERG [6], Jean-Paul DE VRIES [7], Çağdaş ÜNLÜ [1]

[1]Department of Vascular Surgery, Northwest Clinics, Alkmaar, the Netherlands; [2]Department of Surgery, Changi General Hospital, Singapore, Singapore; [3]Department of Surgery, Prince of Wales Hospital, Sydney, Australia; [4]Faculty of Medicine, University of New South Wales, Sydney, Australia; [5]The Vascular Institute, Prince of Wales Hospital, Sydney, Australia; [6]Department of Vascular Surgery, University Medical Center (UMC) Utrecht, Utrecht, the Netherlands; [7]Department of Surgery, Division of Vascular Surgery, University Medical Center Groningen (UMCG), Groningen, the Netherlands

*Corresponding author: Jetty Ipema, Department of Vascular Surgery, Northwest Clinics, Wilhelminalaan 12, 1815 JD Alkmaar, the Netherlands. E-mail: j.ipema@nwz.nl

ABSTRACT

Introduction: Different types of bioresorbable vascular scaffolds (BVSs) have been developed and used in below-the-knee (BTK) arterial diseases. This is the first study reviewing and analyzing the literature on BVS treatment for BTK arterial disease.

Evidence acquisition: MEDLINE, Embase, and Cochrane were searched for studies published until October 21, 2019. The search, study selection, quality assessment, and data extraction were performed by 2 authors independently. Articles that studied the treatment of BTK arterial disease by using BVSs were eligible. Exclusion criteria were studies with a variant design (*e.g.* case reports <5 patients), non-BTK indications for BVS use, and nonhuman studies. Primary endpoint was 12-month primary patency. Secondary endpoints were 12-month freedom from clinically driven target lesion revascularization (CD-TLR), limb salvage, survival, and amputation-free survival (AFS). Study quality was assessed by the Methodological Index for Non-randomized Studies score.

Evidence synthesis: Five studies representing 155 patients with 160 treated limbs met the inclusion criteria. Pooled 12-month primary patency per limb was 90% (143/160; 95% confidence interval [CI]: 0.84-0.95), freedom from CD-TLR 96% (124/130; 95% CI: 0.91-0.99), limb salvage rate 97% (156/160; 95% CI: 0.94-1.00), survival rate 90% (112/125; 95% CI: 0.82-0.96), and AFS rate 89% (110/125; 95% CI: 0.81-0.94). Subgroup analyses of included Absorb BVS studies showed similar results. All studies were assessed as moderate quality.

Conclusions: This meta-analysis of case series showed good 12-month patency and clinical results with BVSs for BTK arterial disease, even in patients with multimorbidity and short but complex lesions. These results encourage a revival of this scaffold.

(*Cite this article as:* Ipema J, Kum S, Huizing E, Schreve MA, Varcoe RL, Hazenberg CE, *et al*. A systematic review and meta-analysis of bioresorbable vascular scaffolds for below-the-knee arterial disease. Int Angiol 2021;40:42-51. DOI: 10.23736/S0392-9590.20.04462-4)

Key words: Blood vessels; Ischemia; Arteries; Meta-analysis; Systematic review.

Introduction

Endovascular treatment is increasingly being used as therapy for patients with chronic limb-threatening ischemia instead of bypass surgery.[1] Although the technology and skills have improved, restenosis rates remain high. Below-the-knee (BTK) use of drug-eluting stents (DESs) has shown superiority over balloon angioplasty and bare-metal stents in preserving patency up to 12 months.[2] However, these permanent implants have disadvantages. First, the metallic alloy of the stent affects the vessel wall, resulting in loss of vasomotor tone, endothelial dysfunction, and chronic inflammation leading to late lumen loss.[3, 4] The stents also make future revascularizations more complicated, and there is a risk of stent fracture.[5]

Bioresorbable vascular scaffolds (BVSs) have been developed to overcome these drawbacks. The short-term effect as with the metallic alloy in preventing acute recoil remains, but late lumen loss resulting from chronic inflammation is prevented due to complete scaffold resorption. Different types of BVSs entered the market, some of which contained a magnesium alloy and others are poly-L-lactide polymer-coated stents impregnated with the antiproliferative drug everolimus.

The first use of BVSs in coronary artery disease was controversial due to high restenosis rates.[6] The results were attributed to suboptimal implantation techniques and inappropriate strut thickness.[7] As a result, the use of these implants in BTK arterial disease also became a topic of discussion. So far, no overview has been provided on short-term clinical outcomes of BVS treatment for BTK arterial disease. New studies have recently been published[8, 9] and a new type of BVS is just launched (ESPRIT™, Abbott Vascular, Santa Clara, CA, USA). Therefore, this systematic review and meta-analysis was performed to give an overview of the short-term clinical outcomes of BVS treatment for BTK arterial disease known so far. The main goal is to study the restenosis rate of BVSs and discuss whether there is a place for BVSs in this population.

Evidence acquisition

This report meets the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Figure 1) guidelines for reporting systematic reviews and meta-analyses.[10] Because this was a literature study, approval from an Institutional Review Board was not required. The study was not registered on the International Prospective Register of Systematic Reviews.

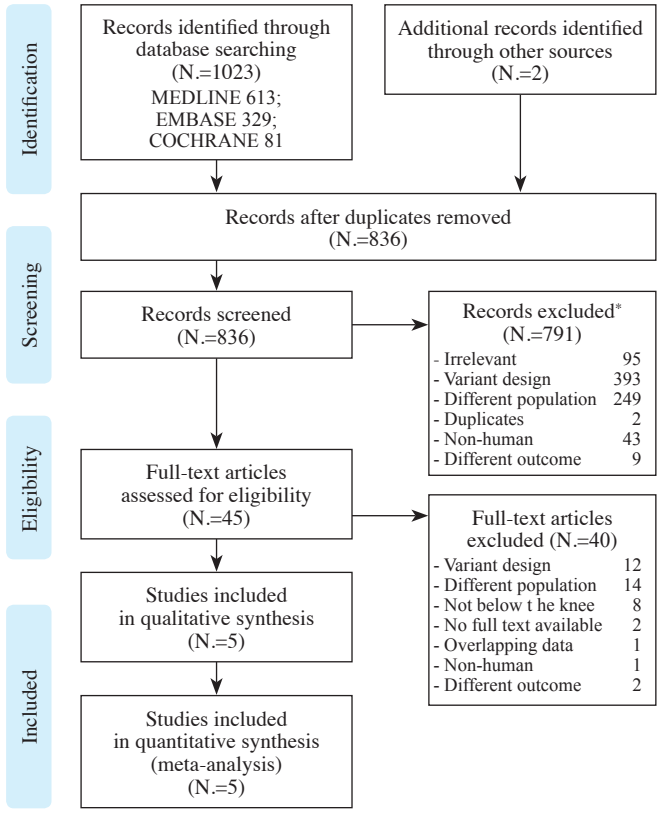

Figure 1.—Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for literature search to identify studies reporting on below-the-knee use of bioresorbable vascular scaffolds. *Some articles had more than one reason to be excluded.

