The Peripheral RegIstry of Endovascular Clinical OutcoMEs (The PRIME Registry): Interim Analysis of the First 328 Subjects With Critical Limb Ischemia

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ABSTRACT: **Purpose.** Subjects with critical limb ischemia (CLI) have high 1-year amputation and mortality rates. PRIME is an ongoing prospective, observational clinical registry that documents the clinical presentation, diagnostic evaluation, endovascular treatment modalities, invasive and non-invasive follow-up, and long-term outcomes of these subjects. The clinical profile and outcomes of CLI subjects were characterized and compared with previous literature to highlight the contemporary knowledge, treatment standards, and challenges in CLI care. **Methods.** Data were analyzed from the first 328 CLI subjects enrolled in the PRIME registry. Baseline demographics, medical history, clinical presentation, testing, treatment modalities, and immediate, 30-day, and 12-month outcomes were evaluated. **Results.** From January 2013 to March 2016, a total of 328 subjects with CLI (Rutherford 4-6) were enrolled. Most subjects were non-Hispanic white males, with type 2 diabetes, hypertension, dyslipidemia, and smoking history, with a mean age of 70.3 years, covered by Medicare. The most common symptoms were claudication, rest pain, and non-healing ulcers. In all, 481 target lesions were treated (average 1.5/procedure). Mean target-lesion prestenosis was 92.7% and over one-half were chronic total occlusions. Balloon angioplasty with atherectomy was the most common treatment, followed by balloon angioplasty alone. Amputation-free survival at 12 months was 84%. **Conclusion.** The study of more patients and a longer follow-up will allow us to derive further knowledge on the endovascular treatment of complex CLI subjects.

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Critical limb ischemia (CLI) represents the terminal stage of peripheral arterial disease (PAD) and occurs when the capillary beds are inadequately perfused and unable to sustain tissue viability. It is defined by the presence of rest pain and/or tissue loss for at least 2 to 4 weeks that can be

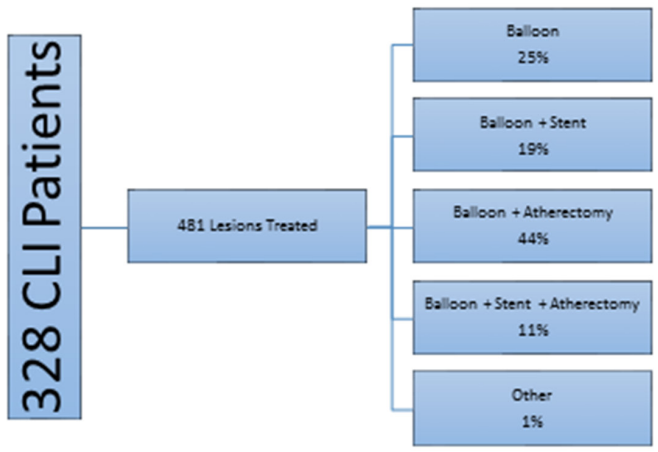

Figure 1. Treatment modalities of 481 treated target lesions.

attributed to occlusive arterial disease. The diagnosis is clinical in nature and classified as Fontaine stages III and IV or Rutherford-Becker classification 4, 5, and 6. The European Consensus Conference has also included the need for analgesia for more than 2 weeks or ischemic tissue loss with an ankle pressure of <50 mm Hg.[1]

Anatomically, CLI is characterized by multilevel and multivessel infrainguinal and tibial-pedal arterial stenoses and occlusions that create a severe imbalance between supply and demand of oxygen in the affected tissues, compromising their viability and threatening limb loss. It is estimated that 1.5 million patients in Europe and 2 million in the United States over age 50 manifest symptoms of CLI. One-year mortality and major amputation rates range from 20%-50%.[2-4] It occurs in approximately 1%-3% of all PAD cases,[5-7] with an incidence between 500-1000 persons per million per year in Europe and the United States.[8-10]

CLI patients have a multitude of comorbidities, significantly increasing their risk for myocardial infarction (MI), stroke, limb loss, and death.[11,12] Within the first year of diagnosis, 25% of patients will die and 30% will be alive but amputated. Two years post below-the-knee (BTK) amputation, 15% will undergo above-the-knee (ATK) amputation and 30% will die.[12] The quality of life of the surviving CLI patient is significantly worse than that of patients with cancer, chronic heart disease, and chronic kidney disease.[13]

