Peripheral Vascular Disease

Helical Centerline Stent Improves Patency
Two-Year Results From the Randomized Mimics Trial

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Background—Reintervention in the femoropopliteal artery is frequent and a major driver of cost-effectiveness. High wall shear generated by swirling blood flow is associated with reduced occurrence of atherosclerosis and restenosis. This trial investigated the clinical and hemodynamic outcomes of the BioMimics 3D self-expanding tubular nitinol stent with helical centerline geometry compared with a straight stent in the femoropopliteal artery.

Methods and Results—In a prospective, multicenter, randomized controlled trial, 76 patients with symptomatic peripheral arterial disease were randomized 2:1 to receive a helical or a straight stent. An independent core laboratory adjudicated angiographic and ultrasound parameters. The primary safety end point was freedom from a composite of all death, target limb amputation, and target lesion revascularization at 30 days. The primary effectiveness end point was freedom from clinically driven target lesion revascularization at 6 months. Patency was a secondary end point. Subjects were followed up for 2 years from intervention. The primary safety (1-sided $P<0.01$) and efficacy (1-sided $P<0.001$) end points for the helical stent were met. The proportion of patients treated with the helical stent who maintained patency at 12 and 24 months was 80% and 72%, respectively, compared with 71% and 55% for the control group. The difference was significant through 24 months ($P=0.05$). Freedom from clinically driven target lesion revascularization for the helical compared with straight stent was 91% versus 92% at 12 months and 91% versus 76% at 24 months.

Conclusions—Both groups had similar safety outcomes and clinically driven target lesion revascularization to 2 years. However, after placement of a BioMimics 3D helical stent, there was improved patency to 2 years.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02163863.

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Key Words: nitinol ■ peripheral arterial disease ■ peripheral vascular diseases ■ prospective studies ■ stents

Peripheral arterial disease (PAD) is common and expensive; in the United States alone, Medicare-funded inpatient costs in 2001 were estimated at $4.4 billion.[1] The superficial femoral artery (SFA) is the most frequently involved segment in symptomatic PAD, irrespective of sex or race.[2,3] Although endovascular intervention in the SFA is generally considered safe and efficacious, simple angioplasty has a poor outcome in the majority of patients. In a review of the outcome in the angioplasty control arm of 3 femoropopliteal stenting studies that resulted in Food and Drug Administration approval, the 12-month vessel patency after angioplasty of lesions 4- to 15-cm long was only 28%.[4] Initial attempts to improve outcome using nondedicated stents proved futile.[5,6] Although contemporary dedicated nitinol stents have shown benefit over simple angioplasty and are now widely used to treat occlusive disease of the femoropopliteal artery, the 12-month patency remains far from ideal.[7,8] Furthermore, when drug-coated balloons are used primarily to treat disease in this area, there will still be a need for stents to treat suboptimal results.

Arterial geometry is commonly helical, generating swirling flow, which is known to elevate wall shear.[9] Atherosclerosis and intimal hyperplasia (IH) mainly occur at locations where wall shear is low.[10–12] A stent that can deform the vessel centerline into a helix has previously been demonstrated in a porcine model to reduce neointimal hyperplasia through mechanisms, including the elevation of wall shear.[13,14] The purpose of the Mimics trial was to evaluate the safety and effectiveness of the BioMimics 3D helical stent (Veryan Medical Ltd, Horsham, United Kingdom) in the treatment of symptomatic PAD affecting the femoropopliteal artery.

Methods

BioMimics 3D Stent
The self-expanding stent is laser cut from a nitinol tube and has a 3D helical centerline geometry set into the nitinol shape memory (Figure 1). The stent is an advanced design with repeating 2 crown units and specific connectors that allow both flexibility and helical geometry. The end 3 crowns have gradually reducing radial force to improve the transition in profile from artery to stent. It is

WHAT IS KNOWN

- Restenosis and the clinical need for reintervention remain the Achilles' heel of endovascular intervention in the SFA.
- The curvature and branching of arteries are commonly nonplanar or helical; there are observational data that the consequent swirling flow elevates vessel wall shear and reduces the development of atherosclerosis and restenosis.

WHAT THE STUDY ADDS

- The Mimics trial, the first randomized trial that compares 2 bare-metal stents to treat the disease of the SFA and popliteal artery, demonstrates that stent design influences clinical outcome.
- A helical stent resulted in higher patency at 2 years when compared with a straight stent.
- This represents the first demonstration that intentionally rendering the curvature of a vessel helical to impart swirling flow improves the outcome of peripheral intervention.

recommended that the stent is oversized to the vessel. The 6-F delivery system is 0.035″-guidewire compatible, and there are 3 highly radio-opaque tantalum markers at each end of the stent to aid accurate deployment.