Literature search

MEDLINE, Embase, and the Cochrane Database of Systematic Reviews were searched for eligible articles published until October 21, 2019. The keywords used were bioabsorbable stent, bioabsorbable scaffold, bioresorbable scaffold, bioresorbable stent, biodegradable stent, biodegradable scaffold, peripheral artery disease, peripheral arterial disease, critical limb ischemia, critical limb ischemia, chronic limb-threatening ischemia, chronic limb-threatening ischemia, below the knee, infrapopliteal, crural, and angioplasty. Supplementary Digital Material 1 (Supplementary Table I) shows the full search strategy.

Study selection

After duplicates were removed, 2 authors (J.I., E.H.) screened the titles and abstracts of the studies identified through the search. The remaining studies were assessed for inclusion by full-text reading. Included were articles that studied the treatment of BTK arterial disease by us-

ing BVSs and reported results on the primary or secondary endpoints, or both. The primary endpoint was 12-month primary patency, which was defined as freedom from binary restenosis and target vessel occlusion. Binary restenosis was defined as a peak systolic velocity >2 m/s, a peak systolic velocity ratio >2.0, doubling of the proximal peak systolic velocity rate, or stenosis >50% assessed by angiography or duplex.[11] Secondary endpoints were 12-month freedom from clinically driven target lesion revascularization (CD-TLR), limb salvage, overall survival, and amputation-free survival (AFS). Limb salvage was defined as freedom from major amputation, defined as amputation above the ankle. Survival was defined as freedom from all-cause death.

Exclusion criteria were studies with a variant design (case reports <5 patients, comments, letters to the editor, guidelines, reviews, book chapters, and articles not available in English, Dutch, German, or Spanish), studies of patients with non-BTK indications for BVS use, and nonhuman studies. A third author (Ç.Ü.) was consulted if disagreement occurred between the authors in the study selection.

Data collection

Study characteristics and baseline data of the included studies were collected by one author (J.I.) and checked by another author (E.H.). Extracted data included year of publication, study design, study period, inclusion criteria, exclusion criteria, number of patients included, baseline patient demographics and comorbidities and Rutherford category. Information on scaffold, lesion, and procedure were also collected. Outcomes data were extracted from the included articles and discussed by 3 authors (J.I., S.K., E.H.). Patient-level data from 3 papers were used after requesting the authors for the original data from these papers.[8, 9, 12]

Data analysis

Meta-Analyst 3.1 software (Tufts University, Medford, MA, USA) was used to perform meta-analyses. Pooled data were analyzed with a random-effects model. Results were presented as the Freeman-Tukey transformed proportion. Tests of heterogeneity between the studies were performed and the results are shown as I^2 indices and p values. I^2 is a test for the variation of point estimates and was rated as <40% for low variation, 30-60% for moderate variation, 50-90% for substantial variation, and 75-100% for considerable variation. A P value of <0.05 indicated a difference between the studies in the underlying magnitude of effect and therefore reflected high heterogeneity.[13]

Study quality assessment

The quality of noncomparative studies was assessed with the Methodological Index for Non-randomized Studies (MINORS) score.[14] Each study was assessed on 8 criteria, for which a total score of 16 could be achieved. A score of ≤8 was considered poor quality, 9 to 14 as moderate quality, and 15 to 16 as good quality.

Evidence synthesis

Included studies

The search identified 1043 articles, of which 834 remained for title and abstract screening after duplicates were removed. There were 43 articles eligible for full-text reading based on title and abstract. Two articles were added from other sources: one was a cross reference and one was our own recent study. Finally, this resulted in 5 articles[8, 9, 12, 15, 16] that met the inclusion criteria: 2 prospective case series,[12, 16] 2 retrospective case series,[8, 9] and 1 retrospective registry study.[15] Reasons for exclusion were variant design (N.=12),[17-28] different population (N.=14),[29-42] not BTK (N.=8),[43-50] full text not available (N.=2),[51, 52] overlapping data (N.=1),[53] nonhuman (N.=1),[54] and different outcome (N.=2).[55, 56]

Characteristics of the included studies

The 5 included studies represented the results of 160 limbs treated in 155 patients, because 1 study included 5 patients with bilateral treatment.[12] Rutherford category of the included patients ranged from 3 to 6, except for 1 study that did not specify critical limb ischemia by Rutherford classification.[15] The Absorb BVS (Abbott Vascular, Santa Clara, CA, USA) was used in 3 studies,[8, 9, 12] and the Absorbable Metal Stent (Magic, Biotronik, Berlin, Germany)[16] and the Biolimus A9-eluting stent (BES, BioMatrix Flex, Biosensor International, Newport Beach, CA, USA)[15] were used in 1 study each. Available stent lengths were Absorb BVS: 8, 12, 18, 23, and 28 mm;[12] Magic: 10 and 15 mm;[16] and BES: 8, 11, 14, 18, 24, 28, 33 and 36 mm.[57]

Treated vessels of all included patients were the anterior tibial artery, posterior tibial artery, and peroneal artery. Four studies also included treatment of the tibioperoneal trunk,[9, 12, 15, 16] and 2 also of the P3 segment of the popliteal artery.[9, 12] Two studies performed standard predilatation,[8, 12] 2 in part of the cases,[9, 15] and 1 did not mention the use of predilatation.[16] One study performed standard postdilatation,[8] 3 studies performed postdilatation in part of the cases[9, 12, 16] and one did not mention it.[15]