In a study of 20,464 Medicare subjects with CLI who underwent amputations, 71% had no revascularization and 54% had no angiogram, underscoring the underutilization of interventional procedures.[5] Prospective randomized studies comparing endovascular revascularization with surgical bypass are in the works, but currently there is a paucity of randomized data comparing strategies.[14] Since the BASIL trial found that endovascular therapy (EVT) paralleled amputation-free survival and quality of life at 6 months, and was less morbid and significantly more economic than surgery,[15,16] there has been a widespread adoption of the "EVT-first" approach along with continuous innovations in endovascular techniques and devices.[17]

To further elucidate the most promising diagnostic and endovascular therapeutic modalities for advanced PAD and CLI, the multicenter, prospective, observational Peripheral RegIstry of endovascular clinical outcoMEs (PRIME) was initiated. PRIME collects comprehensive clinical, diagnostic, procedural, and follow-up data for 3 years following an index endovascular procedure for advanced PAD and CLI.

We present a descriptive analysis of the first 328 CLI subjects enrolled in PRIME, and compare their clinical profile, procedural, 30-day, and 12-month outcomes to the existing body of literature in an effort to highlight the existing limitations in CLI knowledge and care.

METHODS

PRIME represents the collaborative effort among three endovascular, high-volume, research-focused CLI centers across the United States with the goal of reaching ten sites globally. Site participation is voluntary and sites were not reimbursed for participation.

CLI subjects at each center were identified through physician referral and review of admitting diagnoses. Eligible subjects were over the age of 18 years, with symptoms classified as Rutherford 4-6, who were scheduled to undergo EVT of a lower extremity, were willing and able to provide informed consent, and intended to keep their follow-up appointments at the enrolling site. Each site's Institutional Review Board (IRB) approved the study and all subjects signed the informed consent form prior to participation. If all consecutive CLI subjects were not able to be approached at a site, an IRB-approved enrollment algorithm was followed to avoid selection bias. EVT approach and modality were left to the discretion of the treating physician and follow-up was performed per sites' routine standards of care.

The medical records of subjects undergoing revascularization for CLI were the source of clinical information entered into PRIME. Information collected included: demographics (gender, age, race, ethnicity, and insurance type); medical history (angina, coronary artery disease [CAD], chronic obstructive pulmonary disease [COPD], coronary artery bypass graft [CABG], diabetes, dialysis, dyslipidemia, hypertension, MI, tobacco use); previous vascular procedures; presenting symptoms (claudication, rest pain, non-healing wounds); clinical characteristics; medications; ankle-brachial index (ABI); toe-brachial index (TBI); endovascular procedural modalities and details; and immediate outcomes (complications and technical success prior to discharge).

Follow-up data were gathered at 30 days and at 3, 6, and 12 months, with ongoing collection at 24 and 36 months. Follow-up data included history (symptom status: improvement, deterioration, resolution; co-morbidities and procedural complications) and physical examination, non-invasive and invasive imaging, and mortality.

Data were captured in a web-based, electronic data capture system (iMednet version 1.161.3; Mednet Solutions, Inc) and were collected using standardized variable definitions. Definitions relevant to this publication can be found in Appendix 1. Missing data were flagged for review by the dedicated site staff and remote data validation and monitoring occurred for all initial site submissions and at predetermined intervals.

STATISTICAL ANALYSIS

Continuous variables are reported as mean ± standard deviation and range (min-max) depending on normality assumptions. Categorical variables are presented as numbers with percentages. Amputation-free survival was analyzed using Kaplan-Meier non-parametric statistical analysis.

RESULTS

From January 2013 to March 2016, a total of 328 CLI subjects consented and were enrolled in the PRIME registry. The subjects underwent 328 index endovascular revascularization procedures to treat 481 target lesions using combinations of percutaneous transluminal angioplasty (balloon), stenting, and atherectomy (Figure

