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Primary Cryoplasty Therapy Provides Durable Support for Limb Salvage in Critical Limb Ischemia Patients With Infrapopliteal Lesions: 12-month Follow-up Results From the BTK Chill Trial

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Purpose: To report the 12-month follow-up data from the prospective 16-center Below-the-Knee (BTK) Chill Trial, which examined the use of primary cryoplasty for BTK occlusive disease in patients with critical limb ischemia (CLI).

Methods: The trial included 108 patients (77 men; mean age 73±11 years, range 41–101) with CLI (Rutherford categories 4–6) involving 111 limbs with 115 target infrapopliteal lesions. Angiographic inclusion criteria were reference vessel diameter ≥2.5 mm and ≤5.0 mm and target lesion stenosis ≥50%. The primary study endpoints were acute technical success (the ability to achieve ≤50% residual stenosis and continuous inline flow to the foot) and absence of major amputation of the target limb at 6 months. Secondary endpoints were serious adverse events specifically related to use of primary cryoplasty and absence of major amputation of the target limb at 1, 3, and 12 months.

Results: Acute technical success was achieved in 108 (97.3%) of treated limbs, with only 1 clinically significant dissection (≥type C) and 2 residual stenoses >50%; stent placement was required following cryoplasty in only 3 (2.7%) procedures. At 6 months and 1 year, major amputation was avoided in 93.4% (85/91) and 85.2% (69/81) of patients, respectively. Through 1 year, 21% (17/81) of patients underwent target limb revascularization. Rates of major amputation and death at 1 year were 0% for limbs of patients with initial Rutherford category 4; 11.4% and 0%, respectively, for initial category 5; and 40.0% and 31.8% for initial category 6. One-year rates of major amputation and death were 20.4% and 8.8%,

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respectively, for diabetics, versus 4.0% and 10.7% for non-diabetics. At 1 year, major amputation occurred in 16.7% (2/12) of limbs that were expected to be amputated at the time of treatment.

Conclusion: Cryoplasty therapy is a safe and effective method of treating infrapopliteal disease, providing excellent results and a high rate of limb salvage in patients with CLI. Study outcomes through 1 year support the use of cryoplasty as a primary treatment option for patients with CLI secondary to BTK occlusive disease.

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Endovascular intervention is being employed with increasing frequency as a first-line treatment for preventing or delaying amputation in patients with critical limb ischemia (CLI).[1–5] Cryoplasty therapy (cold balloon angioplasty) has been used as an effective primary strategy for limiting the incidence of dissection, vessel recoil, and subsequent intimal hyperplasia and restenosis associated with the endovascular dilation of atherosclerotic lesions in the peripheral vasculature.[6–9] Specialized cryoplasty balloon catheters, approved by the US Food and Drug Administration, are inflated not with the standard mixture of saline solution and contrast medium but rather with nitrous oxide, which causes the plaque in the artery to freeze. Previous scientific studies have shown that this process results in: (1) weakening of the plaque, promoting uniform dilation and reducing vessel trauma; (2) alteration of elastin fibers to reduce vessel wall recoil, while collagen fibers remain unperturbed and capable of maintaining architectural integrity[10,11]; and (3) induction of smooth muscle cell apoptosis, which is associated with reduced neointima formation and subsequent restenosis.[12] In the primary treatment of patients with claudication and femoropopliteal disease, cryoplasty therapy has yielded excellent periprocedural results, with a low rate of dissection and a reduced need for bailout stenting. Clinical patency rates (freedom from target lesion revascularization) of 82.2% through 9 months and 75.0% through 3.4 years have been reported.[8,9]