The postprocedural antiplatelet regimen consisted of as-

TABLE I.—*Characteristics of the included studies.*

Study	Study design	Study period	Inclusion criteria	Exclusion criteria
Bosiers 2005[16]	Prospective case series	December 2003 till 3 January 2004	Symptomatic critical limb ischemia patients, defined as an ankle pressure <50-70 mmHg, a reduced toe pressure 30-50 mmHg, or a reduced transcutaneous oxygen pressure <30-50 mmHg), high-grade (80% to 100%) atherosclerotic lesions in the proximal two thirds of one or more of the infrapopliteal arteries. Rutherford 4-5. Stent implantation for suboptimal angioplasty (*i.e.* residual stenosis or dissection) in lesions ≤30 mm long.	Not mentioned
Stabile 2016[15]	Retrospective registry	May 2012 till May 2014	Patients with lower limb ischemia undergoing primary BES placement in focal infrapopliteal lesions (67% critical limb ischemia), patients on aspirin (75-160 mg/day) and ticlopidine (250 mg twice daily) for at least 7 days	Not mentioned
Varcoe 2016[12]	Prospective case series	September 2013 till November 2015	Rutherford 3-6, chronic, *de-novo* stenotic lesion >60% severity in tibial or distal popliteal arteries, length ≤5 cm, vessel diameter 2.5-4.0 mm, successfully treated inflow lesions, at least 1 single vessel outflow to the foot	Unable to give consent, life expectancy <12 months, significant renal failure precluding angiography, contrast allergy, intolerant for DAPT, calcified lesions
Dia 2019[8]	Retrospective case series	December 2016 till January 2017	Rutherford 3-6, chronic, *de-novo* stenotic lesion >60% severity in anterior tibial artery, posterior tibial artery, peroneal artery between 2.5-4.0 mm	Unable to give consent, life expectancy <12 months, significant renal failure precluding angiography, intolerant for DAPT
Kum 2019[9]	Retrospective case series	August 2012 and June 2017	Rutherford 4-6, age >21 years, *de-novo* stenotic lesions in infrapopliteal arteries, visual angiographic RVD 2.5 and 4.0 mm, angiographic stenosis >50%	BVS in tibial artery within 8 cm of or below the ankle joint

BES: Biolimus A9-eluting stent. BVS: bioresorbable vascular scaffold. DAPT: dual antiplatelet therapy. RVD: reference vessel diameter.

pirin and clopidogrel for 6 months in 3 of the studies.[9, 12, 15] One study prescribed the same form of dual-antiplatelet therapy but specified no duration[8] and 1 study did not specify the type or duration of antiplatelet therapy.[16] A detailed description of the patient, scaffold, and lesion characteristics and procedural data of the included studies is provided in Table I, II.[8, 9, 12, 15, 16]

Study quality of the included studies

The 5 studies were of moderate quality as assessed by MINORS score (Table III).[8, 9, 12, 15, 16] None of the studies described unbiased assessment of the study endpoints, and none of the studies described a prospectively calculated sample size. In addition, the 2 retrospective studies scored 0 on the criterion "prospective collection of data" and the retrospective registry scored 1 on this point.

Meta-analysis

Primary patency was calculated per limb and per scaffold. The 5 included studies reported primary patency rates per limb and were pooled, resulting in 12-month primary patency per limb of 90% (143 of 160; proportion: 0.90; 95% confidence interval [CI]: 0.84 to 0.95) (Figure 2A). 12-month primary patency per limb for the Absorb BVS studies was 91% (99 of 110; proportion: 0.91; 95% CI: 0.83 to 0.96).

Data on primary patency per scaffold were available from 4 studies.[8, 9, 12, 16] These were pooled, resulting in 12-month primary patency per scaffold of 91% (172 of 191; proportion: 0.91; 95% CI: 0.83 to 0.96) (Figure 2B). For the Absorb BVS studies only 12-month primary patency per scaffold was 92% (153 of 168; proportion: 0.92; 95% CI: 0.84 to 0.98).

One study reported scaffold thrombosis in two scaffolds of the same patient. The other studies reported no scaffold thrombosis. Thrombosis rates per type of scaffold were: Absorbable metal stent Biotronik 0/23 scaffolds, Biolimus A9-eluting stent 0/30 limbs, and Everolimus eluting bioresorbable scaffold 2/168 scaffolds.

Four studies reported data on CD-TLR and were therefore pooled, resulting in 12-month freedom from CD-TLR of 96% (124 of 130; proportion: 0.96; 95% CI: 0.91 to 0.99) (Figure 2C).[8, 9, 12, 16] Combining results from the Absorb BVS studies, 12-month CD-TLR was 96% (105 of 110; proportion: 0.96; 95% CI: 0.91 to 0.99).

The 12-month limb salvage rate of the pooled data of the 5 studies was 97% (156 of 160; proportion: 0.97; 95% CI: 0.94 to 1.00) (Figure 2D). However, none of the stud-

TABLE II.—*Patient characteristics, scaffold, lesion and procedural data of the included studies.*

