

A Battle Cry for CLI Patient Advocacy is Needed to Increase Awareness

Michael R. Jaff, DO, FACC, FAHA



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The management of patients with critical limb ischemia (CLI) has become a major topic of conversation in the peer-reviewed literature and at major vascular scientific symposia. This

attention is likely due to interest in advances in technologies to manage CLI via endovascular methods. In addition, the continued enrollment of patients in the BEST-CLI National Institutes of Health trial keeps the discussion of surgical versus catheter-based therapy at the forefront.

Recently, using administrative claims from Medicare patients with a diagnosis of CLI in 2011, we learned that surgical and endovascular revascularization strategies offer similar survival rates and cost.¹ In this analysis, amputation rates were lower when catheter-based interventions were offered. Of no surprise, presentation (ischemic rest pain, ulceration, gangrene) predicted survival, with gangrene demonstrating the poorest survival over 4 years of follow-up.

It is important to note from these data that selecting primary amputation, as the first strategy after presentation of CLI, results in the poorest outcomes, including highest overall costs, shortest survival, and highest risk of subsequent amputation.

“It is of paramount importance that all practitioners recruit multiple specialties to manage patients with CLI.”

Therefore, what are the messages? First and foremost, early diagnosis of CLI is important, and consideration of revascularization as a first-line strategy is prudent. Second, until we get the results from the BEST-CLI trial, local expertise based on a team approach remains the key to deciding the optimal option. It is of paramount importance that all practitioners recruit multiple specialties to manage patients with CLI. Finally, advocacy for patients with CLI remains of great importance, as this patient population requires a loud voice from all of us to increase public awareness, which helps lead to prompt diagnosis. In

addition, advocacy will help to expand a battalion of effective revascularization strategies that will result in restoration of a functioning limb and a preserved quality of life. ■

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Disclosures: None.

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A Call to Action: Join the CLI Global Society to Raise Awareness and Elicit Action

Barry T. Katzen, MD, FACC, FACR, FSIR



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The recently published article in the *Journal of the American Heart Association* that was supported by the work of the Critical Limb Ischemia (CLI) Global Society points out that we have a critical disease affecting large numbers of American patients that may be completely unrecognized. That comment may be viewed as hyperbole, but the fact is, we have identified a disease that is associated with a mortality rate as high as many of the malignant cancers in our population. Yet, CLI remains unrecognized as a diagnosis associated with death at the same levels.

The Society, as a result, is very interested in launching an awareness campaign among physicians to recognize this link between CLI and other morbidities and mortalities. And importantly, the Society is also very interested in doing something about it. We don't just want to identify something as a diagnosis that produces mortality without taking definitive action steps. For those of us working in hospitals or other organized healthcare systems, one of the first steps is to create recognition in the healthcare system for CLI and to promote ways for the diagnosis to be recognized. Depending on

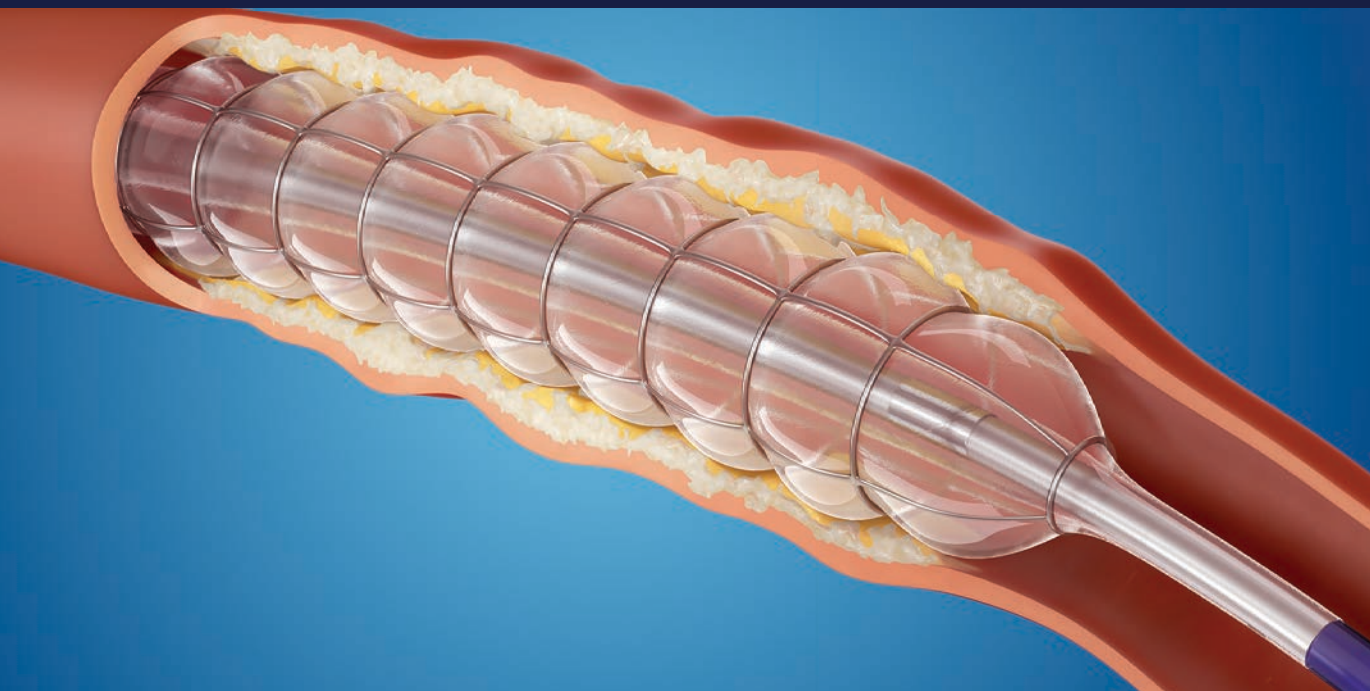
your electronic medical record and the methodologies that you use to collect data, this can vary. In our own institution, we have taken steps to include the words CLI in reports, consultations, and procedural dictations to facilitate word-based searches, which is perhaps the most primitive way to identify the actual number of patients. What we have found is that many institutions, principally because of the absence of codes appropriate to the diagnosis, have no idea what their actual CLI and amputation rates are. The CLI Global Society

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The Spectrum of Revascularization in the CLI Patient to Prevent Amputation: Endovascular and Surgical Modalities

Richard F. Neville, MD



Richard F. Neville, MD, FACS

Techniques used for revascularization of the limb with critical limb ischemia (CLI) have evolved immensely and continue to develop. A consistent increase in the number of endovascular procedures has been accompanied by a corresponding reduction in the number of lower extremity bypass procedures.¹ However, there have been significant advances in technique and technology associated with both modalities. Although both modalities continue to have an important role in revascularization for CLI, individual patient



Figure 1. DVP Patch: distal vein patch.

therapy is often based upon the judgment and the skill of the operator with a lack of recognized data to guide the decision. Analysis of the national VQI database shows a mean percentage of open surgical bypass of 30% at vascular programs involved in CLI. This is reflected in our own practice as well, with 76% of patients presenting with CLI undergoing endovascular revascularization, with 24% initially treated with bypass.

Factors to be considered in this decision include the indication for revascularization, medical comorbidity and life expectancy, specific arterial anatomy, and a history of prior failed vascular therapy. The above tenets were affirmed in a survey of vascular specialists that

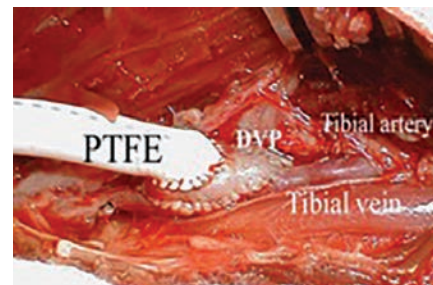


Figure 2. DVP bypass: patch with arterio-venous technique.

performed both endovascular and bypass procedures.² This survey queried physicians who performed both endovascular therapy and open surgical bypass in terms of criteria used to identify those patients best served by bypass as the initial mode of revascularization. The survey supported a surgical bypass first approach for common femoral artery pathology, extensive tissue loss, younger patients with a longer life expectancy, those requiring extensive soft tissue reconstruction, and those with long-segment tibial occlusive disease, especially those with only a single distal tibial target.

