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A multicenter prospective observational study appraising the effectiveness of the Supera stent after subintimal recanalization of femoro-popliteal artery occlusion: The SUPERSUB II study

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Abstract

Background: Complex femoropopliteal artery disease represents a challenge. The Supera stent holds the promise of improving the results of endovascular therapy for complex femoropopliteal disease.

Aims: We aimed at appraising the early and long-term effectiveness of the Supera stent after successful subintimal angioplasty (SuperSUB strategy) for complex femoropopliteal lesions.

Methods: We conducted a multicenter, prospective, single-arm observational study including consecutive patients at participating centers in whom Supera was implanted after successful subintimal angioplasty for complex femoropopliteal lesions.

Results: A total of 92 patients were included Femoropopliteal arteries were the most common target, and lesion length was 261 ± 102 mm. Most procedures were technically demanding, with antegrade femoral access in 35 (38%) and retrograde distal access in 55 (60%). Supera stent length was 281 ± 111 mm, with 4, 5, and 6 mm devices being most commonly used: 32 (35%), 35 (38%), and 23 (25%), respectively. Technical success was achieved in 100% of subjects, as was clinical success (per subject), whereas procedural success (per subject) was obtained in 98%. At 24 months, freedom from clinically driven target lesion revascularization was 93%, whereas primary patency was 87%. When compared

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with a similar historical cohort, Supera stent use appeared to be associated with a reduction in resources.

Conclusion: Use of Supera stent after successful subintimal recanalization of complex lower limb arterial lesions yields favorable procedural results, which are maintained over follow-up, and are associated also with a favorable resource use profile.

KEYWORDS
endovascular therapy, femoropopliteal disease, peripheral artery disease, stent, subintimal angioplasty, Supera stent

1 | INTRODUCTION

The burden of peripheral artery disease continues to expand, with substantial impact of mortality, morbidity, and resource use.[1,2] While surgical revascularization remains the best therapeutic option in eligible patients, endovascular therapy has improved substantially over the last few decades thanks to many key developments.[3] Indeed, endovascular therapy is strongly recommended when medical therapy fails and when surgical revascularization is not indicated. Among the many key improvements in endovascular therapy, refinements in techniques and devices have been momentous.[4,5] For instance, subintimal recanalization and retrograde approaches have improved procedural success rates substantially.[6] Similarly, devices, ranging from sheaths and catheters, to guidewires, balloons, and stents, have improved dramatically, such that devices used 15 or 20 years ago would be considered obsolete if not unethical for contemporary clinical use.[5]

Indeed, success rates and durability of femoropopliteal endovascular therapy are typically less favorable in lesions with heavy plaque burden, significant calcification, and chronic total occlusions (CTOs), especially in patients with critical limb ischemia (CLI), which render balloon angioplasty results, especially in case of subintimal recanalization, often disappointing.[7] Similarly, stents face constant exposure to simultaneous and opposing biodynamic forces (compression, torsion, flexion, extension, and rotation). Furthermore, the lack of native intima-media tissues, may lead, on one hand, to compression, kinking, and fractures, and, on the other hand, enhanced inflammatory response of the arterial wall, potentially leading to accelerated restenosis or thrombosis.[8] Accordingly, there is ongoing debate on the most appropriate optimization strategy in patients with CLI exhibiting femoropopliteal occlusions who have been successfully recanalized using a subintimal tracking technique. The optimal management strategy in these patients is debated, with some operators preferring a stent-less approach with drug-coated balloons, and other endovascular specialists opting for drug-eluting stents, despite the limited comparative evidence based.[9]

The Supera stent is a novel endovascular device that is based on a unique braided, interwoven, self-expanding, nitinol platform, explicitly designed to address the anatomic challenges of the femoropopliteal segment.[10] Basically, it is characterized by superior flexibility and resistance to kinking and deformation, and it has already performed satisfactorily in several registries and observational comparative studies (Supporting Information: Table 1S). Accordingly, it could prove an excellent tool for challenging femoropopliteal lesions in patients with CLI, but uncertainty persists on this specific indication, especially when aggressive revascularization approaches (e.g., subintimal angioplasty) are used.