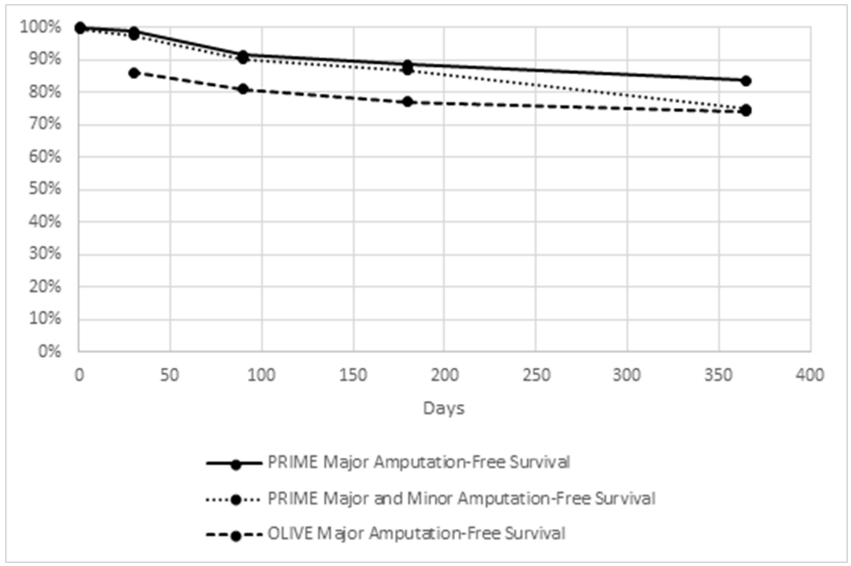

Figure 2. PRIME major amputation-free survival and major and minor amputation-free survival compared with OLIVE major amputation-free survival.

1). As of April 2016, all subjects (328) had reached their 30-day follow-up window and data were collected on 300 subjects (91.2%). By April 2016, a total of 240 of the 328 subjects had entered the 12-month follow-up window and data were able to be collected on 165 subjects (68.8%).

DEMOGRAPHICS AND COMORBIDITIES

Mean patient age was 70.3 ± 11.7 years. Most subjects were white, non-Hispanic, male, and claimed Medicare as primary insurance payer. Over 50% of patients had type II diabetes mellitus, hypertension, and dyslipidemia. Approximately three-quarters of the subjects were current or former smokers. Many patients had been treated with endovascular or surgical treatment prior to their enrollment in PRIME (Table 1).

PRESENTING SYMPTOMS AND LABORATORY VALUES

The most common presenting symptom was presence of an ulcer, with the majority of subjects enrolled as Rutherford classification 5 and 6. Mean baseline creatinine value was 1.5 mg/mL, glomerular filtration rate 61.4 mL/min, and hemoglobin was 12.5 g/dL. These values changed minimally at discharge. At enrollment, most subjects were taking an antihypertensive (beta-blocker, angiotensin-converting enzyme [ACE] inhibitor), and/or angiotensin-II receptor blocker (ARB) and statin medication. At least 75% of subjects were taking aspirin and over 50% were taking clopidogrel (Table 2).

BASELINE EVALUATION MODALITIES AND LEVEL OF DISEASE

Diagnostic angiography was the primary imaging modality followed by ABI and duplex ultrasound. ABIs and TBIs were misleading, as most patients had values consistent with mild PAD. Level of disease (above the knee only, below the knee only, or multilevel) was determined through visual estimate during angiography, and hemodynamic significance was defined as ≥70% stenosis. The majority of CLI patients enrolled in PRIME had multilevel disease in the target limb (Table 3).

TARGET-LESION CHARACTERISTICS

A *target lesion* is defined as any lesion attempted to be crossed or treated during the index endovascular procedure. Data on 481 target lesions were collected from the index endovascular interventions, averaging 1.5 lesions treated per procedure. Mean target-lesion stenosis was 92.3% and over one-half were chronic total occlusions (CTOs). About 25% of the subjects' target lesions had been previously intervened upon and about 40% required multiple (staged) procedures to provide adequate perfusion (Table 4).

ENDOVASCULAR PROCEDURE

Average time from successful access into the artery (percutaneous stick) to sheath pull was about 93 min.

Table 1. Demographics and comorbidities of patients with advanced peripheral arterial disease.