Study	Bosiers 2005[16]	Stabile 2016[15]	Varcoe 2016[12]	Dia 2019[8]	Kum 2019[9]
Patient (N.)	20	30	33	31	41
Age, year, mean or median (range)	76±8	69.7±10.0	81.1±7.9	68.6±8.2	64 (15)
Male	10 (50)	21 (70)	18 (55)	16 (51.6)	23 (56)
DM	10 (50)	19 (63)	11 (33)	19 (61.3)	37 (90)
HL	8 (40)	19 (64)	24 (73)	17 (54.8)	36 (88)
HT	14 (70)	25 (84)	31 (94)	12 (38.7)	37 (90)
IHD	11 (55)	17 (57)	12 (36)	18 (58.1)	24 (59)
RD	4 (20)	11 (36)	9 (27)	4 (1.3)	5 (12)
Smoking	10 (50)	12 (40)	25 (76)	18 (58.1)	16 (48)
Rutherford category					
3	-	NS	12 (32)	3 (9.7)	-
4	9 (45)	NS	1 (3)	7 (22.6)	2 (4.9)
5	11 (55)	NS	20 (53)	14 (45.2)	24 (58.5)
6	-	NS	5 (13)	7 (22.6)	15 (36.6)
Limbs	20	30	38	31	41
Vessels	20	30	-	41	53
Lesions	20	-	43	-	53
Lesion site					
P3	-	NS	2/43* (4.7)	-	5/53 (9.4)
TPT	5/20 (25)	NS	18/43* (41.9)	-	17/53 (32.1)
ATA	7/20 (35)	NS	11/43* (25.6)	16/49 (32.7) per scaffold	14/53 (26.4)
ATP	1/20 (5)	NS	9/43* (20.9)	22/49 (44.9) per scaffold	11/53 (20.8)
PER	7/20 (35)	NS	8/43* (18.6)	11/49 (22.4) per scaffold	6/53 (11.3)
RVD, mm, mean±SD or median (range)	3.0=mean	3.10±0.91	3.0 (2.5-4.0)	3.5 (2.75-3.5) NB stent diameter	3.0 (2.5-3.5)
Stenosis percentage, mean±SD or median (range)	84 (70-95)		80 (60-100)	100 (80-100)	80 (50-100)
Lesion length (mm)	11=mean (2-20)	23.5±9.4	19.2 (5-50)	30.9 (10-60)	22.7 ± 17.2
Scaffolds	23	-	50	49	69
Scaffold type	Absorbable metal stent Biotronik	Biolimus A9-eluting stent	Everolimus eluting bioresorbable scaffold	Everolimus eluting bioresorbable scaffold	Everolimus eluting bioresorbable scaffold

Values are expressed as N. (%).
ATA: anterior tibial artery; ATP: posterior tibial artery; DM: diabetes mellitus. HL: hyperlipidemia; HT: hypertension; IHD: ischemic heart disease; NB: nota bene; NS: not further specified; P3: distal poplitea; PER: peroneal artery; Pt: patient; RD: renal disease; RVD: reference vessel diameter; SD: standard deviation.; PT: tibioperoneal trunk.
*A lesion could involve more than one vessel.

ies gave a definition of major amputation. Limb salvage of the Absorb BVS studies was 98% after 12-monhts (108 of 110; proportion: 0.98; 95% CI: 0.94 to 1.00).

Survival data from 4 included studies were pooled, resulting in a 12-month survival rate of 90% (112 of 125; proportion: 0.90; 95% CI: 0.82 to 0.96) (Figure 2E).[8, 9, 12, 16] One study described only one cardiovascular- and cerebrovascular-related death.[15] Whether there were any all-cause deaths was unclear. This study was therefore not included in the meta-analysis on this outcome parameter. Pooling survival data from the Absorb BVS studies resulted in 12-month survival of 91% (95 of 105; proportion: 0.91; 95% CI: 0.81 to 0.98).

Finally, AFS data from 4 studies were pooled, and the 12-month AFS rate was 89% (110 of 125; proportion: 0.89; 95% CI: 0.81 to 0.94) (Figure 2F).[8, 9, 12, 16] 12-month AFS rate from the 3 studies using the Absorb BVS was also 89% (93 of 105; proportion: 0.89; 95% CI: 0.80 to 0.96).

Heterogeneity based on I^2 showed moderate variation

TABLE III.—*Methodological index for non-randomized studies to assess the quality of noncomparative studies.*

Criterion	Article				
	Bosiers 2005[16]	Stabile 2016[15]	Varcoe 2016[12]	Dia 2019[8]	Kum 2019[9]
1. A clearly stated aim	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	2	2
3. Prospective collection of data	2	1	2	0	0
4. Endpoint appropriate to the aim of the study	2	2	2	2	2
5. Unbiased assessment of the study end point	0	0	0	0	0
6. Follow-up period appropriate to the aim of the study	2	2	2	2	2
7. Loss to follow-up less than 5%	2	2	2	2	2
8. Prospective calculation of the study size	0	0	0	0	0
Total MINORS score	12	11	12	10	10
Maximum possible score	16	16	16	16	16

0: not reported; 1: reported, but inadequate; 2: reported and adequate.

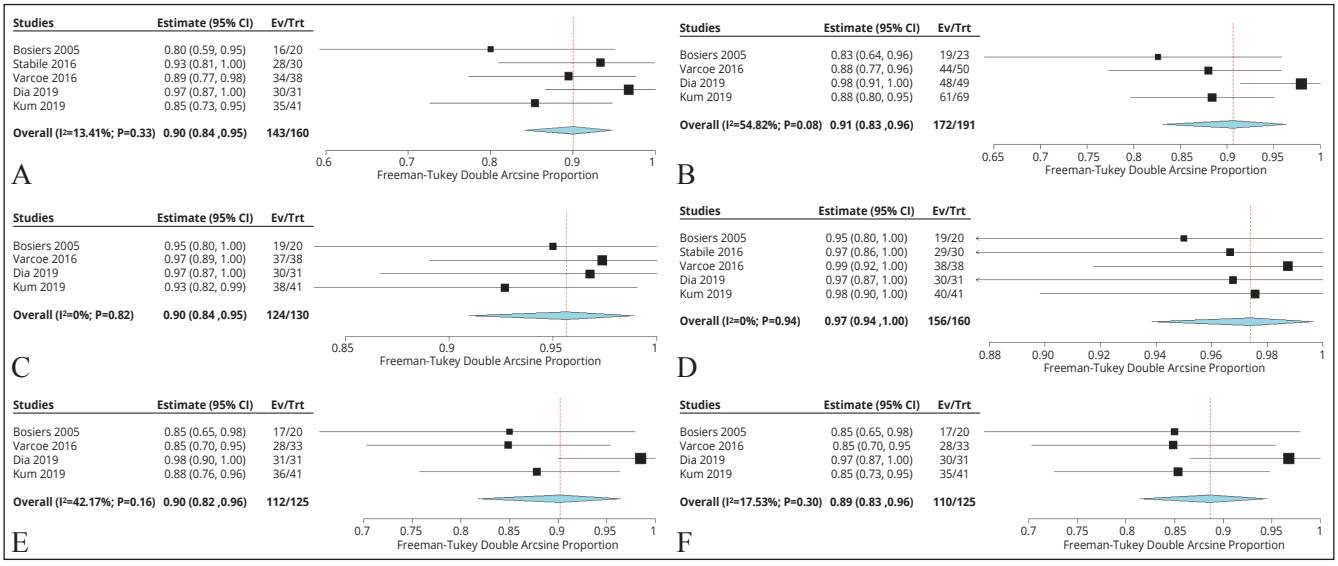

Figure 2.—A) Forest plots of the pooled 12-month rates for primary patency per limb; B) forest plots of the pooled 12-month rates for primary patency per scaffold; C) forest plots of the pooled 12-month rates for freedom from clinically-driven target lesion revascularization; D) forest plots of the pooled 12-month rates for limb salvage; E) forest plots of the pooled 12-month rates for survival; F) forest plots of the pooled 12-month rates for amputation-free survival.

for primary patency per scaffold and survival, and low variation for the other outcomes. None of the P values showed significant heterogeneity.

