

Original Studies

Major Adverse Limb Events and Wound Healing Following Infrapopliteal Artery Stent Implantation in Patients with Critical Limb Ischemia: The XCELL Trial

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Background: Percutaneous transluminal angioplasty (PTA) with stent deployment of infrapopliteal arteries is an accepted but unproven therapy for patients with critical limb ischemia (CLI). We evaluated the safety and effectiveness of the Xpert™ self-expanding nitinol stent (Abbott Vascular, Redwood City, CA) in Rutherford Class 4–6 subjects with infrapopliteal lesions of 4–15 cm in length. **Methods and Results:** 120 patients (140 limbs, 212 implanted devices) underwent primary infrapopliteal nitinol stent deployment as part of this multicenter registry. The primary endpoint was 12-month amputation-free survival (AFS); secondary endpoints included limb salvage, target lesion revascularization (TLR), 6-month angiographic patency, and 6- and 12-month outcomes of wound healing and pain relief. Despite a 6-month binary stent restenosis rate of 68.5%, the 12-month AFS rate was 78.3%. Stratified according to baseline Rutherford classes 4, 5 and 6, the 12-month AFS rates were 100%, 77.3%, and 55.2%, respectively, and freedom from major amputation rates were 100%, 90.9%, and 70.1%, respectively. The 12-month freedom from major amputation rate and clinically driven TLR were 89.6% and 70.1%, respectively. The 6- and 12-month complete wound-healing rates were 49.0% and 54.4%, respectively. Rutherford class 4 patients had significant pain relief through 12-months ($P < 0.05$). **Conclusions:** Primary infrapopliteal nitinol stenting to treat CLI is safe and effective in improving 6- and 12-month clinical outcomes. © 2012 Wiley Periodicals, Inc.

Key words: peripheral vascular disease; critical limb ischemia; infrapopliteal; stents

INTRODUCTION

Critical limb ischemia (CLI) is characterized by chronic lower extremity ischemic rest pain or the presence of ischemic ulcers with or without gangrene [1],

and affects ~27 million people in Europe and North America [2]. Current treatment options aim to relieve pain, heal ischemic ulcers, prevent limb loss, improve overall quality of life, and prolong survival [2].

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However, amputation rates vary between 10 and 40% in the first year following the diagnosis of CLI, with mortality rates as high as 20% [3–5]. The annual number of amputations in the United States due to peripheral artery disease (PAD) is estimated at 160,000, resulting in significant cost to society. The Sage Group reports that a 25% reduction in amputations may save as much as \$29 billion in health care costs [5]. As the incidence of diabetes escalates [6] and the patient population ages, CLI rates are projected to increase [1]. Therefore, the need to define the safety, clinical effectiveness, and durability of less invasive endovascular strategies is essential.

Over the last decade, the use of percutaneous transluminal angioplasty (PTA), in contrast to the historical standard of surgical bypass, has evolved into a primary therapy for CLI patients [7–10]. The primary patency rates reported for PTA are relatively low at 47–58% in the first year, in part due to intimal hyperplasia, residual plaque burden, vascular recoil, and dissection [8,11]. Recently, self-expanding nitinol stents have been used in an attempt to reduce restenosis and improve clinical results [11,12]. However, rigorous prospective independently adjudicated data to evaluate the safety and effectiveness of infrapopliteal stenting to preserve limbs, heal ischemic wounds, reduce pain, and improve mobility are lacking.

The primary objective of the “Xpert™ Nitinol Stenting For Critically Ischemic Lower Limbs” (XCELL) trial was to evaluate the safety and effectiveness of the Xpert™ self-expanding nitinol stent (Abbott Vascular, Inc., Redwood City, CA) in Rutherford class 4–6 CLI patients undergoing primary infrapopliteal stent deployment. We report amputation-free survival (AFS), limb salvage, wound healing, and pain relief at 6 and 12 months endpoints, and angiographic core laboratory-adjudicated assessments of 6-month stent patency and integrity in this challenging patient population.

METHODS

Ethics

The study protocol was approved by each site’s Institutional Review Board and was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki; all patients gave written informed consent prior to inclusion in the study.

Study End Points

The primary endpoint was 12-month AFS, defined as freedom from all-cause death or major amputation (defined as unplanned amputation of the target limb

where a prosthesis was required for standing or walking). Secondary endpoints included freedom from major amputation (i.e., limb salvage), target lesion revascularization (TLR), improvement in the ankle/brachial index (ABI) and toe/brachial index (TBI), core laboratory-adjudicated stent patency, stent fracture rates, and 6- and 12-month wound healing rates, along with self-reported pain relief assessments.

