Intravascular treatment of long segments of experimental peripheral arteries with multiple, serial, balloon-expandable, resorbable scaffolds

Rym El Khoury, MD,[a] Ivan Tzvetanov, MS,[a] Edward A. Estrada, BS,[a] Edward McCarroll, BS,[a] Eugene Michal, BA,[a] Jack Blumeyer, BS,[a] Louis-Georges Guy, PhD,[b] Martin Laflamme, AHT,[b] *and* Lewis B. Schwartz, MD,[a,c] *Park Ridge, IL; Los Altos, CA; and Boisbriand, Quebec, Canada*

ABSTRACT

Symptomatic femoropopliteal occlusive disease has been increasingly treated using endovascular methods. However, restenosis, especially after implantation of permanent metallic stents, has remained common. To date, resorbable scaffolds have failed to achieve sufficient radial strength to enable the successful treatment of long, mobile, peripheral arteries. In the present nonsurvival, large animal experiment, a novel device consisting of multiple, short, serial, balloon-expandable, bioresorbable scaffolds was deployed in arteries subjected to supraphysiologic deformation. Compared with native vessels, the scaffolded arteries continued to bend (113° ± 19° vs 110° ± 20°; $P = .10$) and shorten (15% ± 15% vs 20% ± 14%; $P = .16$), unencumbered by the placement of the investigational device. The mean luminal diameter of the scaffolded arteries was preserved without kinks or occlusions in exaggerated flexion (4.7 ± 0.7 vs 4.7 ± 0.5 mm in extension vs flexion; $P = .80$). Arterial deformation was borne by shortening of the interscaffold spaces (2.2 ± 0.8 mm vs 1.9 ± 0.7 mm in extension vs flexion; $P < .01$) and the scaffolds themselves (10.7 ± 1.4 mm vs 9.9 ± 1.1 mm in extension vs flexion; $P < .01$). The results from the present study challenge the perceived limitations of balloon-expandable devices implanted in peripheral mobile arteries. We have presented a bioresorbable scaffold that combines sufficient radial strength to preserve the mean luminal diameter with movement and the flexibility to accommodate femoropopliteal deformation. (JVS—Vascular Science 2022;3:205-10.)

Clinical Relevance: In the present study, we have described a novel treatment paradigm for femoropopliteal arterial occlusive disease using bioresorbable scaffolds. The balloon-expandable nature and material properties of the polylactide-based scaffolds combined with the short and segmented configuration provided the radial force to resist the physiologic mechanical deformation of the lower extremity artery while accompanying its natural motion. In the present study an acute animal model was tested, and the experimental device is now undergoing a first-in-human clinical trial (ClinicalTrials.gov identifier, NCT04584632).

Keywords: Animal model; Bioresorbable; Endovascular; Femoropopliteal; Preclinical testing; Stents

Percutaneous revascularization has become a vital treatment of symptomatic peripheral arterial occlusive disease.[1] However, its durability has remained poor. After 1 year, >50% of all endovascular femoropopliteal interventions will be attended by symptomatic recurrence and/or restenosis requiring reintervention.[2]

Most devices currently used in peripheral vascular interventions have been adaptations of designs for the coronary arteries. In contrast to the coronary arteries, the superficial femoral and popliteal arteries exhibit diffuse, often severely calcified, long-segment disease, which is often inadequately treated by plain balloon angioplasty.[3-5] Moreover, as the leg bends, this arterial segment will bend, shorten, and twist.[6-8] Self-expanding stent placement after suboptimal angioplasty results in device stress with an inherent risk for stent

From the Efemoral Medical, Inc, Los Altos[a]; the Charles River Laboratories, Boisbriand[b]; and the Department of Surgery, University of Illinois, Advocate Lutheran General Hospital, Park Ridge.[c]

The present study was partially funded by the National Institutes of Health (grant 1-R43-HL145671).