To more precisely and validly appraise the risk-benefit of the Supera stent in patients with class C-D lesions according to the Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC), successfully recanalized by means of subintimal tracking, and building upon our prior experience with Supera stent after subintimal angioplasty,[11] we designed and conducted a multicenter prospective observational trial: the SUPERa stenting after SUBintimal crossing of TASC C-D femoropopliteal lesions in CLI patients (SUPERSUB) II study.

2 | METHODS

2.1 | Design

The SUPERSUB II study was designed as an international, multicenter, prospective, post-marketing, open-label, observational study, focusing on patients receiving a Supera stent after subintimal recanalization of a complex femoropopliteal CTO. The study was approved by the competent ethics committee, including the coordinating center committee (Casa di Cura Abano Terme Polispecialistica e Termale, Abano Terme, Italy; protocol ID: 2018-190E), and was registered in an online registry (NCT00933270).

2.2 | Patients and procedures

Details on the study flow chart are provided in Supporting Information: Table 2S. Specifically, the following inclusion criteria were applied: age ≥18 years, CLI with Rutherford category 4, 5, or 6, de novo TASC C-D femoropopliteal CTO, patent inflow and hemodynamically normal iliac and common femoral arteries, ≥1 patent and healthy tibial vessel runoff to the foot, subintimal crossing of the occluded femoropopliteal vessel, successful Supera stenting from healthy to healthy arterial segment, and signing of approved written consent form, These exclusion criteria were instead applied: acute or subacute limb ischemia, poor inflow in the iliac and common femoral vessels, prior stenting of the target lesion, stenosis in the distal vessels that could impede runoff, endoluminal crossing of the CTO, inability to stent from healthy to healthy arterial segments, known allergy to aspirin, clopidogrel or heparin, or patient unwilling or unlikely to comply with follow-up schedule.

Vascular access (ipsilateral, contralateral, and retrograde) was at operator's discretion, but antegrade access was recommended to ensure support and control.[12] Only one target lesion per patient was selected for intervention. When proximal superficial femoral artery (SFA) stenting was indicated, the proximal stent had to be deployed using a retrograde access, for precise and safe implant, avoiding any risk to stent the common femoral artery or covering the profunda femoris. Pre-dilatation of the target lesion was mandatory in all cases and had to be performed with a balloon, 1 mm bigger in diameter than the reference Supera stent diameter. Commercially available Supera stents were used, and stent sizing matched the reference vessel diameter and fully covered and extended slightly beyond the lesion length. When more than one stent was used, overlapping by at least 1 cm between both stents was recommended.

If the patient was not already under chronic treatment with aspirin at a dose of 75–325 mg, a loading dose of 500 mg had to be administered within 24 h before the index procedure. If the patient was already under chronic treatment with aspirin, this had to be continued under the same dose. Based on body weight, a 5000–10,000 IU bolus of heparin (or other thrombin inhibitors) had to be administered as per standard practice. Antiplatelet and anticoagulant therapy after revascularization were prescribed as per the standard of care at the site. Other medications were left to investigators' discretion based on the patient's clinical needs. A selection of the most relevant previous and concomitant medications was recorded.

After discharge, all patients attended clinic visits at 30 days (±14 days), 6 months (±30 days), 12 months (±30 days), and 24 months (±30 days) that was the final visit. Qualitative and quantitative assessment for diagnostic and therapeutic imaging in all aspects of selective cardio-vascular disease (qualitative and quantitative peripheral arterial segments analysis, angiography/CO_2 angiography, duplex ultrasound, computed tomography scan, magnetic resonance angiography and X-ray visualization of study device) was recommended, as per local institutional practice.

