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The BioMimics 3D Helical Centreline Nitinol Stent in Chronic Limb Threatening Ischaemia and Complex Lesions: Three Year Outcomes of the MIMICS-3D Registry

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WHAT THIS PAPER ADDS

Patients with chronic limb threatening ischaemia (CLTI) or complex lesions have impaired outcomes after endovascular therapy and the optimal strategy is unknown as data are scarce. This analysis assessed the performance of the helical centreline BioMimics 3D stent in three high risk subgroups: complex lesions with calcification, chronic total occlusions, and CLTI. Through to 36 months outcomes were good in all high risk groups with 36 month freedom from target lesion revascularisation ranging from 73.8% to 81.0%. After propensity score matching, there was no difference in clinical outcomes comparing highly calcified with less calcified arteries and occlusion with stenosis, whereas a higher major amputation rate and lower survival in the CLTI group remained.

Objective: There is a need for improved outcomes in the endovascular treatment of patients suffering from chronic limb threatening ischaemia (CLTI), highly calcified lesions, and chronic total occlusions (CTOs). The helical centreline self expanding BioMimics 3D stent might be particularly useful in these high risk subsets, combining flexibility and fracture resistance with radial strength. Herein, the performance of the BioMimics 3D stent was assessed in these high risk subsets.

Methods: MIMICS-3D is a prospective, multicentre, European real world registry. This was a *post hoc* analysis, comparing patients with CLTI *vs.* intermittent claudication (IC), lesions with bilateral calcification *vs*. those without (peripheral arterial calcium scoring system [PACSS] 3,4 *vs*. PACSS 0 − 2), and CTO *vs*. no CTO. Propensity score matching was performed to reduce the impact of baseline variables. The 36 month endpoints were clinically driven target lesion revascularisation (CD-TLR), death, major target limb amputation, and stent patency.

Results: A total of 507 patients were enrolled. At 36 months, patients with CLTI had lower freedom from major amputation than patients with IC (92.6% *vs*. 100%, $p < .001$). In terms of primary patency, patients with CTO had lower patency rates than those without (63.9% *vs.* 77.8%, $p = .003$), but the difference reduced after propensity score matching (70.5% *vs.* 76.8%, $p = .43$). Primary patency was not impaired for patients with PACSS 3,4 or patients with CLTI. Freedom from CD-TLR was not significantly different among the groups and was 73.8% for CLTI *vs.* 78.9% for IC ($p = .15$), 77.6% for PACSS 3,4 *vs.* 78.7% for PACSS 0 − 2 ($p = .55$), and 75.6% for CTO *vs.* 81.0% for no CTO ($p = .11$).

Conclusions: The outcome of the MIMICS-3D registry suggests that the BioMimics 3D stent is effective in the endovascular treatment of complex femoropopliteal lesions and in CLTI. Future randomised controlled trials should confirm its non-inferiority or superiority compared with existing alternatives.

Keywords: Bare metal stent, Calcification, Chronic limb threatening ischaemia, Chronic total occlusion, Femoropopliteal lesions
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INTRODUCTION

Peripheral artery disease (PAD) is associated with high morbidity and mortality rates. Its prevalence is increasing, e.g., the global prevalence of PAD increased by 72% from 1990 to 2019,[1,2] yet its treatment still lacks satisfying long term efficacy and there remains a need to improve treatment strategies,[1,3] particularly in complex femoropopliteal lesions and patients with chronic limb threatening ischaemia (CLTI).

Improving results in patients with CLTI, who suffer from more cardiovascular events after interventions,[4–8] is a major medical need. Furthermore, for severely calcified lesions, the optimal endovascular treatment strategy remains a matter of dispute as none of the treatment modalities has yet demonstrated a clear advantage. Debulking strategies have not yet been proven to have clear benefits,[7] albeit positive outcomes have been reported.[9] In patients with chronic total occlusion (CTO), bailout stenting is often required due to recoil and dissection.[10]

Considering physiomechanics, the mobile femoropopliteal segment itself brings challenges, as the artery undergoes significant deformation during limb flexion,[7,11] e.g., the distal superficial femoral artery and proximal popliteal artery shorten under sitting or stair climbing conditions by 13.9% in the axial direction, and have a local compression of 4.6%.[12]

With its helical centreline geometry, the BioMimics 3D self expanding nitinol stent system (Veryan Medical Ltd, Horsham, UK) has been designed to mimic natural movement and torsions in this highly mobile region. Additionally, the stent has transition zones at its ends where the crowns are increased in length to reduce the outward force to avoid flow disturbances that might arise due to a step change between the stent and the native vessel segments.[13] This helical stent has already been shown to have superior 24 month patency compared with a straight stent in a randomised trial.[14] The current study was performed to obtain real world data in a large set of patients; 36 month outcomes of the overall cohort have been reported previously.[15]

To elucidate the performance of BioMimics 3D in endovascular high risk settings, a *post hoc* analysis in three high risk patient groups was performed: CLTI[4,5] *vs.* intermittent claudication (IC), lesions with severe calcification *vs.* those with less calcification, and CTO *vs.* no CTO lesions. Propensity score matching (PSM) was performed to reduce the impact of baseline variables.

MATERIALS AND METHODS

Study design

The study design has been published previously.[15,16] In brief, this prospective, multicentre, real world observational study enrolled 507 patients at 23 sites in Europe. Enrolment ran from September 2016 to June 2018. Patients were evaluated at 30 days, and at 12, 24, and 36 months.

