

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Spectranetics Corporation
2 September 2003

LASER ANGIOPLASTY FOR CRITICAL LIMB ISCHEMIA **LACI**

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 draft 27 August 2003

LASER ANGIOPLASTY FOR CRITICAL LIMB ISCHEMIA - LACI

I. General Information

Device Generic Name:	Laser Catheter
Device Trade Names:	Vitesse Catheters Models 110-003, 114-009, 117-016, 120-009
	Vitesse E Catheter Model 120-008
	Extreme Catheters Models 110-001, 110-002, 114-001, 220-001, 222-005, 225-004
	Extreme II Catheters Models 220-006, 223-001, and 225-010
Applicant's Name and Address:	Spectranetics Corporation 96 Talamine Court Colorado Springs, Colorado 8097
PMA Application Number:	PMA P910001 / Supplement 022

II. Intended Use/Indications

Facilitation of limb salvage in patients with critical limb ischemia (associated with Rutherford Categories 4, 5 and 6) who have angiographically evident culprit stenoses and/or occlusions in the SFA, popliteal and/or infrapopliteal arteries, who are poor surgical candidates, and who are acceptable candidates for revascularization.

III. Device Description

Spectranetics Excimer Laser Atherectomy (ELA) catheters consist of a bundle of optical fibers, arranged around a guidewire lumen. Two (2) basic types of ELA catheters have been evaluated regarding Laser Angioplasty for Critical Limb Ischemia (LACI): Extreme[®] brand catheters are over-the-wire (OTW) models; Vitesse[®] brand catheters are rapid exchange (Rx) models. All models consist of a proximal length, which couples exclusively with the Spectranetics CVX 300 Excimer Laser, and a distal portion having direct patient contact. In Extreme models, a bifurcation at the juncture of the proximal

and distal catheter portions permits insertion of an appropriately sized guidewire (between 0.014" and 0.035" diameter) through the lumen of the catheter. In Vitesse models, the guidewire lumen begins 9 cm from the distal tip, to facilitate speedier removal of the laser catheter.

Within the Extreme catheter family, the Extreme catheter models are OTW devices originally designed for coronary applications. The Extreme II catheter models comprise larger-diameter OTW devices (from 2.0 mm to 2.5 mm diameter) with increased pushability requested by physicians for use in the legs. All catheters in the Extreme family have a fiber bundle that is concentrically and symmetrically disposed around the guidewire lumen at the distal tip.

Within the Vitesse catheter family, all models are rapid exchange, but models with specific features can be distinguished. Catheters with the simple name "Vitesse" have a fiber bundle that is concentrically and symmetrically disposed around the guidewire lumen at the distal tip. The Vitesse-E model has an eccentrically arranged fiber bundle at the distal tip; the guidewire exits the distal tip in an off-center position. Vitesse E models are equipped with a torque wire extending through the distal portion of the catheter. A torque handle controls rotation of the distal catheter tip through a full 360° arc, around the eccentrically positioned guidewire lumen.

All ELA catheters conduct pulsed 308 nm laser light, from the CVX 300 laser source to the atherosclerotic lesion within an artery. The ultraviolet pulses ablate and debulk the lesion as the catheter tip is slowly advanced through the blockage, without thermal damage to surrounding tissues. Thus, ELA has the ability to traverse long complex vascular lesions, transforming them into treated arteries more amenable to further intervention.

IV. Contraindications, Warnings, and Precautions

Contraindications:

?? No known contraindications

Warnings:

Spectranetics Excimer Laser Catheters require CVX-300® software version 3.7 or higher.

When the laser catheter is in the body, it should be manipulated only while it is under fluoroscopic observation with radiographic equipment that provides high quality images.

The use of the CVX-300[®] Excimer Laser System is restricted to physicians who are trained in angioplasty, Percutaneous Transluminal Angioplasty (PTA) and who meet the training requirements listed below. These requirements include, but are not limited to:

1. Training of laser safety and physics.
2. Review of patient films of lesions that meet the indications for use.
3. A review of cases demonstrating the CLiRpath technique in lesions that meet the indications for use.
4. A review of laser operation followed by a demonstration of the CVX-300[®] Excimer Laser System.
5. Hands on training with the CVX-300[®] Excimer Laser System and appropriate model.
6. A fully trained Spectranetics representative will be present to assist for a minimum of the first three cases.
7. Following the formal training session, Spectranetics will make available additional training if so requested by the physician, support personnel, the institution or Spectranetics.

Precautions:

This catheter has been sterilized using Ethylene Oxide and is supplied STERILE. The device is designated and intended for **SINGLE USE ONLY** and must not be resterilized and/or reused.

Store in a cool, dry place. Protect from direct sunlight and high temperatures (*greater than 60°C or 140°F*).

The sterility of the product is guaranteed only if the package is unopened and undamaged. Prior to use, visually inspect the sterile package to ensure that the seals have not been broken. Do not use the catheter if the integrity of the package has been compromised. Do not use catheter product if its "Use Before Date," found on package labeling, has been passed.

Before use, examine carefully all of the equipment to be used in the procedure for defects. Do not use any equipment if it is damaged.

After use, dispose of all equipment in accordance with applicable specific requirements relating to hospital waste, and potentially biohazardous materials.

Read the Operator's Manual (7030-0035 or 7030-0068) thoroughly before operating the Excimer Laser System. Pay particular attention to the Warnings and Responsibility section of the manual which explains Notes, Cautions, and Warnings to be followed to ensure safe operation of the CVX-300®.

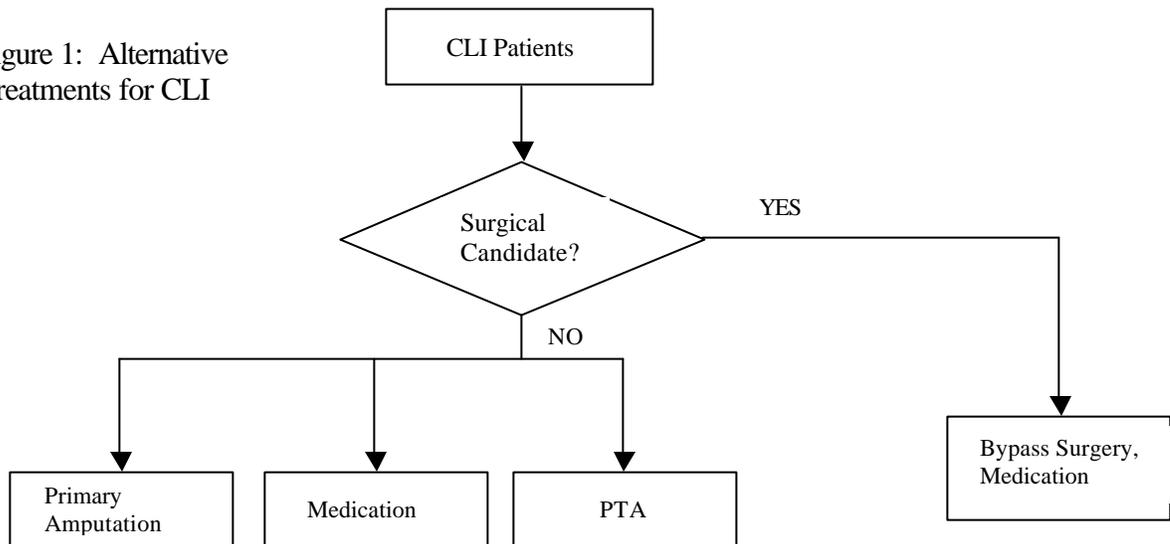
During the procedure, appropriate anticoagulant and vasodilator therapy must be provided to the patient per the institution's PTA protocol.