Demographics	
Age (years)	70.3 ± 11.7 (Range, 35.5-93.1)
Male gender	211/328 (64.3%)
Race	
Black	27/328 (8.2%)
White	298/328 (90.9%)
Native-American	2/328 (0.6%)
Asian	0/328 (0.0%)
Unknown	2/328 (0.6%)
Ethnicity	
Hispanic	10/328 (3.0%)
Non-Hispanic	316/328 (96.3%)
Unknown	3/328 (0.9%)
Insurance Type	
Commercial	43/328 (13.1%)
Medicaid	22/328 (6.7%)
Medicare	263/328 (80.2%)
Self-pay	1/328 (0.3%)
Comorbidities	
Angina	28/326 (8.6%)
Coronary artery disease	145/327 (44.3%)
Cerebrovascular disease	53/327 (16.2%)
Stroke	34/327 (10.4%)
Transient ischemic attack	17/327 (5.2%)
Congestive heart failure	66/328 (20.1%)
Chronic obstructive pulmonary disease	57/325 (17.5%)
Diabetes	211/328 (64.3%)
Type I	11/328 (3.4%)
Type II	200/328 (61.0%)
Dialysis	22/324 (6.8%)
Dyslipidemia	299/328 (90.9%)
Hypertension	295/328 (89.7%)
Myocardial infarction	68/327 (20.8%)
Renal Transplant	
Smoker	5/327 (1.5%)
Never	97/328 (29.5%)
Current	64/328 (19.5%)
Former	168/328 (51.1%)
Prior intervention - lower extremities	
Bypass	37/328 (11.3%)
Endarterectomy	16/328 (4.9%)
Amputation	47/328 (14.3%)
Major	20/328 (6.1%)
Minor	27/328 (8.2%)
Endovascular procedure	132/328 (40.2%)

Data provided as mean ± standard deviation (range) or n/N (%). Denominator of reported responses is reported if different than the total cohort size to account for missing data.

Arterial access was most commonly attempted in the common femoral artery followed by the tibiopedal arteries. Balloon angioplasty (plain, scoring, cutting, or drug coated) used in conjunction with atherectomy (orbital, directional, rotational, or laser) was the most commonly used treatment modality. In <5% of the procedures, no devices were utilized due to the inability to cross the target lesion. (Table 5).

OUTCOMES POST ENDOVASCULAR PROCEDURE

Immediate outcomes data include information from the index endovascular procedures to discharge from the hospital. As of April 2016, 30-day follow-up data were collected on 300 subjects (91.2%) and 12-month follow-up data were available on 165 subjects (68.8% of the subjects who have reached 12-month follow-up status) (Table 6). Amputation-free survival (AFS) was based on the patients who returned or were contacted for each follow-up window and can be seen in Figure 2. Based on these results, 12-month major AFS was predicted by Kaplan-Meier to be 84%, while major and minor AFS rate was determined to be 75%.

DISCUSSION

The PRIME registry was launched with the goal of collecting data on 5000 subjects with advanced PAD and CLI. To date, over 300 subjects with CLI (Rutherford 4 [39.2%], Rutherford 5 [55.3%], and Rutherford 6 [5.5%]) have been enrolled at three high-volume academic and community-based centers in the United States.

Of the first 328 subjects, 64% were male, with a mean age of 70.3 years (range, 35.5-93.1 years). This demographic information correlates with previous

Table 2. Baseline presentation and laboratory values.

Symptoms	
Cellulitis	27/306 (8.8%)
Claudication	187/306 (61.1%)
Neuropathy	110/306 (35.9%)
Osteomyelitis	35/306 (11.4%)
Rest pain	192/306 (62.7%)
Rutherford category	
IV	129/329 (39.2%)
V	182/329 (55.3%)
VI	18/329 (5.5%)
Laboratory values	
Baseline creatinine (mg/mL)	1.5 ± 1.5 (0.3-11.0)
Discharge creatinine (mg/mL)	1.5 ± 1.7 (0.3-13.5)
Baseline glomerular filtration rate (mL/min)	61.4 ± 29.6 (3.0-317.9)
Discharge glomerular filtration rate (mL/min)	64.4 ± 29.5 (3.0-228.1)
Baseline hemoglobin (g/dL)	12.5 ± 1.9 (7.3-17.8)
Discharge hemoglobin (g/dL)	11.4 ± 1.8 (6.8-16.9)
Baseline low-density lipoprotein (mg/dL)	81.6 ± 37.2 (9.0-223.0)
Medications	
Antihypertensive	258/328 (78.7%)
Nitrate	51/328 (15.5%)
Statin	233/328 (71.0%)
Aspirin	252/328 (76.8%)
Warfarin	20/328 (6.1%)
Clopidogrel	178/328 (54.3%)
Prasugrel	5/328 (1.5%)
Insulin	107/328 (32.6%)

Data provided as mean ± standard deviation (range) or n/N (%). Denominator of reported responses is reported if different than the total cohort size to account for missing data. Antihypertensives = beta-blocker, angiotensin-converting enzyme inhibitor, and/or angiotensin II receptor blockers.