The study was approved by the local or national ethics committees and all patients provided written informed consent prior to any study procedure. The study was conducted according to the Declaration of Helsinki, international standards and regulations applicable to medical device registries, relevant data protection guidelines, and local and national regulations. An independent clinical events committee adjudicated all major adverse events and any potentially device related adverse events.

Study participants

Inclusion criteria were age $\geq$ 18 years and $\leq$ 85 years, written informed consent, and PAD involving the femoropopliteal artery scheduled for treatment with the BioMimics 3D stent in accordance with the instructions for use. The main exclusion criteria included patients whose lesions could not be crossed with a wire and/or balloon catheter and could not be dilated sufficiently to allow passage of the delivery system, and patients with known hypersensitivity to nickel—titanium. The full list of inclusion and exclusion criteria is accessible at ClinicalTrials.gov (NCT02900924).

Endpoints and definitions

The primary and secondary endpoints of the overall cohort have been reported previously.[15,16]

The 3 year endpoints of this *post hoc* analysis were clinically driven target lesion revascularisation (CD-TLR) (evidence of recurrent symptoms associated with angiographic evidence of $\geq$ 50% stenosis) as the primary endpoint, and the secondary endpoints were death, major amputation of the index limb, stent patency assessed by duplex ultrasound (as available, peak systolic velocity ratio $\leq$ 2.4), Rutherford category, ankle brachial index (ABI), amputation free survival, and stent fractures (assessed by angiography or, if performed, by radiography).

CLTI was defined as Rutherford class $\geq$ 4, CTO lesions were defined as 100% chronic occlusion of the artery, and the peripheral arterial calcium scoring system (PACSS) grade[17] was assessed during the intervention by the operator. Thereby, PACSS grade 3 and 4 reflected bilateral wall calcifications $<$ 5 cm (grade 3) and $\geq$ 5 cm (grade 4), whereas PACSS 0 — 2 represents no (grade 0) or unilateral (grade 1 and 2) calcification.

Study procedure

The unique features of the BioMimics 3D stent (Fig. 1) have been described above. The stents were to be implanted according to the instructions for use, and concomitant antiplatelet and medication were to be in accordance with the site's standard of care and the recommendations in the instructions for use. Full lesion coverage, spot stenting, direct stenting, and stenting as a bailout therapy were allowed at the physician's discretion. There were no prohibited concomitant treatments.

Statistics

There was no statistically based sample size, but the planned sample size of at least 500 patients was believed to be adequate to provide an accurate characterisation of BioMimics 3D in real world clinical settings.

The data were visually checked for normality using Q-Q plots and if no substantial deviation from normality was

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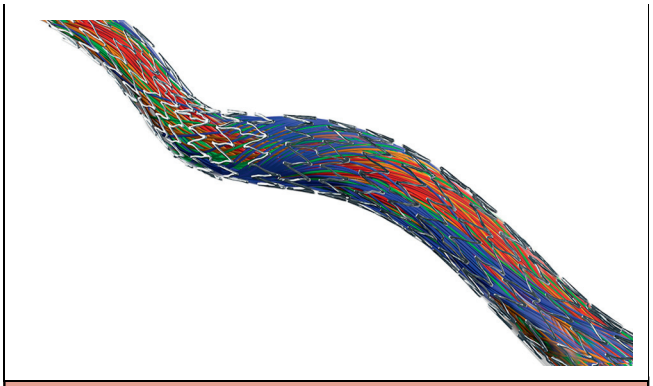

Figure 1. Computational fluid dynamics representation of swirling flow within a BioMimics 3D stent. Image provided by Veryan Medical Ltd.

noted, continuous endpoints were summarised by numbers, means, and standard deviations. Categorical endpoints were summarised by numbers and percentages. Kaplan–Meier analyses with 95% confidence interval (CI) were used to display and summarise time to event data. The analyses were performed based on the data available.

In a *post hoc* analysis, three subgroup analyses were performed for CLTI, complex lesions (PACSS grade 3, 4[17]), and CTO using Fisher's exact test for categorical variables, Student's *t* test for continuous variables, and log rank test for Kaplan–Meier estimates. A p value $< .050$ was considered statistically significant. To minimise the impact of baseline and procedural variables, a propensity score model was employed using logistic regression to model the propensity and greedy matching algorithm with a calliper of 0.1 to find matched pairs. Missing data in the covariables were imputed using a single imputation via Monte Carlo Markov chain methodology. Model fit was assessed via the c statistic, and the propensity scores before and after matching were plotted to examine the overlap between groups. Commonly known variables that might impact outcomes were selected for PSM and are provided in Supplementary Table S1. The analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Overall, 507 patients were enrolled in the MIMICS-3D registry (Fig. 2, Supplementary Figure S1).

