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

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REVIEW
PERIPHERAL ARTERIAL DISEASE A systematic review and meta-analysis
of bioresorbable vascular scaffolds
for below-the-knee arterial diseaseJetty IPEMA ¹ *, Steven KUM ², Eline HUIZING ¹, Michiel A. SCHREVE ¹,
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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.

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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>i.e.</i> 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, <i>de-novo</i> 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, <i>de-novo</i> 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, <i>de-novo</i> 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 duration⁸ 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 worthwhile. 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.

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