In terms of indications for revascularization, patients with large volume tissue loss may be best served by robust, in-line

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Wound Healing and CLI Treatment: Use of a Team Approach

Jos C. van den Berg, MD, PhD



Jos C. van den Berg, MD, PhD

CASE DESCRIPTION

An 85-year-old female patient was referred to our institution with a non-healing ulcer of the proximal part of the dorsum of the right foot and rest pain. Medical history revealed type II diabetes mellitus, ischemic cardiopathy, and arterial hypertension. Medical therapy consisted of single antiplatelet therapy, a calcium-antagonist for use as an anti-hypertensive treatment, cholesterol-lowering drugs, and an oral anti-diabetic (metformin). Clinical examination confirmed the presence of a critical limb ischemia (CLI) with an ulcerative lesion at the proximal

“Wound care, as well as glycemic control, was optimized in collaboration with a wound care nurse, vascular surgeon, and diabetologist.”

part of the dorsum of the foot and two smaller distal pre-tibial ulcerations, corresponding to the anterior tibial artery and fibular artery angiosome (Figure 1).

Normal pulses were present at the level of the common femoral artery. Peripheral pulses were absent bilaterally. Ankle-brachial index could not be measured on the right side, and was 0.51 on the left leg. Duplex examination demonstrated patency of the common and deep femoral artery and an occlusion of the distal superficial femoral artery (SFA) and proximal popliteal artery. In addition, an occlusion



Figure 1. Clinical examination confirmed the presence of a critical limb ischemia (CLI) with ulcers in the pre-tibial region and dorsum of the foot.

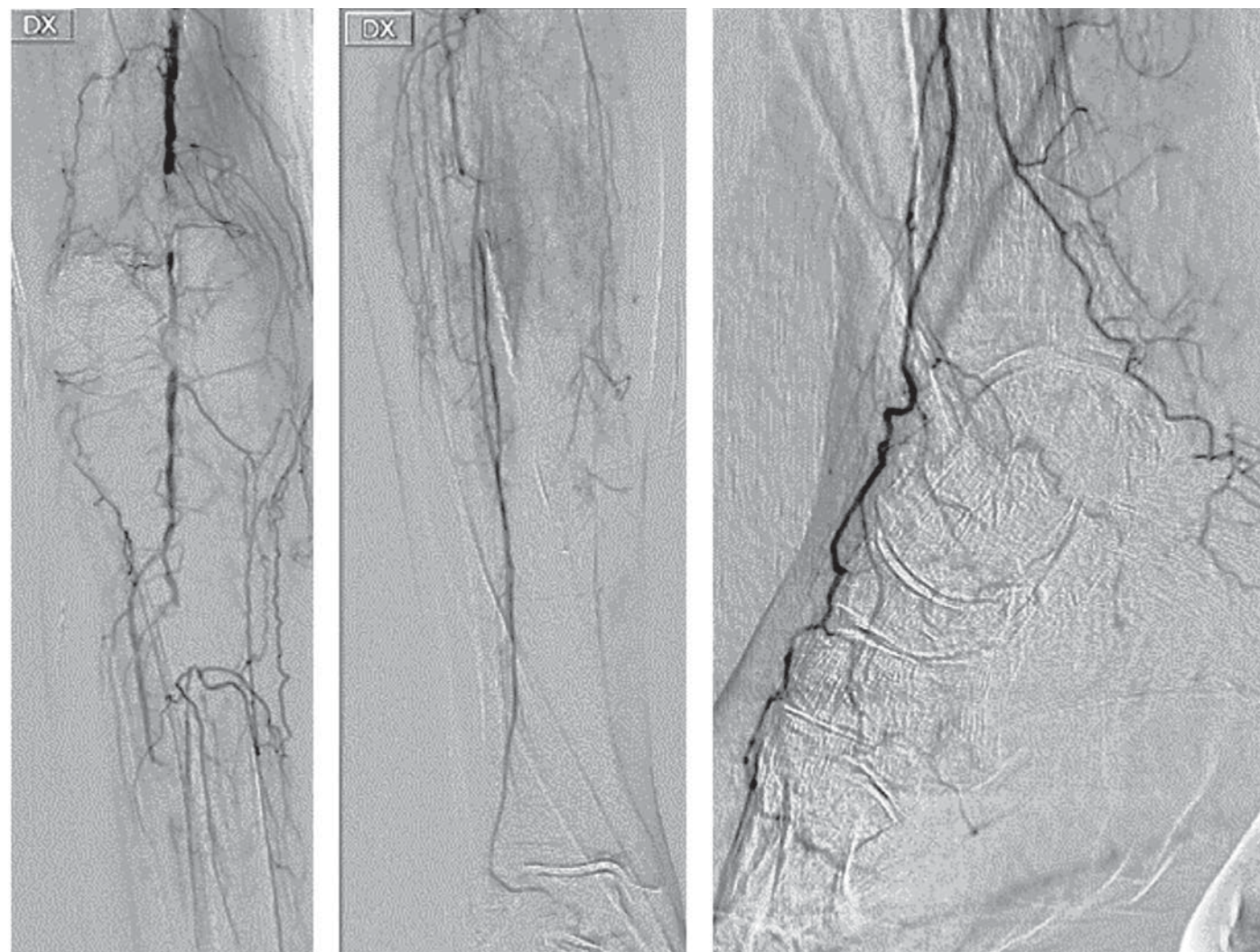


Figure 2. Diagnostic angiography shows an occlusion of the distal SFA and popliteal artery, anterior and posterior tibial artery, as well as tibioperoneal trunk.

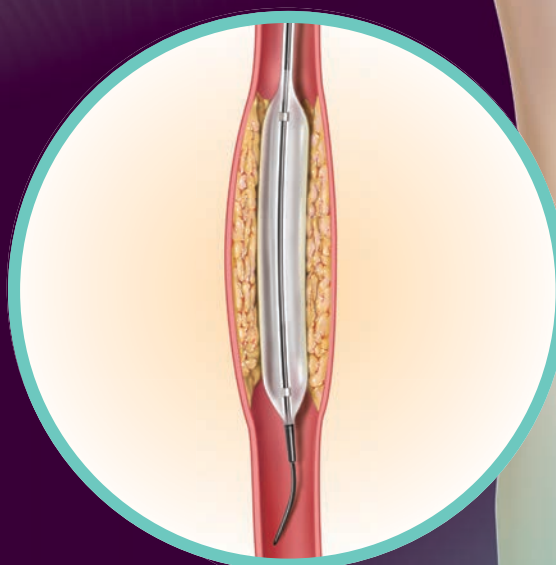
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Figure 3. Control angiography after angioplasty of SFA, popliteal and anterior tibial arteries demonstrated good reconstitution of the flow in the previously occluded segments.