Study Design and Clinical Protocol

The study was a prospective, nonrandomized, multicenter, single-arm study with clinical follow-up at 1, 3, 6, and 12 months (Fig. 1). Patients were eligible for participation if they met the following clinical inclusion criteria: age >18 and <90 years, documented chronic CLI (Rutherford class 4–6); in patients with wounds, documented wound care >2 weeks prior to enrollment was required. Additionally, the patient was required to have documentation of one of the following results involving the target limb in the 2 weeks prior to enrollment: pulse volume recording grade of 0, 1, or 2, nonpulsatile plethysmographic tracing, TcPO₂ < 30 mm Hg, or ankle systolic pressure <40 mm Hg.

Major angiographic inclusion criteria included a target solitary infrapopliteal vessel (>50% stenosis or occluded) with angiographically visible above-the-ankle reconstitution; total estimated stented length ≤15 cm and a reference vessel diameter between 2.0 and 5.0 mm. Excessive lesion length and poor run-off vessels were the major reasons for angiographic screen failure. Major exclusion criteria included a life expectancy of <12 months; cerebrovascular event or myocardial infarction within 3 months of enrollment; inability to walk for any reason; serum creatinine ≥2.5 mg/dl and a target lesion location that would require study stent deployment distal to the inferior cortical margin of the talus bone.

Lesion pretreatment was not restricted and included conventional PTA, atherectomy devices, and cryoplasty. Angiographic procedural success was defined as <30% residual stenosis poststenting; 6-month follow-up angiography to determine binary in-stent restenosis (>50% diameter stenosis) was performed. An independent core laboratory (Beth Israel Deaconess Medical Center Angiographic Core Laboratory, Boston, MA) performed all angiographic and stent integrity analyses. Stent integrity was evaluated via fluoroscopy or flat plate X-ray at 6 and 12 months using a standard 5-point scoring system (Grade 1, single tine fracture; Grade 2, multiple tine fractures; Grade 3, stent fracture(s) with preserved stent alignment; Grade 4, stent fracture(s) with stent mal-alignment; Grade 5, Stent fractures with a transaxial spiral configuration [13].