Disclosures: Efemoral Medical, Inc, is a for-profit research and development medical device company. I.T., E.A.E., E. McCarroll, E. Michal, and J.B. serve as consultants, and L.B.S. serves as chief medical officer. R.E.K., L.-G.G., and M.L. have no conflicts of interest.

Presented at the Forty-fifth Annual Meeting of the Midwestern Vascular Surgical Society, Chicago, IL, September 9-11, 2021.

Correspondence: Lewis B. Schwartz, MD, Department of Surgery, University of Illinois, Advocate Lutheran General Hospital, 1875 W Dempster St, Ste 550, Park Ridge, IL 60068 (e-mail: lewis.schwartz@aah.com).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS-Vascular Science policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2666-3503

https://doi.org/10.1016/j.jvssci.2022.03.002

fracture with mechanical deformation and subsequent thrombosis.[9-11] To date, the risk of external compression and longitudinal axis deformation has significantly hindered the use of balloon-expandable stents in the femoropopliteal axis.[12]

To overcome the shortcomings of permanent metallic devices, bioresorbable devices have emerged, with the goal of providing effective scaffolding, limiting vessel recoil, and attenuating postintervention neointimal hyperplasia. Met with initial promise in the coronary arteries, the success of absorbable scaffolds was shortlived.[13,14] In the periphery, attempts at bioresorbable scaffolding have generated modest results in the treatment of femoropopliteal disease.[15-17] Below the knee, however, resorbable scaffolds have demonstrated satisfactory 36-month primary patency (81%) and freedom from clinically driven target lesion revascularization (87%).[18]

In the present study, we tested the hypothesis in an acute (nonsurvival) animal experiment that long segments of mobile arteries could be effectively treated with multiple, serial, short, balloon-expandable, and resorbable scaffolds.

ARTICLE HIGHLIGHTS

- **Type of Research:** Acute large animal study of investigational peripheral arterial device
- **Key Findings:** In this animal model, the treatment of long and mobile peripheral arteries using novel, short, balloon-expandable, serial bioresorbable scaffolds allowed for continued and unencumbered hindlimb movement.
- **Take Home Message:** This animal model challenges the perceived limitations of balloon-expandable devices implanted in peripheral mobile arteries and presents a bioresorbable scaffold combining sufficient radial strength to preserve mean luminal diameter with movement and flexibility to absorb lower extremity arterial deformation.

METHODS

Study design. In the present nonsurvival animal study, experimental devices were serially implanted into the hindlimb arteries of large mammals that were subjected to exaggerated flexion before and after device deployment. Quantitative assessments of the arterial diameter, deformation, and device apposition were performed. Overall device integrity was verified immediately after sacrifice.

Experimental device. The Efemoral device (Efemoral Medical, Inc, Los Altos, CA) is a novel, balloon-expandable, resorbable scaffold specifically designed for femoropopliteal percutaneous intervention. It consists of small, independent, 10-mm polylactide-based stents serially mounted on a 60-mm angioplasty balloon (Fig 1). The purpose of the interscaffold space is to allow for the artery to bend and twist unencumbered during movement. In the present preclinical study, each device was configured with two scaffolds crimped onto a balloon (Fig 2). The balloons were subsequently deployed in series to allow for long-segment artery scaffolding.

Animal experiment. All animal operations were performed in a facility compliant with 21 Code of Federal Regulations Part 58 (Food and Drug Administration) Good Laboratory Practice for Nonclinical Laboratory Studies (AccelLAB Inc, Boisbriand, Quebec, Canada). The Comité Institutionnel de Protection des Animaux d'AccelLAB (the test facility's institutional animal care and use committee) reviewed and approved the protocol. The test facility is accredited by both the Association for Assessment and Accreditation of Laboratory Animal Care and the Canadian Council on Animal Care.

Peripheral contrast angiography was performed in four female Yorkshire-Landrace pigs weighing 25 to 35 kg. After the induction of general anesthesia, intubation, and mechanical ventilation, the carotid artery was surgically exposed with the pig in dorsal recumbency. A sheath was inserted into the common carotid artery under direct vision and advanced to the aortic bifurcation using fluoroscopy. Heparin was administered to achieve an activated clotting time >300 seconds. Nitroglycerin boluses were administered to mitigate secondary arterial vasospasm.