V. Alternative Practices and Procedures

Unrelieved Critical Limb Ischemia (CLI) most often leads to amputation. Up to 500,000 individuals suffer from CLI, with approximately 80,000 amputations performed annually in the United States (1). Surgical bypass presents doctors and patients with an alternative, which is more successful when autologous vein grafts are used than when synthetic grafts are used (2-5). However, for the large portion of the CLI patient population that presents with multiple profound comorbid conditions, the option of surgical intervention carries an unacceptable risk. Renal dysfunction, advanced cardiac disease, and a lack of veins suitable as bypass grafts may all contribute to a patient's lack of surgical candidacy. What are the treatment plan options for these CLI patients presenting in ASA Class 4 or higher?

Reviewing literature data on CLI patients, one can see that there have been three (3) options historically available to poor surgical candidates with complex CLI. LACI does not appear as a historical option. Treatment options appear as parallel pathways in Figure 1.

Figure 1: Alternative Treatments for CLI



Considering each of the three (3) alternatives to LACI, for non-surgical candidates:

Primary amputation, among ASA class 4 and higher patients, not only results in a reduced perceived quality of life (6), the literature also reports longer hospital stays of about 3 weeks for amputees (7, 8, 9) compared to 2.6 days for LACI patients. Perioperative deaths were as high as 11% (8) among amputees, whereas LACI intervention resulted in no perioperative deaths. Reintervention risk was 19% for amputees (7, 8), including conversions from below-the-knee to above-the-knee surgeries, compared to 15% for LACI, and up to 11% of the amputations resulted in non-healing wounds (8).

Medication for CLI, referred to as “conservative” treatment, has reportedly resulted in rates for major amputation and death equal to between 37% and 38% (10, 11), and 8% to 42% (10, 11, 12) respectively. These rates for LACI were only 14% and 6%, respectively, for Registry Group patients in surgical class ASA 4 or higher. In spite of the known high risk, the literature reports that 11% of conservatively treated CLI patients still underwent bypass surgery.

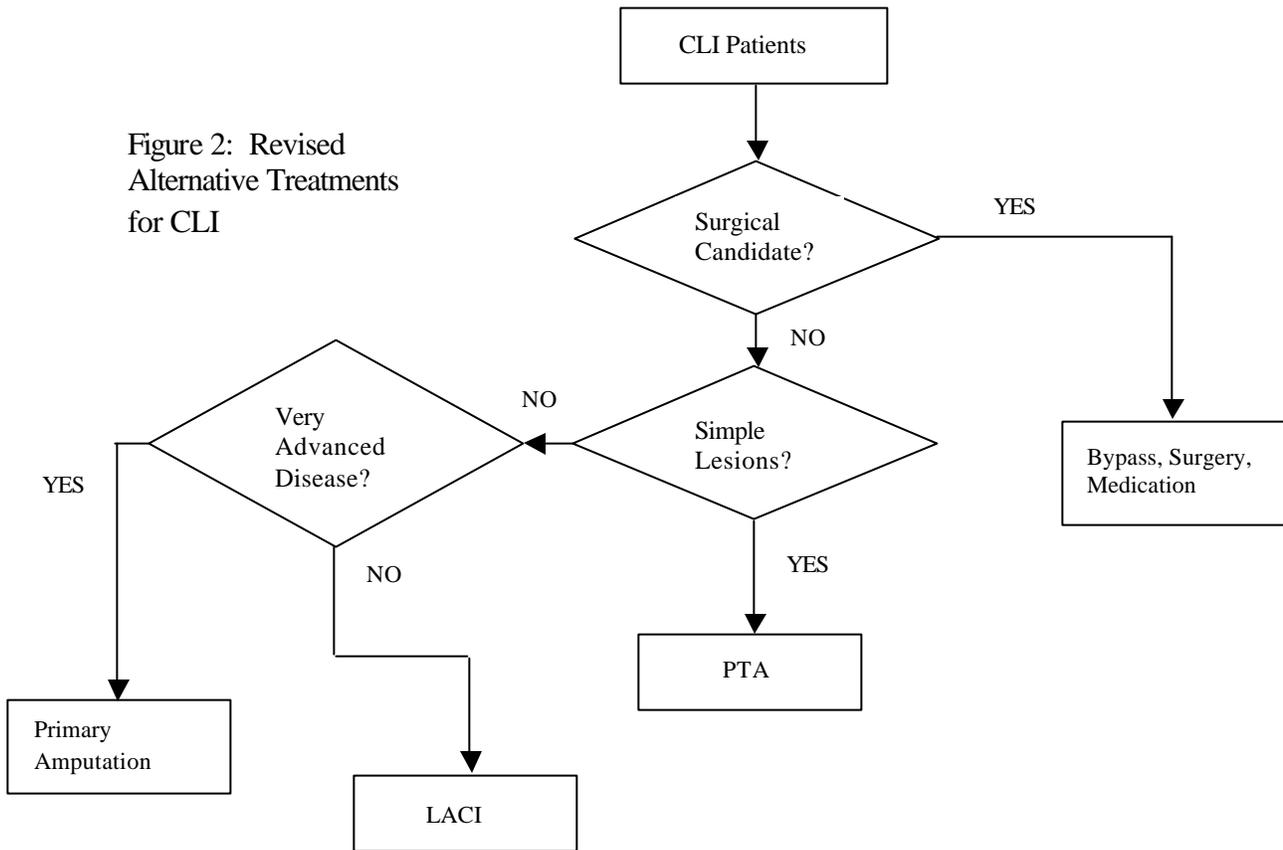
Percutaneous transluminal angioplasty (PTA), using balloons and stents, have shown promising results in some cases (13, 14, 15). However, in other studies certain patterns of CLI disease were identified that are not well suited to PTA (16, 17). In cases of diffuse lesions plaque remodeling tends to mitigate the effects of PTA. When disease extends throughout the legs, and many sites in the femoral-popliteal-tibial-pedal arch are blocked, PTA at a few local sites is ineffective in establishing sufficient blood flow to help the patient. Even when PTA is applied among CLI patients with less complex stenotic disease patterns, LACI shows only a marginally higher reintervention rate of 15%, compared to between 9% and 12% reported in the literature (18, 19, 20, 21) for follow-up intervals in the 6 - 12 month range. LACI showed noticeably lower rates for bypass surgery and major amputation (2% and 7% respectively), compared to 6-15% bypass (19, 20, 21, 22), and 9% to 21% major amputations in PTA patients.