2.3 | Outcomes

The primary efficacy endpoint was freedom from clinically driven-target lesion revascularization (CD-TLR) at 12 months. Other efficacy endpoints were freedom from CD-TLR at 24 months, primary patency rates at 12 and 24 months. Safety endpoints included: freedom from device and procedure-related death through 30 days postprocedure, freedom from target limb major amputation and clinically-driven target lesion revascularization through 12 months postprocedure, and up to 24 months, composite of all major adverse events (MAEs, including death from any cause, major target limb amputation, and CD-TLR) at 12 and 24 months, and individual components of MAE at 12 and 24 months.

Other endpoints of interest were: technical success (defined as achievement of an angiographic core lab-sanctioned final in-lesion residual diameter stenosis of ≤30% using the Supera stent after wire passage through the lesion, clinical success (per-subject, defined as technical success without the occurrence of major adverse limb events during hospitalization), procedural success (per subject, defined as lesion success without the occurrence of major adverse events during the procedure), amputation (distinguishing major and minor amputations) at 1, 6, 12, and 24 months, primary sustained clinical improvement (improvement of ≥1 Rutherford class without CD-TLR) at 1, 6, 12, and 24 months, clinical improvement as assessed by Rutherford class changes at 1, 6, 12, and 24 months, quality of life improvements at 6, 12, and 24 months (according to EQ5D 5L and SF12 questionnaires), and stent integrity at 12 and 24 months.

Furthermore, an outcome and cost comparative analysis was conducted for exploratory purposes, based on yearly procedural-related costs and hospital stay(s) between included patients in comparison to a historical cohort of patients matched by age, gender, and lesion type (TASC C-D), treated by PTA alone, after subintimal crossing, and leveraging Diagnosis-Related Group (DRG) reimbursements, as allocated by the Italian National Health Service.

2.4 | Analysis

Descriptive statistics (arithmetic mean, median as indicated, range, and standard deviation) were calculated for continuous variables. Absolute frequencies and percentages were obtained for qualitative variables. In calculation of percentages, patients with missing data have not been considered, unless otherwise specified. Inferential analysis was based on chi-squared test, Kruskal–Wallis' test, and Wilcoxon's test. Finally, Kaplan–Meier analysis was used for censored variables. Statistical significance was set at the two-tailed 0.05, without multiplicity adjustment. Computations were performed with SPSS, Version 24.

2.5 | Sample size

From historical site data, the primary endpoint (CD-TLR) rate was assumed as 60%; and by using the device under investigation, a relative reduction (RR) of 35% had been estimated.

Taking into consideration a power of 0.95, an alpha error of 0.05%, the estimated sample size calculated via two-sided Fisher's exact test was 73 subjects. Accounting a 20% of attrition the sample size was eventually computed as 92 (rounded up from 91.3).

3 | RESULTS

A total of 92 patients were included, enrolled in 15 sites (Supporting Information: Table 3S). Of these patients, eight were identified as major protocol violators. The final number of subjects included in the per-protocol analysis was thus 84.

Patient features are presented in Table 1. Notably, the mean age was 73.2 ± 9.2 years, with 11 (12%) women and as many as 56 (61%) diabetic individuals. Several comorbidities were evident, including pulmonary disease in 16 (17%), chronic renal failure in 28 (30%), including 11 (12%) patients with end-stage renal failure, and cerebrovascular disease in 17 (18%). Bilateral peripheral artery disease was present in 54 (58%), with prior surgical revascularization in 6 (6%), and prior endovascular therapy in 55 (60%), with a history of amputation in 8 (8%) for the target limb and 4 (4%) for the contralateral limb. Rutherford class was distributed as follows: 4 in 27 (29.4%), 5 in 41 (45.1%), and 6 in 24 (25.5%).