Anteroposterior angiographic images were obtained with the pig in the neutral position and the hindlimb naturally extended and were repeated following manual, exaggerated hindlimb flexion.[19] After identification and flexion angiography of the native arteries, the scaffolds were deployed into the porcine bilateral iliofemoral arteries using slow balloon inflation necessary to achieve complete wall apposition. Angiography was then repeated with the stented hindlimb in both extension and exaggerated flexion. Repeated extension—flexion cycles were not performed in our acute animal model. Intraluminal scaffold imaging was performed using optimal coherence tomography (Illumien Optis Imaging System; Abbott Laboratories, Abbott Park, IL).

Immediately after device implantation and angiography, the pigs were sacrificed, and the scaffolded arteries were excised, treated with graded alcohol, and scanned using the Nikon XT H 225 microcomputed tomography system (Nikon, Tokyo, Japan).

Quantitative analysis. Retrospective quantitative vascular analysis was used to assess the deformation of the arteries, scaffolds, and interscaffold segments. The measurements included the diameter and length of the scaffolds, intervening spaces between scaffolds, and proximal and distal arterial margins. The diameters are reported as the mean luminal diameter (meanD). Axial

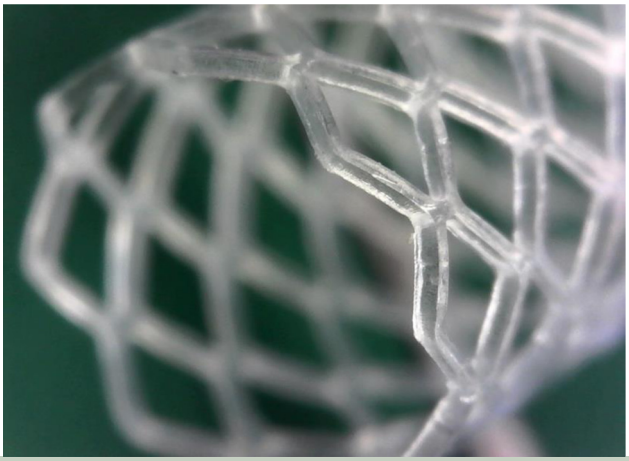

Fig 1. High-resolution photograph of a single Efemoral scaffold.

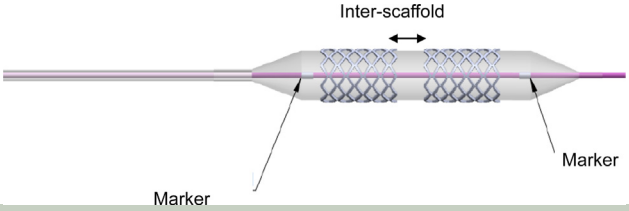

Fig 2. Diagram of two serial scaffolds mounted on a balloon.

compression (expressed as a percentage) was defined as the difference between the arterial target segment lengths in the neutral, extended position minus the length in the flexed position divided by length in the neutral position. The bend angle (expressed in degrees) was measured using planimetry, defined as the approximate angle between the proximal and distal border of the sample target arterial segment.[19]

Statistical analysis. The results are reported as the mean ± standard deviation. Continuous variables were compared using a paired *t* test between the native and scaffolded arteries. Statistical analysis was performed using SPSS, version 20.0 (IBM Corp, Armonk, NY).

RESULTS

Native arteries. Passive hindlimb flexion produced profound and reproducible native arterial deformation, as expected (quantitative vascular analysis revealed a 110° ± 20° bending and 20% ± 14% axial compression). Despite its deformation, the meanD was reliably preserved, without kinking (4.7 ± 0.4 mm in extension vs 5.0 ± 0.2 mm in flexion; $P = .16$).