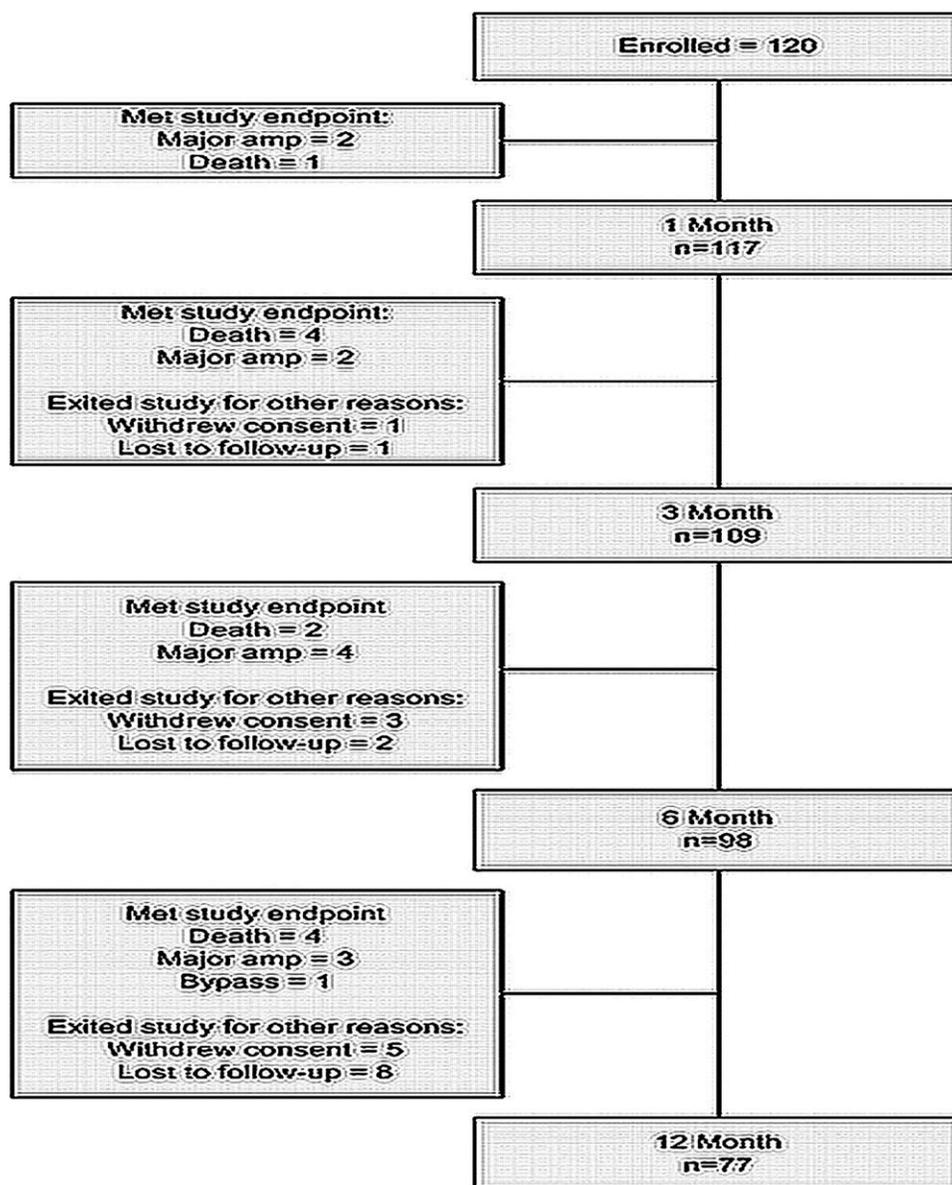


Fig. 1. Study flow.

The protocol required ABI/TBI assessments at pre-procedure, discharge, 1-, 3-, 6-, and 12-month time intervals. ABI and TBI values were calculated by an independent hemodynamic core laboratory (VasCore, Boston, MA) from pressures collected by the site.

Ischemic wound size was measured by acetate tracings of the wound perimeter and photometric assessments at baseline, 1, 3, 6, and 12 months and analyzed by an independent wound core laboratory (Canfield Scientific, Inc., Fairfield, NJ).

Self-reported pain score was measured with an 11-point pain scale ranging from 0 (no pain) to 10 (worst possible pain) at baseline, 1, 6, and 12 months [14,15].

All adverse events were adjudicated by an independent Data and Safety Monitoring Board.

Statistical Analyses

Discrete variables are reported as frequencies (%) and continuous variables as mean \pm standard deviation (SD), or median (interquartile range), as appropriate. Pain assessments were compared by the Wilcoxon Signed Rank Test. The Kaplan-Meier method was used to produce actuarial survival estimates for amputation, death, and TLR. Results were considered statistically significant at $P < 0.05$. Statistical analyses

were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL).

RESULTS

Baseline Characteristics

Between July 2006 and April 2009, 733 subjects were evaluated and 120 subjects (140 target limbs, 212 implanted devices) at 12 United States sites were en-

rolled; a mean of 10 patients per site were enrolled (median 10.5 patients). Complete 12-month data assessment was available in 100 subjects (83.3%); the other 20 subjects (16.7%) were either lost to follow up (national death registries were not queried) or withdrew from the study. The clinical and target lesion characteristics are described in Table I. The baseline angiographic core laboratory target lesion assessments are shown in Table II.

TABLE I. Baseline Characteristics of the Study Subjects and Target Lesions

Demographic and clinical characteristics	Study subjects (<i>N</i> = 120)
Age, y (mean ± SD)	75.5 ± 9.3
Male gender	62 (51.7)
Diabetes	80 (66.7)
Current or former smoker	64 (53.3)
Hypertension	103 (85.8)
Rutherford Classification	
Rutherford 4	21 (17.5)
Rutherford 5	82 (68.3)
Rutherford 6	17 (14.2)
Estimated glomerular filtration rate, ml/min (mean ± SD)	59.2 ± 25.2
Number of runoff vessels	
1	76 (63.3)
≥2	44 (36.7)
Inflow vessel treatment	72 (60.0)
Nontarget infrapopliteal vessel treatment	9 (7.5)
Lesion characteristics	Target lesions (<i>N</i> = 140)
Target Lesion Location	
Popliteal	7 (5.0)
TP trunk	29 (20.7)
Peroneal	32 (22.9)
Posterior tibial	20 (14.3)
Anterior tibial	52 (37.1)
Occlusions	42 (30.0)
Reference vessel diameter, cm (mean ± SD)	2.8 ± 0.7
Lesion length, cm (mean ± SD)	
All	4.7 ± 4.2
Occlusions	7.1 ± 4.5
Stented length, cm (mean ± SD)	7.6 ± 4.2
Total number of stents placed	212
Number of stents/subject	1.8
Number of stents/lesion	1.5

Unless otherwise specified, values indicate number (%) of patients in the corresponding group.