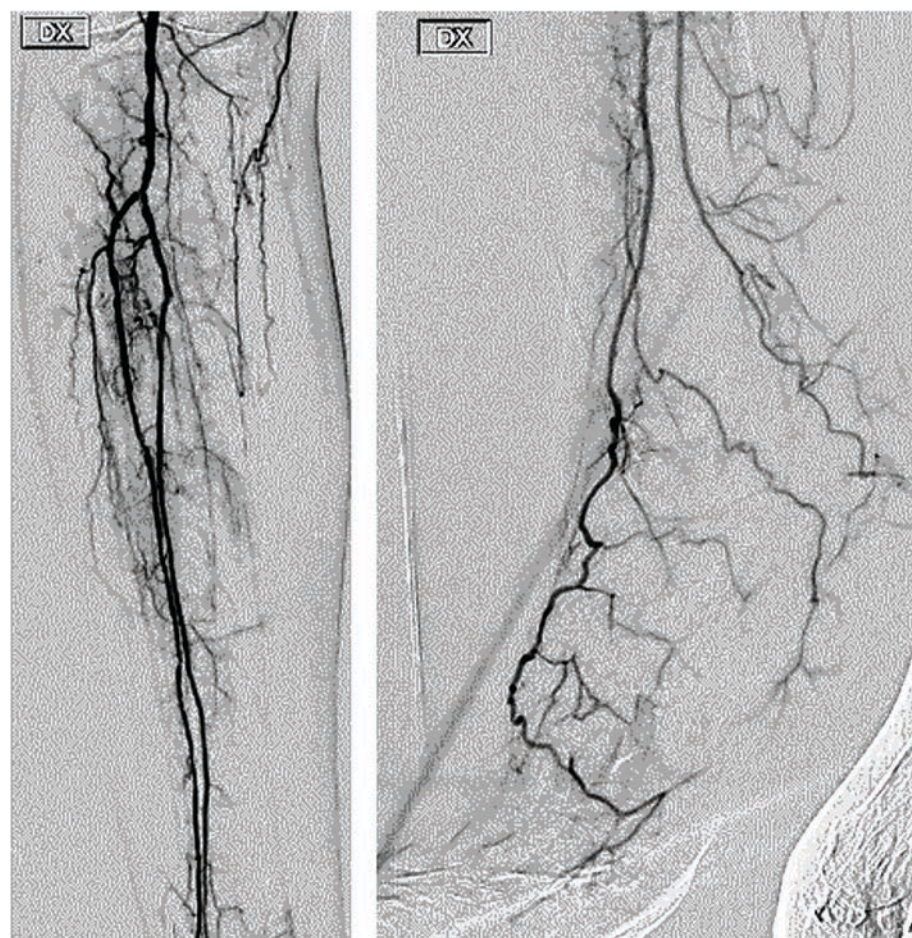


Figure 4. Control angiography demonstrating patency of anterior tibial artery, tibioperoneal trunk and fibular artery; note improved perfusion in the pre-tibial region and dorsum of the foot and visualization of some plantar circulation.

VAN DEN BERG *from page 4*

of the posterior tibial artery was seen. The anterior tibial artery demonstrated severe calcifications and monophasic flow (20 cm/s). The peroneal artery could not be visualized. The patient was referred to our service for percutaneous revascularization on an outpatient basis.

After obtaining antegrade access to the right common femoral artery and placement of a 4-F sheath (Ultimum, St. Jude Medical), diagnostic angiography was performed. Good patency of the proximal segment of the SFA was seen, however, an occlusion starting in the distal portion was evident, with an extension up to the P1 segment of the popliteal artery (length, 3 cm). The distal popliteal artery showed several stenotic areas. The proximal segment of the anterior tibial artery was patent, and an occlusion of 3 cm was seen at

10 cm from its origin. Distally, perfusion was evident, with patency of the a. dorsalis pedis. The tibio-peroneal trunk was occluded distally and the fibular artery demonstrated flow. The posterior tibial artery was occluded, with absence of flow in the plantar artery (Figure 2).

A 4-F diagnostic catheter (multipurpose shape) was advanced over a 0.035-inch Glidewire (Terumo Corporation) to a position close to the origin of the occlusion of the SFA and intraluminal recanalization was performed using an 0.018-inch Gaia guidewire (Asahi Intecc Co., Ltd.). Subsequently, percutaneous transluminal angioplasty (PTA) was performed using a 4- x 40-mm Paseo angioplasty balloon (Biotronik) that was kept inflated for 3 minutes. A control angiography demonstrated a hemodynamically significant residual stenosis, and therefore it was decided to proceed with stenting using

a 5- x 40-mm self-expanding Pulsar 18 stent (Biotronik). Post-dilation with the same 4- x 40-mm angioplasty balloon was performed. Next, an exchange was made for a 0.014-inch Halberd guidewire (Asahi Intecc Co., Ltd.) and the occlusion of the anterior tibial artery was crossed and subsequently dilated with a 2.5- x 40-mm PTA balloon (Armada; Abbott Vascular). A control angiography demonstrated good reconstitution of the flow in the previously occluded segments (Figure 3). No distal embolization was observed.

Given the distribution of the ulcerative lesions, it was decided to attempt an additional recanalization of the occluded distal tibio-peroneal segment and proximal fibular artery. This was achieved using the 0.014-inch Halberd guidewire; PTA was performed with the 2.5- x 40-mm Armada balloon. A control angiography demonstrated straight two-vessel flow toward the foot, with increased flow of the ulcer regions, and absence of distal embolization (Figure 4).

Hemostasis of the puncture site was obtained with manual compression, and the patient could be discharged in good clinical conditions after 6 hours of immobilization. Wound care, as well as glycemic control, was optimized in collaboration with a wound care nurse, vascular surgeon, and diabetologist. The rest pain disappeared, and the wound showed progressive healing over the following weeks.

CONCLUSION

This case demonstrates that revascularization for CLI is feasible in an outpatient setting and emphasizes the need for a multi-disciplinary approach in order to optimize wound care and glycemic control in diabetic patients. ■

CONTRIBUTE TO THE CONVERSATION ON TWITTER: #CLIFIGHTERS

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KATZEN *from cover*

is committed to improving quality of life, reducing amputation rates and mortality from CLI, and establishing national goals to reach these objectives. However, to do so, we must first establish what the actual national rates are, for both of these catastrophic events, and work backward to establish therapeutic public health goals.

As a result, the CLI Global Society is growing in membership and support

to establish appropriate codes to identify CLI patients, develop quality metrics, and establish national standards and goals on which we can improve. In our institution, led by a multidisciplinary collaborative group within the institute's performance improvement process, we have developed algorithms and order sets to be used in patients with CLI that promote early identification and the early involvement of vascular specialists (of any discipline). These efforts involve considerable work and

commitment by those involved to bring about a successful result and require leadership from physicians involved in CLI therapy.

If you believe in these goals, you can help. Take positive action by joining the CLI Global Society as a member, participating in committees, and supporting these initiatives both locally and nationally. We welcome your participation in this important initiative for our patients. ■

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Have Outcomes with Infrapopliteal Angioplasty Improved Over the Last 30 Years?

J.A. Mustapha, MD and Larry E. Miller, PhD



J.A. Mustapha, MD

Individuals suffering from critical limb ischemia (CLI) with involvement of the infrapopliteal arteries should receive surgical or endovascular revascularization in an attempt to salvage the affected limb. Endovascular revascularization is often the only feasible treatment option in patients at high surgical risk or with runoff vessels unsuitable for use as a conduit. Among endovascular treatments for infrapopliteal disease, percutaneous transluminal angioplasty (PTA) remains the standard of care at most centers. The first studies of PTA for treatment of infrapopliteal disease were published 30 years ago. Since then, significant advancements in technology and techniques have been made to expand vascular access options, improve lesion crossing success, and lower the risk for early failures. Yet it is unclear whether patient outcomes with infrapopliteal PTA have improved over this period.

In 2008, Romiti and colleagues¹ performed the first meta-analysis of infrapopliteal PTA in patients with CLI. Their review included 30 studies published between 1990 and 2006. In 2016, Mustapha and colleagues² performed a similar review of 52 contemporary studies published between 2005 and 2015. When comparing key data from these meta-analyses side-by-side (Table 1), patient characteristics generally appear comparable, although diabetes mellitus, hypertension, renal disease, and occlusive disease were slightly more common in the recent meta-analysis. Inspection of outcomes through 1-year follow-up shows nearly identical rates of technical success, primary patency, major amputation, and all-cause mortality.

How should one interpret these findings? At first glance, it appears that infrapopliteal PTA outcomes are not improving with time. However, there is so much variability among studies in trial design, diagnostic standards, patient characteristics, outcome definitions, and imaging review

that interpretation of results is difficult. An example of the extreme variability in outcomes observed among infrapopliteal PTA studies is provided in Figure 1, which shows the range of primary patency rates through 1 year in each study included in Mustapha's meta-analysis.²

Another important consideration with these results relates to patient mortality rates. In each meta-analysis, the overall mortality rate at 1 year was approximately 15%. Yet in a review of more than 28,000 Medicare claims in which CLI patients were treated with endovascular revascularization (most treated with PTA), 1-year mortality was 23%.³ This might suggest that not only are infrapopliteal PTA outcomes in published studies not noticeably improving with time, but these outcomes in real-world settings may be even worse than previously thought.