Focusing on lesion features (Table 2), femoropopliteal arteries were the most common target, with Trans-Atlantic Inter-Society Consensus class C in 40 (44%) and D in 52 (56%), and mean lesion length of 261 ± 102 mm. Most procedures were technically demanding, with antegrade femoral access in 35 (38%) and retrograde distal access in 55 (60%). Mean Supera stent length was 281 ± 111 mm, with 4, 5, and 6 mm devices being most commonly used: 32 (35%), 35 (38%), and 23 (25%), respectively. In terms of procedural results, technical success was achieved in 100% of subjects, as was clinical success (per subject), whereas procedural success (per subject) was obtained in 98% of individuals. Only two major procedural events, one pseudoaneurysm and one vessel perforation during subintimal recanalization, were adjudicated.

Clinical outcomes are summarized in Table 3, whereas long-term pharmacologic therapy is detailed in Supporting Information:

TABLE 1 Patient features.

Feature	*N* (%)* or mean ± standard deviation
Age (years)	73.2 ± 9.2
Female gender	11 (12%)
Caucasian ethnicity	89 (97%)
Hypertension	84 (91%)
Dyslipidemia	70 (76%)
Diabetes	56 (61%)
Previous or current smoking	73 (79%)
Atrial fibrillation	19 (21%)
Coronary artery disease	43 (47%)
Prior coronary artery bypass grafting	18 (19%)
Prior percutaneous coronary intervention	17 (18%)
Pulmonary disease	16 (17%)
Dialysis	11 (12%)
Chronic renal failure	28 (30%)
Cerebrovascular disease	17 (18%)
Carotid artery disease	11 (12%)
Previous carotid revascularization	7 (8%)
Monolateral peripheral artery disease	39 (42%)
Bilateral peripheral artery disease	54 (58%)
Previous surgical revascularization (target limb)	
Femoro-popliteal bypass	3 (3%)
Thromboendoarterectomy	3 (3%)
Previous endovascular treatment	
Target limb	14 (15%)
Contralateral limb	41 (45%)
Percutaneous transluminal angioplasty	21 (23%)
Prior stenting (nontarget limb)	22 (24%)
Target limb amputation	
Toe	6 (6%)
Transmetatarsal	2 (2%)
Contralateral limb amputation	
Toes	2 (2%)
Below-the-ankle	2 (2%)
Rutherford class	
4	27 (29%)
5	41 (45%)
6	24 (26%)

*Sample size = 92.

TABLE 2 Lesion and procedural features.

Feature	N (%) or mean ± standard deviation[a]
Target lesion distribution	
Superficial femoral artery	39 (42%)
Femoropopliteal arteries	49 (53%)
Popliteal artery	5 (6%)
Below the knee	84 (91%)
Calcification	
Mild	12 (13%)
Moderate	41 (45%)
Severe	39 (42%)
Trans-Atlantic Inter-Society Consensus II class	
C	40 (44%)
D	52 (56%)
Lesion length (mm)	261 ± 102
Lesion length range (mm)	150–500
Type of lesion	
De novo	79 (86%)
Re-occlusion	13 (15%)
Access	
Antegrade femoral access	35 (38%)
Retrograde femoral and cross-over	57 (62%)
Retrograde distal access	55 (60%)
Supera stent length (mm)	281 ± 111
Supera stent length range (mm)	160–530
Supera stent diameter	
4.5 mm	32 (35%)
5.0 mm	35 (38%)
5.5 mm	23 (25%)
6.0 mm	2 (2%)
Patent below the knee vessels at baseline	239 (94.8%)
Patent below the knee vessels at baseline	252 (100%)

[a]Sample size = 92.

TABLE 3 Outcomes.

Outcome	Patients/ total (%)	P versus baseline
Freedom from clinically driven-target lesion revascularization		
12 months	74/79 (94%)	-
24 months	73/78 (93%)	-
Primary patency		
12 months	69/77 (90%)	-
24 months	65/75 (87%)	-
Freedom from target limb major amputation and clinically driven-target lesion revascularization		
12 months	77/79 (98%)	-
24 months	77/79 (98%)	-
Freedom from major adverse events		
12 months	61/66 (93%)	-
24 months	51/57 (89%)	-
Rutherford class		
0		
Baseline	0/92	-
12 months	59/79 (75%)	<0.001
24 months	51/79 (64%)	<0.001
4		
Baseline	27/92 (29%)	
12 months	4/79 (5%)	<0.001
24 months	7/79 (9%)	<0.001
5		
Baseline	41/92 (45%)	-
12 months	10/79 (13%)	<0.001
24 months	15/79 (19%)	<0.001
6		
Baseline	24/92 (26%)	-
12 months	4/79 (6%)	<0.001
24 months	6/79 (8%)	<0.001