In the prospective, multicenter Below-the-Knee (BTK) Chill Trial, primary cryoplasty treatment of BTK occlusive disease in CLI patients yielded favorable technical success: residual stenosis $\leq$50% and continuous flow to the foot were achieved in 108 (97.3%) of treated limbs, with only 1 clinically significant dissection ($\geq$type C) and 2 residual stenoses $>$50%.[6] Bailout stenting was needed in only 2.7% of procedures.[6] Of 91 limbs available for follow-up at 6 months, major amputation was avoided in 85 (93.4%). To better assess the long-term impact of cryoplasty therapy for this seriously ill population, the trial was designed to track adverse events and limb status through 1 year, with attention to high-risk subgroups. Notably, in the BTK Chill trial, over two thirds of the patients were diabetic, representing a subset particularly liable to amputation within 1 year of being diagnosed.[13,14]

METHODS

Study Design and Patient Population

The study design and patient population have been reported and described.[6] Between August 2004 and October 2005, 108 patients (77 men; mean age 73$\pm$11 years, range 41–101) with CLI (Rutherford categories 4–6) involving 111 limbs with 115 target infrapopliteal lesions were enrolled at 16 US institutions. Patients with a diagnosis of CLI (rest pain, non-healing ulcers, or gangrene) based on objective clinical assessments were considered eligible for the study if they had de novo or restenotic stenoses or occlusions in the infrapopliteal arteries amenable to minimally invasive treatment. Angiographic inclusion criteria were a target stenosis of $\geq$50% and reference vessel diameter of $\geq$2.5 and $<$5 mm. Patients were excluded from the study if they had comorbidities that reduced their life expectancy to $<$1 year, myocardial

infarction (MI) with a CK-MB >3 times normal within the previous 48 hours, evolving MI, stroke or transient ischemic attack within the previous 2 months, or serum creatinine levels ≥2.5 mg/dL within 24 hours prior to the procedure. Angiographic exclusion criteria included heavily calcified lesions and an inability to advance a guidewire through the stenosis or occlusion.

The study protocol required follow-up at 1, 3, 6, and 12 months after the index procedure. The primary study endpoints were acute technical success (the ability to cross and dilate the lesion, achieve ≤50% residual angiographic stenosis by visual estimate, and establish continuous inline flow to the foot) and absence of major amputation of the target limb at 6 months. Secondary endpoints were serious adverse events specifically related to use of primary cryoplasty and absence of major amputation of the target limb at 1, 6, and 12 months after the index procedure.

Cryoplasty Procedure

Each patient underwent a baseline clinical examination within 30 days before the intervention, including ankle-brachial index (ABI) measurement. Patients received 325 mg of aspirin on the day of the procedure, and they received clopidogrel either in 75-mg doses for 4 days prior to and then on the day of the intervention or as a 450-mg bolus right before the procedure. Standard diagnostic angiography of the target vessels was performed to confirm the presence of lesions suitable for endovascular therapy, and consenting patients were subsequently enrolled.

All inflow and outflow lesions in the affected limb requiring treatment at the time of intervention were addressed during the index procedure. For all lesions other than the target lesion(s), any commercially available treatment was allowed. Adjunctive predilation and/or debulking of the target lesion were performed at physician discretion. Stenting was permitted as a bailout measure to resolve dissection or significant residual stenosis.

Following identification of the target lesion(s), the PolarCath Peripheral Dilatation System (Boston Scientific, Natick, MA, USA) was prepared according to the instructions for use. The PolarCath cryoplasty system consists of 3 components: the cryoplasty catheter, a microprocessor-based inflation unit, and a cartridge containing the inflation medium (nitrous oxide). Using conventional transluminal percutaneous procedures, the PolarCath catheter is introduced through a 6-F sheath over a 0.014-inch guidewire and positioned at the target lesion. The catheter is then connected to the PolarCath inflation unit, and a nitrous oxide cartridge is inserted. The physician initiates treatment by activating a button on the inflation unit, which causes pressurized liquid nitrous oxide to be delivered into the balloon via an inlet tube integrated into the guidewire lumen. As it enters the balloon, the liquid nitrous oxide rapidly undergoes phase change to a gas. This endothermic reaction draws energy and decreases the temperature inside the balloon while simultaneously dilating the balloon. The system is designed to provide a dilation force of 8 atmospheres and an outer balloon surface temperature of −10°C. The automated 20-second treatment cycle is followed by a passive warming cycle. Subsequently, the balloon is manually deflated and either removed or repositioned. Study target lesions were treated with single or multiple inflations of the PolarCath catheter.