A possible remedy for these issues is to improve the quality of study reporting, especially for key variables that strongly impact patient outcomes. In the meta-analysis of Mustapha et al, for example, the percentage of studies that reported key patient characteristics was 63% for renal disease, 56% for lesion length, 54% for Rutherford class, 19% for calcification, and 19% for reference vessel diameter. Inconsistent and incomplete reporting of

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Table 1. Key Results of Meta-analysis of Infrapopliteal PTA for CLI Treatment

Characteristics	Romiti, 2008 ¹	Mustapha, 2016 ²
Studies in Meta-analysis		
Number of studies	30	52
Years of publication	1990–2006	2005–2015
Patient characteristics		
Age (yr)	70	70
Diabetes mellitus	61%	75%
Hypertension	54%	75%
Smoking	50%	40%
Renal disease	23%	34%
Tissue loss	76%	79%
Occlusive disease	41%	52%
Patient outcomes		
Technical success	89%	91%
Primary patency at 1 year	58%	63%
Major amputation at 1 year	14%	15%
All-cause mortality at 1 year	13%	15%

“A possible remedy for these issues is to improve the quality of study reporting, especially for key variables that strongly impact patient outcomes.”

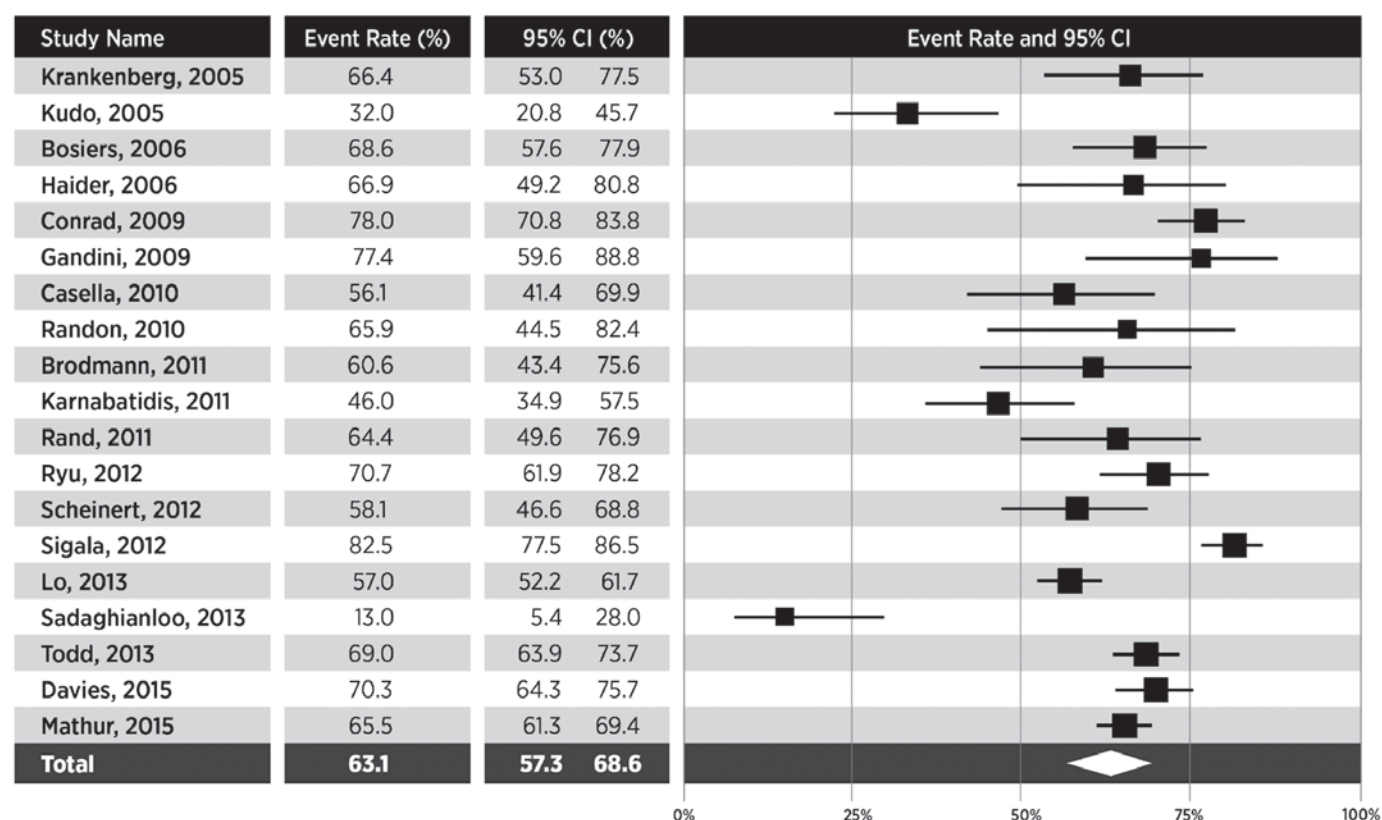


Figure 1. Primary patency through 1 year with PTA in infrapopliteal atherosclerotic lesions.

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Acute Results of Directional Atherectomy for the Treatment of Claudication and Critical Limb Ischemia in the DEFINITIVE LE Study

Lawrence A. Garcia, MD; Michael Jaff, MD; Krishna Rocha-Singh, MD; Thomas Zeller, MD; James McKinsey, MD



Lawrence A. Garcia, MD

Peripheral artery disease (PAD) remains an increasingly common disorder that continues to be a large source of chronic morbidity and mortality worldwide.¹⁻⁶ The endovascular treatment of PAD has become the first-line therapy in most arterial beds.⁷⁻⁹ The treatment of femoropopliteal and tibial-peroneal disease is one such example. Treatment options in this territory include percutaneous transluminal angioplasty (PTA),¹⁰⁻¹³ PTA combined with adjunctive stenting, either bare-metal stent (BMS) or drug-eluting stent (DES) implantation,^{7,12,14-16} drug-coated balloon (DCB),^{17,18} and atheroablative technologies including directional atherectomy (DA)¹⁹⁻²⁴ with devices such as the SilverHawk and TurboHawk Peripheral Plaque Excision Systems (Medtronic).

No single device is considered the gold standard primarily because of the heterogeneity of the patient population and lesion morphologies being treated and the lack of direct comparisons between technologies. In the DEFINITIVE LE Study, DA was used to treat subjects with infrainguinal PAD. Up until this study, there was limited scientific literature on DA given previous study design limitations and a lack of independent evaluation of outcomes.^{20,23,24} Further, previous reports have suggested a higher complication rate and inferior durability with DA as compared with other endovascular strategies.^{21,22}

Herein, we focus on the acute 30-day safety outcomes with respect to procedural complications and 30 day quality-of-life outcomes of the SilverHawk and TurboHawk Plaque Excision Systems in the DEFINITIVE LE study in the treatment of lower-limb arterial disease.

ABSTRACT: Objectives. Assess the acute safety of directional atherectomy (DA) for endovascular treatment of peripheral arterial disease (PAD) in infrainguinal arteries. **Background.** Single-center studies and uncontrolled registries have demonstrated 12-month clinical benefit of DA for the treatment of PAD; however, large-scale, independently assessed multicenter data on acute procedural safety have previously been lacking. **Methods.** DEFINITIVE-LE was a prospective, multicenter, single-arm study. Endpoints were assessed by independent angiographic and duplex ultrasound core laboratories and adverse events were adjudicated by a Clinical Events Committee. For claudicants, the primary endpoint was primary patency at 1 year (estimated by Kaplan-Meier methods). For patients with critical limb ischemia (CLI), the primary endpoint was freedom from major amputation of the target limb at 1 year. **Results.** A total of 800 subjects with 1022 infrainguinal lesions were enrolled; 201 subjects had CLI and 52.3% had diabetes mellitus. Mean lesion length was 7.4 ± 5.3 cm, mean percent diameter stenosis was 73.6%, and 20.8% of patients had occluded lesions. Periprocedural adverse events included distal embolization (3.8%), perforation (5.3%), and abrupt closure (1.9%). Procedural success was achieved in 89.0% of all lesions treated per angiographic core laboratory assessment, with a bailout stenting rate of 3.2%. Additionally, quality-of-life scores were significantly improved at 30 days compared with baseline. **Conclusions.** This large, prospective, multicenter, independently adjudicated study produced acute outcomes indicating that directional atherectomy is safe, with low rates of periprocedural events. Results were promising for PAD patients with claudication or CLI, and there were minimal differences between diabetics and non-diabetics.