Table 3. Baseline evaluation modalities and level of disease.

Parameter	
Duplex ultrasound	172/314 (54.8%)
Extravascular ultrasound (intraprocedure)	75/314 (23.9%)
Ankle-brachial index	189/306 (61.8%)
Right ankle-brachial index	0.84 ± 0.29 (0.15-2.0)
Left ankle-brachial index	0.83 ± 0.27 (0.19-1.58)
Toe-brachial index	136/306 (44.4%)
Right toe-brachial index	0.48 ± 0.24 (0.0-1.13)
Left toe-brachial index	0.49 ± 0.26 (0.0-1.79)
Diagnostic angiogram	284/314 (90.4%)
Level of disease by angiography	
Target limb	
Above the knee	55/261 (21.1)%
Below the knee	79/261 (30.3%)
Multilevel	118/261 (45.2%)
Non-target limb	
Above the knee	53/246 (21.5%)
Below the knee	85/246 (34.6%)
Multilevel	57/246 (23.2%)

Data provided as mean ± standard deviation (range) or n/N (%). Denominator of reported responses is reported if different than the total cohort size to account for missing data.

literature showing that advanced PAD and CLI are more frequently seen in men and are age related, with increased incidence among subjects 65 years and older.[18] The majority of these subjects (80.2%) had Medicare coverage.

Previous literature has shown that the prevalence of PAD and CLI is higher among African-Americans.[18] Interestingly, enrollment in the PRIME registry has thus far drawn subjects primarily from areas highly populated with white, non-Hispanic individuals. As an increased number of sites join in data collection, a less ethnically-biased cohort will become available, and a more in-depth conclusion about the prevalence of disease among different ethnicities will become available.[19,20]

The demographic features and cardiovascular risk factors of the subjects enrolled in PRIME corroborate with those previously published for PAD and CLI, which include CAD, diabetes, dyslipidemia, hypertension, and tobacco use.[6] The prevalence of renal disease and dialysis was higher among the registry subjects in comparison to the general population. Average baseline creatinine was 1.5 mg/dL (0.3 mg/dL higher than most institutions' upper limit of normal). The mean GFR would classify PRIME subjects as having stage 2-3 chronic kidney disease, and almost 7% of subjects are dialysis dependent, compared with 348 subjects per million in the United States (United States Renal Data system, 2010). Therefore, the PRIME population represents a cohort with an even

Table 4. Target-lesion characteristics.

Parameter	Lesions (n = 481)
Lesions treated/procedure	1.5 ± 0.8 (1.0-5.0)
Prestenosis (%)	92.7 ± 10.7 (50.0-100.0)
Chronic total occlusion	214/418 (51.2%)
Lesion length (mm)	156.1 ± 130.9 (8.0-600.0)
Reference diameter (mm)	4.6 ± 1.7 (1.5-10.0)
Calcification present	321/365 (87.9%)
In-stent restenosis	38/385 (9.9%)
Target-lesion revascularization	77/327 (23.5%)
Target-vessel revascularization	83/327 (25.4%)
Staged procedure	131/327 (40.1%)
Technically unsuccessful revascularization	49/388 (12.6%)

Data provided as mean ± standard deviation (range) or n/N (%). Denominator of reported responses is reported if different than the total cohort size to account for missing data. Technically unsuccessful revascularization defined as >30% residual stenosis.

Table 5. Endovascular procedure.

Parameter	
Duration (min)	92.9 ± 49.7 (18-377)
Priority	
Elective	284/324 (87.7%)
Urgent	38/324 (11.7%)
Emergent	2/324 (0.6%)
Access site	
Total number	454
Sites/procedure	1.4 ± 0.63 (1.0-4.0)
Arteries	
Brachial	4/454 (0.9%)
Radial	4/454 (0.9%)
Common femoral	287/454 (63.2%)
Superficial femoral	21/454 (4.6%)
Popliteal	3/454 (0.7%)
Anterior tibial	60/454 (13.2%)
Posterior tibial	57/454 (12.6%)
Peroneal	3/454 (0.7%)
Dorsalis pedis	14/454 (3.1%)
Other	1/454 (0.2%)
Interventions	
Balloon	78/312 (25.0%)
Balloon + stent	60/312 (19.2%)
Balloon + atherectomy	138/312 (44.2%)
Balloon + stent + atherectomy	34/312 (10.9%)
Other	2/312 (0.6%)

