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PERIPHERAL VASCULAR DISEASE

Original Studies

Feasibility and 1-Year Outcomes of Subintimal Revascularization with Supera® Stenting of Long Femoropopliteal Occlusions in Critical Limb Ischemia: The "Supersub" Study

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Background: Stent-based revascularization of long femoro-popliteal (FP) lesions has been mainly studied in claudicants and compromised by restenosis and stent fractures. The Supera® stent's biomimetic design allows enhanced fracture resistance. Data for Supera® stenting to treat long chronic total occlusions (CTOs) in patients with critical limb ischemia (CLI), are scarce. Objective: To assess long-term outcomes of subintimal revascularization with Supera® stenting, for long FP CTOs in patients with CLI. Methods: Prospective, single-center, single-arm study of 34 consecutive CLI patients with FP TASC C and D CTOs, who underwent Supera® stenting after subintimal crossing. Primary efficacy endpoint was 1-year patency and freedom from target lesion revascularization (TLR). Primary safety endpoint was the composite rate of freedom from death from any cause, major amputations, and TLR at a year. Secondary endpoints were stent integrity, clinical improvement, amputation free-survival, quality of life, and cost-efficiency. Results: Mean lesion length was 27.9 ± 10.2 cm. Acute technical success was 100%. Primary patency was 94.1%. Freedom from TLR was 97.1%. Limb salvage was 100%. Clinical improvement was observed in 100% of patients: T_CPO_2 increased from 12.7 ± 6.2 to 54.8 ± 8.4 mm Hg ($p < 0{,}0001$); and 100% of patients experienced a shift in Rutherford to class 0 ($p < 0.0001$). There were no stents fractures. Amputation free-survival was 82.4%. Conclusions: Subintimal revascularization with Supera® stenting in CLI patients with long FP occlusions, is feasible and superior to validated efficacy performance goals. Larger multicenter studies are needed to validate the safety and efficacy of this novel alternative approach. © 2016 Wiley Periodicals, Inc.

Key words: peripheral artery disease; stenting; biomimetic; cost-effectiveness

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INTRODUCTION

Peripheral arterial disease (PAD) affects over 200 million patients worldwide. Its prevalence has increased between 13 and 27% in the past decade [1]. Critical limb ischemia (CLI) patients typically have multilevel and multivessel involvement, with 67% of them presenting with femoropopliteal (FP) and infrapopliteal disease [2]. Endovascular therapy (EVT) has become the preferred initial approach [3]. Success and durability of FP EVT have been limited by heavy plaque burden, calcification, and high prevalence of chronic total occlusions (CTOs), which render balloon angioplasty results suboptimal. Multiple studies [4–15] have already shown favorable results of primary stenting compared with angioplasty with provisional stenting or to predefined performance goals (PG); however, restenosis and fracture rates remain major limitations [5,6,8,13–15].

METHODS

Study Design

SUPERSUB was a prospective, single center, single-arm clinical trial of symptomatic CLI patients with de novo or re-occlusive long CTOs (TASC II C and D) in the FP segment, who underwent **SUPERa**® stenting after **SUB**intimal crossing of the lesion. The study was conducted in full conformance with the Declaration of Helsinki, and approved by the local Institutional Review Board. All patients provided informed consent before the procedure.

Patient Population

From January 2014 to August 2015, all CLI patients (Rutherford 4-6), with transcutaneous partial pressure of Oxygen ($TcPO_2$) $\leq$30 mm Hg, were referred for EVT. Patients were enrolled if they had no evidence of iliac disease, and if they had FP CTO's of at least 15 cm in length (TASC II C-D), which were crossed subintimally. The occlusions were defined as "de novo" if no previous EVT attempt was made, and "re-occlusive" if previously treated with angioplasty. All images were obtained using an Integris Allura 12 DSA system (Philips Medical Systems, Best, The Netherlands). Lesion length, diameter, and post-deployment stent length were automatically measured using the Philips Allura software. All patients underwent subintimal Supera® stenting. Patients were excluded if they had short (TASC II A-B) or stenotic lesions, if endoluminal crossing was achieved, or if they presented with acute limb ischemia. Tibial arteries were treated concomitantly with balloon angioplasty if they exhibited $\geq$70% stenosis, fed the compromised angiosome, or were felt to represent the best option to provide indirect perfusion to the target angiosome when a direct approach was not feasible. Atherectomy, drug coated balloons, focal force balloons and nonbiomimetic stents were not used in this study.

End Points, Definitions

Enrolled patients underwent 3, 6, 9, and 12 months follow-up visits, with performance of clinical (physical examination, review of symptoms, and wound assessment), sonographic (FP duplex ultrasound), and X-ray surveillance (FP fluoroscopic evaluation in anteroposterior and "bent-knee" projections). The primary efficacy end point was primary patency rate (PPR) at 12 months, defined as freedom from restenosis (diameter stenosis $>$ 50%, determined by peak systolic velocity ratio (PSVR) $>$2.0 by duplex ultrasonography), and freedom from clinically driven target lesion revascularization (TLR). Patency rates were analyzed using Kaplan-Meier analysis and the plots were to be truncated at a standard error of $<$7%. Secondary patency was defined as freedom from restenosis and clinically driven TLR after a second EVT was performed in the target lesion following the index procedure. Acute technical success was defined as subintimal recanalization, reentry at the "Ideal Landing Zone" (ILZ: first 2 cm of patent arterial lumen distal to the reconstitution point determined by angiography, to avoid extending the dissection plane over the patent distal vessel), gradual predilatation with creation of a smooth neolumen, and precise stent deployment (defined as a final stent length that equaled the nominal length of the device $\pm$ 5%).