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Key words: peripheral arterial disease, angioplasty, atherosclerosis

METHODS

Study Design

DEFINITIVE LE was a prospective, global, multicenter, single-arm, non-randomized study designed to evaluate the acute and long-term safety and effectiveness of DA for endovascular treatment of PAD in femoropopliteal and tibial-peroneal arteries.²⁵

Candidates for DA in the infrainguinal arteries provided written informed consent prior to screening. Inclusion criteria are listed in Table 1 and included a Rutherford Clinical Category (RCC) score of 1-6, infrainguinal artery stenosis $\geq 50\%$, a reference vessel diameter of 1.5-7.0 mm, and a lesion length of up to 20 cm as assessed by the treating physician. Lesions in the superficial femoral (SFA) or popliteal artery separated by more than 3 cm or those separated by more than 2 cm distal to the popliteal artery were considered separate lesions. Major exclusion criteria included presence of severe calcification (defined as fluoroscopic evidence of calcium present in two walls of the lesion that exceeded 1 cm in length), in-stent restenosis, and lesions located within an aneurysmal segment.

Each site's Institutional Review Board/Ethics Committee approved the study protocol. Subjects were considered enrolled in the study after informed consent was signed and all of the inclusion criteria and none of the exclusion criteria were met.

The study was conducted in accordance with Good Clinical Practice and overseen by a steering committee and an independent Clinical Events Committee (CEC). Angiographic findings (such as dissections, distal embolization, etc) identified and classified by the core laboratory were presented to the CEC for consider-

ation as adverse events. Independent core laboratories conducted analyses of angiographic (SynvaCor) and duplex ultrasonography images (VasCore, Massachusetts General Hospital).

Regular monitoring visits were conducted to ensure that collected data were complete and accurate. Angiographic classification provided by the angiographic core laboratory was final, but the CEC had final say as to relatedness and seriousness of the resulting adverse event.

INTERVENTIONS

Preprocedure data collection included an ankle-brachial index (ABI) and EQ-5D questionnaire (a patient-reported measure of overall health) for all patients, a Walking Impairment questionnaire (WIQ) for subjects with RCC 1-4, and wound assessment via the Wagner scoring scale in subjects with RCC 5 or 6.

Significant stenosis or occlusion of inflow vessels (iliac or common femoral) required successful revascularization prior to enrollment. Infrainguinal arterial lesions intended for treatment at the time of the index procedure that met the inclusion and exclusion criteria were enrolled and considered target lesions. There was no limit on the number of target lesions per patient. If multiple outflow vessels were present, then the treatment of any outflow vessel was left to the discretion of the operator as to the method of revascularization.

All subjects underwent percutaneous revascularization of the femoropopliteal and/or tibial-peroneal arteries using a DA device. In cases in which the DA device was unable to cross, the lesions were permitted to be predilated, at the discretion of the investigator. Angiographic

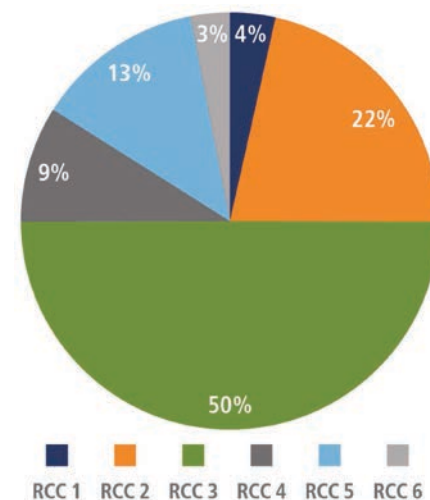


Figure 1. Baseline Rutherford Clinical Category (RCC) of the entire study cohort.

films, including run-off status, were obtained immediately prior to and after DA to document pre- and post-treatment results. Adjunctive procedures were performed at the treating physician's discretion; however, if residual stenosis was $< 30\%$ post-directional atherectomy, additional postdilation was not recommended. A final angiogram of the target lesion(s) and run-off was performed following adjunctive procedures (if required). Residual stenosis was calculated by dividing the native vessel diameter as measured at the most stenotic segment by the estimated reference vessel diameter (mean of the vessel diameters proximal and distal to the lesion) at that location. Distal protection

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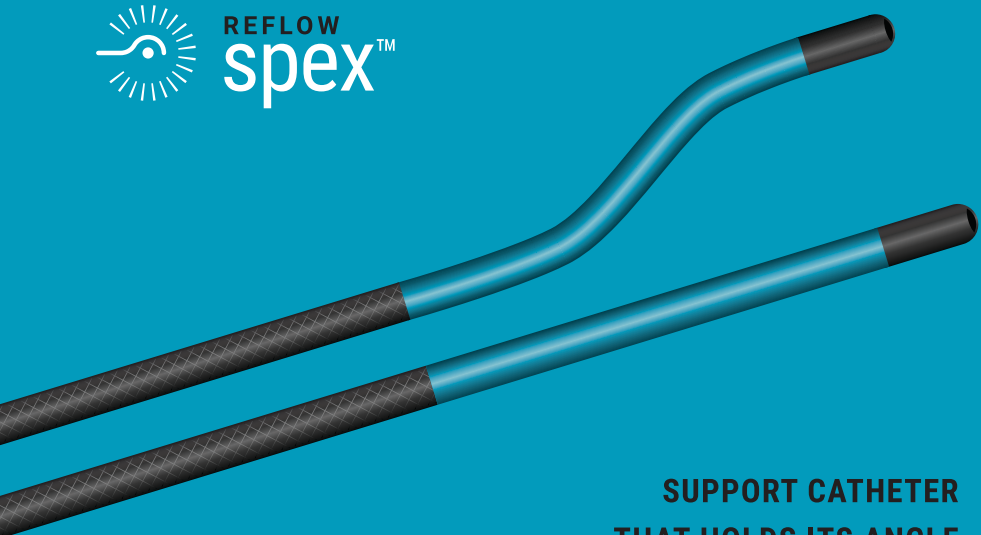
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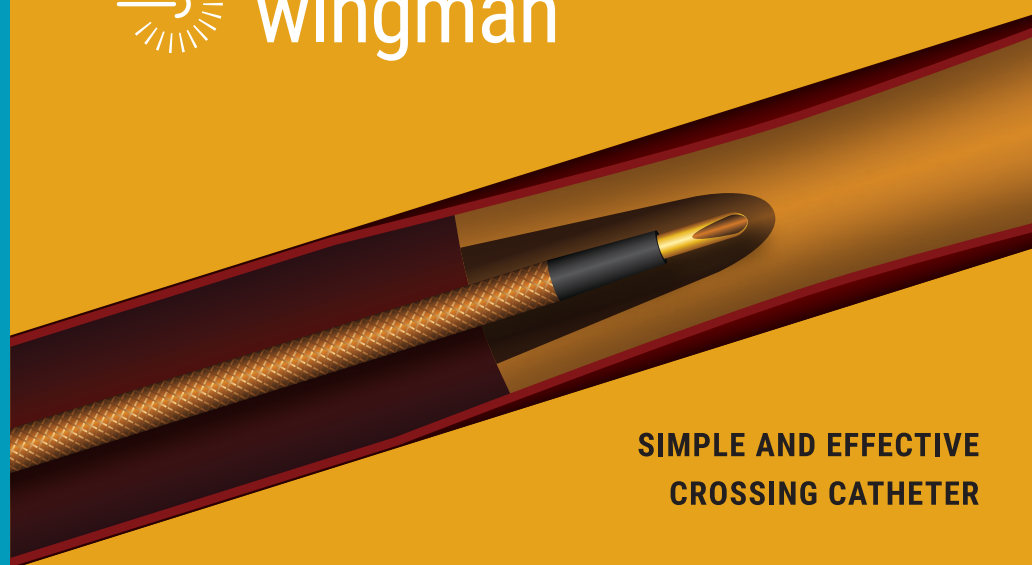
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Table 1. DEFINITIVE-LE inclusion and exclusion criteria.