Table 4S. In particular, at 12 and 24 months, the Kaplan–Meier estimate of freedom from CD-TLR was 94% and 93%, respectively. This can be interpreted as a 93% freedom from CD-TLR post-procedure with Supera stent (Figure 1). The primary end-point at 12 months was assessed on 79 evaluable patients and at 24 months was assessed on 78 evaluable patients. In addition, primary patency was 87% at 24 months, with patency being primarily impacted by technical aspects (stent position from healthy-to-healthy arteries, as per core lab analysis). Notably, favorable results were adjudicated in terms of clinical results (e.g., individual components of adverse events, amputations, and Rutherford class shift) and quality of life (Figure 2; Supporting Information: Figures 1S and 2S).

Focusing on safety, a total number of 61 serious adverse events (SAEs) occurred. The number of patients that showed at least one SAE was 46 (50%). The number of patients reporting more than one SAE was 13 (28% of SAE patients). Deaths were 24, and the outcome of the remaining SAE was as follows: recovered in 32 cases, not recovered in 3 cases and recovered with sequelae

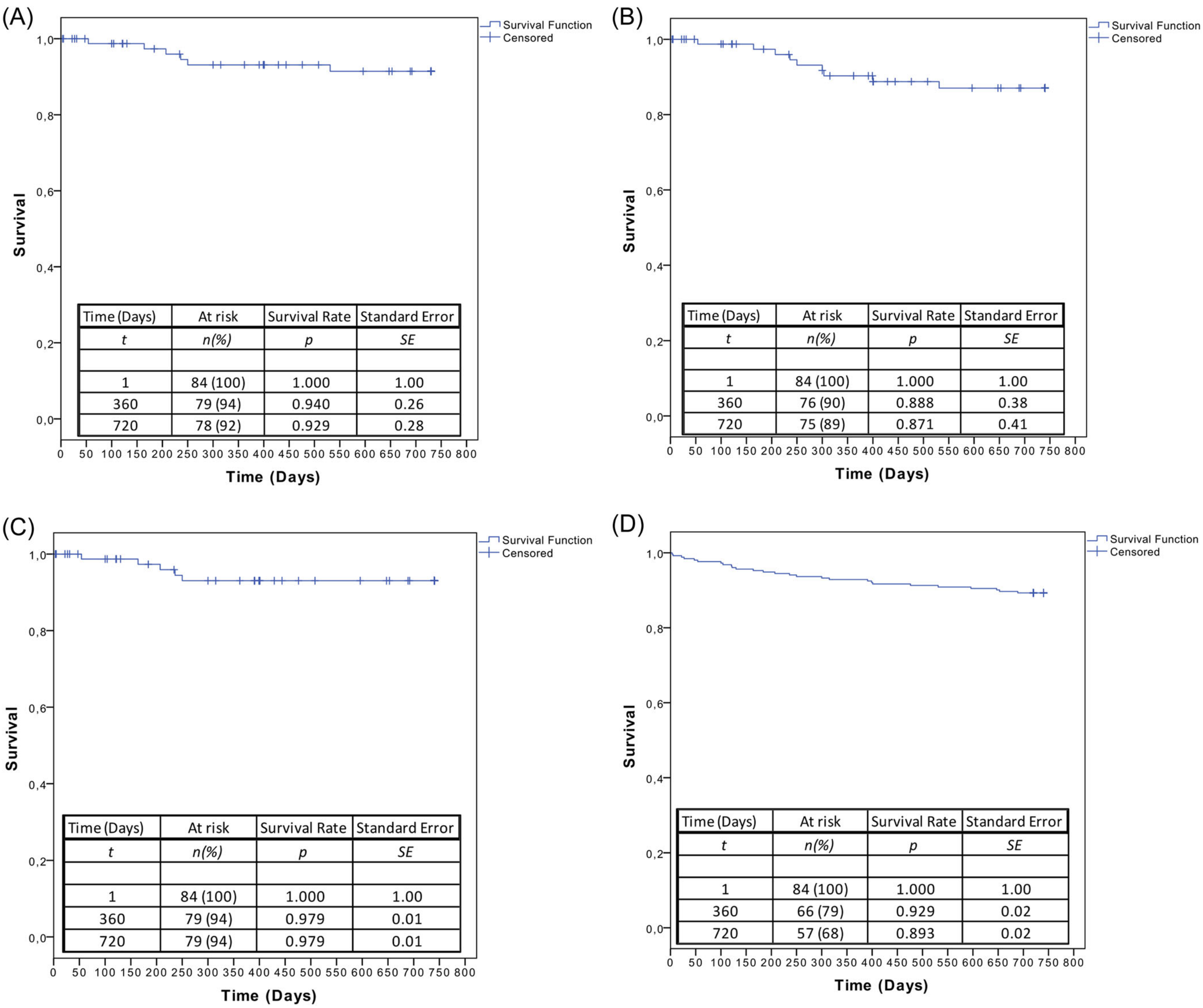

FIGURE 1 Kaplan–Meier analysis of freedom from clinically driven-target lesion revascularization (CD-TLR, panel A), primary patency (panel B), freedom from the composite endpoint of device and procedure-related death through 30-day post-procedure, target limb major amputation, and CD-TLR (panel C), and freedom from death or major target limb amputation (panel D). SE, standard error.

in 2 cases. No event related to accident or malfunctioning of the Supera stent or procedure under study was detected, and no stent fractures were observed.