Acute Procedural and 30-Day Outcomes

Angiographic procedural success was achieved in all lesions. Postprocedure target lesion measurements are presented in Table II, and clinical adverse events through 30 days are noted in Table III. One death occurred 32 days postprocedure secondary to an exacerbation of pre-existing congestive heart failure that became manifest within the 30-day postprocedure window. The single TLR occurred as the result of a periprocedural acute vessel closure, which resolved after thrombectomy and additional Xpert™ stent placement. Two amputations were reported; the first occurred between the procedure and discharge, and the second occurred between discharge and 1-month follow-up. The former subject underwent a planned postprocedure amputation of the left metatarsal and subsequently developed gangrene. The latter subject underwent a planned postprocedure minor amputation to the right 3rd/4th toes, and developed an infection at the surgery site. Both amputations were below-the-knee (BTK).

Long-Term Clinical Results

At 12-month follow-up, 10 additional subjects died; all deaths were adjudicated as unrelated to the study procedure or device. Nine subjects underwent amputation (three between 1 and 3 months, three between 3 and 6 months, and three between 6 and 12 months) because of worsening leg pain, intractable wound infection, or gangrene. One amputation was above-the-knee (the subject developed a wound infection); the other eight were BTK. The overall 12-month Kaplan-Meier AFS rate was 78.3% [95% confidence interval

TABLE II. Angiographic Core Laboratory Target Lesion Assessment

Time of assessment	<i>N</i> Subjects	<i>N</i> Lesions	In-lesion		In-stent	
			Percent diameter stenosis	Minimal lumen diameter	Percent diameter stenosis	Minimal lumen diameter
Preintervention	120	140	81.1 ± 16.5	0.5 ± 0.5	–	–
Postintervention	120	140	23.4 ± 14.0	2.1 ± 0.6	12.3 ± 13.2	2.4 ± 0.6
Discharge—6 month ^a	89	107	62.2 ± 29.7	1.0 ± 0.8	61.0 ± 30.5	1.1 ± 0.9

Unless otherwise specified, values indicate mean ± SD.

^aData analysis is based upon either a 6-month angiographic assessment or a TLR assessment (whichever occurred first).

TABLE III. 30-Day Clinical Adverse Events in 120 Enrolled Patients

Event	Study Subjects (N = 120)
Death	1 (0.8) ^a
Major amputation	2 (1.7)
Myocardial infarction	0
Cerebrovascular accident	1 (0.8)
Target lesion revascularization ^b	1 (0.8)
Target vessel revascularization ^{b†}	2 (1.7)
Access site complication requiring transfusion	1 (0.8)

Unless otherwise specified, values indicate number (%) of patients in the corresponding group.

^aDeath occurred 32 days post-procedure, as the ultimate result of an exacerbation of pre-existing congestive heart failure that began within the 30-day window.

^bTarget lesion and target vessel revascularizations are exclusive events.

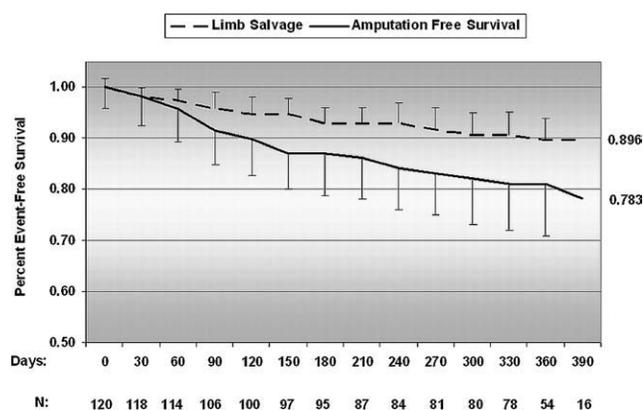


Fig. 2. 12-Month amputation-free survival and limb salvage curves.

(CI) 68.0–86.0] and freedom from major amputation was 89.6% (95% CI 82.0–94.0) (Fig. 2). Freedom from all TLR and “clinically driven” TLR (defined as TLR driven by complaints of leg pain/worsening pain, or a progressing nonhealing ulcer, or a new ulcer formation, with or without the presence of an abnormal noninvasive test) was 54.3% (95% CI 41.0–66.0) and 70.1% (95% CI 56.0–80.0), respectively, at 12 months. Stratified according to baseline Rutherford classes 4, 5, 6, the Kaplan-Meier 12-month AFS and freedom from major amputation rates were 100%, 77.3%, and 55.2%, and 100%, 90.9%, and 70.1%, respectively (Figs. 3 and 4). There were 50 TLR procedures performed through 12 months, with 42 to maintain primary patency and an additional eight to maintain secondary patency.