Finally, CLI patients who underwent *bypass surgery*, in spite of predictions that surgery would be high risk, experienced reintervention in as many as 19% of the cases (23), and death rates of 1% to 2% within 30 days (24, 25, 26), while all LACI patients survived for at least 30 days.

The alternative treatments for CLI patients with high surgical risks are all indicated as either unacceptable, or inferior to LACI, according to literature references. Therefore, acknowledging there are some CLI patients (approximately 10%) whose advanced condition leaves primary amputation as the best alternative (27), and eliminating the portion of the CLI population for whom PTA may be effective due to simple lesion morphology, there remains a large segment of the CLI population without a limb-saving treatment alternative, other than LACI.

Figure 2 depicts the revised treatment alternatives for CLI patients, including LACI, based on the above arguments and literature data.

Figure 2: Revised
Alternative Treatments
for CLI



VI. Marketing History

None of the Spectranetics catheter models have been previously marketed in the USA for critical limb ischemia. Two models (the Extreme catheters, model numbers 222-005 and 225-004) are currently CE Marked, and have been commercially marketed in Europe since November, 1996, without any significant complaints that required a vigilance report to any Notified Body or Competent Authority.

VII. Potential Adverse Effects of the Device on Health

Use of the Spectranetics CVX-300[®] Excimer Laser System may contribute to the following complications:

Dissection of the arterial wall	Embolization
Acute reclosure	Spasm
Aneurysm formation	Thrombus
Nerve Injury	Arrhythmia
Perforation	Hematoma
AV fistula formation	Death

No long term adverse effects of peripheral excimer laser atherectomy are known at this time.

VIII. Summary of Pre-Clinical Studies

Biocompatibility:

Spectranetics has tested all of the materials used in the manufacture of laser catheters, and shown that they conform to the provisions of ISO 10993-1, with reference to Bluebook memo G95-1. Vitesse catheter models, previously marketed only for coronary applications, collectively represent all of the materials used in the new models. Thus, there is no reason to suspect detectable toxicity, or any lack of biocompatibility, in either the previously approved, or re-designed, catheter models suitable for LACI.

Bench Testing:

Extreme Catheter Models – Bench testing, for mechanical integrity, was performed separately for the 2.2 mm and 2.5 mm Extreme catheters, which are manufactured with metal bands at the distal catheter tip, one on the outside diameter of the catheter, and one at the inner diameter surrounding the guidewire lumen.

2.2 mm Extreme catheters (222-005): Testing showed 2.2 Extreme laser catheters maintained physical integrity after fatigue, and tension in excess of the acceptable lower limit. The distal tips of test units showed no deterioration after artificial fatigue, and separation forces for the metal band exceeded 5 pounds. Pull tests on the inner lumen showed that the bond strength to the inner lumen at the catheter tip exceeded 2 pounds, and the bond strength between the inner band and the epoxy-bound fiber array exceeded 5 pounds. All tests exceeded the acceptable lower limits for strength.

2.5 mm Extreme catheters (225-004): Tensile strength testing indicated that tubing-to-tubing fuse had tensile strengths in excess of that measured for the tubing alone. Fatigue and pull tests on the 2.5 mm Extreme catheters showed that, again, the separation forces for the outer band, inner tubing bond, and inner band-to-epoxy junctures were >5 pounds, >2 pounds, and >5 pounds, respectively, which exceeded the acceptable lower limits for strength.

Extreme II Catheter Models (220-006, 223-001, and 225-010) – Bench testing for both mechanical integrity and tissue ablation interactions were conducted on the 2.0 mm, 2.3 mm, and 2.5 mm Extreme II laser catheters. Tissue ablation, using porcine aorta as a substrate, showed comparable performance, and tip wear, when Extreme and Extreme II catheters were compared. The cross-sectional ablation areas were equal to, or greater than, the diameter of the catheter tip in each case. All three (3) catheter sizes were able to negotiate through the iliac arch of a model, held at 37° C, without binding

or prolapsing an appropriately sized guidewire. Finally, the mechanical integrity of each tubing-to-tubing, or tubing-to-band, or epoxy-to-metal, bond was checked using tensile strength as per ISO 10555-1. All bonds exceed either the 5 Newton limit for tubing with diameters between 0.75 mm and 1.15 mm, or the 15 Newton limit for tubing with diameters >1.85 mm.

IX. Summary of Clinical Studies

Design:

The LACI Phase 2 (LACI 2) trial was a multicenter prospective registry of patients, who were poor surgical candidates with critical limb ischemia (CLI) categorized as Rutherford class 4, 5, or 6 (10). The registry group was compared to the ICAI (Ischemia Cronica Critica degli Arti Inferior) Study Group's historical control cohort for a randomized trial of prostaglandin E₁ (alprostadiol-alpha-cyclodextrine, Schwarz Pharma Italia, Milan), treatment of CLI (11). The ICAI control group thus received standard treatment for CLI, including both invasive and noninvasive interventions, but not prostaglandins. Thus, the ICAI control group served as a well balanced reference to currently available treatments for CLI.

Methods:

Patients were screened at twelve (12) clinical sites in the United States and three (3) sites in Germany. Up to (3) patients at new LACI sites* were enrolled as training cases, and data was compiled separately for the training group.

Key inclusion criteria were Rutherford class 4, 5, or 6 CLI, which had been stable for two (2) weeks, angiographically identifiable arterosclerotic lesions in the superficial femoral artery (SFA), popliteal, infrapopliteal or tibial arteries, and poor surgical candidacy. Poor surgical candidates were those with an absence of veins suitable as autologous grafts, absence of vessels suitable as a bypass site, and high risk of surgical complications including death. Upon study completion, there were five (5) instances in which patients who did not meet inclusion criteria were treated with LACI. These five (5) patients, who presented in Rutherford class 3 without ulcers or rest pain, were pooled into the training group at the recommendation of the LACI Steering Committee.

The primary efficacy endpoint was limb salvage (that is, freedom from amputation at or above the ankle) at six months, and the primary safety endpoint was survival at 6 months. Secondary endpoints included procedural and radiographic outcomes, and serious adverse events (SAEs). Although the protocol did not specify that reintervention

* New LACI sites are those which did not participate in LACI Phase 1 feasibility trials.

during the follow-up period would be an SAE, the results were tabulated as if they were, at the direction of the Data Safety Monitoring Committee.