Data provided as mean ± standard deviation (range) or n/N (%). Denominator of reported responses is reported if different than the total cohort size to account for missing data.

higher than usual risk for contrast-induced nephropathy and hence mortality, as established by Abe et al.[21] Medical therapy specific to CLI revolves around the treatment of the myriad of comorbidities with which these subjects typically present. Suboptimal medical therapy was identified in the registry, with only 76.8% of subjects taking aspirin and 71% taking statins at presentation.

Most subjects (>90%) underwent diagnostic angiography prior to their endovascular procedure, showing that a large percentage of CLI subjects (45.2%) have multilevel disease, in agreement with the SCAI Expert Consensus Statement for Infrapopliteal Arterial Intervention Appropriate Use.[22] Over one-half of the lesions were CTOs and almost 90% were calcific, making their treatment more complex. The average number of target lesions treated per procedure was 1.5. The number of staged procedures needed to complete revascularization will be important to research, as each additional procedure leads to added cost and risk to patients. Baseline ABI values were available for 61.8% of patients and the mean values were consistent with mild PAD, as described by Bunte et al.[23] Additional analysis with larger numbers of CLI patients may need to be completed to further analyze the validity of hemodynamic parameters in the characterization and evaluation of patients with CLI.

The wide range of revascularization techniques utilized also underscores the complexity of CLI, as different anatomical locations may require different revascularization techniques. In the BASIL trial, the EVT was primarily focused on plain balloon angioplasty, while the Japanese OLIVE registry mainly featured plain balloon angioplasty, cutting balloon angioplasty, and/or nitinol stenting (for bail-out). As PRIME is not dictating the treatment modalities to be used, it

Table 6. Outcomes post endovascular procedure.

Parameter	Immediate	30-Day	12-Month
Arteriovenous fistula	6/328 (1.8%)	0/300 (0.0%)	—
Embolization	2/328 (0.6%)	—	—
Thrombus	3/328 (0.9%)	0/300 (0.0%)	—
Dissection	41/328 (12.5%)	—	—
Non-flow limiting	33/328 (10.0%)	—	—
Flow-limiting	8/328 (2.4%)	—	—
Abrupt closure	0/328 (0.0%)	—	—
Perforation	10/328 (3.0%)	—	—
Mild	4/328 (1.2%)	—	—
Moderate	4/328 (1.2%)	—	—
Severe	2/328 (0.6%)	—	—
Rupture	1/328 (0.3%)	—	—
Spasm	4/328 (1.2%)	—	—
Aneurysm	0/328 (0.0%)	0/300 (0.0%)	—
Pseudoaneurysm	7/328 (2.1%)	3/300 (1.0%)	—
Hematoma	14/328 (4.3%)	2/300 (0.7%)	—
Compartment syndrome	0/328 (0.0%)	0/300 (0.0%)	—
Amputation	2/328 (0.6%)	13/300 (4.3%)	38/165 (23.0%)
Major	0/328 (0.0%)	3/300 (1.0%)	14/165 (8.5%)
Minor	2/328 (0.6%)	10/300 (3.3%)	24/165 (14.5%)
Death	0/328 (0.0%)	4/322 (1.2%)	32/242 (13.2%)
Ankle-brachial index			
Right	—	0.96 ± 0.27 (0.33-1.89)	0.83 ± 0.32 (0.00-1.97)
Left	—	0.97 ± 0.25 (0.00-1.88)	0.88 ± 0.27 (0.00-1.64)
Toe-brachial index			
Right	—	0.53 ± 0.25 (0.00-1.49)	0.51 ± 0.22 (0.04-1.11)
Left	—	0.49 ± 0.21 (0.00-1.02)	0.49 ± 0.22 (0.00-1.08)

Data provided as mean ± standard deviation (range) or n/N (%). Denominator of reported responses is reported if different than the total cohort size to account for missing data.

shows an evolution of therapy that is different from these previous registries. Further research into these data may help us understand where different modalities excel and fail. Analyses of the short-term and long-term outcomes of these subjects may steer operators in different directions when making decisions on revascularization in subjects with CLI.