Discussion

This systematic review and meta-analysis was performed to give an update on the clinical outcomes of BVSs in patients with BTK arterial disease. The included studies showed good 12-month primary patency, survival, and limb salvage rates, but this was based on case series of moderate quality and no randomized controlled trials. In addition, even in this population with a high risk of cardiovascular adverse events, AFS was 89% after 12 months.

Focusing on the results of the individual studies, the results of the Bosiers *et al*.[16] study showed the lowest patency and limb salvage rates. The Magic stent was used, which does not contain an antiproliferative drug such as everolimus. Animal studies have shown negative remodeling after bioresorbable magnesium alloyed scaffolds on the short-term.[58, 59] Besides, the superiority of DESs for preventing restenosis has been shown over the use of bare-metal stents in different randomized trials.[2] Therefore, drug eluting BVSs seem to be preferred over magnesium alloyed bioresorbable scaffolds.

The study of Dia *et al*.[8] showed excellent results of 97-98% on all outcomes, even though this study population

had severe obstructions (range, 80-100%) and long BTK lesions (median length, 30.9 mm) compared with the other study populations. This was the only study that performed standard predilatation and postdilatation. Patency and freedom from CD-TLR were evidently lower in the Kum *et al*.[9] study. This study population included a large proportion of diabetic patients (90%) and Rutherford 5 and 6 patients (95%) compared with the other studies. Both can explain the lower patency rates found in the latter study. Nevertheless, limb salvage rates were still good.

The 12-month primary patency of 90% for BVSs in this meta-analysis was much higher than the 75.8% for DESs and 47.9% for BMSs, drug-coated balloon angioplasty, and plain old balloon angioplasty shown by another meta-analysis.[60] In addition to the 12-month outcomes of the current study, 5-year results from a single center were recently presented. Besides procedural and technical success, and limb salvage of 100%, primary patency was 72.9%, and freedom from CD-TLR was 90.7%.[61] These results are excellent compared with 5-year follow-up results of the PADI trial (percutaneous angioplasty and drug-eluting stents for infrapopliteal lesions in critical limb ischemia trial), which showed patency rates of 11.6% for DESs and 8.6% for bare-metal stents and percutaneous transluminal angioplasty, although this trial included only patients with critical limb ischemia.[62] The advantage of BVSs over DESs is that the BVS provides a strong structure to prevent elastic recoil, with release of antiproliferative drugs, similar to the DES, but then disappears which makes that it does not hinder future interventions or imaging. However, a direct comparison between BVSs and bare-metal stents and DESs cannot be made since no data from randomized controlled trials on BVSs are available.

Owing to an increase in adverse events and scaffold thrombosis in coronary artery disease compared with standard of care, the Absorb BVS was withdrawn from the market. Coronary and peripheral artery disease are quite similar because both diseases are based on atherosclerosis; however, biochemical differences exist, such as differences in concentrations of low-density lipoprotein cholesterol and C-reactive protein, reflecting the different disease pathologies.[63] Furthermore, treatment goals and effects of complications differ between coronary and peripheral artery disease.[64, 65] If late scaffold thrombosis or restenosis occurs in peripheral arteries after wound healing has taken place, it is not so harmful, whereas late scaffold thrombosis or restenosis in coronary arteries leads to myocardial infarction and possible death. Extrapolating studies including patients with coronary artery disease to studies with peripheral arterial disease patients is therefore not justifiable.

BVSs are still being developed. Second-generation stents have already demonstrated better results in cardiology due to thinner struts and improved expansion characteristics.[66, 67] Adjustment of stent diameter and length specifically for BTK vessels could probably improve results for BTK use. A new type of BVS has just been introduced. In addition, predilatation and postdilatation treatment differed between all included studies, because there is yet no standardized predilatation and postdilatation protocol for BTK use of BVSs. The importance of a dedicated protocol of implantation techniques has shown favorable results in coronary use.[68, 69]

Limitations of the study

This study has some limitations. First, none of the included studies is a comparative or randomized trial; therefore, no direct comparison can be made with other BTK strategies. Second, the numbers of the included studies and numbers per study are relatively small. However, this is the first study giving an overview of all published results on BTK use of BVSs so far, showing promising results. Taking this in mind, the importance of the new randomized controlled LIFE-BTK trial (ClinicalTrials.gov Identifier: NCT04227899) studying an improved bioresorbable stent, in a dedicated study population of 225 patients, will be very worthful. Third, the studies in this meta-analysis use different BVSs with different properties, regarding the use of antiproliferative drugs and resorption time. Therefore, subgroup analyses of studies that used the Absorb BVS were performed and results were similar. Fourth, heterogeneity was seen between the studies regarding study populations, lesion characteristics, and treatment strategies. However, the variety reflects daily practice. Fifth, not all studies gave clear definitions of study endpoints, such as amputation, and comorbidities, such as renal disease, which were not further specified. Because major amputation is commonly defined as amputation above the ankle, we assumed the authors of the different studies used this definition. Sixth, there could be a selection bias, because all studies included relatively short lesions.

Conclusions

The current systematic review and meta-analysis showed good 12-month patency results with BVSs for the treatment of BTK arterial disease, even in high-risk patients with short but complex lesions. This meta-analysis justifies the importance of randomized controlled trials and studies

with long-term follow-up with clearly defined endpoints which are currently missing. A multicenter single-blinded randomized trial will investigate the safety and efficacy of the newest generation BVS.

References

1. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG; TASC II Working Group. Inter-society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg 2007;45:S5–67.

2. Liu X, Zheng G, Wen S. Drug-eluting stents versus control therapy in the infrapopliteal disease: A meta-analysis of eight randomized controlled trials and two cohort studies. Int J Surg 2017;44:166–75.