Inclusion Criteria
• Has a Rutherford Clinical Category score of 1-6
• Is willing and capable of complying with all follow-up evaluations at the specified times
• Is ≥18 years old
• Provides written informed consent prior to study specific procedures
• Has evidence of ≥50% stenosis or occlusion in the superficial femoral, popliteal, anterior tibial, posterior tibial, and/or peroneal arteries, confirmed by angiography
• Has identifiable distal target vessel, which upon completion of the intervention, is anticipated to provide reconstitution of blood flow to the foot
• Exchangeable guidewire must cross lesion(s), with ability of catheter to cross lesion
• Each discrete target lesion's length is ≤20 cm
• Reference vessel diameter is ≥1.5 mm and ≤7 mm
Exclusion Criteria
• Has one or more of the contraindications listed in the SilverHawk Instructions for Use
• Has a contraindication or known untreated allergy to antiplatelet therapy, anticoagulants, thrombolytic drugs, or any other drug anticipated to be used
• Has a hypersensitivity to contrast material that cannot be adequately pretreated
• Has known hypersensitivity to treatment device material
• Has known uncontrollable hypercoagulable condition, or refuses blood transfusion
• Has life expectancy of <12 months
• Has surgical (requiring hospitalization) or endovascular procedure of the target vessel within 14 days prior to the index procedure
• Has planned surgical intervention or endovascular procedure within 30 days after the index procedure
• Is currently participating in an investigational drug or another device study that may clinically interfere with the study endpoints
• Has other co-morbid condition(s) that in the judgment of the physician precludes safe percutaneous intervention
• Has had a previous peripheral bypass affecting the target limb
• Has end-stage renal disease, defined as undergoing hemodialysis for kidney failure
• Has had a previous amputation above the metatarsal line on the target limb
• Has presence of severe calcification in target lesion(s)
• Has in-stent restenosis of the target lesion
• Has an aneurysmal target vessel
• Has significant stenosis or occlusion of inflow tract that has not been revascularized prior to treatment of the target vessel
• Has perforation, dissection, or other injury of the access or target vessel requiring additional stenting or surgical intervention prior to enrollment
• Has disease that precludes safe advancement of the SilverHawk device to the target lesion(s)

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devices, permitted under the study protocol, were used at the discretion of the attending physician.

ADJUVANT MEDICAL THERAPY

It was recommended that all subjects receive antiplatelet or antithrombotic therapy per American Heart Association/

American College of Cardiology/European Society of Cardiology guidelines before and after the procedure. Anticoagulation during the procedure was left to the discretion of the treating physician to maintain appropriate levels of anticoagulation.

FOLLOW-UP

Follow-up assessments occurred prior to discharge and at 30 days, 3 months (for subjects with RCC score 5 or 6 at

Table 2. Baseline demographics.

Subject Characteristics	Claudicants (n = 598)	CLI (n = 201)	Total (n = 799)
Age (years)	69.5 ± 10.4	72.1 ± 11.4	70.1 ± 10.7
Female gender	43.8%	50.2%	45.4%
Caucasian	71.7%	64.7%	70.0%
History and risk factors			
Diabetes	46.8%	68.7%	52.3%
Angina	22.9%	18.4%	21.8%
Arrhythmia	15.6%	22.9%	17.4%
Congestive heart failure	13.2%	17.9%	14.4%
Myocardial infarction	18.6%	18.9%	18.7%
CABG or PCI	39.5%	32.3%	37.7%
Hypertension	92.0%	92.0%	92.0%
Hyperlipidemia	86.1%	76.1%	83.6%
Renal insufficiency	16.7%	23.4%	18.4%
Current or former smoker	53.5%	35.8%	49.1%
Data provided as mean ± standard deviation or percentage. CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.			

baseline), 6 months, and 1 year following the index procedure. Each follow-up visit included assessment of RCC score, WIQ (for subjects with a baseline RCC score 1-4), EQ-5D, ABI, adverse event evaluations, and wound assessments for subjects with a baseline RCC score of 5 or 6.

ENDPOINTS

Briefly, the study's primary endpoints were primary patency and freedom from amputation at 1 year; these results were presented elsewhere.²⁵ Prespecified secondary endpoints included: (1) device success, defined as ≤30% residual stenosis following use of the DA device, as measured by angiography, without adjunctive endovascular interventions or periprocedural complications; (2) procedural success, defined as ≤30% residual stenosis following use of the DA and adjunctive endovascular interventions (if required) as measured by angiography without periprocedural complications; and (3) major adverse event (MAE) rate at 30 days and 1 year, defined as clinically driven target-vessel revascularization (at least 70% lesion stenosis or at least 50% with attendant symptoms), major unplanned amputation of the treated limb (resulting in a limb prosthesis), or all-cause mortality.

STATISTICAL ANALYSIS

Data were evaluated for all subjects enrolled regardless of the treatment delivered; all available data for all such subjects were used in primary analyses of baseline characteristics and study outcomes. All target lesions were analyzed as identified by the angiographic core laboratory.

All statistical analyses were performed using Statistical Analysis System for Windows version 9.1 or higher (SAS Institute, Inc). Unless otherwise noted, continuous variables were evaluated using t-tests, binary categorical variables with Fisher's exact test, and ordinal variables with Mantel-Haenszel χ^2 test; for continuous variables collected at multiple time points,

change scores from baseline were computed and used as the basis for analysis.

RESULTS

Enrollment occurred between April, 2009 and April, 2011 at 47 international centers. Eight hundred subjects were enrolled in the study; however, inadequate informed consent resulted in the exclusion of one subject's data from all analyses. Baseline demographic information is listed in Table 2. Results are provided for the claudicant cohort (n = 598), CLI cohort (n = 201), and the overall study population (n = 799). The mean age was 70.1 ± 10.7 years and 45.4% of the population was female. Co-morbid conditions included diabetes mellitus (52.3%), hypertension (92.0%), and hyperlipidemia (83.6%). The CLI cohort was older (72.1 years vs 69.5 years; $P<.01$) and had a significantly higher percentage of subjects with diabetes mellitus (68.7% vs 46.8%; $P<.001$) and renal insufficiency (23.4% vs 16.7%; $P=.045$).

Baseline RCC scores are shown in Figure 1. Approximately one-half (49.8%) of the subjects were classified as RCC 3. Baseline lesion characteristics are listed in Table 3. A total of 1022 lesions were treated in 799 subjects (1.3 lesions/subject). The mean baseline percent diameter stenosis was 73.6 ± 18.7%, and 20.8% of lesions were occluded. The mean lesion length was 7.4 ± 5.3 cm; 27.8% were ≥10 cm. The total SFA disease burden, defined as the total of the lengths of all SFA lesions per subject, was 9.4 ± 6.3 cm.

Table 4 describes the procedural characteristics. The average procedure time (from arterial access to catheter removal) was 70.9 ± 34.3 minutes, with shorter times observed in the claudicant group (67.7 minutes vs 80.6 minutes; $P<.001$). Predictors of a longer procedure time included patients with CLI (vs claudication), longer target lesion treated, greater baseline severity of stenosis, the number

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Table 3. Lesion characteristics.

Subject Characteristics	Claudicants (n = 743)	CLI (n = 279)	Total (n = 1022)
Target artery			
Superficial femoral artery	72.1%	48.4%	65.7%
Popliteal	15.3%	17.2%	15.9%
Infrapopliteal	12.5%	34.4%	18.5%
Baseline stenosis (%)	72.7 ± 18.1	75.9 ± 20.0	73.6 ± 18.7
Occlusions	17.4%	29.9%	20.8%
Calcification	37.1%	37.1%	37.1%
Lesion length (cm)	7.5 ± 5.3	7.2 ± 5.5	7.4 ± 5.3
Longest lesion per subject (cm)	8.3 ± 5.4	8.3 ± 5.7	8.3 ± 5.5
SFA vessel lesion length (cm)	9.2 ± 6.1	10.0 ± 6.8	9.4 ± 6.3
Target lesion length			
≥10.0 cm	28.9%	24.8%	27.8%
4.0 to 9.9 cm	41.5%	39.9%	41.1%
<4.0 cm	29.6%	35.3%	31.1%

Data provided as mean ± standard deviation or percentage.

Table 4. Procedural characteristics.

Procedural Characteristics	Claudicant	CLI	Total
Procedure time (min)	67.7 ± 33.1	80.6 ± 36.0	70.9 ± 34.3
Contrast administered (cc)	159.2 ± 95.4	159.7 ± 92.0	159.3 ± 94.5
Fluoroscopy time (min)	20.0 ± 18.7	22.1 ± 13.1	20.5 ± 17.5
Use of embolic protection			
All	20.1%	27.4%	22.2%
SpiderFX only	19.6%	27.4%	21.5%
Device success	76.0%	72.1%	74.9%
Post-device stenosis (%)	23.9 ± 13.1	25.6 ± 13.8	24.3 ± 13.3
Procedural success rate	91.2%	83.0%	89.0%
Post-adjunctive stenosis (%)	18.0 ± 11.2	20.9 ± 12.3	18.7 ± 11.5

Data provided as mean ± standard deviation or percentage.