In terms of quality of life, EQ-VAS scores improved significantly from baseline (47.46) to 12-month (63.63, $p < 0.001$) and 24-month follow-up (71.51, $p < 0.001$) (Supporting Information: Figures 3S–6S). Accordingly, benefits were seen for EQ-5D-5L (0.185, 0.053, and 0.051, both $p < 0.001$), Self-Care (0.097, 0.034, and 0.031, both $p < 0.001$), Usual Activities (0.224, 0.049, and 0.032, both $p < 0.001$), and Anxiety/Depression (0.125, 0.047, and 0.027, both $p < 0.001$). Similarly beneficial effects were also adjudicated for SF-12 Physical Component Summary (14.27 increase, $p < 0.001$, from baseline to 12 months and 4.47 increase, $p < 0.001$, between 12 and 24 months) and SF-12 Mental Component Summary (10.41 increase, $p < 0.001$, from baseline to 12 months and 9.70 increase, $p < 0.001$, between 12 months and 24 months).

When comparing the outcomes of the Supera stent group to the historical cohort, the former showed a higher rate of freedom from TLR at 12 months (93% in the study group compared with 26.4% in the historical cohort, $p < 0.001$). Regarding resource use comparisons, cumulative procedural costs and duration of hospitalization (including both index and repeat procedures) in the Supera group were significantly lower (6347 ± 1629€) in comparison to the historic cohort (12,987 ± 6347€, $p < 0.001$) (Supporting Information: Table 5S and Figure 7S). Similarly, the Supera stent group also showed a significant reduction in total hospitalization stay (4.3 ± 4.8 vs. 11.5 ± 8.9 days, $p < 0.001$). Differences in costs were largely due to reductions in repeat