Trial Design

The Mimics trial was a prospective multicenter randomized trial designed to assign patients with symptomatic PAD involving the SFA to treatment with the BioMimics 3D stent (helical stent) or a control straight tubular self-expanding nitinol stent (straight stent; LifeStent, CR Bard, AZ, was the specified control; however, if unavailable, any comparable straight tubular self-expanding nitinol stent was permitted). The safety and effectiveness of the helical stent were established in comparison to objective performance goals (OPGs) based on historical data.[4,7,15,16] The purpose of the control arm in this trial was for the evaluation of secondary end points. The LifeStent is a well-established contemporary SFA stent that has been shown in a randomized trial to have superior outcomes compared with angioplasty in the SFA.[7] All participating centers had institutional review board approval, and each patient provided informed consent. A consort diagram is shown in Figure 2.
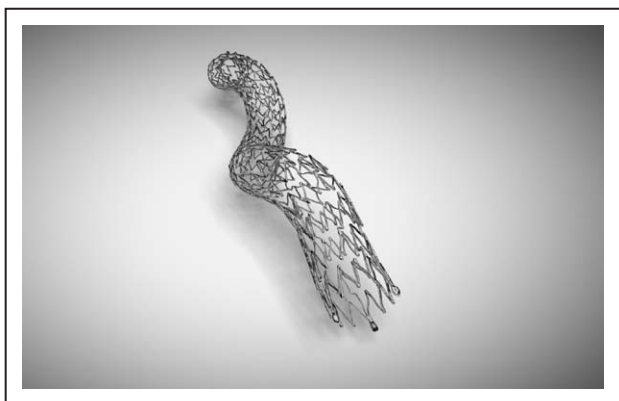

Figure 1. The BioMimics 3D helical stent.

Patients with lower limb arterial disease (Rutherford category, 1–4) whose symptoms were considered clinically and by imaging to be due to SFA disease were included in the trial. Solitary target lesions 4- to 10-cm long were to be treated with a single stent. The decision to predilate was not mandated and was left to the operator. The BioMimics 3D stents were available 5 to 7 mm in diameter and 60, 80, 100, and 125 mm in length. One patent calf vessel (no stenosis >50%) was required. All patients were treated with dual antiplatelet therapy before or at the time of intervention; the dose and duration were left to the operator's discretion. Patients were excluded if there had been previous intervention at the target site within 6 months, previous stent placement in the target limb, a requirement for treatment other than percutaneous transluminal angioplasty before stent placement (eg, laser and cryoplasty), or a contralateral lesion that required intervention during the index procedure or within 30 days unless both limbs were included in the trial.

Primary End Points

The safety end point of 88% of patients free from all cause death, index limb amputation, and target lesion revascularization (TLR) through 30 days was provided by the widely used OPG for femoropopliteal stents developed and published by the VIVA Physicians group in 2007 and supported by the Food and Drug Administration.[4]

Efficacy data were assessed at 6 months to fulfill regulatory requirements. The VIVA OPG does not define the proportion of patients expected to be free of clinically driven TLR (CDTLR) at 6 months, and therefore, using a similar approach to that taken by the authors of the VIVA OPG article, a thorough unbiased review of recent literature was undertaken to establish a 6-month freedom from CDTLR performance goal of 67%.[15–17] The primary efficacy end point of freedom from CDTLR assesses the effect of loss of patency on the patient in terms of both recurrence of symptoms and need for further intervention. It was defined as freedom from TLR after recurrent or worsening symptoms of PAD. In line with contemporary SFA stent studies, patients were prospectively followed up for 24 months.

Secondary Evaluations

Clinical variables, including Rutherford category, walking impairment questionnaire, ankle/brachial indices, and duplex ultrasound, were obtained by hospital visit at screening, discharge, 30 days, and 6, 12, and 24 months.

Procedural success was defined as successful deployment of the stent according to the Instructions for Use, a <30% residual stenosis and no procedural serious adverse event. Primary stent patency, a secondary end point of the study, was defined as freedom from a >50% stenosis identified by formal angiography or duplex since the index procedure. Treated vessel segments that demonstrated an increase in peak systolic velocity ratio of >2.0 or had undergone a CDTLR were deemed to have lost primary stent patency.

Using duplex ultrasound, stent patency was evaluated for both straight and helical stents when the patient's leg was straight. When the leg is straight, the curvature in the helical stent is similar to that in the native vessel, and as such, duplex ultrasound is considered a valid method to evaluate patency in the helical stent.

The secondary outcomes were obtained by randomizing patients 2:1 to receive either a helical or a straight self-expanding nitinol stent. Each center was allocated sequentially numbered, sealed envelopes that ensured 2:1 randomization. The envelopes were opened in order once angiography confirmed that the lesion conformed to the protocol.

Angiography and duplex examinations were reviewed by coreLab Bad Krozingen. The trial was registered with clinicaltrials.gov (identifier, NCT02163863).