ABI measurements were performed after the procedure and prior to hospital discharge. Patients received aspirin (325 mg/d) and clopidogrel (75 mg/d) indefinitely after the index procedure or according to the accepted standard of care for the institution or investigator. At 1, 3, 6, and 12 months after intervention, the patients were required to return for clinical examination, including assessment of wounds and ABI measurements of both the dorsalis pedis and posterior tibial arteries.

Statistical Analysis

All primary and secondary endpoint data were analyzed on an intent-to-treat basis. Quantitative baseline, procedural, and follow-up data are expressed as counts (percentages) for categorical variables and means ± stan-

dard deviations for continuous variables. Adverse events are presented as cumulative data at 1, 3, 6, and 12 months.

RESULTS

The baseline risk factors, comorbidities, and lesion characteristics were those typical of patients suffering from CLI (Table 1). Nearly 70% of the patients were diabetics, and there were high rates of hypertension, hyperlipidemia, and coronary artery disease. More than two thirds of the patients were categorized with Rutherford category 5/6 ischemia, with tissue loss (nonhealing ulcers and/or gangrene) noted in the majority of target limbs. Most patients reported multiple lower extremity symptoms. The mean diameter stenosis was 86.9%; a third (33.9%) of the lesions were occlusions with a mean length of 57.7±29.7 mm. In 76 (68.5%) of the 111 treated limbs, there were multiple additional lesions identified; in relation to 40 (36.0%) of the treated BTK lesions, there were proximal lesions (iliac, common femoral, superficial femoral, and/or proximal popliteal arteries) as well.

Outcomes through 6 months after cryoplasty have been reported.[6] Briefly, acute technical success was achieved in 108 (97.3%) of 111 study procedures. Mean target lesion percent diameter stenosis was reduced from 86.9%±13.6% at baseline to 15.5%±16.9% after cryoplasty, and stent placement was performed following cryoplasty in 2.7% of procedures. Procedural success was high for both stenotic (98.7%) and occlusive (95.1%) lesions. There was no vessel perforation, embolization, or major bleeding in any of the study procedures.

Through 1 year of follow-up, 21 of the initial 108 patients had withdrawn or become lost to follow-up (representing 22 of the initial 111 limbs), and 8 (9.2%) patients (8 treated limbs) had died, leaving 79 (73.1%) patients [81 (73.0%) of the treated limbs] available for assessment (Table 2). The event rate for amputation (Table 2) was 6.6% (6/91) at 6 months and 14.8% (12/81) at 1 year; by Kaplan-Meier analysis, the rate of survival free from major amputation was 89.0% at 6 months and 78.5% at 1 year (Figure). Of the 19 limbs for which records indicated that amputation was expected at baseline, major amputation was avoided in 100% of those available for follow-up at 30 days, in 93.3% at 3 months, in 92.3% at 6 months, and in 83.3% at 1 year; amputation of any nature (major or minor) was avoided in 94.7% at 1 month, in 80.0% at 3 months, in 69.2% at 6 months, and in 50.0% at 1 year. Mortality in patients in whom amputation was expected was 18.8% (3/16) at 6 months and 25.0% (4/16) at 1 year.

TABLE 1
Demographics, Risk Factors, and Clinical and Lesion Characteristics for 108 Patients with 115 Below-the-Knee Lesions in 111 Limbs