Hemodynamic core laboratory-calculated ABI and TBI assessments are presented in Table IV. A matched pair analysis was performed to determine the ABI/TBI change from baseline to 6 months in subjects with measurements at both time points, which showed a mean increase of 0.14 ± 0.21 for ABI, and $0.12 \pm$

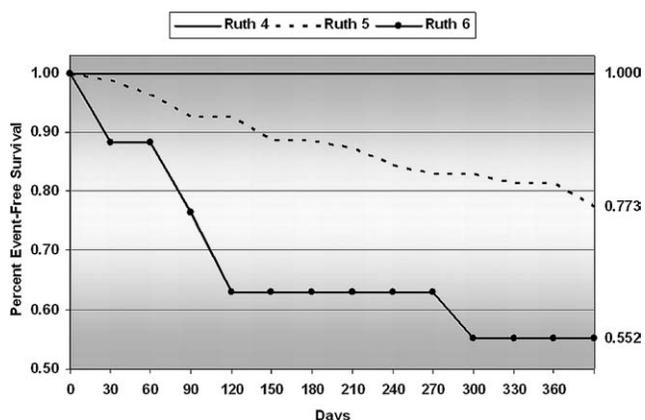


Fig. 3. 12-Month amputation-free survival, stratified by baseline Rutherford class.

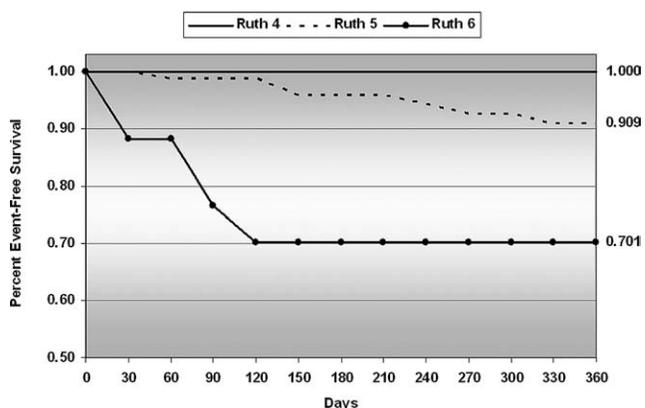


Fig. 4. 12-Month limb salvage, stratified by baseline Rutherford class.

0.22 for TBI. Noncompressible/noncalculable ABI or TBIs were noted in 13/115 (11.3%) patients. Five patients did not have ABI/TBI performed at baseline.

Stent integrity was assessed in 104 stents at 6 months and in 81 stents at 12 months. One grade four stent fracture was identified at 12 months with separation of proximal stent fragments. The 6-month angiographic binary restenosis rate was 63.6% (68 of 107 lesions) in 61 of 89 subjects.

Wound Healing Assessment

A total of 165 wounds (97 subjects) were present at baseline (45.5% were located on the toe); of those, 128 wounds were considered “analyzable” (defined as wounds with a baseline area calculation and at least one follow-up area calculation, or classified as “healed” at any assessment during follow-up). Table V shows the change in wound size and the range of maximum decrease/increase in wound size at each time interval. The reasons for non-analyzable wounds were:

TABLE IV. Hemodynamic Core Laboratory ABI and TBI Measurements

Exam interval	ABI			TBI		
	<i>N</i>	Mean ± SD	Min–Max	<i>N</i>	Mean ± SD	Min–Max
Overall analysis						
Preprocedure	87	0.67 ± 0.23	0–1.14	68	0.37 ± 0.24	0–0.99
Discharge	70	0.88 ± 0.17	0.52–1.17	64	0.48 ± 0.24	0–0.98
1 Month	76	0.93 ± 0.18	0.47–1.19	72	0.51 ± 0.20	0–0.97
3 Month	67	0.87 ± 0.19	0.41–1.18	62	0.49 ± 0.24	0–0.98
6 Month	58	0.82 ± 0.18	0.23–1.16	46	0.43 ± 0.23	0–0.88
12 Month	41	0.85 ± 0.22	0.33–1.18	40	0.46 ± 0.20	0–0.95
Matched pairs analysis						
Preprocedure	52	0.67 ± 0.22	0.20–1.12	32	0.32 ± 0.21	0–0.69
6 Month		0.81 ± 0.18	0.23–1.13		0.44 ± 0.22	0.12–0.88

Non-compressible values (ABI ≥ 1.2 or TBI ≥ 1.0) have been excluded from this analysis.