Statistical Analysis

Using an expected proportion of 98%, a sample size of 40 patients with a helical stent achieves 80% power to detect superiority against the VIVA Physician group OPG of 88% based on the use of a 1-sided test for binomial proportion at a significance level, α_1, of 0.04.
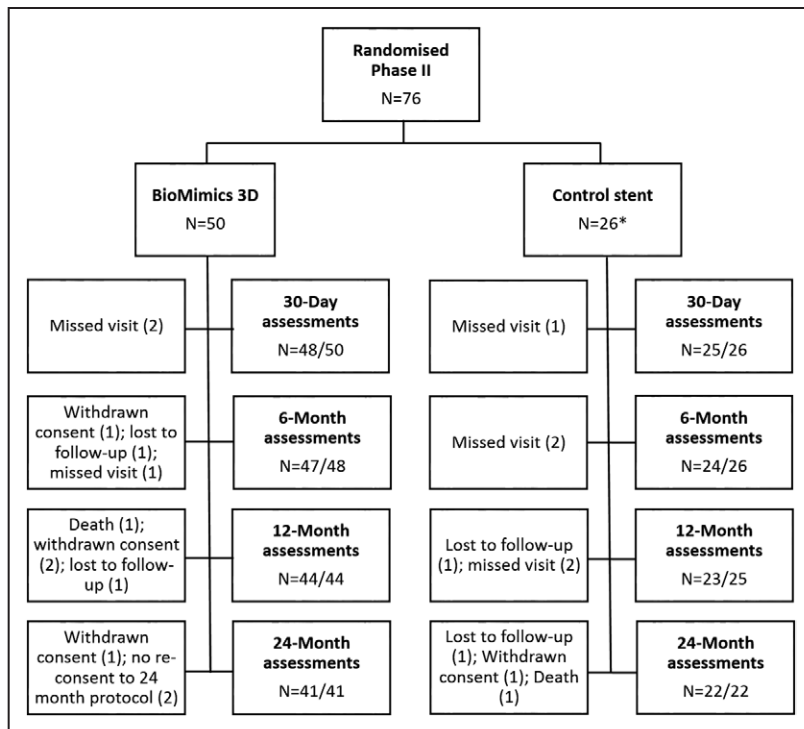
Figure 2. Consort diagram. *Twenty-four of 26 were LifeStent CR Bard.

The primary efficacy end point was freedom from CDTLR at 6 months. Using an expected proportion of 95%, a sample size of 22 patients with a helical stent achieved 85% power to detect superiority against the primary efficacy goal derived from the literature of 67% using a 1-sided test for binomial proportions at a significance level, α_2, of 0.01.

To account for loss to follow-up, the target enrollment for the helical stent was 50 patients. Categorical variables were summarized as proportions, and continuous variables are summarized as a mean and SD. To compare differences in demographics between the arms of the trial, the Student t test was used for continuous variables and the Fisher exact test was used for categorical variables. A P value of ≤0.05 indicated statistical significance, and all hypothesis tests were 2-sided unless otherwise stated. End points were analyzed on an intention-to-treat basis and include all enrolled subjects. For all primary and secondary end points, no imputation of missing data was performed. Subjects who had ascertainment of status at a later follow-up (for example, subjects who are known to be free of major adverse events past 30 days but missed the 30-day visit) are not considered missing as their status was known, and their data were used to evaluate the primary safety and efficacy end points. The number of subjects who attended each follow-up visit is presented in a study consort diagram.

Freedom from the loss of primary patency and freedom from CDTLR were evaluated using a survival analysis through 24 months. The Kaplan–Meier method was used to estimate the survival distribution. Differences between survival distributions were evaluated using the Log-rank test.

Results

Seventy-six patients from 8 investigational sites in Germany were enrolled after 2:1 randomization: 50 in the helical stent arm and 26 in the straight stent arm. The lesion characteristics and patient demographics are shown in Tables 1 and 2. Twenty-four of 26 patients received the LifeStent, one patient a Pulsar (Biotronic), and one a Misago (Terumo) self-expanding nitinol stent. Per protocol, these were not protocol deviations and were included in the analysis. There were 2 patients treated with critical limb ischemia in the helical stent group

but none in the straight stent group. Conversely, a greater proportion of patients with severe claudication (Rutherford category, 3) were treated by a straight stent (P=0.04). In the helical stent group, 98% of lesions were either Trans-Atlantic Inter-Society Consensus (TASC) A or B; in the straight stent group, all lesions were TASC A or B (Table 1). For the helical and straight stent groups, the mean lesion length was 66 and 63 mm, respectively (P=0.72); 44% (22/50) and 46% (12/26) (P=1.0) of patients had total occlusions and 52% (26/50) and 58% (15/26) (P=0.47) had moderate to severe calcification. The degree of calcification was reported by the core laboratory.