3. Grewe PH, Deneke T, Machraoui A, Barmeyer J, Müller KM. Acute and chronic tissue response to coronary stent implantation: pathologic findings in human specimen. J Am Coll Cardiol 2000;35:157–63.

4. Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, *et al.* Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202.

5. Otsuka F, Vorpahl M, Nakano M, Foerst J, Newell JB, Sakakura K, *et al.* Pathology of second-generation everolimus-eluting stents versus first-generation sirolimus- and paclitaxel-eluting stents in humans. Circulation 2014;129:211–23.

6. Ali ZA, Serruys PW, Kimura T, Gao R, Ellis SG, Kereiakes DJ, *et al.* 2-year outcomes with the Absorb bioresorbable scaffold for treatment of coronary artery disease: a systematic review and meta-analysis of seven randomised trials with an individual patient data substudy. Lancet 2017;390:760–72.

7. Omar WA, Kumbhani DJ. The Current Literature on Bioabsorbable Stents: a Review. Curr Atheroscler Rep 2019;21:54.

8. Dia A, Venturini JM, Kalathiya R, Besser S, Estrada R, Friant J, *et al.* Single arm retrospective study of bioresorbable vascular scaffolds to treat patients with severe infrapopliteal arterial disease. Catheter Cardiovasc Interv 2019;94:1028–33.

9. Kum S, Ipema J, Chun-Yin DH, Lim DM, Tan YK, Varcoe RL, *et al.* 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. J Endovasc Ther 2020;27:616–22.

10. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

11. Schäberle W. Ultrasonography in Vascular Diagnosis: A Therapy-Oriented Textbook and Atlas. Third Edition. Berlin: Springer; 2016.

12. Varcoe RL, Schouten O, Thomas SD, Lennox AF. Experience With the Absorb Everolimus-Eluting Bioresorbable Vascular Scaffold in Arteries Below the Knee: 12-Month Clinical and Imaging Outcomes. JACC Cardiovasc Interv 2016;9:1721–8.

13. The GRADE Working Group. GRADE handbook for grading quality of evidence and strength of recommendations; 2013 [Internet]. Available from: https://gdt.gradepro.org/app/handbook/handbook.html [cited 2020, Oct 22].

14. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003;73:712–6.

15. Stabile E, Salemme L, Ferrone M, Arcari A, Cioppa A, Popusoi G, *et al.* Abluminal biodegradable polymer-based Biolimus A9-eluting stent for the treatment of infrapopliteal arteries in critical limb ischemia: long-term follow-up. Int J Cardiol 2016;202:98–9.

16. Bosiers M, Deloose K, Verbist J, Peeters P. First Clinical Application of Absorbable Metal Stents in the Treatment of Critical Limb Ischemia: 12-month results. Vasc Dis Manag. 2005;2.

17. Brugaletta S, Ortega-Paz L, Onuma Y. Data from real-world registries: can it guide development of the bioresorbable scaffolds of tomorrow? EuroIntervention 2017;13:1259–62.

18. Buccheri D, Caramanno G, Geraci S, Cortese B. Should we reconsider dual antiplatelet therapy duration following bioresorbable scaffold angioplasty? J Thorac Dis 2017;9:417–8.

19. Chan KH, Seow SC, Tan HC. Very late bioresorbable vascular scaffold thrombosis at 25 months post implantation. Singapore Med J 2017;58:571–2.

20. Colombo A, Latib A. Can long-term results following balloon angioplasty be the "crystal ball" to predict outcome following bioresorbable vascular scaffolds? J Am Heart Assoc 2012;1:e005272.

21. Cortese B, Buccheri D, Stefanini GG, Mehran R. The Contemporary Pulse of Bioresorbable-Scaffold Thrombosis Among Expert Operators. J Am Coll Cardiol 2016;67:2905–6.

22. Di Mario C, Borgia F. Assimilating the current clinical data of fully bioabsorbable stents. EuroIntervention 2009;5:F103–8.

23. Felix CM, Vlachojannis GJ, IJsselmuiden AJ, Onuma Y, van Geuns RJ. Very Late Scaffold Thrombosis in Absorb BVS: Association With DAPT Termination? JACC Cardiovasc Interv 2017;10:625–6.

24. Nai Fovino L, Barioli A, Tarantini G. 'Full-plastic jacket' with bioresorbable vascular scaffolds: 5-year optical coherence tomography follow-up. Eur Heart J Cardiovasc Imaging 2019;20:370.

25. García-García HM, Schultz C, Duckers E, Regar E, Ligthart J, Serruys PW, *et al.* Five-year follow-up of the ABSORB bioresorbable everolimus-eluting vascular scaffold system: multimodality imaging assessment. EuroIntervention 2013;8:1126–7.

26. Goncalves-Ramírez LR, Gutiérrez H, Rojas P, Cortés C, Serrador A, Ramos B, *et al.* Fully bioresorption of an Absorb bioresorbable vascular scaffold after scaffold restenosis. Cardiol J 2019;26:209–11.

27. Mitomo S, Latib A, Tanaka A, Jabbour RJ, Regazzoli D, Leone PP, *et al.* Dual Antiplatelet Therapy After Bioresorbable Vascular Scaffold Implantation: Insights From the Milan Cohort. JACC Cardiovasc Interv 2017;10:1471–2.

28. Gongora CA, Shibuya M, Ramzipoor K, Lee C, Cheng Y, McGregor JC, *et al.* Vessel Caging Versus Vascular Restoration in the Same Artery: Long-Term Vascular Remodeling and Healing in Response to Overlapping Metal Stent and Bioresorbable Polymer Scaffold. JACC Cardiovasc Interv 2015;8:631–2.

29. Bruining N, Tanimoto S, Otsuka M, Weustink A, Ligthart J, de Winter S, *et al.* Quantitative multi-modality imaging analysis of a bioabsorbable poly-L-lactic acid stent design in the acute phase: a comparison between 2- and 3D-QCA, QCU and QMSCT-CA. EuroIntervention 2008;4:285–91.

30. Liang M, Kajiya T, Lee CH, Chan M, Teo SG, Chan KH, *et al.* Initial experience in the clinical use of everolimus-eluting bioresorbable vascular scaffold (BVS) in a single institution. Int J Cardiol 2013;168:1536–7.