Primary safety endpoint: composite rate of freedom from death from any cause, major amputations (above the ankle), and TLR at a year. Secondary endpoints: stent integrity (lack of fracture, as determined by orthogonal X-ray examinations of the stents), clinical improvement (increase in $TcPO_2$ to $\geq$ 40 mm Hg and Rutherford category improvement of at least one class from baseline), amputation free-survival (freedom from any amputation), quality of life [according to the EuroQoL5D-3 Level version (EQ5D-3L) questionnaire] [16,17], cost-efficiency [determined by comparing hospitalization days and overall annual costs between this cohort and a matched-historical cohort (selected on the basis of similar demographics, CLI stage, complexity and length of the FP CTO, severity of calcification, and subintimal recanalization) of 60 CLI patients previously treated with balloon angioplasty but without stents in the same center], and PPR by lesion subtype (*de novo* vs. reocclusive) at 12 months.

Calcification was considered: (a) mild: orthogonal fluoroscopic examination of the arterial segment revealed calcium in one side of the artery, $<$ 5 cm in

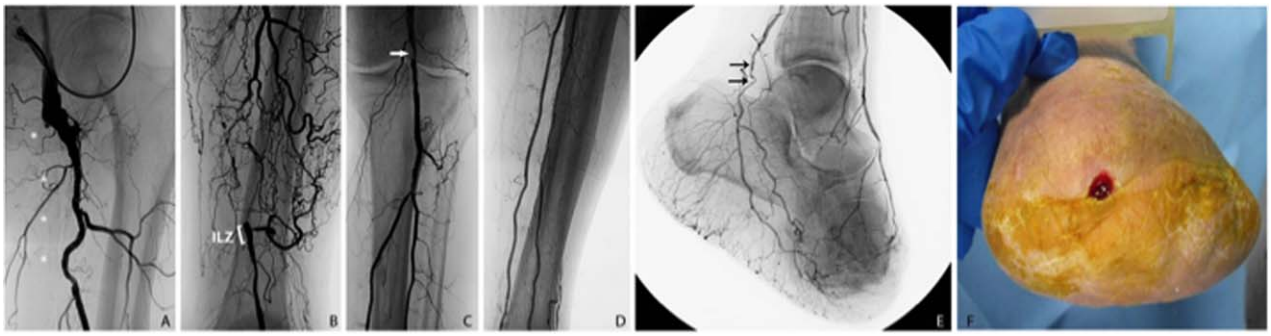


Fig. 1. Diagnostic Angiography and Non-healing Wound. A: Previous Common Femoral Endarterectomy with occluded stent in SFA (asterisks), and TASC D SFA CTO. B: Flow reconstitution and ILZ. C: P2 lesion (arrow). D: Tibial run-off. E: Distal AT reconstitution. Diseased CP (arrows). F: nonhealing wound. SFA: Superficial Femoral Artery. CTO: Chronic Total Occlusion. ILZ: Ideal Landing Zone. PT: Posterior Tibial. AT: Anterior Tibial. CP: Common Plantar. [Color figure can be viewed at wileyonlinelibrary.com]

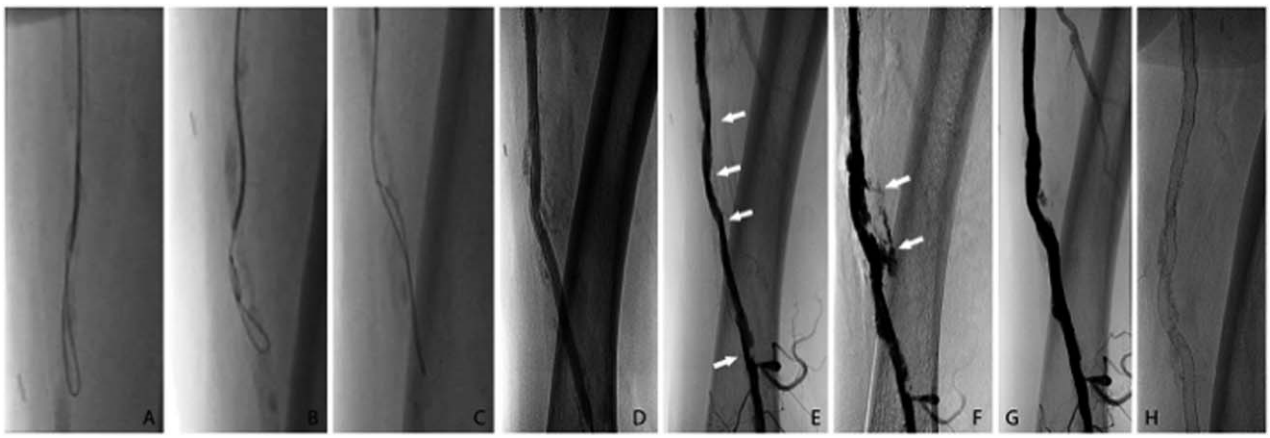


Fig. 2. Subintimal Crossing of TASC D SFA CTO. A: Looped 0.035" Stiff Glide wire and support catheter. B, C: Subintimal dissection carried to distal cap. D: Reentry in the ILZ. Neolumen is created with a high-pressure, noncompliant balloon. E: Multiple recoil points (arrows). F: Recoils treated with 6 × 40 mm balloon, resulting in contrast extravasation (arrows). G: Prolonged PTA (5 min) with high-pressure, noncompliant balloon sealed the perforation. H: Supera® stent lining the neolumen.