Age, y	73±11 (41–101)
Men	77 (71.3%)
Risk factors (per patient)	
Diabetics, all	71 (67.6%)
Diabetics, insulin dependent	47 (44.3%)
Hypertension	89 (84.0%)
Hyperlipidemia	74 (71.8%)
Smoker, current	10 (10.0%)
Smoker, past	73 (72.3%)
Coronary artery disease	75 (70.1%)
Obesity	22 (20.6%)
Symptoms	
Rest pain	71/108 (65.7%)
Nonhealing ulcers	73/110 (66.4%)
Gangrene	28/76 (36.8%)
Claudication	76/108 (70.4%)
Anticipated amputation	19/77 (24.7%)
Skin discoloration	84/110 (76.4%)
Sensory deficit	68/108 (63.0%)
Edema	47/110 (42.7%)
Clinical categories (Rutherford)	
Class 4	22/111 (19.8%)
Class 5	49/111 (44.1%)
Class 6	28/111 (25.2%)
Class unknown	12/111 (10.8%)
Lesion characteristics	
Mean vessel diameter, mm	3.2±0.7 (2.0–6.0)
Mean stenosis, %	86.9±13.6 (50–100)
Mean lesion length, mm	41.1±30.4 (2.0–110.0)
Occlusions	39 (33.9%)
Location	
Anterior tibial	35 (28.5%)
Peroneal	33 (26.8%)
Posterior tibial	23 (18.7%)
Popliteal	19 (15.4%)
Tibioperoneal trunk	11 (8.9%)
Dorsalis pedis	1 (0.8%)
Other	1 (0.8%)

Continuous data are presented as means ± standard deviation (range); categorical data are given as counts (percentages).

TABLE 2
Cumulative Clinical Outcomes for 108 Patients With 111 Treated Limbs

	1 Month	3 Months	6 Months	12 Months
Death	0/104 (0.0%)	2/95 (2.1%)	5/93 (5.4%)	8/87 (9.2%)
Major amputation overall*	3/107 (2.8%)	4/96 (4.2%)	6/91 (6.6%)	12/81 (14.8%)
Minor amputation overall†	1/107 (0.9%)	4/96 (4.2%)	5/91 (5.5%)	7/81 (8.6%)
In 19 limbs with planned amputation at baseline				
Major amputation	0/19 (0.0%)	1/15 (6.7%)	1/13 (7.7%)	2/12 (16.7%)
Minor amputation	1/19 (5.3%)	2/15 (13.3%)	3/13 (23.1%)	4/12 (33.3%)
Target limb revascularization				
Endovascular	1/107 (0.9%)	3/96 (3.1%)	12/91 (13.2%)	13/81 (16.0%)
Surgical bypass	2/107 (1.9%)	2/96 (2.1%)	2/91 (2.2%)	4/81 (4.9%)
Rehospitalization and other‡	6/108 (5.6%)	9/96 (9.4%)	15/91 (16.5%)	23/81 (28.4%)

* Transfemoral (above knee) or transtibial (below knee).
† Transmetatarsal or digital.
‡ Among the 81 limbs followed at 1 year, only 2 of the 23 rehospitalizations or other adverse events were deemed possibly related to the study device (1 thrombosis, 1 pain and discoloration in toes).

Through 1 year of follow-up, 17 (21.0%) of 81 target limbs available for assessment had undergone revascularization: surgical in 4 (4.9%) limbs and percutaneous in 13 (16.0%) limbs. There were 23 instances of rehospitalization or other adverse events in patients available for follow-up through 1 year, but only 2 of these were considered possibly related to the study device (1 thrombosis and a patient who experienced pain and discoloration in toes subsequent to a change in medication regimen, which primarily resolved within ~1 week). These adverse events included individual cases of skin graft, groin hematoma, contralateral limb interventions, coronary artery bypass, and debridement of ulcers.

While procedural outcomes did not differ significantly according to the baseline Rutherford categories of the patients, rates of death and major amputation through 1 year were higher for those classified as category 6 (extensive ischemic lesions that could require major amputation if not cleared): 7 of the 8 deaths reported overall and 6 (50%) of the 12 major amputations reported overall occurred in this group (Table 3). Four of the major amputations occurred in patients who were classified at baseline as Rutherford category 5 (limited ischemic lesions that might require minor amputation if not cleared). The baseline Rutherford category was not known for the patients who underwent the other 2 major amputations.