After recording relevant medical history, a clinician photographed ischemia-associated ulcerations, using a digital camera with a 3x3 cm (9 cm²) reference target visible in the picture. Each patient leg to be treated was angiographed and the locations of lesions, with their percent stenoses, were recorded. Recanalization via laser atherectomy at the target lesion(s), began with the choice of a laser catheter sized with respect to the target vessel's diameter. In some cases, the use of a smaller catheter was followed by a second pass with a larger laser catheter, in order to optimize the reopening of the diseased artery. Standard catheter insertion techniques were used, beginning with sheath insertion. Contralateral or ipsilateral antegrade approach, in the same direction as blood flow, was recommended in the study protocol, but not required if other approaches were indicated. Saline infusion was recommended, to flush blood and contrast media from the field of laser-lesion interaction.

Upon completion of any adjunctive balloon angioplasty and/or stent deployment, the final percent stenosis in any target lesion was visually assessed and recorded. Follow-up visits were scheduled at 1, 3, and 6 months post-treatment. Follow-up visits included digital photography, Rutherford classification, ankle-brachial blood pressure measurement, records of any reinterventions including amputation since the last visit, and general examination. Serious adverse events were reported at the time of occurrence.

Patient Population and Demographics:

The LACI Registry Group contained 145 patients with 155 limbs treated, and the Training Group contained 15 patients with 15 limbs treated. A total of 160 patients were accounted for in both groups, with a total of 170 limbs treated. The ICAI historical control group contained 789 individuals.

The Registry Group patient descriptors were similar to the Control Group in more than one statistic, including age, and past history of smoking. (See Table 1.)

However, more women and more comorbidities were noted in the Registry Group, including more hypertension, prior stroke, prior myocardial infarction, diabetes, hypercholesterolemia, obesity, and high surgical risk. More current smokers were treated in the Control Group. None of these variables correlated with mortality or major amputation. Overall the Registry Group was a more morbid patient group; the difference between 46% of Registry Patients in ASA class 4 or higher 11% of the Control Group (see page 415 of the ICAI paper) in a similar category has statistical significance.

Table 1: Baseline patient characteristics, Registry Group vs. Control Group; Training Group

	Registry Group n= 145		Control Group n=789				Training Group n=15	
					Difference	95% CI in Difference		
Age	72 ? 10 (45 - 91)		71 ? 10		1	-0.8 to 2.8	73 ? 12 (52 - 91)	
	n	%	n	%	Difference	95% CI in Difference	n	%
Gender:								
Male	77	53%	572	72%	-19.4%	-28.5% to -10.3%	6	40%
Previous Cardiovascular Illness:								
Stroke (CVA)	30	21%	92	12%	9.0%	1.7% to 16.4%	2	13%
Myocardial Infarction (MI)	33	23%	120	15.5%	7.5%	1.9% TO 16.1%	2	13%
Coronary Artery Disease (CAD)	72	50%	DN A				7	47%
Previous Surgical Interventions:								
Coronary Artery Bypass (CABG)	24	17%	DN A				4	27%
Coronary Angioplasty (PCTA)	21	14%	DN A				2	13%
Risk Factors Present at Enrollment:								
Diabetes	95	66%	309	39%	26.4%	17.5% to 35.2%	7	47%
Hypertension	121	83%	384	49%	34.8%	27.4% to 42.2%	12	80%
Hypercholesterolemia	81	56%	126	16%	39.9%	31.0% to 48.8%	8	53%
Obesity	51	35%	53	7%	28.5%	20.1% to 36.8%	3	20%
Smoking Past	57	39%	352	45%	-5.3%	-14.4% to 38%	5	33%
Smoking Current	20	14%	201	25%	-11.7%	-18.5% TO -4.9%	3	20%
Other	21	14%	DN A				0	0%
Renal Function:								
Creatinine (144)	1.7 ? 1.9 (0.4 - 11)		DNA				1.5 ? 1.2 (0.6 - 4.5)	
BUN (140)	34.0 ? 22.1 (7 - 139)		DNA				26.0 ? 13.3 (6 - 48)	
Poor Surgical Candidate:								
High Surgical Risk	66	46%	84	11%	35%	27% to 44%	2	13%
Absence of Venous Autologous Graft	47	32%	DN A				3	20%
Poor/No Distal	98	68%	DN A				12	80%
Any two Reasons	48	33%	DN A				2	13%
Any three Reasons	9	6%	DN A				0	0%

Notes: DNA = Data was not available for Control
Other (Risk Factors) = History of Infection, Neuropathy, Limb Pain, and Interventions in Limbs

CLI presentation was similar between the Registry Group and the Control Group, with the same ratios of Rutherford Category 4 (rest pain without ulcers) and Category 5-6. (See Table 2.) The recruited LACI Registry Group showed a noticeable similarity to the ICAI historical control group.

Table 2: Baseline Patient characteristics, Registry Group vs. Control Group

	Registry n = 145 n %	Control n = 789 n %	Difference [95%CI]
% Right Legs	75 (48%)	DNA	
Rutherford category:			
4	40 (28%)	240 (30%)	-2.8% [-10.8%, 5.1%]
5 or 6	105 (72%)	549 (70%)	2.8% [-5.1% , 10.8%]
5	94 (65%)	DNA	
6	11 (7%)	DNA	
CLI presentation:			
Rest pain	118 (81%)	729 (92%)	-11.0% [-17.6% , -4.4%]
Ulcers or Gangrene	105 (72%)	549 (70%)	2.8% [-5.1% , 10.8%]
Ulcers	96 (66%)	DNA	
Gangrene	39 (27%)	DNA	
Neuropathy	72 (50%)	DNA	
Duration of CLI (weeks)	25 ± 37 (1 - 261)	"AT LEAST 2 WEEKS"	
Location of ulcers/gangrene:	n %	n %	
Lower Leg(above ankle)	14 (9%)	DNA	
Ankle	12 (8%)	DNA	
Foot(below ankle)	65 (45%)	DNA	
Heel	17 (12%)	DNA	
Toe	33 (23%)	DNA	
Sole	3 (2%)	DNA	
Previous major amputation	0 (0%)	35 (4%)	-4.4% [-5.9%, -3.0%]
Previous minor amputation	18 (12%)	44 (6%)	6.8% [1.2% , 12.4%]
Post-procedure planned minor amp.	23 (16%)	DNA	
Amputation indicated (note 1)	56 (39%)	DNA	
Previous interventions (including bypass)	32 (22%)	176 (22%)	-0.2% [-7.6% , 7.1%]

NOTES:

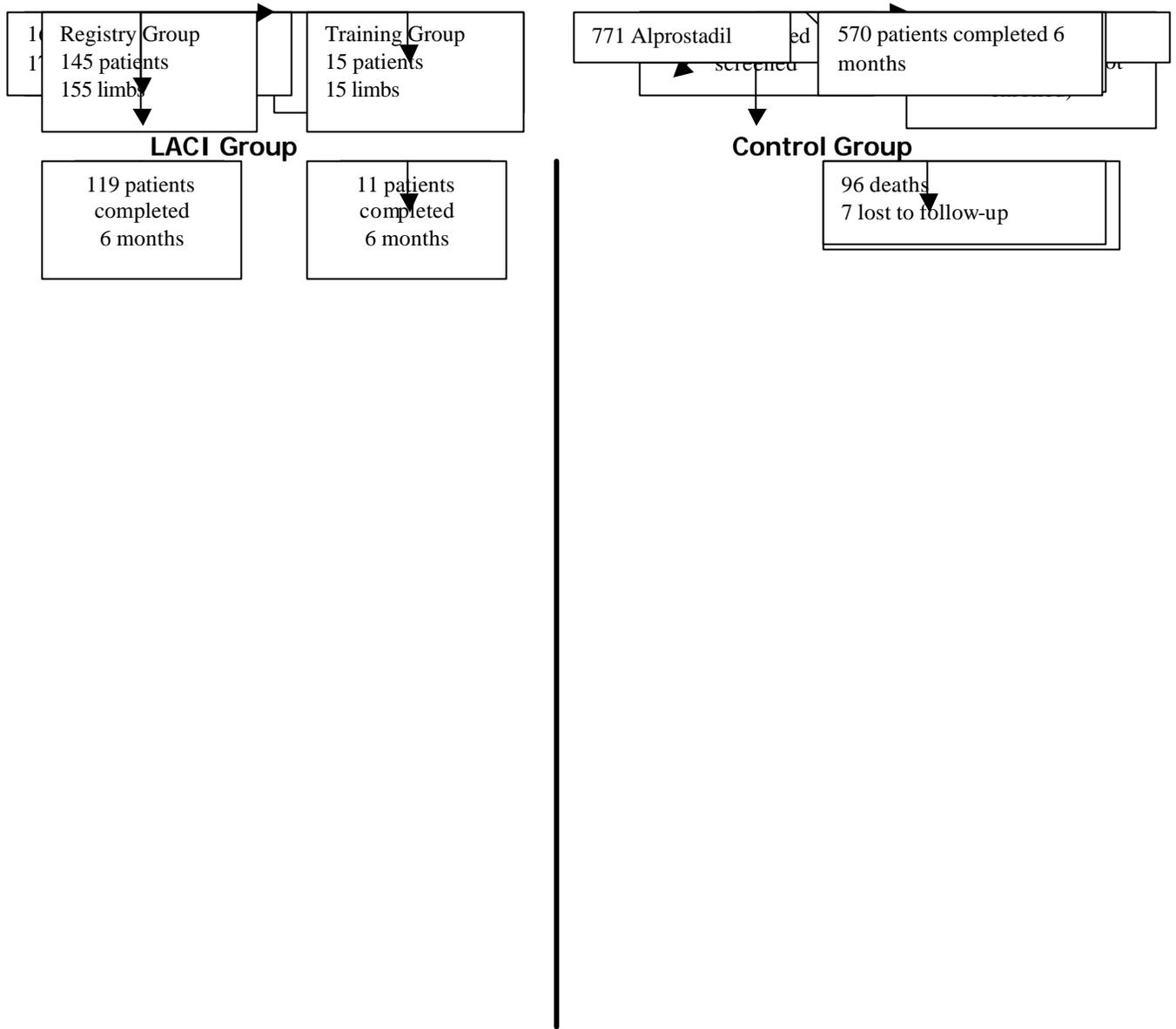
1. "In the absence of intervention, would this patient be referred for amputation?"

DNA = data was not available for the Control group

CLI = critical limb ischemia

Final enrollment and patient accountability data are summarized in Figure 3 below. ICAI control group data were extracted from the reference paper.

Figure 3: Patient flow in LACI Phase 2 Group and Control Group



Data Analysis and Results:

The fact ten (10) patients in the Registry Group had both legs treated necessitated analysis on a per patient basis for Serious Adverse Events such as death, myocardial infarction, and stroke. Other analyses, including the primary endpoint, limb salvage at 6 months, were done on per limb basis.

The primary endpoint was limb salvage (freedom from amputation above the ankle), a short-term efficacy endpoint. Secondary endpoints, to establish safety, included death, persistent CLI, frequency of bypass surgery, and other events. Limb salvage rates may be calculated using two different bases for the LACI Registry Group, either the number of patients or the number of limbs. Also, rates may be calculated on either an intent to treat basis, counting all Registry and Control enrollees, or on a basis censored for deaths, lost-to-follow-up, cases with unreliable or incomplete data, and drop outs. Tables 5 and 6 show that limb salvage was higher for the Registry Group, regardless of basis. The difference between Registry and control limb salvage rates is significant ($p = 0.05$) when the basis is all limbs (Table 3), but insignificant based on the censored cohort (Table 4).

The number of patient limbs reaching the primary endpoint was significantly higher in the Registry Group when compared to the historical control. (See Table 3.) It should be noted that limb salvage in 118, out of the 130 patients living 6 months after LACI, equals a 93% limb salvage rate in non-morbid patients.

Table 3: Limb Salvage Rate Intent to Treat Analysis

	LACI Registry Group	Control Group	Difference [95% CI]
Limb salvage	76% (118/155) limbs	63% (501/789) patients	13% [5%, 20%]
Limb salvage	76% (110/145) patients	63% (501/789) patients	13% [5%, 20%]