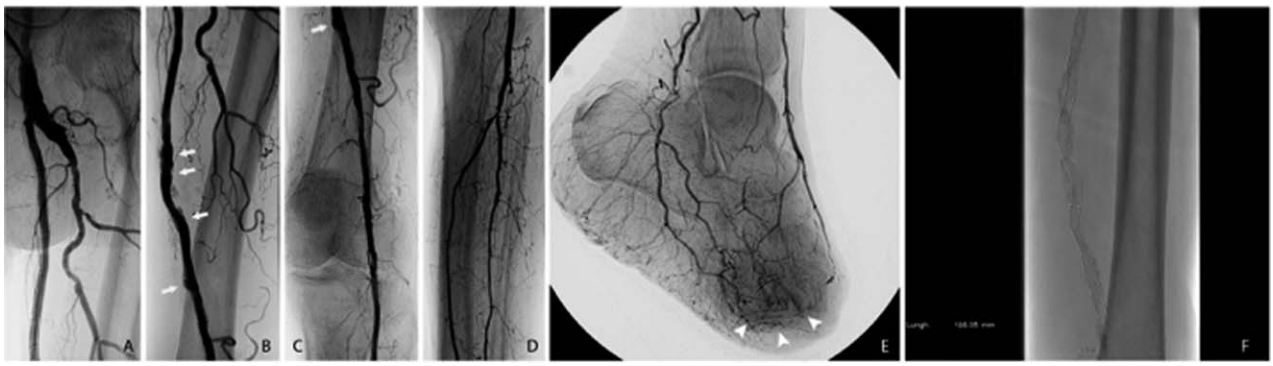


Fig. 3. Final Angiogram. A–C: Residual pseudo-aneurysms (arrows). D–E: Tibial-pedal runoff with improved wound blush (arrow-heads). F: Stent length measurement. The 200 mm Supera® stent was deployed at 198 mm (−1%).

length; (b) moderate: calcium in both sides of an arterial segment 5–10 cm in length; (c) severe: calcium in both sides of an arterial segment >10 cm in length, which also had intraluminal calcium. Tibial arteries were considered patent if they had no lesions $\geq 50\%$.

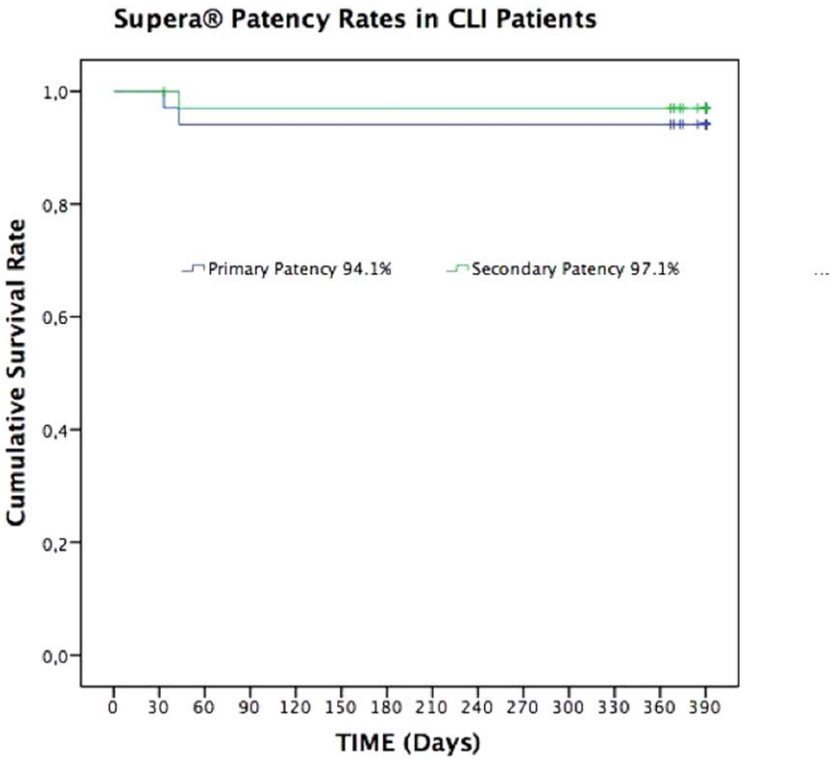
Limb salvage was defined as freedom from major amputation at or above the ankle. Amputation free survival was defined as freedom from any amputations and death. The primary efficacy objective was to establish superiority of the Supera® stent to an objective PG of 66% established by VIVA Physicians (VP). The primary safety objective was to establish superiority of the Supera® stent, compared with a modification of the objective PG of 88% established by VP [18]. The modification consisted of changing the element of any amputation to major amputation (to account for the more complex patient population and lesion subset). Hence, the modified safety objective PG was the combined end point of death from any cause, TLR and major amputation.

Procedure and Technique

All patients were pre-treated with aspirin (75–160 mg) and clopidogrel (300 mg). Antegrade access was obtained in the common femoral artery under ultrasound guidance (GE Logic E9® - 9 MHz, linear probe). A 6 Fr, 11-cm introducer (Radifocus®-Terumo, Somerset NJ) was advanced to perform EVT (Fig. 1). This approach was chosen to increase the likelihood of successfully crossing the CTO, and to safely address any tibial disease that needed concomitant treatment. Patients were anticoagulated with a single 5000 I.U bolus of intra-arterial unfractionated heparin, without weight adjustment or activated clotting time monitoring. After endoluminal failure, the subintimal approach was carried with a 4 French Berenstein type II (Cordis, Fremont CA) or Navicross (Terumo, Somerset, NJ) catheters for support, and a 0.035″ Stiff or Half-stiff Glide wires with a 1.5 mm pre-shaped "J" tip (Terumo), or a 0.018" V18® (Boston Scientific, Marlborough, MA) guide wire, using the catheter/looped-wire-tip technique. Catheter and wire were advanced as a unit keeping the loop as small as possible, until reaching the distal CTO cap. Re-entry was performed with meticulous technique, respecting the ILZ. Re-entry was gained in antegrade (in most cases) or retrograde fashion (when antegrade re-entry could not be achieved into the ILZ), followed by "rendezvous" (encounter of the antegrade and retrograde wires in the ILZ). Once subintimal crossing and re-entry were achieved, predilatation was performed with a 4 mm balloon at nominal pressure for 1 min (Ultraverse® - BARD, Murray Hill, NJ. Lengths: 120, 150, or 300 mm). Then, a 5 or 6 mm high-pressure, ultra noncompliant balloon (Dorado® - BARD. Lengths: 100, 200 mm) was used to dilate the subintimal space for 2 min, to homogenize the neolumen. Angiographic controls were then performed in orthogonal projections, to assess for recoil and to determine stent diameter. If recoiling was observed, the neolumen was further treated with a 6 or 7×40 mm high-pressure balloon (Pacific Plus® - Medtronic, Minneapolis, MN), to focally treat the recoil points. The final predeployment balloons were 1 mm larger than the estimated stent diameter, which is

TABLE I. Demographics, Clinical, and Angiographic Features at Baseline and Post-treatment.