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of lesions treated, and the presence of arterial calcification. Predilation to allow passage of the DA device was performed in 8.3% of lesions in subjects treated for claudication and 15.8% of those in CLI subjects ($P<.001$), typically using PTA balloons, which were predominantly (75.0%) ≤3 mm in diameter. There was no significant difference in the percentage of lesions predilated in femoropopliteal vs tibial-peroneal arteries (10.1% vs 11.6%). After initial therapy with DA, adjunctive therapy was performed in 35.3% of the target lesions. The majority of adjunctive therapy was PTA; the adjunctive stent rate was 3.2%. Distal embolic protection (DEP) via a filter device was used in 22.2% of subjects, with the SpiderFX Embolic Protection System (Medtronic, Inc) used in 97.2% of those cases. DEP use was significantly more frequent in conjunction with the TurboHawk device than with SilverHawk (39.8% vs 14.2%, respectively; $P<.001$) and in CLI subjects than in claudicants (27.4% vs 20.4%, respectively; $P=.049$) and occurred qualitatively more often with longer, more heavily stenotic, and calcified lesions. Device success (defined as ≤30% residual stenosis following use of the DA device) was achieved in 74.9% of all target lesions

and did not differ significantly between the claudicant and CLI groups or between femoropopliteal and tibial-peroneal lesions. Procedural success (defined as ≤30% residual stenosis at the conclusion of the procedure) was achieved in 89.0% of target lesions, including 91.2% of lesions in claudicants compared with 83.0% of lesions in the CLI subjects ($P<.001$) and was more often achieved in femoropopliteal lesions than in tibial-peroneal lesions (90.1% vs 84.0%; $P=.02$). Following DA, the mean percent diameter stenosis was $24.3 \pm 13.3\%$. For those lesions treated with adjunctive therapy, the residual stenosis was $18.7 \pm 11.5\%$. Predictors of greater procedural success included female gender, SFA lesion location, lower baseline percent diameter stenosis, absence of vascular calcification, and shorter lesion length. Table 5 shows the periprocedural adverse events in the study. The most common event noted was arterial perforation (5.3%), which occurred more frequently in the claudicant group than in the CLI group (6.2% vs 2.5%, respectively; $P=.04$). Abrupt closure occurred in 15 cases (1.9%). Distal embolization was noted in 30 of 799 subjects (3.8%) as adjudicated by the CEC and angiographic core lab. This includes 24 events in 542 subjects (4.4%) with evaluable angiograms of run-off and 6

Table 5. Periprocedural events.

Periprocedural Event	Day 0 (Index Procedure Date)	Days 1-30 (Post Procedure)	Days 0-30 (Total Periprocedural Events)
All periprocedural events (distal embolization, abrupt closure, flow-limiting dissection, perforation, aneurysm)	82 (10.3%)	16 (2.0%)	90 (11.3%)
All periprocedural events requiring treatment	51 (6.4%)	16 (2.0%)	61 (7.6%)
Distal embolization	30 (3.8%)	0 (0.0%)	30 (3.8%)
Requiring treatment	13 (1.6%)	0 (0.0%)	13 (1.6%)
Surgical intervention	1 (0.1%)	0 (0.0%)	1 (0.1%)
Stenting	1 (0.1%)	0 (0.0%)	1 (0.1%)
PTA/lysis/embolectomy/aspiration	11 (1.4%)	0 (0.0%)	11 (1.4%)
Abrupt closure	5 (0.6%)	10 (1.3%)	15 (1.9%)
Requiring treatment	2 (0.3%)	10 (1.3%)	12 (1.5%)
Surgical intervention	1 (0.1%)	7 (0.9%)	8 (1.0%)
Stenting	0 (0.0%)	1 (0.1%)	1 (0.1%)
PTA	1 (0.1%)	2 (0.3%)	3 (0.4%)
Associated to dissection	1 (0.1%)	2 (0.3%)	3 (0.4%)
Associated to embolization	2 (0.3%)	5 (0.6%)	7 (0.9%)
Associated to thrombosis	1 (0.1%)	7 (0.9%)	9 (1.1%)
Associated to perforation	0 (0.0%)	2 (0.3%)	2 (0.3%)
Dissection (flow limiting)	18 (2.3%)	0 (0.0%)	18 (2.3%)
Requiring treatment	12 (1.5%)	0 (0.0%)	12 (1.5%)
Surgical intervention	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stenting	8 (1.0%)	0 (0.0%)	8 (1.0%)
PTA	4 (0.5%)	0 (0.0%)	4 (0.5%)
Perforation	39 (4.9%)	4 (0.5%)	42 (5.3%)
Requiring treatment	30 (3.8%)	4 (0.5%)	33 (4.1%)
Surgical intervention	1 (0.1%)	0 (0.0%)	1 (0.1%)
Stenting	12 (1.5%)	4 (0.5%)	15 (1.9%)
PTA	17 (2.1%)	0 (0.0%)	17 (2.1%)
Aneurysm	1 (0.1%)	2 (0.3%)	3 (0.4%)
Requiring treatment	0 (0.0%)	2 (0.3%)	2 (0.3%)
Surgical intervention	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stenting	0 (0.0%)	2 (0.3%)	2 (0.3%)
PTA	0 (0.0%)	0 (0.0%)	0 (0.0%)

Data provided as number (percentage). PTA = percutaneous transluminal angioplasty.

additional embolic events adjudicated by the CEC in the remaining 257 subjects without evaluable run-off angiograms. In total, 13 subjects (1.6%) had distal embolizations that were subsequently treated. The use of DEP devices was at the discretion of the implanting physician. No significant differences were noted in the rate of distal embolization by use of DEP (22/622 without DEP [3.5%] vs 8/177 with DEP [4.5%]; $P=NS$). Moreover, within the group of subjects treated without DEP, the embolic event rates were not statistically different between patients treated with TurboHawk or SilverHawk devices (4/150 [2.7%] vs 18/472 [3.8%]; $P=NS$). There were no significant differences in rates of periprocedural events between femoropopliteal and tibial-peroneal lesions. Rates of distal embolization were also not significantly associated

with other lesion characteristics, although greater rates of embolization in smaller target vessels, longer lesions, calcified lesions, and cases with multiple target lesions were observed.

The 30-day MAE rate was 1.6% including 4 deaths (0.5%), 6 clinically driven target-lesion revascularizations (0.9%), and 3 major unplanned amputations (0.4%; 1 above the knee, 1 below the knee, and 1 Syme's), all in CLI patients. MAEs were more common among CLI subjects, with a rate of 3.5% vs 1.0% among claudicants ($P=.02$). None of the 4 deaths within 30 days were adjudicated as related to either the study device or the index procedure by the CEC (3 were due to myocardial infarction and 1 was due to cardiogenic shock).

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Table 6. Secondary endpoints.		
Outcome	Baseline	30-Day Follow-Up
Rutherford clinical category	3.1 ± 1.1	1.5 ± 1.7
Ankle-brachial index	0.65 ± 0.16	0.90 ± 0.18
Walking Impact Questionnaire (claudicants only)		
Pain	54.9 ± 26.0	77.3 ± 23.6
Walking distance	19.9 ± 24.2	46.5 ± 39.1
Walking speed	20.3 ± 20.7	36.9 ± 29.4
Stair climbing	32.0 ± 31.0	49.9 ± 38.9
EQ-5D index score	0.71 ± 0.19	0.80 ± 0.19
EQ-5D visual analog scale	65.0 ± 19.2	71.0 ± 20.1
Data provided as mean ± standard deviation. EQ-5D = EuroQol Five Dimensions Questionnaire.		