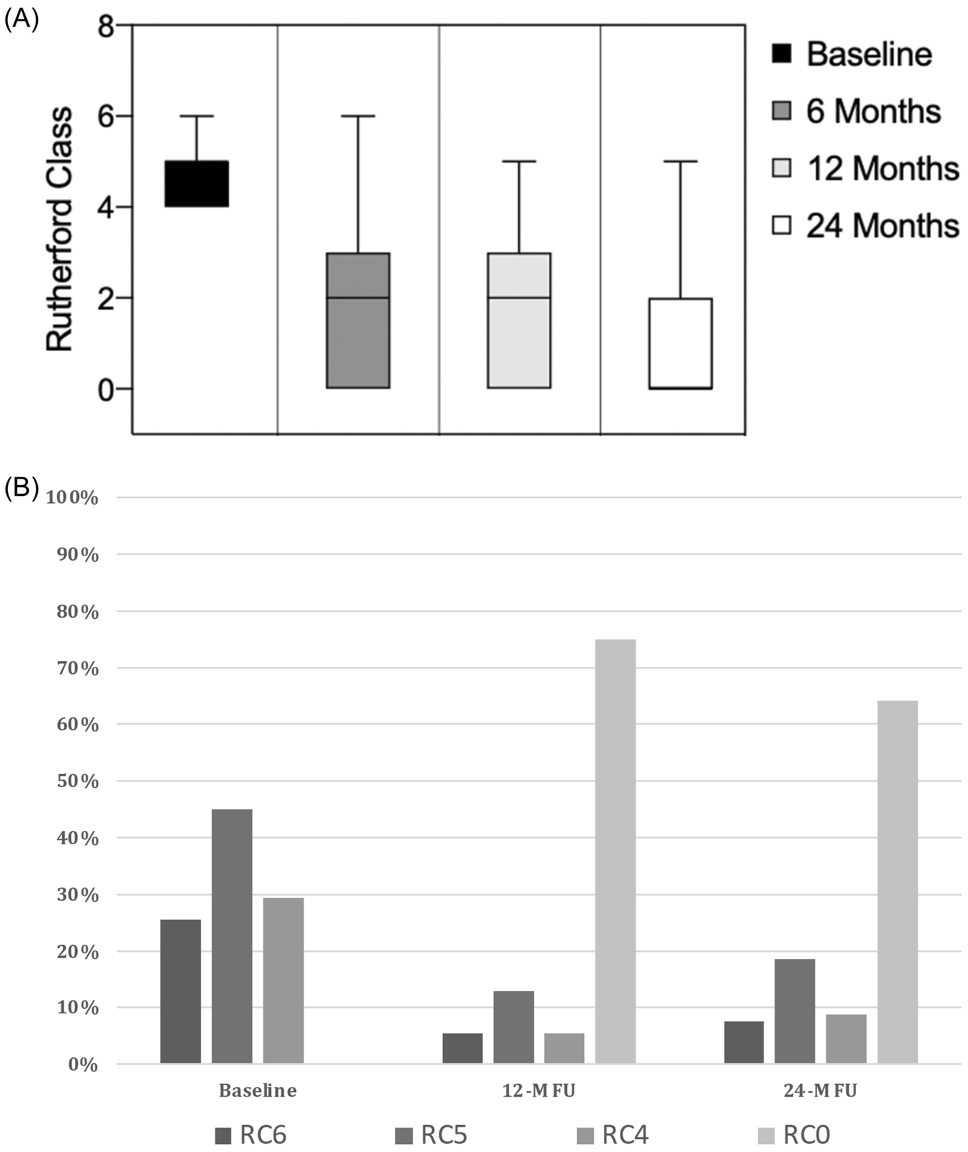

FIGURE 2 Rutherford class (RC) distribution at baseline, 6-, 12-, and 24-month follow-up ($p < 0.001$ when comparing 6-, 12-, and 24-month follow-up vs. baseline; panel A), and corresponding shift over time (panel B).

revascularization and hospital stay (either repeat or prolonged ones, in the Supera stent group; Supporting Information: Figure 8S).