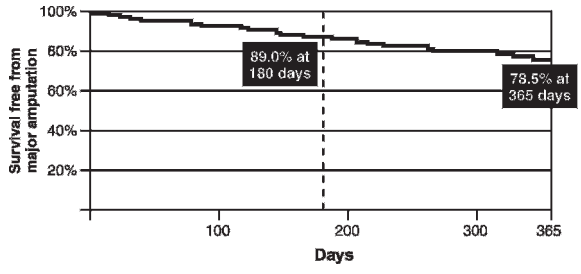

Figure ◆ Survival free from major amputation at 180 and 365 days by Kaplan-Meier analysis.

The data through 1 year of follow-up were also stratified according to baseline diabetes and smoking status of the patients (Table 4). At baseline, 71 patients with 73 treated limbs were known to be diabetics, while 34 patients with 35 treated limbs were registered as non-diabetic (3 subjects did not report diabetes status). Among patients available for follow-up, rates of major amputation and death at 1 year were 20.4% and 8.8%, respectively, for diabetics versus 4.0% and 10.7%, respectively, for non-diabetics. At baseline, 73 patients with 76 treated limbs were known to have a history of smoking (7 subjects did not report history of tobacco use). Among patients available for follow-up, rates of major amputation and death at 1 year were 13.2% and 10.5%, respectively, for smokers versus 13.0% and 4.2%, respectively, for the 28 nonsmokers.

TABLE 3
Cumulative Clinical Outcomes by Baseline Rutherford Category for 108 Patients With 111 Treated Limbs

	Unknown	Category 4	Category 5	Category 6
Technical success*	12/12 (100%)	21/22 (95.5%)	48/49 (98.0%)	27/28 (96.4%)
Death				
1 mo	0/12 (0.0%)	0/22 (0.0%)	0/44 (0.0%)	0/27 (0.0%)
3 mo	0/12 (0.0%)	0/21 (0.0%)	0/40 (0.0%)	2/23 (8.7%)
6 mo	0/12 (0.0%)	0/21 (0.0%)	0/38 (0.0%)	5/23 (21.7%)
12 mo	1/12 (8.3%)	0/21 (0.0%)	0/34 (0.0%)	7/22 (31.8%)
Major amputation†				
1 mo	0/12 (0.0%)	0/22 (0.0%)	2/47 (4.3%)	1/27 (3.7%)
3 mo	0/12 (0.0%)	0/21 (0.0%)	2/42 (4.8%)	2/21 (9.5%)
6 mo	1/12 (8.3%)	0/21 (0.0%)	2/40 (5.0%)	3/18 (16.7%)
12 mo	2/11 (18.2%)	0/21 (0.0%)	4/35 (11.4%)	6/15 (40.0%)

* Per limb; acute technical success was the ability to cross and dilate the lesion, achieve ≤50% residual angiographic stenosis by visual estimate, and establish continuous inline flow to the foot.
† Per limb; transfemoral (above knee) or transtibial (below knee).

For lesions classified at baseline as stenoses (angiographic stenosis <100%) and available for follow-up at 1 year, the rates of major amputation and death were 14.0% and 7.5%, respectively, while for lesions classified as occlusions, the respective rates were 19.4% and 12.1%.

DISCUSSION

According to the 2000 report of the TransAtlantic Inter-Society Consensus (TASC I),[15] the universally accepted indication for angioplasty of infrapopliteal lesions is limb salvage. This consensus was upheld by the abbreviated

TABLE 4
Cumulative Clinical Outcomes by Baseline Diabetes and Smoking Status for 108 Patients With 111 Treated Limbs