Patient Demographics	Number/Total (%) or mean ± SD
Gender	
Male	32/34 (94.1%)
Female	2/34 (5.9%)
Age (years)	
Average	76.4
SD	7.5
Range	61–86
Comorbidities	
Diabetes	33/34 (97.1%)
Dyslipidemia	12/34 (35.3%)
Hypertension	24/34 (73.5%)
Coronary artery disease	14/34 (42.2%)
Dialysis	4/34 (11.8%)
Previous Coronary Revascularization	11/34 (32.4%)
Previous Surgical Vascular Revascularization (Target Limb)	12/34 (35.3%)
Previous PTA of Target Limb	16/34 (47.1%)
Previous Amputation of Target Limb	29/34 (85.3%)
Toes	9/34 (26.5%)
Transmetatarsal Amputation	4/34 (11.8%)
Baseline Rutherford Class (Target Limb)	
4	2/34 (5.9%)
5	24/34 (70.6%)
6	8/34 (23.5%)
Number of Patent Runoff Tibials	**Baseline/Post**
0	14 (41.2%)/- (0%)
1	12 (35.3%)/9 (26.5%)
2	8 (23.5%)/22 (64.7%)
3	0/3 (8.8%)
Target Lesion Anatomical Distribution	**Number/Total (%)**
Superficial Femoral	10/34 (29.4%)
FP	16/34 (47.1%)
Popliteal	8/34 (23.5%)
Tibial	33/34 (97.1%)
Calcification	
Mild	5/34 (14.1%)
Moderate	10/34 (29.4%)
Severe	19/34 (55.9%)
TASC II Class	
C	10/34 (29.4%)
D	24/34 (70.6%)
Treated Lesion Length (Mean ± SD)	27.9 ± 10.2 cm
Stent Diameter	
4 mm	2/34 (5.9%)
5 mm	28/34 (82.4%)
6 mm	4/34 (11.8%)



Supera® Patency Rates in CLI Patients

Time period (Month)	At risk *Primary Patency*	At risk *Secondary Patency*	Survival rate *Primary Patency*	Survival rate *Secondary Patency*	Standard error *Primary Patency*	Standard error *Secondary Patency*
t	n	n	p	p		
0	34	34	1.000	1.000	0.000	0.000
3	32	33	0.941	0.971	0.040	0.030
6	32	33	0.941	0.971	0.040	0.030
9	31	32	0.941	0.971	0.040	0.030
12	31	32	0.941	0.971	0.040	0.030

Fig. 4. Kaplan-Meier Estimates of Primary and Secondary Patency Rates. [Color figure can be viewed at wileyonlinelibrary.com]

indispensable to properly deploy the Supera® stent cells, and allow them to acquire their correct geometry (Fig. 2).

Once the neolumen was prepared, the Supera® stent was diligently deployed, respecting its geometry and nominal length. Stents were implanted from distal to proximal, stenting from "healthy to healthy" arterial segments. When more than one stent was used, a one-centimeter overlap was used (Fig. 3).

Statistical Analysis

Continuous variables are reported as mean ± standard deviation (SD). Categorical variables are reported as *n* (%). Changes in $TcPO_2$ means and quality of life metrics as determined by the EQ5D-3L questionnaire were calculated using a two-tailed Student T test and Mann-Whitney U test. Changes in Rutherford class were assessed by the Kruskal-Wallis test. Patency, limb salvage, and amputation-free survival rates were calculated by Kaplan-Meier analysis. All tests were two-sided, and the threshold for statistical significance was set at $P < 0.05$ using SPSS 16.0 software (SPSS, Chicago; IL).

RESULTS

Thirty-four consecutive CLI patients (32 men; mean age 76.4 ± 7.5 years) underwent EVT of TASC C and D CTOs, by means of subintimal revascularization and Supera® stenting of the neolumen. Mean follow-up was