TABLE V. Change in Wound Area During Follow-Up

Timeframe	<i>N</i> Subjects	<i>N</i> Wounds	Change in wound area from baseline (cm ²)		Data range	
			Mean ± SD	Median (IQR)	Maximum decrease in wound area (cm ²)	Maximum increase in wound area (cm ²)
Baseline – 1 month	67	104	–1.68 ± 6.67	–0.19 (1.38)	–48.00	12.47
Baseline – 3 months	49	72	–2.03 ± 8.96	–0.41 (1.99)	–69.21	7.65
Baseline – 6 months	35	47	–1.38 ± 3.20	–0.33 (2.05)	–12.68	7.62
Baseline – 12 months	19	20	–1.70 ± 8.40	–0.79 (6.41)	–16.84	20.98

IQR, Interquartile range.

Negative numbers represent a decrease in wound area from baseline to follow-up interval; positive numbers represent an increase.

TABLE VI. Complete Wound Healing

Timeframe	Number of wounds
Total number of wounds present at baseline	165
Total number of analyzable wounds	128
Total number of wounds completely healed by 12 months	80
Number healed at:	
1 month	25
3 months	26
6 months	21
12 months	8

(1) missing baseline or follow-up wound area calculations ($n = 7$), (2) death ($n = 6$), (3) minor amputation ($n = 16$), (4) major amputation ($n = 7$), or (5) graft ($n = 1$). The 6- and 12-month complete wound healing rates among analyzable wounds were 56.3% (72/128) and 62.5% (80/128), respectively (Table VI). At 6 months, of the 97 wound patients, 28 (29%) experienced complete wound healing and 46 (47%) experienced healing of at least one wound.

11-Point Pain Score Assessment

The 11-point self-reported pain score was evaluated by a matched pair method, and included only subjects

TABLE VII. Matched Pairs 11-Point Pain Scale for Assessment of Subject-Reported Pain

Rutherford class	<i>N</i>	Baseline	6 Months	12 Months	<i>P</i> value ^a
Rutherford 4	19	6.0 (3.0)	3.0 (4.0)	–	<0.001
Rutherford 5	62	5.0 (3.0)	4.5 (4.0)	–	<0.001
Rutherford 6	9	6.0 (5.0)	3.0 (4.0)	–	0.106
Rutherford 4	16	–	1.5 (5.0)	3.5 (6.0)	0.271
Rutherford 5	47	–	5.0 (4.0)	5.0 (5.0)	0.611
Rutherford 6	7	–	4.0 (3.0)	3.0 (2.0)	0.496
Rutherford 4	16	6.0 (4.0)	–	3.5 (6.0)	0.031
Rutherford 5	48	5.0 (3.0)	–	4.5 (5.0)	0.057
Rutherford 6	7	6.0 (6.0)	–	3.0 (2.0)	0.172

Unless otherwise specified, values indicate median (interquartile range).

^aComparisons by Wilcoxon Signed Rank Test.

who responded at the baseline assessment and at each subsequent time interval (Table VII). Rutherford class 4 subjects reported significant pain relief from baseline to 6 months ($P < 0.001$), and from baseline to 12 months (both $P < 0.05$). Rutherford class 5 subjects reported significant pain relief from baseline to 6 months ($P < 0.001$) with a trend toward a significant pain reduction from baseline to 12 months ($P = 0.051$). 47% of patients had matched pain score assessments, reflecting a potential limitation in this analysis.

DISCUSSION

The XCELL trial is, to date, the largest prospective, multicenter, core laboratory-adjudicated study evaluating the safety and effectiveness of a bare metal self-expanding stent for infrapopliteal interventions in CLI patients. The study enrolled 120 patients for 12-month primary end point assessment of AFS. Importantly, all protocol-mandated safety and effectiveness end points were consistent with the objective performance goals for evaluating catheter-based treatment of CLI recently proposed by Conte et al. [16].

The main findings of the present study are: (1) procedural success was achieved in 100% of lesions; (2) in-hospital and 30-day adverse events were few, with rates of death, myocardial infarction, cerebrovascular accident, and major amputation of 0.8%, 0.0%, 0.8%, and 1.7%, respectively; (3) the rate of clinically driven TLR was low at 29.9% despite a 6-month binary restenosis rate of 68.5%; (4) 12-month rates of AFS, overall survival, limb salvage and were 78.3%, 87.5%, and 89.6%, respectively; and (5) 12-month outcomes of wound healing and pain relief improved significantly, with 62.5% of analyzable wounds completely healed (56.3% by 6 months). With low rates of periprocedural and follow-up adverse events, our results collectively demonstrate the safety and effectiveness of BTK stenting with the Xpert™ self-expanding nitinol stent as an endovascular strategy in CLI patients.