	Diabetics	Nondiabetics	Smokers	Nonsmokers
Patients (limbs) treated*	71 (73)	34 (35)	73 (76)	28 (28)
Technical success†	71/73 (97.3%)	34/35 (97.1%)	76/76 (100.0%)	26/28 (92.9%)
Death				
1 mo	0/71 (0.0%)	0/33 (0.0%)	0/71 (0.0%)	0/26 (0.0%)
3 mo	1/63 (1.6%)	1/30 (3.3%)	2/64 (3.1%)	0/25 (0.0%)
6 mo	3/61 (4.9%)	2/30 (6.7%)	4/62 (6.5%)	1/25 (4.0%)
12 mo	5/57 (8.8%)	3/28 (10.7%)	6/57 (10.5%)	1/24 (4.2%)
Major amputation‡				
1 mo	3/71 (4.2%)	0/34 (0.0%)	1/74 (1.4%)	2/26 (7.7%)
3 mo	4/64 (6.3%)	0/30 (0.0%)	2/65 (3.1%)	2/25 (8.0%)
6 mo	6/60 (10.0%	0/29 (0.0%)	4/61 (6.6%)	2/24 (8.3%)
12 mo	11/54 (20.4%)	1/25 (4.0%)	7/53 (13.2%)	3/23 (13.0%)

* Diabetic status was not reported by 3 patients (3 limbs), and history of tobacco use was not reported by 7 patients (7 limbs).
† Per limb; acute technical success was the ability to cross and dilate the lesion, achieve ≤50% residual angiographic stenosis by visual estimate, and establish continuous inline flow to the foot.
‡ Per limb; transfemoral (above knee) or transtibial (below knee).

2007 TASC II report[16] and by the 2005 practice guidelines of the American College of Cardiology/American Heart Association,[17] which affirm the evolution of endovascular technology as a viable first-line alternative to the traditional choices of bypass surgery or primary amputation in treatment of CLI, as noted by other investigators.[1,3,18–22] Many patients first receive the diagnosis of peripheral artery disease only when they present with symptoms of rest pain, nonhealing ulcers on the foot or lower leg, tissue loss, and/or gangrene. Primary amputation remains a distressingly common initial treatment for CLI (67% of cases in one data analysis), without any attempt at revascularization, and often without any diagnostic vascular evaluation (49% of the primary amputation cases in the same data analysis).[23] Major amputation, often deemed necessary for stemming progression of the disease (in as many as 25% of patients at 1 year[23]), is clearly not a benign procedure, with high subsequent mortality. Furthermore, recovery from major amputation is compromised by the significant comorbidities and advanced cardiovascular disease state of the CLI population.[24–26] All considered, the costs to the health system associated with major amputation are high compared to those for revascularization and limb salvage.[23] While lower extremity bypass surgery has been reasonably effective as a limb salvage strategy, it carries substantial morbidity and mortality risks due to the high-risk disease profiles. Moreover, the procedures are technically challenging and can be compromised by poor-quality or inadequate venous conduits.[27–31]

The evolved rationale for a primary endovascular approach to treatment of infrapopliteal lesions associated with CLI is based on the potential for more rapid and minimally invasive re-establishment of pulsatile blood flow to the foot, an outcome associated with prompt relief of rest pain, facilitated clearing of infection, and speeded wound healing. These benefits of improved blood flow plus good wound care usually result in limb salvage, with amputation either prevented altogether or else limited to below the ankle (toes or transmetatarsals). It is understood that even short-term patency of 3 to 6 months may be sufficient to accomplish these goals. Thus the acknowledged shortcoming of sometimes short-term loss of primary patency following endovascular therapies need not nullify the clinical benefit. Such loss is rarely associated with a degree of ischemia that is worse than before treatment. In contrast, failure of a distal bypass graft can prompt amputation if the surgical wound has not healed or is infected. Repeat/redo surgery is usually more difficult than the initial surgery, whereas repeat endovascular treatments are frequently technically easier than the initial treatment, due either to less severe or extensive restenoses or to easier traversal of reocclusions (because they are shorter or softer). Further, failure of endovascular therapies is usually not associated with vascular bed alterations that make surgical treatment more difficult.[3,20,22]

Conventional balloon angioplasty in infrapopliteal vessels is frequently supported by subintimal recanalization[32–35] and occasionally by bailout stenting (bare metal and, more recently, drug-eluting) in the characteristic instances of flow-limiting dissection, elastic recoil, and postangioplasty residual stenosis $>$30%.[35–37] The concerns related to stent deployment — the potential for in-stent restenosis (apparently less likely with the drug-eluting stents[37,38]), thrombosis, and fracture — are heightened in the infrapopliteal vasculature due to the smaller caliber and increased motion of the vessels and the more diffuse nature of the atherosclerotic disease.[38,39] In addition to cryoplasty, other specialized forms of angioplasty that have been used for infrapopliteal lesions involve the use of the cutting balloon[40] or the excimer laser.[41]