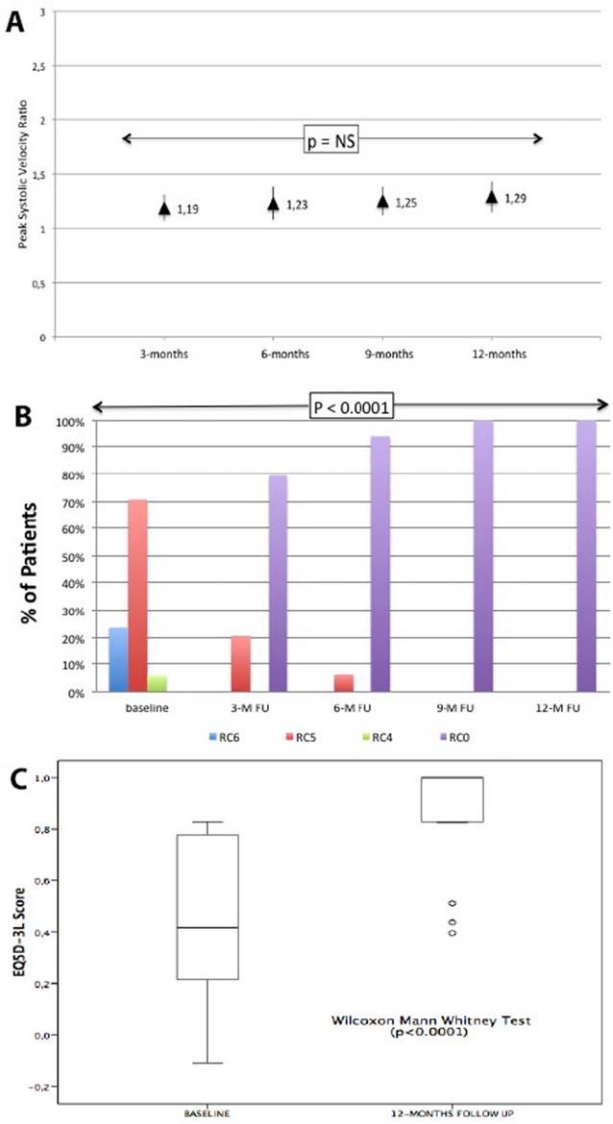


Fig. 5. Changes in PSVR, Rutherford class and Quality of Life During Follow-u. A: PSVR by US. Error bars: ± SD. B: Rutherford class shift. C: Median ± SD and Interquartile ranges of the European Quality of Life (EQ5D-3L) score. [Color figure can be viewed at wileyonlinelibrary.com]

493.2 ± 143.6 (range: 367–903), and all patients completed at least 12-months of follow-up. Data from all patients has been available at the 3, 6, 9, and 12 months follow-up, except 1 patient who died at 7 months from cardiovascular causes. Baseline demographics, risk factors, and clinical characteristics of the cohort were typical of patients with CLI (Table I). At baseline, most patients (70.6%) were Rutherford class 5 and had moderate to severely calcified lesions (85.3%), with 0 to 1 patent tibial runoff (76.5%). Mean lesion length was 27.9 ± 10.2 (range 15–53) cm, with a mean implanted stent length of 30.6 ± 11 (range 17–58) cm and a mean number of implanted stents of 2.2 ± 0.9 (range 1–4). Retrograde techniques were required in 12 cases (35.3%) to achieve re-entry in the ILZ. Of 29 patients (85.3%) who underwent concomitant tibial revascularization, 27 featured CTOs (22 had one, and 5 had 2 tibials opened), and 2 had 1 patent runoff with ≥ 70% stenosis in a second tibial, which were also treated.

Efficacy and Safety End Points

The PPR was 94.1% (Fig. 4) by Kaplan Meier analysis, and the standard error was 4%. The mean PSVR was 1.2 at 3 months and 1.3 at 12 months follow-up (Figs. 5A and 6C–E). Freedom from clinically driven TLR was 97.1% with a standard error of 6.1%.

Two Supera® stent occlusions were censored after the first month follow-up: one patient re-occluded a popliteal aneurysm after successful index procedure, and declined further intervention. The second patient had colon cancer and suspended antiplatelet therapy to undergo colon resection. At 2 months follow-up, the stent occluded. Repeat EVT was performed. The stent was patent at 1-year. Secondary patency rate was 97.1%.

Acute technical success and precise stent deployment was achieved in 100% of patients: 21.4% of stents were deployed at nominal length; 60.7% had 2.2 ± 1.7% elongation; and 17.8% had 2.2 ± 0.2% shortening with respect to their nominal length (all within the pre-specified ± 5%). Freedom from death of any cause and major amputations was 97.1%. Clinical improvement was achieved and maintained during follow-up in all patients (100%), with clinically documented wound healing [supported by T_CPO_2 increments from 12.7 ± 6.2 mm Hg to 54.8 ± 8.4 mm Hg ($P < 0.0001$)]; and shift in Rutherford class to 0 at 12 months (Fig. 5B). Patients also experienced improvement in quality of life metrics related to mobility, ability to perform daily activities and pain (Fig. 5C).

Freedom from intraprocedural complication was 85.3%. Five patients (14.7%) experienced superficial femoral artery pseudoaneurysms from the aggressive predilatation strategy. All these cases were managed by Supera® stenting and duplex ultrasound surveillance at 24 hr, 1 week, and all programmed follow-up visits (Fig. 6C–E). There were no adverse sequelae in any of these patients. No deaths related to the procedure were recorded. No stents fractures were identified at any of the follow-up points, and there were no major amputations, with 100% limb salvage rate (Fig. 6A,B,F, and G). Amputation free survival rate was 82.4%, as 6 patients (17.6%) underwent preplanned minor amputations.

Cost Efficiency

To determine if subintimal Supera® stenting could achieve long-term cost savings, a comparison was