At index procedure, predilation was performed in 88% (44/50) and 69% (18/26) (P=0.06) of BioMimics 3D and control cases, respectively. Postdilation was performed for all BioMimics 3D and control cases. There was no difference in the residual stenosis between groups (Table 1).

The proportion of patients taking dual antiplatelet therapy in the helical stent arm at index procedure, discharge, and 1, 6, 12, and 24 months was 78%, 96%, 50%, 13%, 5%, and 7%, respectively. In the straight stent arm, the proportions were 77%, 92%, 44%, 17%, 21%, and 9%. There was no statistical difference between the 2 groups at any time point.

End Points and Secondary Evaluations

The primary analyses in this randomized study compared the helical stent group with performance goals for both safety and efficacy and did not involve comparing the primary outcomes of the 2 groups. There were no deaths, amputations, or TLR through 30 days, and there was no CDTLR through 6 months for the helical and straight stent groups. Therefore, both primary safety (1-sided P<0.01) and efficacy (1-sided P<0.001) end points for the helical stent group were met. For the straight stent group, primary safety (1-sided P=0.04) and efficacy (1-sided P<0.001) end points were also met.

Table 1.   Lesion Morphology, Stent Details, and Immediate Outcome

	Helical Stent (n=50)	Straight Stent (n=26)	P Value
SFA location, %			
Prox SFA	0 (0/50)	4 (1/26)	0.34
Prox Mid SFA	0 (0/50)	0 (0/26)	1.00
Mid SFA	10 (5/50)	19 (5/26)	0.30
Mid distal SFA	16 (8/50)	8 (2/26)	0.48
Distal SFA	66 (33/50)	46 (12/26)	0.14
Distal SFA—Prox PA	8 (4/50)	23 (6/26)	0.08
Preprocedure stenosis, % (SD)	84.3 (16.6)	87.9 (14.3)	0.33
Total occlusion, %	44 (22/50)	46 (12/26)	1.0
Calcification, %	64 (32/50)	73 (19/26)	0.46
None	36 (18/50)	27 (7/26)	0.46
Mild	12 (6/50)	15 (4/26)	0.73
Moderate	10 (5/50)	15 (4/26)	0.48
Severe	42 (21/50)	42 (11/26)	1.0
TASC II, %			
A	42 (21/50)	42 (11/26)	1.0
B	56 (28/50)	58 (15/26)	1.0
C	2 (1/50)	0 (0/26)	1.0
Lesion length, mm (SD)	65.8 (29.3)	63.3 (27.5)	0.72
Stent length, mm (SD)	98.5 (27.5)	87.8 (22.1)	0.07
Stent diameter, mm (SD)	4.5 (0.8)	4.5 (0.9)	1.0
Postprocedural stenosis, % (SD)	22.0 (7.7)	22.7 (10.0)	0.76
Postprocedural ABI (SD [n])	0.88 (0.16 [48])	0.94 (0.21 [24])	0.21

Numbers in parentheses are the proportion of patients with that characteristic. ABI indicates ankle/brachial indices; PA, popliteal artery; SFA, superficial femoral artery; and TASC, Trans-Atlantic Inter-Society Consensus.

Procedural success (<30% residual stenosis and no procedural serious adverse event) as judged by the core laboratory was 86% (43/50) after the helical stent and 85% (22/26) (P=1.0) after the straight stent.

There was substantial improvement in the Rutherford Category at both 12 and 24 months after stent implantation in both groups (Figure 3). At 1 and 2 years, the proportion of patients that had improved by at least 1 Rutherford category after the helical stent was 86% (38/44) and 88% (36/41), respectively. The equivalent proportion after the straight stent was 82% (18/22) and 86% (19/22), respectively. There was no difference between groups at either time point (Figure 4).

There was a sustained increase in mean ankle/brachial indices after treatment with the helical stent from 0.58 pretreatment to 0.93 and 0.87 at 1 and 2 years. The equivalent mean ankle/brachial indices after the straight stent were 0.59, 0.88, and 0.94. There was no difference between the groups at any time point (Figure 5).

The Kaplan–Meier survival estimate for target lesion primary patency (<50% stenosis without further intervention) after helical stent placement was 80% at 1 year and 72% at 2 years compared with 71% and 55% after the straight stent. Although the trial was not specifically powered to detect differences in primary patency, during the 2-year trial period, the Log-rank test suggests that the difference in survival distributions of the 2 groups was statistically different in favor of the helical stent (Log-rank test, P=0.05; Figure 6).

The Kaplan–Meier survival estimate for freedom from CDTLR was 91% at 12 months and 91% at 24 months (day 730) after treatment with the helical stent compared with 92% and 76% after the straight stent (Figure 7). Although there is a trend toward better freedom from clinically driven reintervention with the BioMimics 3D in the second year compared with the straight control stent, the difference noted was not significant (Log-rank test, P=0.14).