Rationale for Stenting in Critical Limb Ischemia

Although surgical bypass has long been considered the gold standard treatment for CLI patients, its use is limited by absence of suitable conduits, advanced age and presence of comorbidities, resulting in high morbidity and mortality rates [1]. With the advent of new interventional techniques and devices, PTA has evolved into a primary therapy for appropriate CLI patients [7–10], despite relatively low 1-year primary patency rates between 47 and 58% [8,11]. Interestingly, the BASIL trial, which compared PTA with surgical bypass in patient appropriate for either therapy, did not demonstrate a significant difference in clinical outcomes between the two revascularization strategies at 1-year follow-up [10].

Recently, self-expanding nitinol stents have been used in conjunction with PTA in an attempt to further reduce restenosis and improve clinical outcomes [11]. In a prospective nonrandomized study, Bosiers et al. reported limb salvage rates of 95.9% and 90.8% at 1- and 2- years, respectively, following nitinol stent implantation for infrapopliteal lesions in CLI patients [12,17]. The retrospective findings of Donas et al. [18], support the extended durability of nitinol stent results

in a similar study population, with an AFS rate of 88.7% at 2 years. Limb salvage was 95.9% and 90.8% at 1- and 2-year follow-up [12,17] with 2-year AFS of 85.7% [18]. However, prospective, independently adjudicated trials to evaluate the safety and effectiveness of infrapopliteal stenting to heal ischemic wounds and preserve limbs are lacking.

Amputation-Free Survival

In the XCELL trial, the overall 12-month AFS was 78.3%. When stratified according to baseline Rutherford class, AFS was 100%, 77.3%, and 55.2% for Rutherford classes 4, 5, and 6, respectively. Of the 11 patients who had an amputation, two occurred within the first 30 days postprocedure, six occurred between 30 days and 6-month follow-up, and three occurred between 6- and 12-month follow-up. However, limb revascularization in CLI patient does not have the primary intent of improving overall survival. In CLI outcome trials, effectiveness endpoints that combine limb-related outcomes (e.g., amputation) and patient survival can be misleading, as such an endpoint is influenced by patient mortality which may be unrelated to endovascular or surgical intervention [16]. While AFS must remain an important study endpoint, however, because it is defined as freedom from major amputation or all-cause death, which may not be procedure related, the true rate of limb salvage may be underestimated. To more accurately estimate the frequency of major amputation, we calculated the rate of limb salvage (freedom from major amputation). In our study population, the 12-month Kaplan-Meier estimate for limb salvage was 89.6%. When stratified according to baseline Rutherford categories, limb salvage was 100%, 90.9%, and 70.1% for class 4, 5, and 6, respectively. Nevertheless, our results compare favorably with previous studies using bare metal stents (BMS) for treating CLI. Notably, our trial included 14.2% Rutherford 6 patients, a population typically neglected or under-represented in endovascular CLI trials. Compared with other BMS, limb salvage ranged from 91.5% to 100% at 1-year follow-up [19–22] and 82% at 3-year follow-up [23].

Major Adverse Limb Events

The deployment of the Xpert™ nitinol stent was successful in 100% of the lesions, with a 30-day adverse event rate of 6.7%, despite the fact that 30% of the lesions were chronic total occlusions. At 12-month follow-up, the overall cumulative rate of adverse events increased to 63.3%, largely driven by

the increased rate of TLR to maintain vessel patency. Nevertheless, the overall survival was 87.5%.

Vessel Patency

Primary patency of the treated vessel is an important effectiveness end point following endovascular therapy, as sustained vessel patency is hypothesized to improve limb salvage. In our study, the 12-month freedom from TLR for all patients was 54.3%. However, we made the observation, well appreciated in interventional coronary trials, that because of the per-protocol required 6-month angiogram, a preponderance of TLRs occurred in the absence of an associated deterioration in patient-related symptoms (i.e., failure to heal a wound, worsening wound status or increasing limb pain). Therefore, post-hoc, we defined “clinically driven” TLR as a revascularization indicated due to complaints of leg pain/worsening pain, a progressing nonhealing ulcer, or a new ulcer formation, with or without the presence of an abnormal noninvasive test. The freedom from clinically driven TLR was a notable 70.1%; as such, the nonclinically driven TLRs were termed “incidental TLRs”. These observations, while limited by the post-hoc determination, challenge the current paradigm that a high stent (or vessel) patency rate will necessarily translate into improved wound healing and/or limb salvage. It also challenges the growing use of drug-eluting stents and suggests that the use of a less costly device (i.e., a BMS) may be as effective in improving limb salvage in the short- to midterm, despite improving angiographic vessel patency. The clinically driven TLR results are presented here not for the purpose of scientific conclusions, but rather as a hypothesis-generating observation that warrants future investigation.