Scaffolded arteries. A total of 38 resorbable scaffolds were implanted in eight iliofemoral arteries in four pigs. The devices were implanted in a configuration of two serial scaffolds in two arteries, four scaffolds in two arteries, six scaffolds in three arteries, and eight scaffolds in one artery. The total scaffolded arterial length ranged from 32 to 97 mm.

After scaffold implantation, passive hindlimb flexion produced patterns of profound deformation similar to those observed in the native arteries (bending, 113° ± 19°; compression, 15% ± 15%; $P = .16$). Despite accommodating multiple, rigid scaffolds, all arteries remained widely patent without kinking or luminal narrowing, even in extreme flexion (meanD, 4.8 ± 0.3 mm in extension vs 4.7 ± 0.3 mm in flexion; $P = .80$). We found no evidence of crushing, crimping, or compression in any scaffolded vessel, including the artery treated with a "full scaffold jacket" of eight stents traversing a total length of 10 cm (Fig 3).

Quantitative analysis of the individual scaffolds and interscaffold spaces revealed that the deformation of arterial flexion was borne by both segments (Fig 4). We found significant shortening of the spaces between the scaffolds (n = 30 spaces; mean length in extension, 2.2 ± 08 mm; mean length in flexion, 1.9 ± 0.7 mm; $P < .01$) and of the axially flexible scaffolds themselves (n = 38 scaffolds; mean length in extension, 10.7 ± 1.4 mm; mean length in flexion, 9.9 ± 1.1 mm; $P < .01$).

Scaffold integrity. Qualitative examination of the indwelling scaffolds using optimal coherence tomography demonstrated complete and consistent wall apposition in all devices. Qualitative examination of the explanted arteries using three-dimensional microcomputed tomography revealed intact scaffolds without fracture or deformation (Fig 5).

DISCUSSION

In the present study, long-segment porcine peripheral artery stenting using novel, bioresorbable, balloon-expandable, short, serial scaffolds did not affect the luminal diameter. Acute supraphysiologic hindlimb deformation did not generate significant compression of the scaffolded artery. Arterial deformation was effectively borne, not only by the interscaffold spaces, but also by the scaffolds of the tested device.

It has long been believed that metal balloon-expandable stent implantation is contraindicated for femoropopliteal arteries because a rigid device can be crushed as the leg moves.[12] However, implantation of short, metal, balloon-expandable stents in the superficial femoral artery has been previously shown to be safe and effective. In 1995, Bergeron et al[20] implanted 55 first-generation balloon-expandable metal stents in short lesions in 42 femoropopliteal arteries of 39 patients and found that 77% had remained primarily patent after 2 years. In that same year, Henry et al[21] reported their experience with metal balloon-expandable stent implantation in 310 patients, including 126 with short lesions confined to the femoropopliteal arteries.