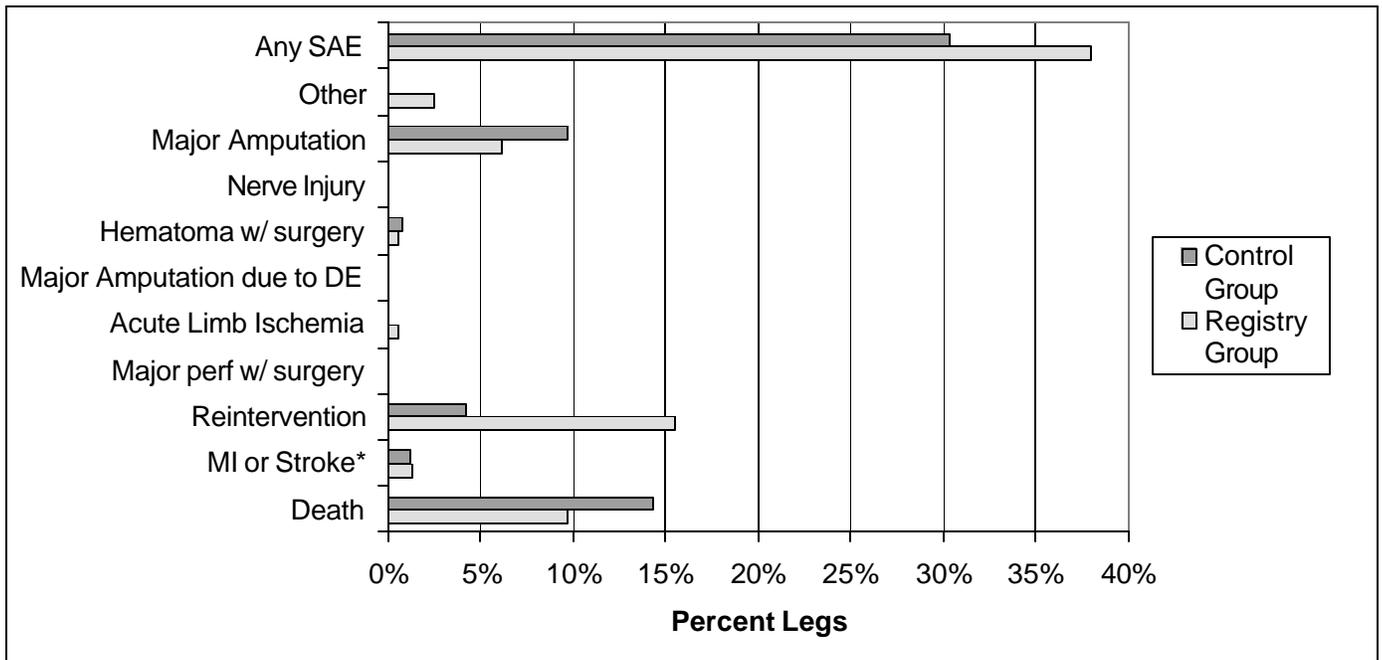
Table 4: Limb Salvage Rate Censored Population Analysis

	LACI Registry Group	Control Group	Difference [95% CI]
Limb salvage	93% (118/127) limbs	87% (494/570) patients	6% [0.5%, 12%]
Limb salvage	92% (110/119) patients	87% (494/570) patients	6% [-0.2%, 12%]

The overall SAE rate for the Registry Group, including a 17% rate (24/145 patients) for reinterventions, was 35% based on 155 legs, or 38% (55/145) based on 145 patients. The overall SAE rate for the literature Control Group was 30% (239/789) including 4% (34/789) reinterventions. Death, stroke, and complication rates were either equivalent or lower for the Registry Group when compared to the historical control. Bypass surgery was rare in the Registry Group (2.1%), but deemed necessary in almost one third (29.7%) of the control group. Refer to Figure 4.

Furthermore, LACI treatment led to shorter hospital stays, 3 days on the average, for CLI patients, than that observed for the control group, 23 days on the average.

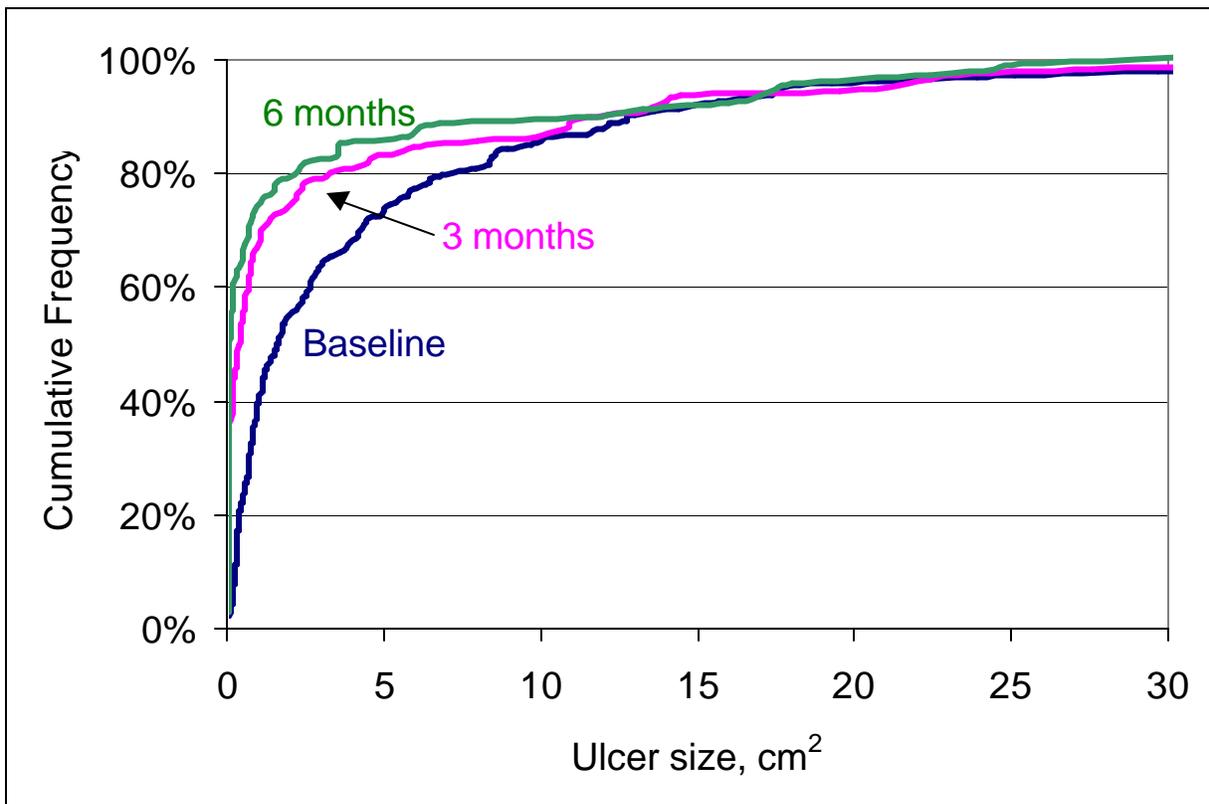
Figure 4: Adjudicated serious adverse events, Registry Group vs. Control Group