Chronic limb threatening ischaemia vs. intermittent claudication

Patients with CLTI (121/502, 24.1%) were slightly older (72.2 ± 10.6 years *vs.* 69.4 ± 9.8 years, $p = .007$), had more cerebrovascular events in their medical history (16.5% *vs.* 9.7%, $p = .048$), more diabetes mellitus (47.2% *vs.* 33.9%, $p = .003$), more renal insufficiency (13.2% *vs.* 6.8%, $p = .037$), more non-healing wounds (57.9% *vs.* 0.8%, $p < .001$), and fewer patent outflow vessels at baseline (absence of patent infrapopliteal vessels in 9.9% *vs.* 2.6%, $p = .002$) than patients with IC. In the PSM cohort, the number of non-healing wounds remained as a difference (57.1% *vs.* 1.7%, $p < .001$), and the CLTI lesions had a higher diameter stenosis and were more frequently occluded (95.3 ± 7.9% *vs.* 93.5 ± 9.0%, $p = .036$, and 63.4% *vs.* 48.8%, $p = .028$, respectively) (Tables 1 and 2; for the PSM population, see Supplementary Tables S2–S4).

CD-TLR at 12, 24, and 36 months was 82.5%, 75.1%, and 73.8% in the unmatched CLTI group and 90.7%, 84.0%, and 78.9% in the IC group, respectively.

At the final 36 month follow up, patients with CLTI had significantly lower survival (64.0% *vs.* 91.5%, $p < .001$), a lower freedom from major amputations (92.6% *vs.* 100%, $p < .001$), and subsequently lower amputation free survival and CD-TLR free survival than those with IC. This difference remained

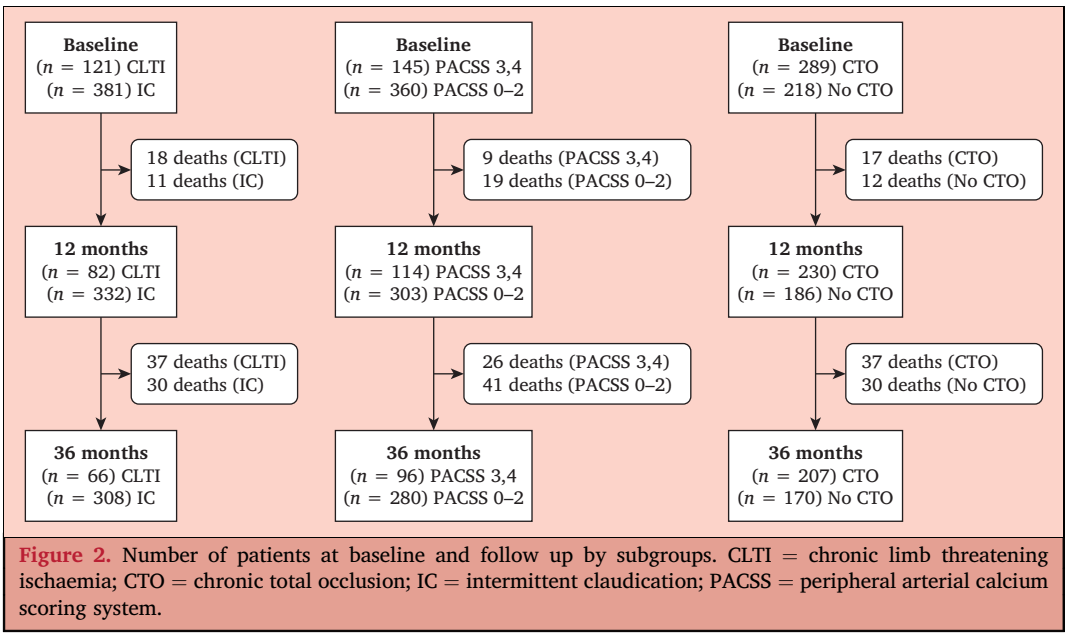

Figure 2. Number of patients at baseline and follow up by subgroups. CLTI = chronic limb threatening ischaemia; CTO = chronic total occlusion; IC = intermittent claudication; PACSS = peripheral arterial calcium scoring system.

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Table 1. Baseline characteristics by subgroup