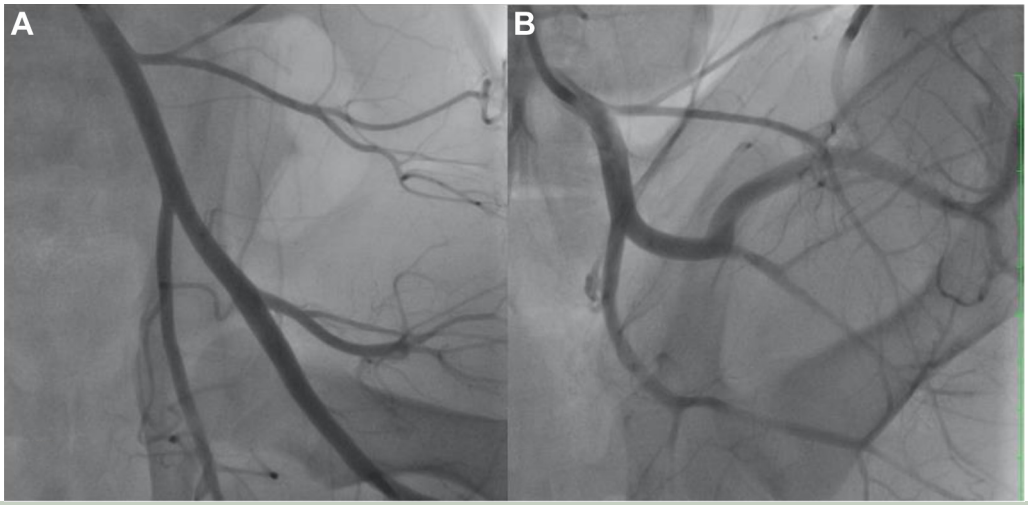

Fig 3. Porcine iliofemoral arterial deformation after deployment of the eight serial scaffolds. Anteroposterior angiograms after implantation of four serial scaffolds in extension **(A)** and exaggerated flexion **(B)**.

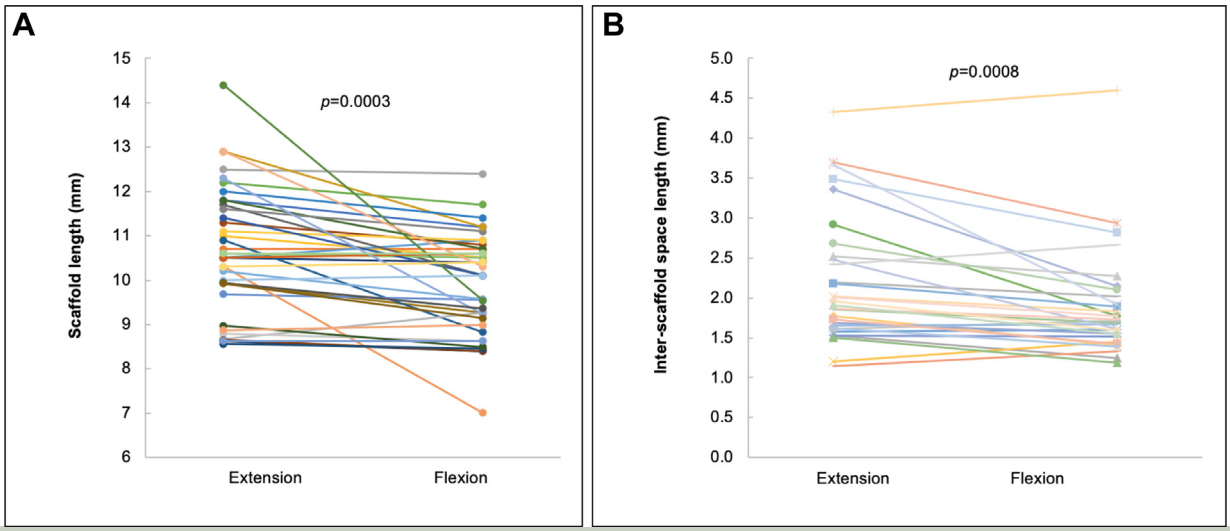

Fig 4. Mechanism of axial deformation of scaffolded arteries in scaffolded segments **(A)** and interscaffold spaces **(B)**.

Restenosis after 6 months was observed in only 13% of the cases, including 18% in distal lesions but only 4.4% of the lesions in the proximal superficial femoral artery.[21] In the present animal study, we demonstrated a preserved luminal diameter after implantation of balloon-expandable scaffolds.

Numerous clinical investigators have theorized that bioresorbable vascular scaffolds might represent a favorable paradigm shift in endovascular therapy, notably by offering the advantages of avoiding a chronic foreign body reaction and enhancing adaptive remodeling.[22,23] Nevertheless, the initial enthusiasm for this technology has been met by skepticism.[24] In the ESPRIT I [a clinical evaluation of the Abbott vascular ESPRIT BVS (bioresorbable vascular scaffold) system] trial, an everolimus-coated 1:1 mixture of poly-D and L-lactide 6- × 60-mm scaffold was tested in 35 patients and yielded 100% technical success and 94% primary patency at 12 months.[15] In that prospective trial, the short average lesion length of 35.2 mm challenged the generalizability of these excellent results.[15] In contrast, the Remedy scaffold (Kyoto Medical, Kyoto, Japan) failed to demonstrate durability, with a primary patency of 32.1% to 58% at 12 months in similarly short lesions (average length, 37.9 and 59 mm). However, its excellent secondary patency (>85%) highlighted the advantage of this flexible and nonpermanent device.[16,17]