31. Sato K, Latib A, Panoulas VF, Kawamoto H, Naganuma T, Miyazaki T, *et al.* Procedural feasibility and clinical outcomes in propensity-matched patients treated with bioresorbable scaffolds vs new-generation drug-eluting stents. Can J Cardiol 2015;31:328–34.

32. Costopoulos C, Latib A, Naganuma T, Miyazaki T, Sato K, Figini F, *et al.* Comparison of early clinical outcomes between ABSORB bioresorbable vascular scaffold and everolimus-eluting stent implantation in a real-world population. Catheter Cardiovasc Interv 2015;85:E10–5.

33. Brugaletta S, Gomez-Lara J, Serruys PW, Farooq V, van Geuns RJ, Thuesen L, *et al.* Serial in vivo intravascular ultrasound-based echogenicity changes of everolimus-eluting bioresorbable vascular scaffold during the first 12 months after implantation insights from the ABSORB B trial. JACC Cardiovasc Interv 2011;4:1281–9.

34. Onuma Y, Serruys PW, Gomez J, de Bruyne B, Dudek D, Thuesen L, *et al.*; ABSORB Cohort A and B investigators. Comparison of in vivo acute stent recoil between the bioresorbable everolimus-eluting coronary scaffolds (revision 1.0 and 1.1) and the metallic everolimus-eluting stent. Catheter Cardiovasc Interv 2011;78:3–12.

35. Naganuma T, Ishiguro H, Takagi K, Fujino Y, Mitomo S, Nakamu-

ra S, *et al.* Provisional T-stenting with bioresorbable vascular scaffolds in vivo: insights from optical frequency domain imaging. JACC Cardiovasc Interv 2015;8:635–7.

36. Ellis SG, Steffenino G, Kereiakes DJ, Stone GW, van Geuns RJ, Abizaid A, *et al.* Clinical, Angiographic, and Procedural Correlates of Acute, Subacute, and Late Absorb Scaffold Thrombosis. JACC Cardiovasc Interv 2017;10:1809–15.

37. Azzalini L, Giustino G, Ojeda S, Serra A, La Manna A, Ly HQ, *et al.* Procedural and Long-Term Outcomes of Bioresorbable Scaffolds Versus Drug-Eluting Stents in Chronic Total Occlusions: The BONITO Registry (Bioresorbable Scaffolds Versus Drug-Eluting Stents in Chronic Total Occlusions). Circ Cardiovasc Interv 2016;9:e004284.

38. Windecker S, Haude M, Neumann FJ, Stangl K, Witzenbichler B, Slagboom T, *et al.* Comparison of a novel biodegradable polymer sirolimus-eluting stent with a durable polymer everolimus-eluting stent: results of the randomized BIOFLOW-II trial. Circ Cardiovasc Interv 2015;8:e001441.

39. Ribeiro EE, Campos CM, Ribeiro HB, Lopes AC, Esper RB, Meirelles GX, *et al.* First-in-man randomised comparison of a novel sirolimus-eluting stent with abluminal biodegradable polymer and thin-strut cobalt-chromium alloy: INSPIRON-I trial. EuroIntervention 2014;9:1380–4.

40. Wykrzykowska JJ, Serruys PW, Onuma Y, de Vries T, van Es GA, Buszman P, *et al.* Impact of vessel size on angiographic and clinical outcomes of revascularization with biolimus-eluting stent with biodegradable polymer and sirolimus-eluting stent with durable polymer the LEADERS trial substudy. JACC Cardiovasc Interv 2009;2:861–70.

41. Ellis SG, Gori T, Serruys PW, Nef H, Steffenino G, Brugaletta S, *et al.* Clinical, Angiographic, and Procedural Correlates of Very Late Absorb Scaffold Thrombosis: Multistudy Registry Results. JACC Cardiovasc Interv 2018;11:638–44.

42. Yew KL. The buddy balloon technique to release a sticky ABSORB bioresorbable vascular scaffold balloon post-scaffolding. Int J Cardiol 2016;207:1–2.

43. Linni K, Ugurluoglu A, Hitzl W, Aspalter M, Hölzenbein T. Bioabsorbable stent implantation vs. common femoral artery endarterectomy: early results of a randomized trial. J Endovasc Ther 2014;21:493–502.

44. Bontinck J, Goverde P, Schroë H, Hendriks J, Maene L, Vermassen F. Treatment of the femoropopliteal artery with the bioresorbable REMEDY stent. J Vasc Surg 2016;64:1311–9.

45. Werner M, Schmidt A, Scheinert S, Banning-Eichenseer U, Ulrich M, Bausback Y, *et al.* Evaluation of the Biodegradable Igaki-Tamai Scaffold After Drug-Eluting Balloon Treatment of De Novo Superficial Femoral Artery Lesions: the GAIA-DEB Study. J Endovasc Ther 2016;23:92–7.

46. Werner M, Micari A, Cioppa A, Vadalà G, Schmidt A, Sievert H, *et al.* Evaluation of the biodegradable peripheral Igaki-Tamai stent in the treatment of de novo lesions in the superficial femoral artery: the GAIA study. JACC Cardiovasc Interv 2014;7:305–12.

47. Silingardi R, Lauricella A, Coppi G, Nicolosi E, Gennai S, Coppi G. Midterm results of endovascular treatment of superficial femoral artery disease with biodegradable stents: single-center experience. J Vasc Interv Radiol 2015;26:374–81.e1.

48. Tiryakioglu SK, Tiryakioglu O, Karahan O, Demirtas S, Gokalp F, Erkoc K, *et al.* Clinical features and patency rates of Remedy® biodegradable peripheral stents. Cardiovasc J Afr 2016;27:238–41.

49. Giordano A, Ferraro P, Corcione N, Messina S, Maresca G, Coscioni E, *et al.* Endovascular Therapy for Infrainguinal Artery Disease With Coronary Devices: A Retrospective Observational Study Comparing Drug-Eluting Stents Versus Bioresorbable Vascular Scaffolds. Angiology 2017;68:59–66.

50. Lammer J, Bosiers M, Deloose K, Schmidt A, Zeller T, Wolf F, *et al.* Bioresorbable Everolimus-Eluting Vascular Scaffold for Patients With Peripheral Artery Disease (ESPRIT I): 2-Year Clinical and Imaging Results. JACC Cardiovasc Interv 2016;9:1178–87.