Characteristics	CLTI			Calcification			CTO		
	CLTI (n = 121 P) (n = 125 L)	IC (n = 381 P) (n = 388 L)	p value	PACSS 3,4 (n = 145 P) (n = 150 L)	PACSS 0–2 (n = 360 P) (n = 366 L)	p value	CTO (n = 289 P) (n = 296 L)	No CTO (n = 218 P) (n = 222 L)	p value
Age – y	72.2 ± 10.6	69.4 ± 9.8	.007	71.1 ± 10.6	69.6 ± 9.7	.11	68.7 ± 10.2	71.9 ± 9.4	<.001
Male	74 (61.2)	255 (66.9)	.27	109 (75.2)	222 (61.7)	.004	181 (62.6)	151 (69.3)	.13
Female	47 (38.8)	126 (33.1)	.27	36 (24.8)	138 (38.3)	.004	108 (37.4)	67 (30.7)	.13
CVA or TIA	20 (16.5)	37 (9.7)	.048	18 (12.4)	39 (10.8)	.64	37 (12.8)	20 (9.2)	.26
Hypertension	103 (85.1)	326 (85.6)	.88	130 (89.7)	303 (84.2)	.12	244 (84.4)	190 (87.2)	.44
Hypercholesterolaemia or dyslipidaemia	74 (61.2)	247 (64.8)	.52	93 (64.1)	229 (63.6)	1.0	181 (62.6)	143 (65.6)	.51
Coronary artery disease	14 (11.6)	36 (9.4)	.49	18 (12.4)	32 (8.9)	.25	32 (11.1)	19 (8.7)	.46
Smoking	75 (62.0)	266 (69.8)	.13	96 (66.2)	248 (68.9)	.60	203 (70.2)	142 (65.1)	.25
Current	46 (38.0)	144 (37.8)	1.0	48 (33.1)	142 (39.4)	.19	127 (43.9)	64 (29.4)	<.001
Diabetes mellitus	57 (47.1)	129 (33.9)	.010	68 (46.9)	119 (33.1)	.004	106 (36.7)	81 (37.2)	.93
Insulin dependent	31 (25.6)	51 (13.4)	.003	36 (24.8)	46 (12.8)	.001	44 (15.2)	38 (17.4)	.54
Renal insufficiency	16 (13.2)	26 (6.8)	.037	19 (13.1)	22 (6.1)	.012	19 (6.6)	23 (10.6)	.14
Dialysis	7 (5.8)	3 (0.8)	.003	8 (5.5)	2 (0.6)	.001	5 (1.7)	5 (2.3)	.75
CLTI*	121 (100)	0 (0.0)	<.001	38 (26.8)	82 (22.8)	.35	77 (26.7)	44 (20.4)	.11
Non-healing wound on the target limb	70 (57.9)	3 (0.8)§	<.001	22 (15.2)	51 (14.2)	.78	45 (15.6)	28 (12.8)	.44
De novo lesions	113 (90.4)	350 (90.2)	1.0	133 (88.7)	333 (91.0)	.42	272 (91.9)	195 (87.8)	.14
Restenotic lesions	12 (9.6)	38 (9.8)	1.0	17 (11.3)	33 (9.0)	.42	24 (8.1)	27 (12.2)	.14
Maximum RVD – mm	5.4 ± 0.7	5.5 ± 0.7	.77	5.4 ± 0.8	5.5 ± 0.6	.32	5.4 ± 0.7	5.5 ± 0.7	.015
Lesion length – mm	125.8 ± 88.1	126.2 ± 92.6	.72	144.3 ± 94.0	118.5 ± 89.0	<.001	156.5 ± 99.6	85.1 ± 56.7	<.001
Diameter stenosis – %	95.4 ± 7.9	94.4 ± 8.1	.090	94.9 ± 8.6	94.5 ± 7.8	.44	99.9 ± 1.8	87.6 ± 7.8	<.001
Occlusion	80 (64.0)	211 (54.4)	.062	88 (58.7)	205 (56.0)	.63	294 (99.3)†	0 (0.0)	<.001
Calcification									
Grade 0, no visible calcium	16 (12.9)	74 (19.1)	.14	0 (0.0)	91 (24.9)	<.001	57 (19.3)	34 (15.4)	.29
Grade 1, unilateral, < 5 cm	34 (27.4)	117 (30.2)	.57	3 (2.0)‡	149 (40.7)	<.001	89 (30.2)	63 (28.5)	.70
Grade 2 unilateral, ≥ 5 cm	35 (28.2)	91 (23.5)	.29	0 (0.0)	126 (34.4)	<.001	61 (20.7)	65 (29.4)	.023
Grade 3, bilateral, < 5 cm	27 (21.8)	48 (12.4)	.013	76 (50.7)	0 (0.0)	<.001	42 (14.2)	34 (15.4)	.80
Grade 4, bilateral, ≥ 5 cm	12 (9.7)	57 (14.7)	.18	71 (47.3)	0 (0.0)	<.001	46 (15.6)	25 (11.3)	.12

Data are displayed as mean ± standard deviation or n (%). Rutherford class and calcification grade were not available for all patients; thus, the subgroups do not add up to the total of 507 patients. CLTI = chronic limb threatening ischaemia; CTO = chronic total occlusion; CVA = cerebrovascular accident; IC = intermittent claudication; L = lesions; P = patients; PACSS = peripheral arterial calcium scoring system; RVD = reference vessel diameter; TIA = transient ischaemic attack.

* Data not available for all patients.

† Two patients had one lesion with CTO and one without.

‡ Patients with two lesions were classified into PACSS grade 3,4 as soon as one of the lesions was classified as PACSS grade 3,4. Data are site assessed.

§ Subjects were not classified as Rutherford ≥4.

after PSM. However, CD-TLR and patency did not differ among the groups (Fig. 3, Table 3, Supplementary Figures S2–S4).

Patients with CLTI also had a lower ABI at baseline compared with patients with IC and a greater clinical improvement at 36 months than patients with IC (100% *vs.* 84.4%, $p < .001$ in the unmatched cohort) (Supplementary Tables S5 and S6).

Patients with severe calcification (peripheral arterial calcium scoring system grade 3,4) vs. less severe calcification (peripheral arterial calcium scoring system grade 0 – 2)

Patients with PACSS 3,4 (145/505, 28.7%) were more often male (75.2% *vs.* 61.7%, $p = .004$), more frequently had diabetes mellitus (46.9% *vs.* 33.1%, $p = .004$), renal insufficiency (13.1% *vs.* 6.1%, $p = .012$), and longer lesions (144.3 ± 94.0 mm *vs.* 118.5 ± 89.0 mm, $p < .001$) compared with the patients with less calcification (Tables 1 and 2; for the PSM population, see Supplementary Tables S2–S4).

CD-TLR at 12, 24, and 36 months was 84.8%, 79.5%, and 77.6% in the unmatched PACSS 3,4 group and 91.4%, 83.9%, and 78.7% in the PACSS 0 – 2 group, respectively.