Death	0 (0.0%)	15 (10.3%)	15 (10.3%)	113 (14.3%)	-4.0%	[-9.9% , 2.0%]
Myocardial Infarction	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (1.1%)	-1.1%	[-2.3% , 0.0%]
Stroke	0 (0.0%)	1 (0.7%)	1 (0.7%)	1 (0.1%)	0.6%	[-1.2% , 2.3%]
MI or Stroke*	0 (0.0%)	1 (0.7%)	1 (0.7%)	10 (1.3%)	-0.6%	[-2.5% , 1.4%]
Reintervention	2 (1.4%)	22 (15.2%)	24 (16.6%)	34 (4.3%)	12.2%	[5.6% , 18.9%]
Major perf w/ surgery	0 (0.0%)	0 (0.0%)	0 (0.0%)	DNA		
Acute Limb	0 (0.0%)	1 (0.7%)	1 (0.7%)	DNA		
Major Amp. due to DE	0 (0.0%)	0 (0.0%)	0 (0.0%)	DNA		
Hematoma w/ surgery	1 (0.7%)	0 (0.0%)	1 (0.7%)	6 (0.8%)	-0.1%	[-2.0% , 1.8%]
Nerve Injury	0 (0.0%)	0 (0.0%)	0 (0.0%)	DNA		
Major Amputation	1 (0.7%)	8 (5.5%)	9 (6.2%)	76 (9.6%)	-3.4%	[-8.3% , 1.4%]
AKA	0 (0.0%)	2 (1.4%)	2 (1.4%)	DNA		
BKA	1 (0.7%)	6 (4.1%)	7 (4.8%)	DNA		
Other	0 (0.0%)	4 (2.8%)	4 (2.8%)	N/A		
Bypass	0 (0.0%)	3 (2.1%)	3 (2.1%)	N/A		
Endarterectomy	0 (0.0%)	1 (0.7%)	1 (0.7%)	N/A		
Any	5 (3.4%)	53 (36.6%)	55 (37.9%)	239 (30.3%)	7.6%	[-1.3% , 16.6%]

LACI treatment reduced wound areas in 41 out of 109 ulcers, for which baseline wound area measurements were available. Eighteen (18) of the 41 improved wounds healed completely. Wound areas were measured using a validated, software based, technique in which the areas were calculated from digital ulcer images internally calibrated to the 9 cm² target included in each image. Most of the healing, as measured by wound area, occurred within the first 3 months after LACI, as indicated by the small difference between a cumulative frequency plot of ulceration size at 3 months vs. that at 6 months. For instance, Figure 5 shows that the percentage of wounds \leq 5 cm² in area increased from a baseline of 65% to 80% within 3 months. That is 15% of wounds observed during LACI screening procedures healed to an area of \leq 5 cm², during the first half of the follow-up period. The percentage of wounds \leq 5 cm² in size increased to 82% in the time period between 3 and 6 months post-treatment, a differential of only 2%.

Figure 5: Cumulative Frequency of Ulceration (Wound) Areas at Baseline, 3 Months, and 6 Months



The data presented in Table 5 indicate that the average wound area decreased 44% within 3 months, and 50% within 6 months. In 7 cases, wound size increased, and there were 8 cases in which wounds were lost to amputation, totaling 15 cases in which no wound healing was documented with certainty. Additionally, there were wounds for which the 6-month status was indeterminate. In spite of the incomplete data set, Spectranetics is compelled to point out that many ulcerations, but not all, heal after LACI treatment.

Table 5: *Wound Mean Areas at Baseline, 3 Months, and 6 Months, for 109 ulcers with known baseline areas*

<i>Ulcer Areas:</i>			
	Mean Area cm ² ? Standard Deviation	Range cm ²	Mean % Healed vs. Baseline
Wound area at Baseline	7 ? 21	0 to 263 cm ²	0%
Wound area at 3 months	4 ? 8	0 to 40 cm ²	44%
Wound area at 6 months	3 ? 9	0 to 51 cm ²	50%
<i>Numbers of Ulcers showing Changes after 6 Months:</i>			
	Number of Wounds = N		
Improved	23		
Healed 100%	18		
Worse	7		
Amputated	8		

Device Failures and Replacements:

No device failures, which required product replacement, were recorded during the LACI Phase 2 clinical study.

X. Conclusions Drawn from the LACI Phase 2 Clinical Trial

Protocol Endpoints:

Primary Endpoint Efficacy– The proportion of cases with clinical success, i.e. limb salvage at 6 months, was nonsignificantly higher among LACI patients than for the ICAI historical control group. The intent-to-treat data in Table 3, of section IX above, lists clinical success for 76% of LACI Registry Group limbs and 63% for ICAI control group limbs. If the analysis is based on living limbs, (with the number of deaths, cases lost follow-up, and/or cases without reliable data, are subtracted prior to calculations) the 6-month values become 93% and 87% for LACI patients and control patients, respectively. Even though not statistically different, the odds of limb salvage are better after LACI. This meets the standard for efficacy established in the LACI Phase 2 Study Protocol, in which it was hypothesized that limb salvage after LACI would be as good as that for the ICAI control group.

Secondary Endpoints and Safety – Rates of overall serious adverse events (SAE's) were statistically equivalent for LACI patients vs. the literature Control Group. The SAE rate for the Registry Group, as reported in Figure 4 above, was 37.9%, slightly higher than the 30.3% drawn from the ICAI publication for the Control Group. However, two (2) mitigating points apply to the Registry Group's SAE rate. First, post-procedural re-angioplasty was not considered a serious adverse event according the LACI Phase 2 protocol approved under IDE #G981099. In spite of this fact, re-interventions were tallied as part of the reported 37.9% SAE rate. The reinterventions, representing on-going potential for limb salvage, would likely have been impossible without the associated original LACI success. Should reinterventions be excluded as SAE's, the overall rate for LACI becomes significantly lower for the Registry Group – only 21.3%. Second, 46% of the LACI Registry Group presented with combinations of medical conditions associated with high risk of surgical mortality and morbidity (ASA class 4 or above), vs. 11% in the Control Group. Significantly more comorbid conditions were present in LACI patients, potentially leading to more adverse events among the Registry Group. The statistically equivalent SAE rates emphasize LACI's safety, even within a desperately ill population. Also, the probability of surgical intervention, such as bypass and endarterectomy, was low in the LACI Registry Group. Only 2.6% of the Registry Group required either bypass or endarterectomy. This fact is most significant in the CLI population, whose membership includes many poor surgical candidates, having significant comorbidities.

Death rates were likewise statistically equivalent for the Registry and Control Groups.

Risk Benefit Statement for LACI as Alternative CLI Treatment:

CLI treatment plans available in the absence of LACI, as discussed in Section V above, are all associated with higher serious adverse event rates than is LACI, according to literature reports. Published data show primary amputation leads to more reintervention (19%) than LACI (15.5%), not to mention the continued disease state represented by non-healing wounds in 11% of amputees. CLI patients, treated conservatively with medications, show historical trends toward higher rates for bypass (11%), amputation (38%), and even death (42%), when compared to LACI. Percutaneous Transluminal Angioplasty (PTA), available only to the subset CLI patients with relatively simple arterial lesion patterns, was associated with amputation rates as high as 21%.