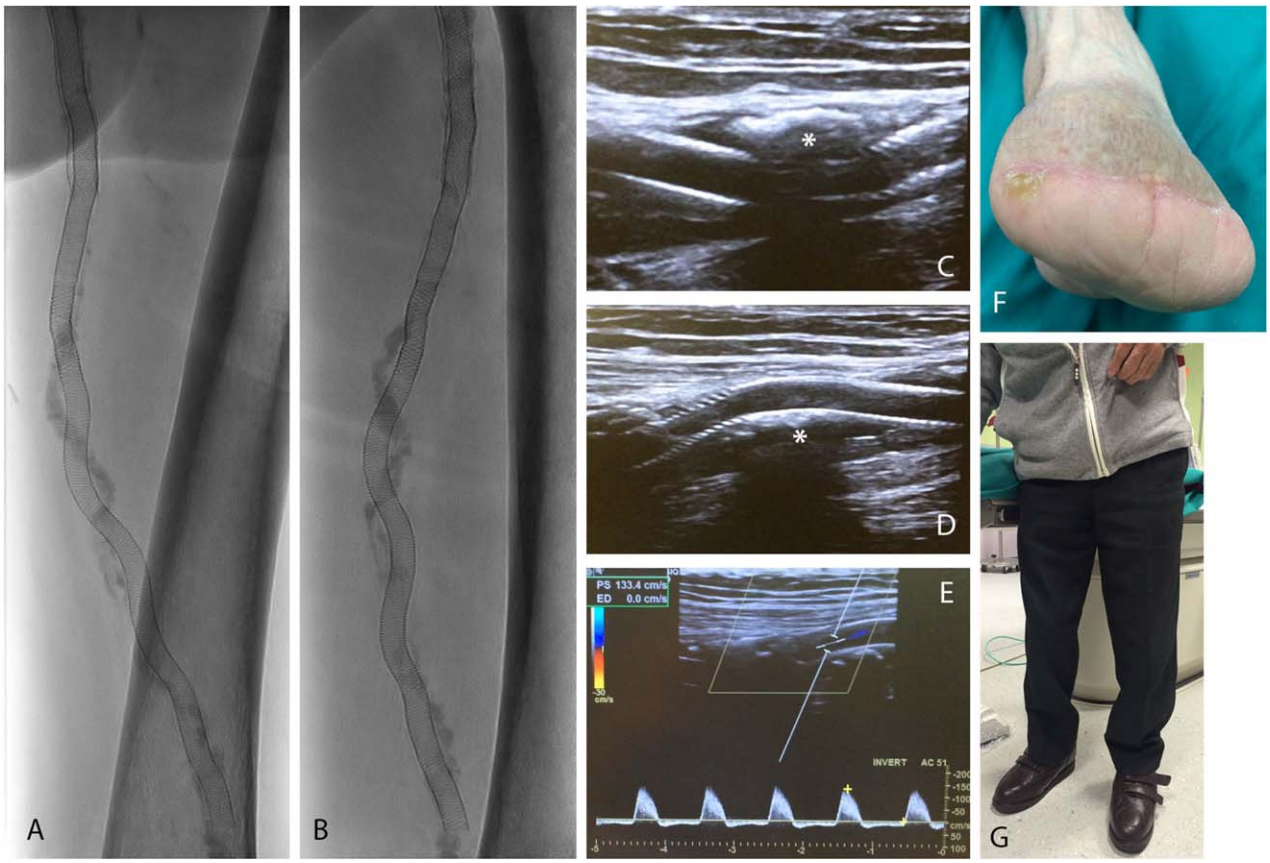


Fig. 6. 1-Year Follow-up. A,B: Orthogonal X-rays of the Supera Stent without fractures. C,D: Duplex US illustrates radial strength: calcium fails to compress the stent (asterisk). E: Patent stent with biphasic flow. F: Healed amputation. G: Ambulatory patient with customized shoes. [Color figure can be viewed at wileyonlinelibrary.com]

performed to a matched historical cohort of 60 CLI patients previously treated with angioplasty in the same center (Table II). Freedom from TLR at 12 months by Kaplan-Meier analysis was 97.1% in the study group compared with 26.4% in the historical cohort ($P < 0.0001$; Fig. 7). This translated in increased need for repeat procedures and prolonged hospitalizations in the historical cohort treated with angioplasty (Fig. 8A), generating higher costs to the health-care system (9564.9 euros) than when treated with Supera® (4427.3 euros, Fig. 8B). These calculations are based on Diagnosis-Related Group (DRG) reimbursements, which are allocated by the Italian National Health Service on a region-specific basis and therefore vary across the country. The amounts shown are specific to the Veneto region.

Lesion Subtypes

Patients who undergo failed FP angioplasty followed by surgery, have a worse outcome than those who undergo primary surgical intervention [19]. Based on this precept, we conducted a subgroup analysis to compare outcomes of CLI patients with *de novo* versus reocclusive lesions. There were no differences in baseline characteristics. PPRs determined by Kaplan-Meier analysis were equivalent for de novo (94.4%) and reocclusive (93.8%) lesions at 1 year ($P = 0.915$). Both groups experienced similar improvements in Rutherford Class and quality of life.

Efficacy and Safety Objectives

The PPR by Kaplan-Meier survival estimate was 94.1%, significantly higher than the PG of 66% established by VP ($P < 0.0001$). The rate of freedom from the combined end point of death from any cause, TLR and major amputation was also superior to the objective safety PG (91.2 vs. 88%), albeit not statistically significant ($P = 0.132$).

DISCUSSION

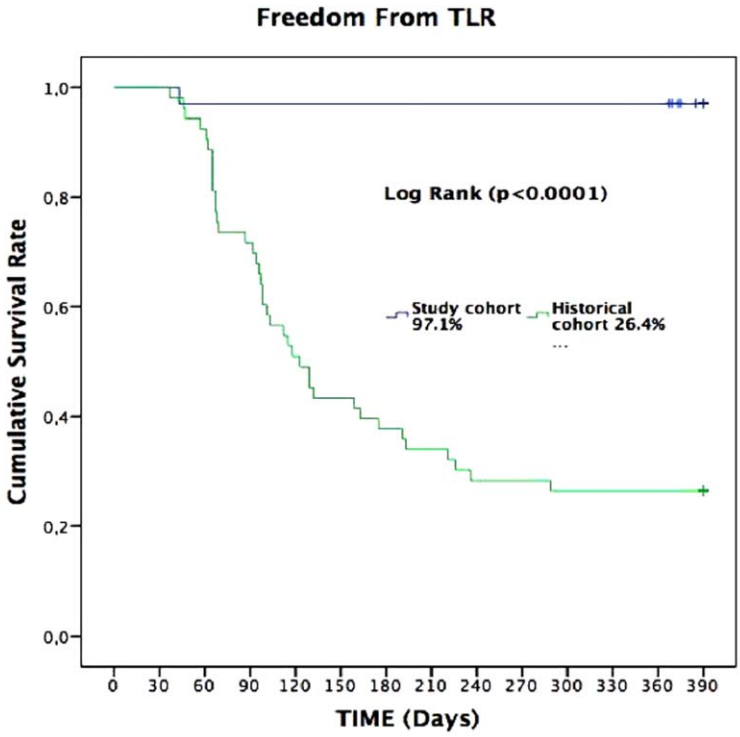
Maintenance of long-term patency after revascularization of the FP segment remains the Achilles heel of

TABLE II. Historical Matched Cohort.