Discussion

The study was powered to address the primary safety and efficacy end points. Patients who received the helical stent in the Mimics trial had no deaths, amputations, or TLR through 30 days and no CDTLR through 6 months. This group, therefore, met the safety end point in comparison to the VIVA OPG and the 6-month primary efficacy end point of freedom from CDTLR of at least 67%. It is noted that the straight stent group also met the same outcomes. The trial was extended to 2 years to investigate the medium term effect of a helical stent on patency and clinically driven reintervention in comparison to a straight stent.

There is an understandable correlation between arterial patency and continued benefit after endovascular arterial intervention.[18,19] The majority of clinical failure in patients having claudication and treated by angioplasty of the SFA is because of reocclusion.[19] In patients with critical limb ischemia repeated reintervention is required to maintain good outcome.[18] Unfortunately, reintervention after the loss of patency in the SFA has limited success and exposes the patient to repeat hospitalization and clinical risk.[20] In addition, the rate of reintervention is a major driver of the difference in costs between competing interventions and therefore of cost-effectiveness.[21] Optimizing primary patency is, therefore, important when managing patients with PAD.

The BioMimics 3D helical stent was designed to improve outcomes by using the ability of laminar swirling flow to generate protective elevation in wall shear. In 1969, Caro et al[11] published their observations that atherosclerosis develops in areas of low wall shear. After they reported that arterial curvature is commonly helical, resulting in swirling flow and elevation of wall shear,[9] many important observations have been made: (1) IH also develops at areas of low wall shear and conversely is less likely at areas of elevated wall shear[10,12,22–24]; (2) straight stents reduce the natural helical curvature of an artery; and (3) individual stent designs affect the volume of IH that develops, which is not solely dependent on the degree of injury.[25–28] Swirling flow induced by a helix has high wall shear[9–14] and when generated by a helical dialysis graft reduces the IH when compared with a conventional graft.[29] Recently,
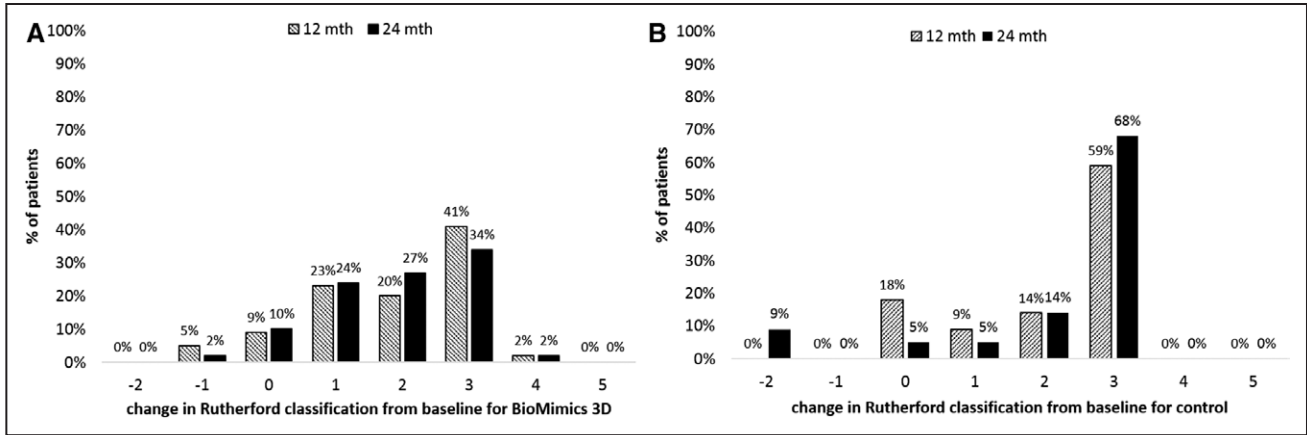
Figure 3. Rutherford classification after treatment with both stents. The figure shows the change in Rutherford classification between baseline and 12 and 24 months. **A**, BioMimics 3D stent. **B**, Control stent.

it has been demonstrated in an animal model that a helical nitinol stent is capable of modifying the centerline of an artery and that this not only induces swirling flow and therefore high wall shear but also reduces the amount of IH when compared with a straight nitinol stent.[13,14,30] It is proposed that the following mechanisms may contribute to a reduced risk of IH after shaping an artery to have a helical centerline: elevation of wall shear and, particularly relevant, reduction of low wall shear; cross-mixing augmenting blood wall mass transport, including of oxygen; and rendering of wall shear more uniform circumferentially than in a planar (2 dimensionally) curved vessel or conduit.[9,13,30]

Restenosis is a process not limited to the primary efficacy assessment undertaken at 6 months. Within the SFA, Iida et al[31] have shown that although the most frequent time to identify restenosis is at 12 months, the period of reocclusion extends beyond this. The assessment of restenosis and reintervention in the Mimics trial was, therefore, extended to 24 months. During the 24 months of follow-up, there was a

significant improvement in the primary patency of the helical stent compared with the straight stent ($P=0.05$) and a trend toward better freedom from clinically driven reintervention was noted with the BioMimics 3D stent group.