At the final assessment at 36 months, survival was lower in the high calcification group (79.5% *vs.* 87.6%, $p = .034$), and the amputation free survival was lower too. Major

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Table 2. Procedural characteristics by subgroup

	CLTI			Calcification			CTO		
	CLTI (n = 121 P) (n = 125 L)	IC (n = 381 P) (n = 388 L)	p value	PACSS 3,4 (n = 145 P) (n = 150 L)	PACSS 0–2 (n = 360 P) (n = 366 L)	p value	CTO (n = 289 P) (n = 296 L)	No CTO (n = 218 P) (n = 222 L)	p value
Procedure time − min	84.3 ± 59.9	71.6 ± 44.3	.053	87.2 ± 55.0	69.6 ± 45.3	.001	85.1 ± 54.8	60.4 ± 34.7	<.001
Total fluoroscopy time − min	16.8 ± 13.0	14.3 ± 10.4	.056	16.9 ± 13.5	14.1 ± 10.0	.016	17.4 ± 12.7	11.5 ± 7.5	<.001
Total contrast volume − mL	115.0 ± 61.5	111.6 ± 59.8	.49	103.8 ± 61.1	114.8 ± 59.6	.045	116.9 ± 59.8	104.9 ± 60.1	.004
Number of BioMimics stent deployed									
1	94 (75.2)	296 (76.3)	.81	115 (76.7)	278 (76.0)	.91	193 (65.2)	202 (91.0)	<.001
2	24 (19.2)	72 (18.6)	.90	25 (16.7)	71 (19.4)	.53	78 (26.4)	18 (8.1)	<.001
3	4 (3.2)	15 (3.9)	1.0	7 (4.7)	12 (3.3)	.45	17 (5.7)	2 (0.9)	.040
4	3 (2.4)	5 (1.3)	.41	3 (2.0)	5 (1.4)	0.70	8 (2.7)	0 (0.0)	.012
Total stented length − mm	135.6 ± 81.9	130.0 ± 80.0	.24	134.5 ± 77.7	130.0 ± 81.3	.18	153.3 ± 91.2	101.8 ± 48.7	<.001
No patent infrapopliteal vessel	12 (9.9)	10 (2.6)	.002	6 (4.1)	16 (4.4)	1.0	18 (6.2)	4 (1.8)	.016
PTA balloon									
Pre-dilatation	111 (88.8)	340 (87.6)	.88	136 (90.7)	318 (86.9)	.30	273 (92.2)	181 (81.5)	<.001
Post-dilatation	100 (80.0)	248 (63.9)	.001	126 (84.0)	225 (61.5)	<.001	203 (68.6)	150 (67.6)	.85
Drug coated balloon									
Pre-BioMimics stent placement	29 (23.2)	93 (24.0)	.90	34 (22.7)	89 (24.3)	.73	87 (29.4)	36 (16.2)	<.001
Post-BioMimics stent placement	21 (16.8)	116 (29.9)	.004	25 (16.7)	112 (30.6)	.001	79 (26.7)	58 (26.1)	.92
Technical success, lesion based	124 (99.2)	383 (99.0)	1.0	148 (98.7)	362 (99.2)	.63	284 (98.6)	217 (99.5)	.34
Acute procedural success	116 (95.9)	373 (97.9)	.32	140 (96.6)	352 (97.8)	.53	280 (96.9)	214 (98.2)	.41

Data are displayed as mean ± standard deviation or n (%). Rutherford class and calcification grade were not available for all patients; thus, the subgroups do not add up to the total of 507 patients. CLTI = chronic limb threatening ischaemia; CTO = chronic total occlusion; IC = intermittent claudication; PACSS = peripheral arterial calcium scoring system; PTA = percutaneous transluminal angioplasty.

amputations, CD-TLR, and primary patency did not differ significantly among the groups and after PSM there was no difference in outcomes (Fig. 3, Table 3, Supplementary Figures S2—S4). There was also no significant difference in terms of ABI and Rutherford class among the groups for the matched and unmatched cohorts (Supplementary Tables S5 and S6).

All four stent fractures observed in MIMICS-3D occurred in PACSS 0 − 2 patients with CTO, one was in a patient with CLTI, the remaining three were in patients with IC.

Patients with chronic total occlusion vs. those without

Patients with CTO lesions (n = 289/507, 57.0%) were slightly younger (68.7 ± 10.2 years *vs.* 71.9 ± 9.4 years, $p < .001$), had longer lesions (156.5 ± 99.6 mm *vs.* 85.1 ± 56.7 mm, $p < .001$), and fewer patent outflow vessels (absence of patent outflow vessels 6.2% *vs.* 1.8%, $p = .016$) (Tables 1 and 2; for the PSM population, see Supplementary Tables S2—S4).

CD-TLR at 12, 24, and 36 months was 86.1%, 79.7%, and 75.6% in the unmatched CTO group and 93.0%, 85.6%, and 81.0% in the no CTO group, respectively.

In the unmatched cohort, patients with CTO lesions had lower 36 month primary patency than patients without CTO (63.9% *vs.* 77.8%, $p = .003$), but this difference diminished after PSM. There was no difference in survival, rate of major amputation, or CD-TLR (Fig. 3, Table 3, Supplementary Figures S2—S4).