Therefore, considering three (3) points:

- 1) The LACI alternative showed equivalency with the mixture of various treatment modes reported in the ICAI control publication, and cited in the approved study protocol (IDE G980199);
- 2) LACI treatment presents CLI patients with improved adverse event rates, when specifically compared one-on-one to reported event rates for primary amputation, medication, and PTA; and
- 3) The attached Risk Management Analysis Table, LACI presents no unacceptable risks, as evaluated by international standards;

then the benefits for LACI exceed the otherwise equivalent risks. The decreased probability for serious adverse events, i.e. improved safety when compared to literature reports for alternatives, combined with formally equivalent efficacy data collected under the auspices of a controlled clinical trial, fits the model for an acceptable risk/benefit profile for a new medical device indication.

Therefore, Spectranetics believes that the results of the LACI Phase 2 , pivotal trial, show LACI to be both safe and efficacious. The company furthermore believes LACI to be the best alternative treatment for CLI patients, whose quality of life could be maintained through limb-saving revascularization.

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ATTACHMENT

**RISK MANAGEMENT TABLE
WITH REFERENCE TO ISO 14791**

Hazard/Risk	Potential Cause	Possible Risk Reduction Measures	Probability ¹	Severity ²	Risk Category ³	Acceptable?	Comment
COMPLICATIONS:							
Spasm	Decreased blood supply during treatment and trauma to limb	Nirtoglycerin Injection Therapy	3% = I	N	A	Yes	Risk Level in lowest category
Major Dissection	Inadvertent misalignment of guidewire and/or catheter alignment or technical errors	Stent implantation	4% = I	M	A	Yes	
Thrombus	Treatment trauma	Anticoagulant Therapy	3% = I	M	A	Yes	
Distal Embolization	Inadequate lysis of occlusion	Anticoagulant Therapy as appropriate	3% = I	M	T	Yes	
Perforation	Inadvertent misalignment of guidewire and/or catheter alignment or technical errors	Physician Training; prolonged balloon inflation; stent implantation	3% = I	M	A	Yes	
Surgical Reconstruction	Perforation or major dissection associated with improper guidewire and catheter alignment or technical errors	Physician Training/Post-market Education	0% = U	S	A	Yes	
Reocclusion	Physiological and anatomical patient makeup; progress of disease	Stenting, Drug Therapy	1% = I	M	A	Yes	
Venous Thrombosis	Treatment trauma	Anticoagulant Therapy	0% = U	S	A	Yes	
Pseudoaneurism	Treatment trauma	Physician Training	1% = I	M	A	Yes	
Arterio-Venous Fistula	Treatment trauma	Physician Training	0% = U	M	A	Yes	
Renal Failure	Contrast overload and/or Pre-existing Renal Disease	Dialysis	1% = I	S	T	Yes	

Hazard/Risk	Potential Cause	Possible Risk Reduction Measures	Probability ¹	Severity ²	Risk Category ³	Acceptable?	Comment
COMPLICATIONS: continued							
Infection	Lack of aseptic technique or conditions; progress of existing infection	Antibiotics	1% = I	M	A	Yes	Risk Level in lowest category, but no foreseeable Risk Reduction Measure
Other ⁴	Comorbidities and/or malfunction in other devices used as accessories	Patient Screening	7% = I	M	A	Yes	
SERIOUS ADVERSE EVENTS:							
Death	Comorbidities	Management of comorbid conditions	10% = R	C	T	Yes (No)	Death is never considered Acceptable. However the rate for LACI is lower, but not Statistically Lower than that for the Control.
Non-fatal Myocardial Infarction	Coronary artery disease	Cardiac care	0% = U	C	A	Yes	Risk Level in lowest category
Non-fatal Stroke - CVA	Comorbid cardiac or vascular disease at/above the heart	Management of comorbid conditions	1% = I	C	T	Yes	Risk Level in acceptable category
Reintervention	Progress of peripheral vascular disease; reclosure/reocclusion	Lifestyle change; prolonged anticoagulation	17% = O	M	T	Yes	Reintervention was similar between groups based on the number of patients who underwent an initial percutaneous intervention
Major Perforation	Improper guidewire and catheter alignment or technical errors	Physician Training/Post-market Education	0% = U	M	A	Yes	
Acute Reclosure	Physiological and anatomical patient makeup	Stenting	1% = I	M	A	Yes	
Major Amputation due to Embolization	Inadequate lysis of occlusion	Anticoagulant Therapy as appropriate	0% = U	C	A	Yes	
Major Amputation	Disease progressed beyond ability to heal; Failure to re-establish adequate blood flow	LACI Treatment	8% = I	C	T	Yes	Major Amputation was lowered after LACI, as compared to the Control Group. The difference was not statistically different.

Hazard/Risk	Potential Cause	Possible Risk Reduction Measures	Probability ¹	Severity ²	Risk Category ³	Acceptable?	Comment
SERIOUS ADVERSE EVENTS: continued							
Nerve Injury	Technical error resulting in nerve damage	Physican Training	0% = U	S	A	Yes	
Bypass Surgery	Failure to re-establish adequate blood flow with laser catheter	LACI Treatment	2% = I	S	T	Yes	This rate in the literature control group was significantly higher - 30%. LACI patients who are poor surgical candidates avoided surgery in significant numbers.
Endarterectomy	Failure to re-establish adequate blood flow with laser catheter	LACI Treatment	1% = I	S	T	Yes	Risk Level in acceptable category, but no foreseeable Risk Reduction Measure
OTHER OUTCOMES							
Extended Hospital Stay	Comorbidities, Infection, Complications necessitating treatment	LACI Treatment	8%=I	S	T	Yes	Average hospital stay was 3 days.
Persistent CLI	Restenosis as part of disease; Inadequate blood flow established	Reintervention	28%=P	M	U	Yes	Equivalent to 31% Observed in ICAI Control Group
Non-improving Wound	Restenosis as part of disease; Inadequate blood flow established; Colateral disease too extensive.	LaCI Treatment, Wound treatment	12%=R	M	T	Yes	24% of wounds healed completely
¹ Categories for Probability		² Categories for Severity		³ Categories of Risk			
F = Frequent, >50%		C = Catastrophic; permanent disability or death		I = Intolerable & Unacceptable			
P = Probable, 21%-50%		S = Serious; surgery required		U = Undesirable & Unacceptable			
O = Occasional, 16% -20%		M = Marginal; risk of surgery or hospitalization		T = Tolerable & Acceptable			
R = Rare, 10% - 15%		N= Negligible; no risk of additional therapy		A = Ameliorated/None Perceived & Acceptable			
I = Improbable, >0% to < 10%							
U = Unbelievable, 0% or none observed/expected							
⁴ Other Complications were those related to other devices used as accessories during LACI, or due to co-existing conditions such as heart failure or hematoma occurrences in locations not anatomically associated with LACI.							
NOTE: 10% is set as the threshold for "Improbable" based on the literature "ICAI" control publication. The rate for Major Amputation was reported as 9.6% (10% to 2 significant figures) in the publication. Any value less than 10% is considered relatively improbable based on this piece of data.							