4 | DISCUSSION

The present SuperSUB II prospective registry provides important clinical data on the effectiveness of the Supera stent for the endovascular treatment of patients with highly complex lower limb peripheral artery disease requiring subintimal recanalization. In particular, our study confirms the favorable results on this device, highlighting that subintimal revascularization encompassing Supera stenting in CLI patients with long BTK occlusions is feasible and provides excellent results when considering validated efficacy performance goals.

Endovascular therapy for challenging lower limb arterial disease has evolved momentously in the last few decades, from the pioneering experiences of Dotter, Gruntzig, and Kaltenbach, to the innovative concept of subintimal recanalization championed by Bolia.[13] Stents have proved over time, despite several setbacks and their evident inherent limitations, a key adjunct to optimize results of suboptimal angioplasty.[14] However, most stents, irrespective of coatings, face enormous challenges in the lower limb districts, given the everyday mechanical stresses imposed on them. While improvements in alloy and coating have translated into improved clinical results, the risk of stent compression, fracture, and similar mechanical issues is substantial.[15,16]

The recent introduction of the Supera stent, with its unique interwoven design, appears as a major improvement to currently available technologies, especially when stenting is envisioned in challenging settings, for example, after subintimal angioplasty.[17] We indeed hereby report on the benefits associated with the use of the Supera stent in terms of clinical results, quality of life, and resource use, providing reassuring results on the acute and midterm outlook of patients treated with this intriguing SuperSUB strategy, as well as on the feasibility of adopting such strategy in routine clinical practice. Indeed, our findings provide further support to a more liberal adoption of the SuperSUB strategy, given the excellent technical, device, and procedural results, and the high rate of freedom from clinically driven revascularization up to 24 months, resulting in improved quality of life and the potential cost savings for the healthcare system. These favorable findings are in line with the high rates of primary and secondary patency up to 24 months. Most of reinterventions occurred in patients with adverse anatomical features (i.e., diffuse disease impeding healthy-to-healthy stenting). Such findings are in keeping with those reported by Saratzis et al., in a series of 121 cases matched pairs created with a propensity score based on patient details and plaque features appraised at computed tomography.[18]

While awaiting dedicated comparative studies, including randomized trials, our results support a wider adoption of the SuperSUB approach whenever facing challenging lower limb lesions. Another promising avenue is the combination of the favorable features of the Supera stent with the anti-restenotic effects of drug-coated balloons (DCB). In selected cases, DCB could be used during lesion preparation or otherwise after Supera stent implantation to reduce the risk of restenosis in the body or at stent edges.[19] Notably, some experts claim to exploit the unique features of Supera by using it selectively, that is, in case of suboptimal results after prolonged balloon inflation or at the re-entry site. However, our exploratory analysis for patency factors suggests that extensive and default Supera stenting of all treated segments is associated with the best early and long-term clinical results.

5 | LIMITATIONS

Drawbacks of our work are several, including single-arm design, pragmatic scope, lack of centralized quantitative vascular analysis, and use of historical controls to perform clinical and cost comparisons, with limited external validity making and mainly hypothesis-generating. In addition, the sample is only moderate. Accordingly, our results and the relevant discussion should be viewed in the context of other studies reporting on the SuperSUB strategy as well as other competing revascularization and stenting strategies for lower limb arterial revascularization.[20-21]

6 | CONCLUSIONS

Use of the Supera stent after successful subintimal recanalization of complex lower limb arterial lesions is associated with favorable procedural results, which are largely maintained over follow-up up to 24 months. Notably, the favorable impact of such SuperSUB strategy appears evident in terms of long-term patency, clinical outcomes, quality of life dimensions, and reduced resource use in comparison to a historical cohort of similarly complex patients.

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CONFLICT OF INTEREST STATEMENT

Dr. Giuseppe Biondi-Zoccai has consulted for Amarin, Balmed, Cardionovum, Crannmedical, Endocore Lab, Eukon, Guidotti, Innovheart, Meditrial, Microport, Opsens Medical, Terumo, and Translumina. Dr. Lorenzo Patrone has consulted for Abbott, Bard, Cordis, Pathfinder Medical, and Shockwave. All other authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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