In the matched and unmatched cohorts, patients with CTO had a lower ABI at baseline compared with patients with IC or patients with no CTO, but this difference diminished after 36 months (Supplementary Tables S5 and S6).

DISCUSSION

The Mimics 3D subgroup analysis suggests good safety and performance outcomes in patients with CLTI or in complex lesions (highly calcified or CTO lesions) similar to patients with IC or simple lesions.

Chronic limb threatening ischaemia

CLTI is the most severe form of PAD,[5] and the optimal treatment strategy is still debated. As seen in the study,

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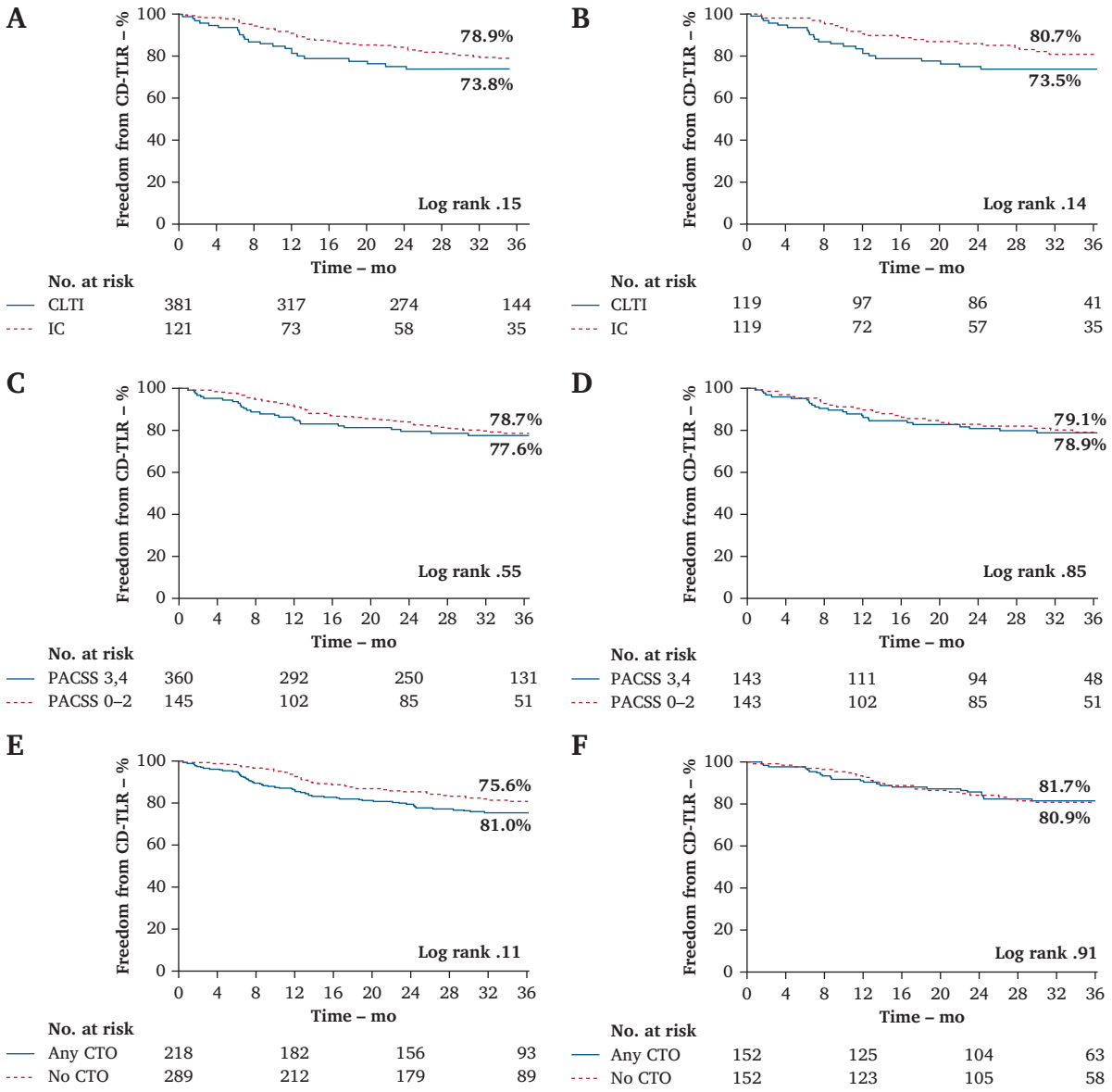

Figure 3. Cumulative Kaplan–Meier estimate of freedom from clinically driven target lesion revascularisation (CD-TLR) by subgroup. (A,B) Critical limb threating ischaemia (CLTI) *vs.* intermittent claudication (IC): (A) unmatched cohort and (B) matched cohort. (C.D) Peripheral arterial calcium scoring system (PACSS) 3,4 *vs.* PACSS 0–2: (C) unmatched cohort and (D) matched cohort. (E,F) Chronic total occlusion (CTO) *vs.* no CTO lesions: (E) unmatched cohort and (F) matched cohort. Data are displayed as Kaplan-Meier survival and 95% confidence interval.

patients with CLTI suffer from multiple comorbidities. CLTI treatment entails surgical therapy or endovascular treatment, with endovascular therapy considered the primary strategy for comorbid patients. Recently, it was associated with an improved amputation free survival in BASIL-2,[18] while conflicting data were shown in the BEST-CLI trial in younger patients with an adequate great saphenous vein graft.[19] Moreover, the optimal endovascular modality has not been identified in randomised controlled trials. Balloon angioplasty is a common endovascular therapy, but has the limitation of vessel recoil and dissections, thus bailout stenting is commonly required.[7]