Comparison between series of CLI cases in which angioplasty was employed as a first-line strategy for treating infrapopliteal lesions is difficult because many studies include claudicants (with infrapopliteal lesions) as well as CLI patients; often, the studies feature femoropopliteal as well as infrapopliteal lesions and do not stratify for lesion length or runoff status.[3] Whereas patients with Rutherford category 6 ischemia have been excluded in many studies involving placement of infrapopliteal stents, a

quarter (25.2%) of the patients in our cryoplasty trial had category 6 ischemia and 44.1% had category 5 ischemia. Many studies of infrapopliteal stenting have excluded lesions beyond a minimal length owing to limitations in available stent lengths and the cost of deploying multiple stents. Our trial, however, included lesions ranging up to 11 cm in length (mean 4.11 cm). It is also the case that many studies have not reported on the extent of adjunctive use of subintimal angioplasty or other procedures or on the percentage of cases requiring bailout stent placement.

Among the studies of endovascular treatment for CLI, a high degree of variance has been observed in terms of acute outcomes, with reported procedural success rates ranging from 79% to 98%.[22,35,42,43] In our multicenter trial, cryoplasty was the primary intervention in a patient population with CLI, skewed toward the clinically worst degree of ischemia, and treatable infrapopliteal lesions; claudicants and patients with only above-the-knee lesions were excluded. Nonetheless, we achieved an acute technical success rate of 97%. The rates of dissection (only 1 that was flow-limiting) and unplanned stent placement (only 3 cases) were low. These excellent success rates were achieved despite a high incidence of occlusions and the most advanced clinical ischemia: technical success rates of 94.9% for occlusions, 98.0% in the Rutherford category 5 subset, and 96.4% in the Rutherford category 6 subset.

Infrapopliteal angioplasty may result in major complications, such as puncture site hematomas and acute arterial occlusions, previously reported in 2% to 17% of cases.[3,15,16,20] In our primary cryoplasty series, only the 1 (subacute) complication was noted: the reocclusion of the target lesion within 24 hours of the index procedure that eventuated in surgical bypass.

The TASC I report noted 2-year rates of limb salvage after infrapopliteal angioplasty ranging between 60% and 86%, depending on anatomical factors such as distal runoff status.[15] In a random-effects meta-regression analysis of 18 studies involving 1280 cases of infrapopliteal angioplasty (14% for claudication, 86% for CLI) between 1984 and 1997, the 1- and 2-year rates of limb salvage were 79% and 74%, respectively.[44] Six-month data from the Bypass versus Angioplasty in Severe Ischemia of the Leg (BASIL) study, which randomized 452 patients with severe leg ischemia to either a surgery-first or an angioplasty-first strategy, demonstrated broadly similar outcomes in terms of amputation-free survival, with death or amputation occurring for 50 of 228 surgery-arm patients and 46 of 224 angioplasty-arm patients (50% of the angioplasties were subintimal; the superficial femoral artery was treated in 80% of the angioplasties and more distal vessels in 62%).[45] In a population of 314 seriously impaired CLI patients who were deemed unsuitable for open surgery and underwent either primary amputation or angioplasty [31.8% (47/148) of procedures on aortoiliac vessels and 68.2% (101/148) on infrainguinal vessels] with optional bailout stenting, angioplasty (along with appropriate wound and foot care) was associated with a 63% 12-month limb salvage rate (by Kaplan-Meier life-table analysis), although the investigators noted that the benefit derived from angioplasty in terms of maintenance of ambulation lasted only 12 months.[46] With primary use of cryoplasty for infrapopliteal lesions in the BTK Chill trial, major amputation was avoided for 85.2% through 1 year. By Kaplan-Meier analysis, the 1-year rate of survival free from major amputation was 78.5%.