The treatment of a long, occlusive, atherosclerotic lesion with a single intravascular device has remained challenging. This unmet clinical need informed the design of the Efemoral vascular scaffold system (Efemoral Medical, Inc), which, akin to a freight train

Fig 5. Three-dimensional microcomputed tomography image of an artery treated with eight scaffolds using a computer-generated wall.

rounding a tight curve, provides spaces between its multiple, short, rigid scaffolds to allow for absorption of the arterial deformation caused by flexion. Implantation of stents that overlap, although common in clinical medicine, creates bulk and noncompliance within the artery, leading to aggressive neointimal hyperplasia, restenosis, and therapeutic failure. In contrast, the lengths of the scaffolds and interscaffold spaces of the Efemoral vascular scaffold system are tightly calculated and controlled to accommodate the known degrees of flexion inherent in the human peripheral vasculature while still ensuring that the individual scaffolds do not abut. Moreover, the individual polylactide-based scaffolds were also able to significantly absorb the mechanical forces induced by hindlimb exaggerated flexion.

Study limitations. The limitations of the present study included the sample size and the absence of atherosclerosis in the chosen animal model. The deployment of balloon-expandable plastic stents in heavily diseased human peripheral arteries could produce different results. Also, iterative mechanical stress related to hindlimb repeated flexion was not assessed in the present acute preclinical study nor was the histologic vascular response over time.

CONCLUSIONS

In the present study, we found that experimental peripheral arteries can be acutely treated with multiple, short, balloon-expandable, bioresorbable scaffolds without luminal compromise. Subsequent studies will focus on the chronic vascular response to this interventional strategy. An acute animal model was tested in the present study, and the experimental device is now undergoing a first-in-human clinical trial (ClinicalTrials.gov identifier, NCT04584632).

AUTHOR CONTRIBUTIONS

Conception and design: RE, IT, EE, E McCarroll, E Michal, JB, LG, ML, LS
Analysis and interpretation: RE, JB, LG, LS
Data collection: RE, LS
Writing the article: RE, LG, LS
Critical revision of the article: IT, EE, E McCarroll, E Michal, JB, LG, ML, LS
Final approval of the article: RE, IT, EE, E McCarroll, E Michal, JB, LG, ML, LS
Statistical analysis: RE, LS
Obtained funding: RE, IT, LS
Overall responsibility: LS