The 2 groups within the trial were generally well matched although slightly more straight stents were placed in the distal SFA compared with the helical stent group. When the groups were stratified by implant location, there was no difference in loss of primary patency or CDTLR between the 2 groups. The numbers are too small, however, to draw any definite conclusion.

A plausible explanation for these patency findings is that the helical centerline structure of the BioMimics 3D stent produced laminar swirling flow, leading to elevated wall shear and a reduced volume of IH within the stented segment. The peak timing of restenosis as identified by Iida et al[31] and the delay in both presentation and management of patients representing with symptoms probably explain the observed trend in reintervention in the second year.
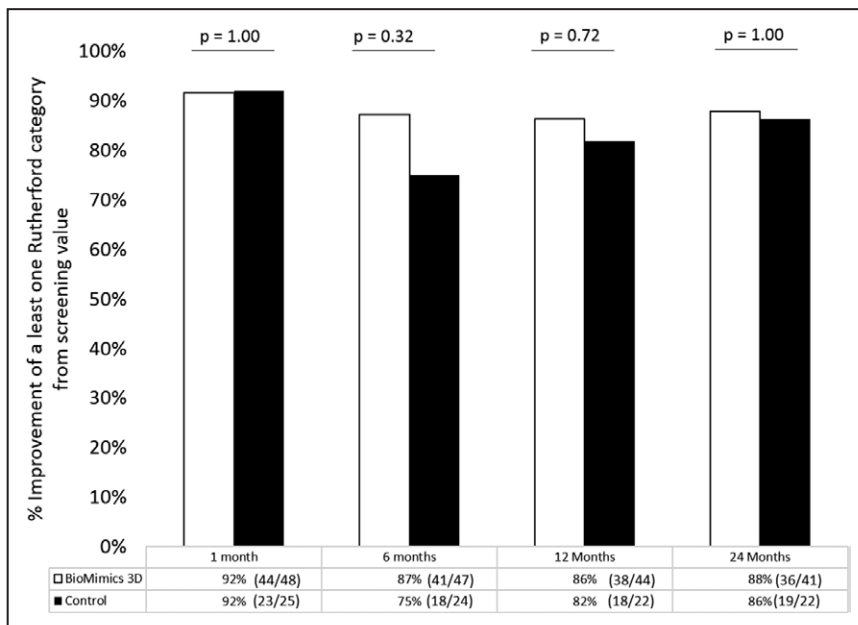

Figure 4. Improvement by at least 1 Rutherford category. The figure shows the proportion of patients in each group that had improved by at least 1 Rutherford category through 24 months. The number in parentheses are patient numbers with data available at that time interval.
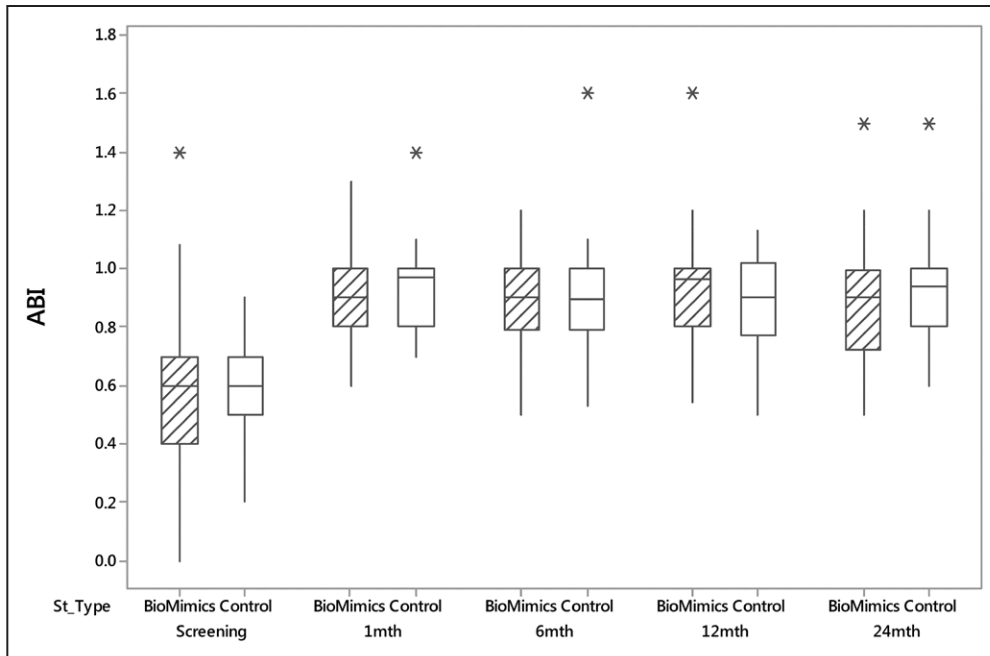
	1 month	6 months	12 Months	24 Months
☐ BioMimics 3D	92% (44/48)	87% (41/47)	86% (38/44)	88% (36/41)
■ Control	92% (23/25)	75% (18/24)	82% (18/22)	86% (19/22)