Table 7. Outcomes by diabetic status.			
Outcome	Diabetics	Non-Diabetics	Total
Device success	75.9%	73.9%	74.9%
Procedural success	88.2%	89.8%	89.0%
Change from baseline to 30 days in clinical endpoints			
Rutherford clinical category	-1.5 ± 1.4	-1.7 ± 1.2	-1.6 ± 1.3
Ankle-brachial index	0.24 ± 0.23	0.26 ± 0.19	0.25 ± 0.21
Periprocedural events			
Distal embolization	15 (3.6%)	15 (3.9%)	30 (3.8%)
Abrupt closure	10 (2.4%)	5 (1.3%)	15 (1.9%)
Dissection (flow limiting)	11 (2.6%)	7 (1.8%)	18 (2.3%)
Perforation	18 (4.3%)	24 (6.3%)	42 (5.3%)
Aneurysm	0 (0.0%)	3 (0.8%)	3 (0.4%)
Data provided as mean ± standard deviation or number (percentage).			

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All secondary outcomes are listed in Table 6, including ABI, RCC, the WIQ and EQ-5D questionnaires, and wound healing. Each outcome demonstrated statistically significant improvement at the 30 day follow-up visit compared with baseline. Procedural success and adverse events were no greater among patients with diabetes (Table 7). A small but significant difference favoring non-diabetics was found in improvement in RCC from baseline to 30 days ($P<.01$), but was not seen in ABI measurements.

DISCUSSION

The DEFINITIVE LE study was undertaken to establish clinical and scientific data for DA using the SilverHawk and TurboHawk devices as treatment of infrainguinal PAD in both claudicants and CLI patients. The trial, although not randomized, was prospective, and all outcomes were determined by an independent CEC as well as adjudication of events by independent core laboratories (both angiographic and duplex ultrasonographic), which provides a scientific basis for the efficacy and outcome of DA in one of the largest prospective registries in the lower limb to date.

The overall trial results have already been published,²⁵ and the outcomes demonstrated that DA was safe for the treatment of either claudicants or patients with

CLI out to the endpoint of 12 months. However, several questions remain regarding the acute safety and results. Therefore, we report herein the specific outcomes with regard to acute and periprocedural outcomes to 30 days. These outcomes of this heterogeneous group of patients enrolled support the early positive findings seen elsewhere.^{19,20,24,26} However, these results were the first to be reported with independent core lab and clinical events committee adjudication not seen in prior single-center and multicenter registries. Additionally, despite having more adjunctive therapy in the longer-lesion subset and less in the shorter-lesion subset, there was no difference in acute complications or 30-day outcomes. The overall procedure time was longer for the CLI group, as could be expected with the multilevel nature of PAD in this patient population, but did not differ in fluoroscopy time or iodinated contrast dose. Unsurprisingly, more than 2 lesions and multilevel disease were independent predictors of longer procedure times. Furthermore, calcified lesions resulted in longer procedure times, although the use of DEP in these patients did not affect the 30-day outcome. The embolic events were very low at 3.8% overall. No significant difference in the rate of distal embolization by use of DEP was noted. However, the study was not powered to detect such differences and the use of DEP with more complex lesions, which tend toward greater rates of

embolization, makes direct comparisons difficult. Within the group of subjects treated without DEP, the embolic event rates were not statistically different between patients treated with TurboHawk or SilverHawk devices (4/150 [2.7%] vs 18/472 [3.8%]; $P=NS$). Within the group of subjects treated with DEP, the embolic event rates were 4.0% (4/99 subjects treated with TurboHawk) and 5.1% (4/78 subjects treated with SilverHawk; $P=NS$). While no statistical differences can be detected, the embolic rates were slightly lower in subjects treated with TurboHawk than in SilverHawk models despite the treatment of more complex lesions. This event rate, which is lower than those reported elsewhere,^{21,26,27} and importantly, independently reported by the angiographic core laboratory, is acceptable for this device when compared with other devices used in the infrainguinal arteries. Perforation rate for this study was 5.3%, and all events were associated with wire passage, DA use, or adjunctive therapy to include PTA and/or stenting. We did not delineate the complication from one device to another in the process of the procedure because completion arteriography may not have been performed after each step. Therefore, the event was adjudicated as an event regardless of primary cause. Effective debulking to $\leq 30\%$ diameter stenosis using DA alone was achieved in 74.9% of all procedures and in 89.0% of patients requiring adjunctive therapy. Average post-DA diameter stenosis was 24.3% and 18.7% following adjunctive therapy. The need for predilation to facilitate the passage and use of an atherectomy device occurred in 9% of lesions. This was noted in subjects with longer and more calcified lesions at baseline. Our findings suggest that optimal debulking in a challenging lower-limb location of the infrainguinal segments can be achieved using DA and that this method of revascularization is a viable alternative to PTA and stent approaches, with excellent safety and 30-day results for the treatment of patients with PAD.

STUDY LIMITATIONS

There are several key limitations to this trial and report. First, this study is a non-randomized registry. However, given that this protocol was not driven for device approval and more toward the scientific pursuit of the objective outcomes from therapy, it becomes noteworthy and makes this trial unique to other registries. Also, this report only details the events to 30 days. Furthermore, any complications that may occur after 30 days are not captured here. However, it should be noted that no further anatomic complications (aneurysm, etc) were reported in the final 12-month report. Lastly, these data and acute outcomes should not be extrapolated to other FDA-approved or pending approval atherectomy or atheroablative devices. Any potential inference should be performed in a direct fashion with direct comparator trials.

CONCLUSION

In summary, the findings of the DEFINITIVE LE registry establish the periprocedural and acute safety of the SilverHawk and TurboHawk systems for DA. As the primary outcome from DEFINITIVE LE provided evidence of a primary patency similar to other trials of stenting and drug-coated balloons, DA may provide an additional primary strategy for PAD without implantable scaffolds in this challenging anatomic territory.

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Figure 3. Before: pre-pedal loop angiography.

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flow to the limb as evidenced by restoration of a palpable distal pulse. Surgical bypass should be considered to accomplish this result in those patients with significant tissue loss or in need of plastic surgical flap reconstruction for the soft tissue defect. Intravascular ultrasound routinely



Figure 4. After: post-pedal loop angiography.

demonstrates that arterial disease associated with CLI often extends along the entire length of the tibial artery segments and may be underestimated by angiography. Patients with larger wounds (> 2 cm at the largest transverse diameter) may have better healing rates with open surgical bypass, while smaller wounds or ulceration may heal equally well with both endovascular therapy or bypass.

Arterial anatomy may be a factor as well, with differentiation of the femoral-popliteal and tibial artery segments. Common femoral artery disease is best treated with open techniques especially

if the femoral bifurcation including the profunda femoris artery is involved. In the femoral-popliteal segment, TASC A, B, and C lesions may be appropriate for endovascular therapy realizing that this level of arterial disease rarely results in CLI without additional multilevel involvement. TASC D, or long occlusive lesions in the femoral-popliteal segment, may be better served with surgical bypass although endovascular advances including drug-elution technology may impact this conclusion. In terms of tibial artery disease, the evidence remains unclear. However, if endovascular therapy is chosen for tibial occlusive disease, in-line flow to the foot should be the goal with assessment of the increase in foot perfusion post-procedure. Pedal arch revascularization and retrograde pedal access have certainly expanded the scope of endovascular procedures that can be offered to the patient with CLI. The medium- and long-term outcomes associated with these advanced endovascular approaches remain an important area of investigation.

The choice of revascularization may also be impacted by the angiosome concept. There are six distinct angiosomes in the lower leg and foot. Revascularization of the appropriate angiosome in which the wound is primarily located has been shown to enhance healing.³ All else being equal, the modality that best establishes

perfusion into the artery feeding the wound's angiosome can be considered in the decision-making process to result in rapid and complete healing. However, not at the expense of other factors which may be important and should certainly be considered in concert with revascularization of the appropriate angiosome. Surgical bypass should be considered after failed endovascular therapy on a timely basis. Multiple failed endovascular interventions can decrease the chance of a successful bypass. ■

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these key patient characteristics makes it impossible to reliably determine if patient outcomes are changing with time or whether treatment of increasingly complex cases may be influencing these results.

Overall, it is unclear whether infrapopliteal PTA outcomes are improving with time. If outcomes are improving with time, it is not obvious and likely complicated by study- and patient-specific factors that vary considerably from study to study. However, it is clear that clinical studies of infrapopliteal PTA in

CLI patients should improve transparency and consistency in data reporting in order to facilitate more robust data analysis efforts that could answer this important question. ■

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“How should one interpret these findings? At first glance, it appears that infrapopliteal PTA outcomes are not improving with time.”



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