Major amputation had been anticipated in 19 known cases at baseline (90% of those limbs were Rutherford category 6) but was averted with primary cryoplasty treatment in 83.3% at 1 year; the 1-year survival rate in those patients was 75.0%. Regardless of whether amputation had been anticipated, primary cryoplasty was effective overall in avoiding major amputation and death in the most seriously ill patients with the most severe atherosclerosis.

People with diabetes mellitus are at particularly high risk of developing CLI,[14,47] and their prognosis is considerably worse.[48] According to the TASC II report, the need for a major amputation is 5 to 10 times higher for diabetics versus non-diabetics.[16] Whereas current smoking is closely related to proximal peripheral artery disease, diabetes affects the arterial tree in a centrifugal pattern, predisposing to infra-

genicular atherosclerotic disease.[49,50] The spread of atherosclerosis is accelerated in diabetics, with faster progression of intimal hyperplasia at anastomoses or angioplasty sites.[16,48] In our trial of primary cryoplasty for treatment of infrapopliteal disease, more than two thirds of the CLI patients were diabetics. The 1-year rate of limb salvage was 79.6% for diabetics versus 96.0% for non-diabetics; the survival rates were comparable: 91.2% for diabetics versus 89.3% for non-diabetics. Target limb revascularization occurred in 20.4% (11/54; 8 percutaneous and 3 surgical) of diabetics and in 24.0% (6/25; 5 percutaneous and 1 surgical) of non-diabetics available for 1-year follow-up.

The positive outcomes reported with primary use of the PolarCath device in this prospective study may be attributed to the unique combination of effects that cryoplasty exerts on the vessel wall, which differentiate this therapy from other conventional endovascular revascularization methods. By inducing phase change in the tissue during dilation, cryoplasty generates thermal stresses that lead to a weakening of the plaque,[51] while ice formation in interstitial fluids can lead to fragmentation of elastin fibers and uncoiling of elastic layers. Dissections during conventional angioplasty tend to be due to the differences in elastic properties in regions where plaque abuts adjacent normal arterial tissue.[52] Taking advantage of the known propensity of freezing to alter the mechanical properties of both normal and abnormal tissue,[53] cryoplasty promotes a more uniform response to dilation with less barotrauma. The consequent reduction in vessel trauma, flow-limiting dissection, and postdilation elastic recoil can mean less need for bailout stent placement, as seen in the current trial.

Restenosis may also be inhibited by cryoplasty due to the induction of apoptosis in arterial smooth muscle cells (facilitated by the cooling algorithm of the PolarCath device), which may inhibit neointima formation.[12] Taking the rate of target limb revascularization (only 21.0% at 1 year) as an indicator of restenosis, this trial of primary cryoplasty for infrapopliteal lesions would seem to bear out that advantage.

Conclusion

Clinical trials have now demonstrated the mid- to long-term safety and efficacy of primary cryoplasty in the treatment of both femoropopliteal and infrapopliteal arterial disease. Cryoplasty therapy has been shown to safely dilate stenotic and occluded lesions, with excellent acute success characterized by low rates of dissection and bailout stenting. Through 1 year of follow-up in the current trial involving CLI patients with infrapopliteal lesions and primarily Rutherford category 5/6 ischemia, cryoplasty provided durable outcomes, delaying the need for revascularization and supporting limb salvage and survival. Cryoplasty is readily performed in conjunction with other minimally invasive percutaneous methods and does not preclude additional treatment, including bypass surgery. The 1-year data from this trial support the use of cryoplasty in patients with CLI as a primary treatment strategy for restoring blood flow and promoting healing while avoiding or minimizing amputation. More extended follow-up will be important for further evaluating the durability of the outcomes with cryoplasty in the infrapopliteal region, particularly for the high-risk diabetic patients who comprised over two thirds of this population. Randomized trials including cryoplasty will also be important for developing our comparative understanding of the outcomes with various interventional treatment strategies in the management of CLI.

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