Patient demographics	Number/total (%) or mean ± SD
Gender	
Male	45/60 (75%)
Female	15/60 (25%)
Age (years)	
Average	72.9
SD	9.7
Range	43–90
Comorbidities	
Diabetes	51/60 (85%)
Dyslipidemia	35/60 (58.3%)
Hypertension	46/60 (76.6%)
Coronary artery disease	26/60 (43.3%)
Dialysis	17/60 (28.3%)
Previous coronary revascularization	20/60 (33.3%)
Previous PTA target limb	23/60 (38.1%)
Baseline Rutherford class (target limb)	
4	4/60 (6.7%)
5	40/60 (66.7%)
6	16/60 (26.7%)
Anatomical distribution	
Superficial Femoral artery	16/34 (26.6%)
FP arteries	32/60 (53.3%)
Popliteal artery	12/60 (20%)
Tibial arteries	56/60 (93.3%)
Calcification	
Mild	21/60 (35%)
Moderate	11/60 (18.3%)
Severe	28/60 (46.6%)
TASC II class	
C	25/60 (41.6%)
D	35/60 (58.3%)
Treated lesion length	
Mean ± SD	24.7 ± 9.4 cm
Range	15–48 cm

EVT. Nitinol stents have improved results of EVT in the FP segment; however, lesion morphology remains the most important predictor of long-term outcomes. Long occlusions constitute the most complex lesion subtype, and are associated with the highest incidence of stent fractures [20]. Moreover, the constant exposure to simultaneous and opposing biodynamic forces (compression, torsion, flexion, extension, rotation) in the FP segment [21], exerts significant stress on metallic endoprostheses, leading to compression, kinking and fractures with an ensuing enhanced inflammatory response on the arterial wall, manifested as accelerated restenosis [22]. To our knowledge, this is the first study reporting on subintimal revascularization with Supera® stenting of TASC C and D femoropopliteal occlusions in advanced CLI patients, which exceeded both safety and efficacy PGs previously set for claudicants [18]. This study is also the first to show cost-efficiency and improvement in quality of life metrics related to a revascularization strategy in CLI patients. This was demonstrated by significant clinical improvements in $TcPO_2$, wound healing, improvement in Rutherford class, decrease in hospitalization time, and need for repeat procedures, as well as in Euros spent. Our mean length of stay (5.5 days) compared favorably with reports from a recent manuscript by Agarwal et al. [23], which showed that from 2003 to 2011, the mean length of stay for patients with critical limb ischemia treated with endovascular revascularization was 8.7 days. In our study, the large volume of patients with Rutherford V and VI who remained hospitalized after their procedure drove the mean length of stay, as they typically undergo evaluation by members of a multidisciplinary team including infectious disease specialists, podiatrists and plastic surgeons, and then undergo debridements, minor amputations and hyperbaric treatments during the same hospitalization.

The PPR was 94.1% in SUPERSUB. The recently published 1 year outcomes of Supera® in the FP segment in SUPERB, revealed a PPR of 86.3%, with a 72% shorter lesion length (7.8 vs. 27.9 cm in SUPERSUB), only 5.7% of TASC C lesions, and no patients with Rutherford 5 or 6 [21]. Despite all SUPERSUB lesions being long total occlusions, there were no fractures at 1 year, consistent with previously reported registries of Supera® in the SFA [20,24] and Popliteal [25]. Previous reports of Supera® in CLI patients were limited to the popliteal artery with PPRs of 68.4% in lesions 73.5% shorter (7.4 vs. 27.9 cm in SUPERSUB) [26]. Although this study does not allow for direct comparison with other stents, our results reveal superior PPR and lower fracture rates at a year (94.1/0%) than those reported at 12 months (83.1/0.9%), and more recently at 5 years (66.4/1.9%) for the Zilver PTX drug-eluting nitinol stent despite a lesion length that was 81% shorter (5.4 vs. 27.9 cm in SUPERSUB) [10,27]. Results of SUPERSUB also compare favorably with studies of differently designed self-expanding; slotted-tube nitinol stents in the FP segment, which have revealed PPR and fracture rates of 81.3/3.1% (RESILIENT [13]); 81.7/1.8% (STROLL [28]); and 77.2/0.4% (DURABILITY II [29]). The primary efficacy and safety objectives of the study were superior to the proposed objective PG set by VP, which currently represents the benchmark commonly used to assess therapies in the femoropopliteal space [18]. The difference in outcomes with previously published literature is believed to be at least partially explained by the diligent technique employed and the proposed mechanism of action of the SUPERSUB approach. The technique consisted of the meticulous dissection of the subintimal space with a tightly looped wire (1.5 mm loop), advanced in straight fashion (avoiding expansion of the subintimal space), and reentering within a prespecified



Freedom From TLR Comparison

Time period (Month)	At risk *Supera cohort*	At risk *Historical cohort*	Survival rate *Supera cohort*	Survival rate *Historical cohort*	Standard error *Supera cohort*	Standard error *Historical cohort*
t	n	n	p	p		
0	34	60	1.000	1.000	0.000	0.000
3	33	38	0.971	0.717	0.029	0.062
6	33	20	0.971	0.377	0.029	0.067
9	32	15	0.971	0.283	0.029	0.062
12	32	14	0.971	0.264	0.029	0.061