Patients with CLTI have generalised, severe atherosclerosis with a three fold increased risk of cardiovascular events, including death.[4–8] Despite advances in endovascular interventions, CLTI remains a morbid and deadly disease with a high mortality rate.[20] Likewise, in the current series, 36 month survival was 27.5% lower in patients with CLTI than in those with IC, and even after PSM a significant difference between the groups remained. Moreover, major amputation occurred in 7.4% in the CLTI group at 36 months whilst there were none in the IC group with similar outcomes in the PSM groups. Notably, inherent to the definition of CLTI, no PSM could be done for Rutherford class (4.8 $\pm$ 0.6 for CLTI patients *vs.* 2.7 $\pm$ 0.5 for IC patients, $p < .001$). This, along with a higher rate of occluded lesions (63.4% *vs.* 48.8%, $p = .028$) certainly impacted the major amputation rate, but also seemed to impact survival.

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Table 3. Clinical outcomes and patency at 36 months by subgroup (matched and unmatched cohorts)

	Survival	Ff major TLA	Amputation free survival	Ff CD-TLR	CD-TLR free survival	Primary patency
CLTI	64.0 (54.8–73.2)	92.6 (87.3–97.9)	60.4 (51.0–69.8)	73.8 (64.5–83.1)	49.5 (40.1–59.0)	66.0 (55.7–76.3)
IC	91.5 (88.6–94.4)	100 (100–100)	91.5 (88.6–94.4)	78.9 (74.6–83.3)	73.1 (68.5–77.7)	71.4 (66.4–76.3)
Log rank *p* value	<.001	<.001	<.001	.15	<.001	.14
CLTI PSM	64.4 (55.2–73.7)	92.5 (87.1–97.9)	60.8 (51.3–70.2)	73.5 (64.1–82.9)	49.6 (40.1–59.1)	65.5 (55.1–75.9)
IC PSM	89.4 (83.7–95.1)	100 (100–100)	89.4 (83.7–95.1)	80.7 (73.1–88.4)	73.3 (65.1–81.5)	75.3 (66.6–83.9)
Log rank *p* value	<001	.004	<.001	.14	<.001	.090
PACSS 3,4	79.5 (72.5–86.6)	97.6 (95.0–100)	78.1 (70.9–85.3)	77.6 (70.1–85.1)	64.2 (56.0–72.4)	70.5 (62.2–78.8)
PACSS 0–2	87.6 (84.0–91.1)	98.8 (97.6–100)	87.0 (83.3–90.6)	78.7 (74.1–83.3)	69.6 (64.6–74.5)	70.6 (65.4–75.9)
Log rank *p* value	.034	.36	.019	.55	.19	.43
PACSS 3,4 PSM	80.0 (73.0–87.0)	97.6 (94.9–100)	78.6 (71.4–85.8)	78.9 (71.5–86.3)	65.2 (56.9–73.4)	71.7 (63.4–80.0)
PACSS 0–2 PSM	84.2 (77.7–90.6)	97.7 (95.1–100)	82.7 (76.0–89.4)	79.1 (71.8–86.5)	67.8 (59.7–75.9)	69.5 (60.8: 78.1)
Log rank *p* value	.46	.98	.46	.85	.62	.77
CTO	85.6 (81.3–89.9)	98.0 (96.2–99.7)	84.5 (80.1–88.9)	75.6 (70.1–81.0)	65.4 (59.6–71.1)	63.9 (57.5–70.3)
No CTO	84.8 (79.8–89.7)	99.1 (97.8–100)	84.3 (79.3–89.3)	81.0 (75.4–86.6)	71.0 (64.8–77.2)	77.8 (71.9–83.8)
Log rank *p* value	.87	.40	.72	.11	.14	.003
CTO PSM	86.8 (81.2–92.5)	97.8 (95.3–100)	86.2 (80.4–92.0)	81.7 (75.1–88.4)	72.1 (64.6–79.6)	70.5 (62.2–78.8)
No CTO PSM	82.4 76.1–88.7)	98.7 (96.9–100)	81.7 (75.3–88.1)	80.9 (74.1–87.6)	68.8 (61.2–76.4)	76.8 (69.5–84.1)
Log rank *p* value	.27	.064	.29	.91	.52	.43

Data are presented as Kaplan–Meier estimates of percentage (95% confidence interval). CD-TLR = clinically driven target lesion revascularisation; CLTI = chronic limb threatening ischaemia; CTO = chronic total occlusion; DCB = drug coated balloon; Ff = freedom from; IC = intermittent claudication; PACSS = peripheral arterial calcium scoring system; PSM = propensity score matched; TLA = target limb amputation.

However, outcomes might have also been impacted by factors that were not included in the PSM.