Figure 5. Ankle/brachial indices (ABI) to 24 months. The figure shows the ABI from baseline through 24 months for both groups. The presence of an asterisk (*) above certain box plots indicates the existence and location of an outlier for the data set in question. St_type indicates stent type.

The trial showed similar clinical and hemodynamic outcomes in both groups, but this was associated with rather more interventions in the straight stent group.

Conclusions

The Mimics trial investigated the clinical outcomes of the BioMimics 3D helical stent that is designed to induce laminar swirling blood flow and elevate vascular wall shear in the treated segment. The 2-year results suggest that the BioMimics 3D stent, through promoting an increase in swirling blood flow and wall shear, may have patency benefits when compared with a straight stent. The BioMimics 3D is being studied under

an approved Investigational Device Exemption (IDE) study in the United States, Germany, and Japan (NCT02400905).

Limitations

The construct of the Mimics trial necessarily limited the comparison against only 1 conventional straight self-expanding nitinol stent. Although this reduces the scope for comparison against other devices, the authors are not aware of any data to indicate that the LifeStent is in any way inferior to other conventional straight nitinol stents. Neither are we able to make direct comparison against drug-eluting balloons or stents.
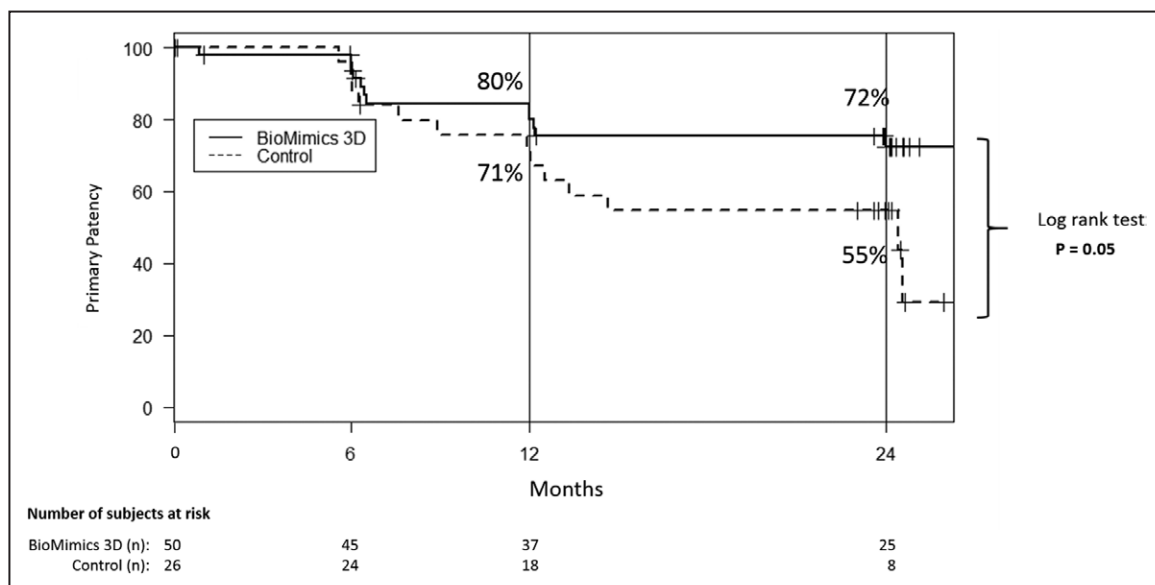