Fig. 7. Kaplan-Meier Estimate of Freedom from TLR. Supera® stent (Study Cohort) versus Angioplasty (Historical Cohort) for TASC C and D Lesions in Patients with CLI. [Color figure can be viewed at wileyonlinelibrary.com]

ILZ to create a smooth "neolumen." This was followed by proper and progressive dilatation to create the proper space for the stent. Slow inflations were performed until the "waists" were smoothed. The mechanism of action is based on two principles: First, the "neolumen" that has been created is devoid of diseased endothelium, plaque burden, and the intimal calcification that occupies the intraluminal space (however, it lacks structure and is bound to collapse and re-occlude without a scaffold that provides it with radial strength). Second, the Supera® stent's design provides this neolumen of the necessary radial strength, as it incorporates six pairs of interwoven nitinol wires that form a closed loop at both ends of the stent, which partially replicate the endogenous reticular network of interconnected collagen and elastin fibers normally present in healthy arterial walls (dissipating radial, axial, and torsional forces, and preventing the creation of focal areas of high wall stress that lead to restenosis). This design confers superior radial strength and biomimetic flexibility that allows the stent to imitate the natural motions of the artery, hence decreasing the incidence of fractures [15,30]. Other factors that may have influenced the outcomes are the fact that the study is generated from a practice dedicated to CLI patients with established multidisciplinary protocols and the experience of the operators. When this technique is properly executed, creates the equivalent to an in situ endovascular bypass, and represents an innovative concept.

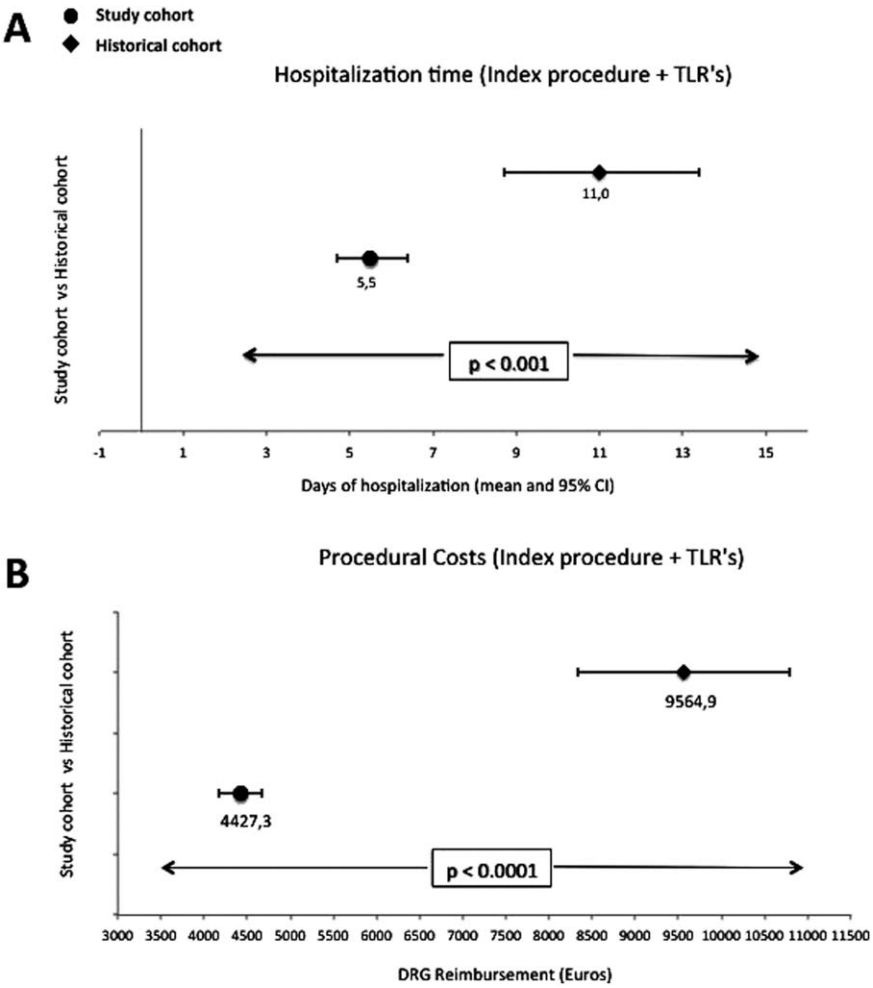


Fig. 8. Cost-Efficacy Analysis. A: Decreased hospitalization days in study cohort. Error bars: 95% CI. B: Decreased procedural costs in study cohort. Error bars: 95% CI.

Limitations of the study include its single-center, single-arm, non-randomized design, and relatively small sample size (although it represents to the best of our knowledge, the largest cohort of severe CLI patients with the longest total occlusions of the FP segment who underwent endovascular revascularization that have ever been studied to this point). Larger, multicenter, randomized-controlled studies comparing this strategy with other more commonly used approaches (such as intraluminal crossing with/without atherectomy, with/without use of bare metal/drug-eluting stents) and with a longer follow-up are warranted to determine the generalizability of our results.

CONCLUSIONS

Stenting of long FP CTOs had not been systematically studied in CLI. In claudicants, Supera® has shown durable patency and no fractures. **SUPERSUB** is the first study to report on the feasibility of using an approach that combines subintimal recanalization with Supera® stenting as the primary strategy to treat long FP CTOs in patients with advanced CLI. This strategy was safe and resulted in wound healing and improved Rutherford class. SUPERSUB is also the first study reporting improvement in quality of life metrics, shorter hospitalization times, and lower costs due to a decreased need for repeat procedures. Caution should be exercised before considering this as a new standard of care. Larger, multicenter studies are needed to validate the efficacy and safety of this proposed alternative treatment option, which for now just represents another "tool in the armamentarium" of the CLI specialist. Exhaustive analysis of our data points toward the urgent need to set updated objective PGs for endovascular revascularization strategies in patients with CLI.

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