51. Mitomo S, Candilio L, Tanaka A, Latib A, Colombo A. "Golden tube" with favorable vessel remodeling at four-year follow-up after bioresorbable vascular scaffold implantation for moderate to severe calcified lesions: insights from intravascular imaging. Cardiol J 2018;25:532–3.

52. Miyazaki T, Latib A, Ruparelia N, Kawamoto H, Sato K, Figini F, *et al.* The use of a scoring balloon for optimal lesion preparation prior to bioresorbable scaffold implantation: a comparison with conventional balloon predilatation. EuroIntervention 2016;11:e1580–8.

53. Varcoe RL, Schouten O, Thomas SD, Lennox AF. Initial experience with the absorb bioresorbable vascular scaffold below the knee: six-month clinical and imaging outcomes. J Endovasc Ther 2015;22:226–32.

54. Lee JH, Kim SJ, Park SI, Ko YG, Choi D, Hong MK, *et al.* Development of a New Hybrid Biodegradable Drug-Eluting Stent for the Treatment of Peripheral Artery Disease. BioMed Res Int 2016;2016:6915789.

55. Danzi GB, Sesana M, Arieti M, Villa G, Rutigliano S, Aprile A, *et al.* Does optimal lesion preparation reduce the amount of acute recoil of the Absorbe BVS? Insights from a real-world population. Catheter Cardiovasc Interv 2015;86:984–91.

56. Ormiston JA, Webber B, Ubod B, Darremont O, Webster MW. An independent bench comparison of two bioresorbable drug-eluting coronary scaffolds (Absorb and DESolve) with a durable metallic drug-eluting stent (ML8/Xpedition). EuroIntervention 2015;11:60–7.

57. Endovascular Today. EUROPEAN Device Guide / Drug-Eluting Stents; 2020 [Internet]. Available from: https://evtoday.com/device-guide/ecember/drug-eluting-stents-2 [cited 2020, Oct 22].

58. Maeng M, Jensen LO, Falk E, Andersen HR, Thuesen L. Negative vascular remodelling after implantation of bioabsorbable magnesium alloy stents in porcine coronary arteries: a randomised comparison with bare-metal and sirolimus-eluting stents. Heart 2009;95:241–6.

59. Di Mario C, Griffiths H, Goktekin O, Peeters N, Verbist J, Bosiers M, *et al.* Drug-eluting bioabsorbable magnesium stent. J Interv Cardiol 2004;17:391–5.

60. Varcoe RL, Paravastu SC, Thomas SD, Bennett MH. The use of drug-eluting stents in infrapopliteal arteries: an updated systematic review and meta-analysis of randomized trials. Int Angiol 2019;38:121–35.

61. Varcoe RL. 5-Year ABSORB BTK Trial Results. Proceedings of the Vascular Interventional Advances Conference 2019; 2019 Nov 2-5; Las Vegas, USA. London: LINC; 2019.

62. Spreen MI, Martens JM, Knippenberg B, van Dijk LC, de Vries JP, Vos JA, *et al.* Long-Term Follow-up of the PADI Trial: Percutaneous Transluminal Angioplasty Versus Drug-Eluting Stents for Infrapopliteal Lesions in Critical Limb Ischemia. J Am Heart Assoc 2017;6:1–11.

63. Agarwal S, Naderi S. Etiopathogenic differences in coronary artery disease and peripheral artery disease: results from the National Health and Nutrition Examination Survey. Angiology 2014;65:883–90.

64. DeRubertis BG, Kum S, Varcoe RL. The Demise of the Absorb BVS: Lessons Learned From the Discontinuation of a Disappearing Stent. J Endovasc Ther 2018;25:706–9.

65. van Haelst ST, Peeters Weem SM, Moll FL, de Borst GJ; Haelst van ST. Current status and future perspectives of bioresorbable stents in peripheral arterial disease. J Vasc Surg 2016;64:1151–1159.e1.

66. Serruys PW, Onuma Y, Dudek D, Smits PC, Koolen J, Chevalier B, *et al.* Evaluation of the second generation of a bioresorbable everolimus-eluting vascular scaffold for the treatment of de novo coronary artery stenosis: 12-month clinical and imaging outcomes. J Am Coll Cardiol 2011;58:1578–88.

67. Regazzoli D, Leone PP, Colombo A, Latib A. New generation bioresorbable scaffold technologies: an update on novel devices and clinical results. J Thorac Dis 2017;9:S979–85.

68. Puricel S, Cuculi F, Weissner M, Schmermund A, Jamshidi P, Nyffenegger T, *et al.* Bioresorbable coronary scaffold thrombosis: multicenter comprehensive analysis of clinical presentation, mechanisms, and predictors. J Am Coll Cardiol 2016;67:921–31.

69. Jukema JW, Verschuren JJ, Ahmed TA, Quax PH. Restenosis after PCI. Part 1: pathophysiology and risk factors. Nat Rev Cardiol 2011;9:53–62.

Conflicts of interest.—Steven Kum has served as consultant for Abbott Vascular; Ramon L. Varcoe has served as consultant for Abbott Vascular, Boston, Medtronic, Intervene, Intact Medical and Surmodics; Constantijn E. Hazenberg has served as consultant for Philips. All other authors have no conflicts of interest to declare.

Authors' contributions.—Jetty Ipema contributed to conception, data acquisition, data analysis, data interpretation, article draft and critical revision; Steven Kum gave substantial contribution to conception, data acquisition, data analysis, data interpretation and to the article draft; Eline Huizing contributed to data acquisition, data analysis, data interpretation and to the article draft; Michiel A. Schreve, Ramon L. Varcoe and Constantijn E. Hazenberg contributed to data interpretation and article draft; Jean-Paul de Vries gave contribution to conception, data interpretation and article draft; Çağdaş Ünlü contributed to conception, data analysis, data interpretation, article draft and critical revision. All authors read and approved the final version of the manuscript.

History.—Article first published online: October 21, 2020. - Manuscript accepted: October 14, 2020. - Manuscript revised: September 28, 2020. - Manuscript received: May 30, 2020.

Supplementary data.—For supplementary materials, please see the HTML version of this article at www.minervamedica.it