Figure 6. Primary patency. Kaplan–Meier curves for primary patency of both groups. Over 2 years, the difference is significant.
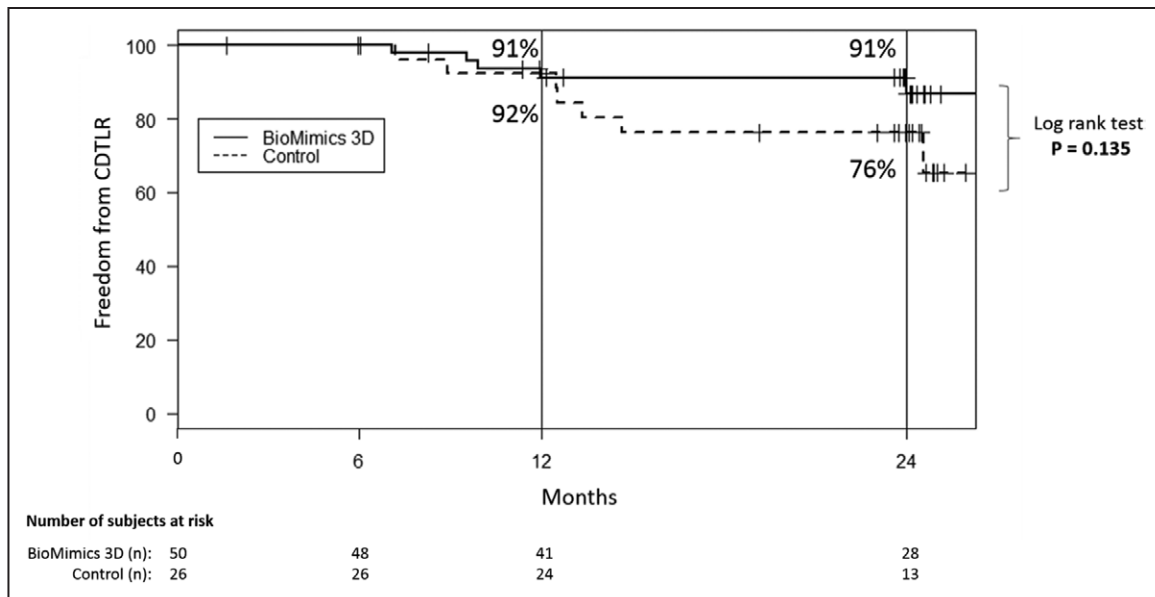
Figure 7. Freedom from clinically driven target lesion revascularization (CDTLR). Kaplan–Meier curves of freedom from CDTLR after independent event adjudication in both groups.

There were more patients with Rutherford category 3 but no patients with rest pain in the straight stent group. In addition, the stent length was longer in the helical stent group.

Table 2. Patient Demographics of Both Groups

	Helical Stent (n=50)	Straight Stent (n=26)	P Value
Demographics			
Age, y (mean±SD)	68.0±10.4	66.8±8.9	0.601
Men	66 (33/50)	65 (17/26)	1.00
White, % (n)	100 (50/50)	100 (26/26)	1.00
Risk factors			
Diabetes mellitus	26 (13/50)	42 (11/26)	0.2
Dyslipidemia	76 (38/50)	77 (20/26)	1.00
Hypertension	88 (44/50)	85 (22/26)	0.73
Smoking (current and former)	76 (38/50)	81 (21/26)	0.58
Medical history			
Carotid artery disease, % (n)	10 (5/50)	8 (2/26)	1.00
Renal disease, % (n)	4 (2/50)	0 (0/26)	0.54
Iliac disease, % (n)	18 (9/50)	15 (4/26)	1.00
Peripheral disease, % (n)	30 (15/50)	27 (7/26)	1.00
Rutherford category			
1	6 (3/50)	4 (1/26)	1.00
2	18 (9/50)	4 (1/26)	0.15
3	72 (36/50)	92 (24/26)	0.04
4	4 (2/50)	0 (0/26)	0.54

Although it is possible that these differences may have affected the outcome, the authors feel that the slight bias is unlikely to account for the significant differences found.

It is noted that there is a slight imbalance between the 2 groups in the distribution of the stent within the SFA and clinical indication (Table 1). Unfortunately, the numbers are too small within each group to allow meaningful direct comparison.

The mean lesion length was ≈7 cm (Table 2), and patients were limited to Rutherford category 1 to 4. Further studies will be required to investigate the effect of increasing wall shear in longer lesions and in patients with critical limb ischemia.

As discussed in the text, the trial was powered to detect superiority to the VIVA OPG at 30 days and superiority in CDTLR at 6 months rather than differences in primary patency or CDTLR to 24 months. Nevertheless, the authors feel that the data are compelling and warrant further clinical investigation.

Disclosures

T. Zeller is a consultant for Boston Scientific, Cook, CR Bard, Medtronic, Spectranetics, Veryan Medical, and WL Gore and received speaking honoraria from Biotronik, Straub Medical, Cordis, Abbott Vascular, Trireme, and Volcano. P.A. Gaines is a consultant for Novate Medical and Veryan Medical and received speaking honoraria for Bard, Cook Medical, and Medtronic. G.M. Ansel is a consultant for Abbott Vascular, Cordis Endovascular, CR Bard, Medtronic, Boston Scientific, Veryan Medical, and WL Gore. C.G. Caro is a consultant to Veryan Medical.

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