Uniform End Points Definitions and “Patient-Centric” Clinical Outcomes

A growing body of evidence suggests that endovascular therapies are a relevant revascularization strategy for high-risk CLI patients. However, because of the relatively small number of patients enrolled in these studies, the controversy regarding the most appropriate efficacy end points and the lack of uniform definitions make meaningful comparisons between studies difficult. For endovascular therapy to achieve long-term credibility, experts have advocated for the standardization of trial designs, end points, and definitions [16,24].

The XCELL trial design utilized many of the objective performance criteria elements proposed by Conte et al. [16], and endorsed by the FDA’s Center for Devices and Radiological Health [25]. We also focused our analysis on frequently neglected “patient-centric”

outcomes such as limb preservation, wound healing, and pain relief. To our knowledge, this is the first endovascular CLI study to correlate these “patient-centric” outcomes with the more traditional study end point of AFS.

Although the Trans-Atlantic Inter-Society Consensus (TASC II) Document recommends wound healing as a primary study end point [1], it is seldom reported in CLI trials. This likely reflects the heterogeneous nature of ischemic wound size and duration and outcomes which may be affected by patient-, external-, and functional-related variables, including, diabetes, quality of and access to specialized wound care centers and pre-existing levels of function. Despite arterial patency, wound healing is slow with 52–63% of patients with incomplete healing at 6-month follow-up [19,26]. The association between index vessel patency (i.e., the wound-related artery), and the location of the ischemic wound is important. The inability to maximize blood flow via the artery perfusing the wound, thereby relying on collateral circulation, has been shown to result in reduced wound healing and limb salvage rates [27]. We were unable to draw any direct conclusions regarding the patency of the wound-related artery and subsequent wound healing rates or limb salvage, as we did not evaluate the patency of pedal vessels or the status of collateral vessels at the ankle. By 6 months, 29% (28) of the patients with analyzable wounds demonstrated complete wound healing and 47% (46) of wound patients had complete healing of at least one wound. Notably, following stenting, complete wound healing was achieved almost twice as rapidly (~106 days) as rates observed following surgical revascularization (~187 days) [26,28,29]. However, it is acknowledged that direct comparisons in wound healing rates between these modalities is complicated by differences in patient mix, local wound care standards, wound duration prior to intervention, etc.

Study Limitations

Our study was subject to the inherent limitations of a single-arm, nonrandomized trial and its results cannot be compared with those of randomized control trials. However, the protocol-mandated safety and effectiveness endpoints of this study were consistent with the trial endpoints recently proposed by Conte et al. [16]. Notably, it is the largest study to date with independent core laboratory-adjudicated assessments of stent patency, stent integrity and wound healing, and self-reported pain relief. Other limitations include the relatively short-term follow-up; however, we noted that the majority of major adverse limb events occurred within the first 6 months of follow-up. Additionally, this

cohort included a majority (82.5%) of Rutherford 5–6 patients, thus capturing clinical insights into this sicker patient population. The “clinically driven” TLR data is limited by the post-hoc nature of the analysis; however, the data is clearly presented as such and is provided simply as a point of discussion. Future studies of larger CLI cohorts, with more extended follow-up are necessary to determine whether these observations can be replicated. Finally, the observed LTF rate of 16.7% could adversely impact the study conclusions. Of note, 17 LTF patients (85%) were either Rutherford class 5–6 and 9 patients (45%) withdrew consent due to their inability or unwillingness to travel to the study center for angiographic, hemodynamic, and/or wound care follow-up. We concede that, assuming the extreme situation that all LTF patients experienced a primary endpoint event on the last day of contact, the hypothetical 12 month AFS rate calculated by Kaplan-Meier analysis was 63.6%, lower than the observed 78.3% AFS rate.

CONCLUSIONS

Implantation of the Xpert™ self-expandable nitinol stent for the treatment of infrapopliteal lesions in Rutherford Class 4–6 CLI patients is safe, with few major adverse events through the first 30 days and excellent 12 month rates of limb preservation, wound healing, and pain relief. Importantly, 12-month wound healing rates are comparable to those of open surgery.

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