REFERENCES

1. Adam DJ, Beard JD, Cleveland T, Bell J, Bradbury AW, Forbes JF, et al. Bypass versus angioplasty in severe ischaemia of the leg (BASIL): multicentre, randomised controlled trial. Lancet 2005;366:1925-34.
2. Cheng SW, Ting AC, Ho P. Angioplasty and primary stenting of high-grade, long-segment superficial femoral artery disease: is it worthwhile? Ann Vasc Surg 2003;17:430-7.
3. Torii S, Mustapha JA, Narula J, Mori H, Saab F, Jinnouchi H, et al. Histopathologic characterization of peripheral arteries in subjects with abundant risk factors: correlating imaging with pathology. JACC Cardiovasc Imaging 2019;12(Pt 1):1501-13.
4. Rocha-Singh KJ, Jaff MR, Crabtree TR, Bloch DA, Ansel G; Viva Physicians Inc. Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. Catheter Cardiovasc Interv 2007;69:910-9.
5. Gray BH, Sullivan TM, Childs MB, Young JR, Olin JW. High incidence of restenosis/reocclusion of stents in the percutaneous treatment of long-segment superficial femoral artery disease after suboptimal angioplasty. J Vasc Surg 1997;25:74-83.
6. Klein AJ, Chen SJ, Messenger JC, Hansgen AR, Plomondon ME, Carroll JD, et al. Quantitative assessment of the conformational change in the femoropopliteal artery with leg movement. Catheter Cardiovasc Interv 2009;74:787-98.
7. Vernon P, Delattre JF, Johnson EJ, Palot JP, Clement C. Dynamic modifications of the popliteal arterial axis in the sagittal plane during flexion of the knee. Surg Radiol Anat 1987;9:37-41.
8. Lederman RJ. Legs bend: why dynamic angiography is important. Catheter Cardiovasc Interv 2009;74:799.
9. Nikanorov A, Schillinger M, Zhao H, Minar E, Schwartz LB. Assessment of self-expanding nitinol stent deformation after chronic implantation into the femoropopliteal arteries. EuroIntervention 2013;9:730-7.
10. Schlager O, Dick P, Sabeti S, Amighi J, Mlekusch W, Minar E, et al. Long-segment SFA stenting—the dark sides: in-stent restenosis, clinical deterioration, and stent fractures. J Endovasc Ther 2005;12:676-84.
11. Scheinert D, Scheinert S, Sax J, Piorkowski C, Braunlich S, Ulrich M, et al. Prevalence and clinical impact of stent fractures after femoropopliteal stenting. J Am Coll Cardiol 2005;45:312-5.
12. Katsanos K, Tepe G, Tsetis D, Fanelli F. Standards of practice for superficial femoral and popliteal artery angioplasty and stenting. Cardiovasc Intervent Radiol 2014;37:592-603.
13. Serruys PW, Chevalier B, Sotomi Y, Cequier A, Carrie D, Piek JJ, et al. Comparison of an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II): a 3 year, randomised, controlled, single-blind, multicentre clinical trial. Lancet 2016;388:2479-91.
14. Ellis SG, Kereiakes DJ, Metzger DC, Caputo RP, Rizik DG, Teirstein PS, et al. Everolimus-eluting bioresorbable scaffolds for coronary artery disease. N Engl J Med 2015;373:1905-15.
15. 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.
16. Werner M, Micari A, Cioppa A, Vadala 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.

17. Bontinck J, Goverde P, Schroe H, Hendriks J, Maene L, Vermassen F. Treatment of the femoropopliteal artery with the bioresorbable REMEDY stent. J Vasc Surg 2016;64:1311-9.
18. Varcoe RL, Thomas SD, Lennox AF. Three-year results of the Absorb everolimus-eluting bioresorbable vascular scaffold in infrapopliteal arteries. J Endovasc Ther 2018;25:694-701.
19. El Khoury R, Nikanorov A, McCarroll E, LeClerc G, Guy LG, Laflamme M, et al. An animal model of human peripheral arterial bending and deformation. J Surg Res 2019;241:240-6.
20. Bergeron P, Pinot JJ, Poyen V, Benichou H, Khanoyan P, Rudondy P, et al. Long-term results with the Palmaz stent in the superficial femoral artery. J Endovasc Surg 1995;2:161-7.
21. Henry M, Amor M, Ethevenot G, Henry I, Amicabile C, Beron R, et al. Palmaz stent placement in iliac and femoropopliteal arteries: primary and secondary patency in 310 patients with 2-4-year follow-up. Radiology 1995;197:167-74.
22. Di Mario C, Caiazzo G. Biodegradable stents: the golden future of angioplasty? Lancet 2015;385:10-2.
23. van Haelst ST, Peeters Weem SM, Moll FL, de Borst GJ. Current status and future perspectives of bioresorbable stents in peripheral arterial disease. J Vasc Surg 2016;64:1151-9.e1.
24. Capodanno D. Time for a debriefing: is there a future for bioresorbable scaffolds? EuroIntervention 2018;13:1857-9.

Submitted Feb 3, 2022; accepted Mar 4, 2022.