Impressively, there was no difference in 36 month CD-TLR or primary patency, even though CLTI is a known predictor for restenosis and re-intervention, which illustrates the performance of the helical centreline stent in this population.[6–8]

As stated above, so far, data are still insufficient to recommend the best treatment for CLTI. In this context, it is relevant to explore how a novel stent design such as BioMimics 3D compares with current drug eluting stents (DESs) as these have been recommended for several indications in femoropopliteal lesions.[21] Furthermore, it is relevant to compare the results to another mimetic self expanding stent, Supera (Abbott Vascular, Santa Clara, CA, USA). Both stents are highly biomechanically compatible with the challenging femoropopliteal environment, however they have completely different designs. Supera is a woven stent consisting of six pairs of nitinol wires that are formed into a braid during deployment.[22] BioMimics 3D is a slotted tube, laser cut, self expanding nitinol stent with a 3D helical centreline. Due to the shape memory properties of nitinol, the stent retains its 3D helical centreline and is therefore able to shorten with the vessel as the knee or hip are flexed. The stent imposes its helical shape onto the vessel, which not only aids biomechanical compatibility but induces swirling flow and creates high wall shear; a phenomenon considered to be patency protective.[13,23–25]

With the caveat that the quoted studies had different patient populations, the results are similar to those of DES and Supera (Supplementary Table S7).[6,26–29] For example, freedom from CD-TLR at 36 months was 73.8% in MIMICS-3D *vs.* 57.4 — 82% for Supera and 80.4% for the Zilver PTX DES.

Calcification

For calcified lesions, bare metal stents are often used to prevent recoil. Calcium deposits may hinder the delivery and penetration depth of the antiproliferative drug, challenging the effectiveness of drug coated balloons (DCBs) and DES.[30–32] Calcification also increases the risk of dissection, incomplete stent expansion, malapposition, stent fractures, and restenosis, and results in a smaller lumen gain;[17,29–31,33] bailout rates after DCB therapy may be as high as 66.7%.[34]

Calcification is also an independent predictor of death.[8,17] Likewise, 3 year survival was lower in the high calcification group (79.5% *vs.* 87.6%, $p = .034$). This difference in survival was attributed to worse baseline characteristics such as higher rates of diabetes mellitus and renal insufficiency, as there was no difference in survival in the PSM cohort.

The BioMimics 3D stent might be particularly useful in calcified lesions. Due to its helical design BioMimics 3D is very flexible, whilst still having a high radial force. This is reflected by the fact that CD-TLR and primary patency were nearly identical in the PACSS 3,4 and the PACSS 0 — 2 group, even though calcification is a known predictor for restenosis.[17,31,33,35] This outcome is attributable to the combination of both high radial strength and flexibility, and to the swirling flow that has been shown to improve the risk of restenosis.[13,24,25]

In MIMICS-3D, the subgroup of patients with PACSS 3,4 lesions had a mean lesion length of 144.3 mm. MIMICS-3D

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is currently the only study of a mimetic stent with 3 year data in this high risk subgroup, therefore 1 year data are compared. Freedom from CD-TLR at one year was 84.8% (95% CI 78.5 — 91.1) compared with 84.7% in lesions with a mean length of 164 mm treated with the Zilver PTX in a retrospective study in Japan.[31] Primary patency at 1 year was 81.5% (95% CI 74.7 — 88.4) *vs.* 70.5% to 75.9% for Supera and Zilver PTX (Supplementary Table S7).[31]

Chronic total occlusion

CTO lesions are difficult to treat. If balloon angioplasty is intended, approximately half of the subjects require stenting, and the plaque burden and calcification can lead to dissection and elastic recoil;[10] a higher stenosis degree at baseline has been proven to be associated with higher re-intervention rates and lower patency.[8,36–41] Likewise, in MIMICS-3D, the 3 year patency in patients with CTO was lower than in those with no CTO; however, the CD-TLR rate was nearly identical. Notably, subjects with CTO had smaller vessel diameters and longer lesions, and after PSM no difference was present.

Studies with CTO lesions are scarce, but the outcomes are within the range of other publications, even if these also include no CTO lesions. For example, the 3 year CD-TLR rate was 75.6% compared with 57.4% and 80.4% for the Supera stent and the Zilver DES, respectively (Supplementary Table S7).[6,42,43]

Limitations are inherent to the design of an observational study, such as the lack of randomisation that hampers the comparison with other devices, and the lack of systematic imaging assessments. Moreover, the patient population is heterogeneous and additional treatments were permitted, which further hampers the comparison with historical data. Screening failures were not recorded, but given the observational character of this series, the risk of bias through screening failures is low as patients only needed to consent to providing their data, albeit a selection bias cannot be excluded. Performing PSM for CLTI *vs.* IC patients is questionable as PSM can only correct for some imbalance in populations and CLTI and IC patients are far from comparable. However, in an attempt to level out large imbalances between the subgroups PSM was performed. Although suboptimal, this method enabled comparison of the results in the different subgroups to some extent. The follow up compliance at 36 months was 88.6%.[15] While this is an expected follow up compliance for observational registries, particularly during the time of COVID-19, the suboptimal follow up might have impacted outcomes. The subgroup analyses and PSM were *post hoc* analyses and hence not powered. The strength of this registry is the real world data that reflect the patient population that the practitioner sees in their daily routine.

Conclusion

MIMICS-3D suggests that BioMimics 3D achieves good results in patients with CLTI and in complex lesions such as severe calcification or CTO. In particular, after PSM, there was no difference in clinical outcomes for patients with severe calcification or with CTO lesions. Ultimately, randomised controlled trials are needed to compare different treatment regimens in these high risk subsets.

CONFLICTS OF INTEREST

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APPENDIX A. SUPPLEMENTARY DATA

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