Vascular access location and number is yet another evolving topic, as CLI subjects frequently require multiple access points (mean of 1.4 access points and up to 4 access points during the same procedure, with a significant number of tibiopedal retrograde accesses). From the PRIME-CLI data, it appears that access complications are few and far between as overall complications rates were all under 5%, but no consensus exists regarding the safest and most effective access method.[24] Further study into the safety and feasibility of using different access techniques and sites should be implemented.

Appendix 1. Definition of parameters.
Target lesion: any arterial stenosis where an attempt was made to cross or intervene during the index endovascular procedure.
Target-lesion revascularization: the patient has had a prior peripheral vascular procedure that included an intervention on one of the current target lesions.
Target-vessel revascularization: the patient has had a prior peripheral vascular procedure that included an intervention on one of the current target vessels.
Technically unsuccessful revascularization: target lesion post-stenosis ≥30% post endovascular treatment.
AV fistula: an abnormal connection between the artery and a vein; may cause a bruit.
Embolization: development of a blood clot distal to the lesion intervened upon. Blood flow is occluded.
Thrombus: development of a blood clot in the artery as a result of the endovascular procedure.
Dissection: a tear or damage to the inner wall of an artery. (a) Non-flow limiting: dissection does not impede blood flow (b) Flow-limiting: dissection impedes blood flow, but does not cause a total occlusion. (c) Abrupt total occlusion: dissection causes complete occlusion of blood flow in artery.
Perforation: a puncture in the artery caused by one of the devices used for intervention; contrast can usually be seen outside the artery wall: (a) Mild: delayed extravasation after initial contrast injection, with continuation beyond extravasation site that resolves with prolonged balloon inflation. (b) Moderate: extravasation is visualized immediately upon contrast injection, with continuation beyond extravasation site that resolves with prolonged balloon inflation. (c) Severe: extravasation is visualized immediately upon contrast injection with minimal blood flow beyond extravasation site; requires treatment with a covered stent, coils, and anticoagulation.
Rupture: the artery is punctured so severely emergent surgery is needed for repair.
Spasm: the smooth muscle in the arterial wall spasms, resulting in vasoconstriction.
Aneurysm: a weakness in the wall of the artery that causes an abnormal widening of the vessel.
Pseudoaneurysm: disruption and dilation of the wall of the artery causing a leak, resulting in a hematoma.
Hematoma: localized swelling filled with blood at the site of arterial access or due to perforation of a traversed artery.
Compartment syndrome: internal bleeding resulting in compression within the limb compromising the circulation and function of the tissues in that area.
Amputation: surgical removal of the limb or part of the limb: (a) Major amputation: removal of the limb above the ankle. (b) Minor amputation: removal of the foot or toes (below the ankle).
Major amputation-free survival: freedom from above-the-ankle amputation of either limb or death (any cause).
Major and minor amputation-free survival: freedom from any amputation of either limb or death (any cause).

As the number of enrolled subjects increases, a better understanding of which patients would not be able to withstand such procedures may become evident. Immediate complications related to EVT in the PRIME population appears to be low, under 5% for all categories except dissection (12.5%). This suggests an achievement of the short-term goal of anatomical revascularization without significant compromise to the subject.

The prognosis of CLI remains extremely poor. Mortality rates in contemporary CLI series have been reported as high as 41% at 2 years[25] and the 30-day morbidity and mortality related to a major amputation ranges from 4%-12% depending on the level of amputation.[26] The overall mortality rates at 30 days and 12 months for the PRIME subjects were 1.2% and 13.6%, respectively. For the patients who reached 12-month follow-up, the major amputation rate was reported at 8.5%, whereas the minor amputation rate was 14.5%.

The PRIME registry major AFS rates at 3, 6, and 12 months trend higher than those presented by the

OLIVE registry (Figure 2). Overall 12-month major AFS was 84% in PRIME, 74% in OLIVE, and 71% in the retrospective cohorts of the PREVENT III, BASIL, and CIRCULASE trials.[27,28] The difference in AFS is most likely due to improved awareness and increasingly available technologies in the United States. The improvement in the AFS in PRIME is a good indicator that current EVT is effective in treating complex CLI patients, but further analysis is warranted.

Although 30-day follow-up compliance was 91.2%, 12-month compliance was only 68.8%. Patients who did not return for follow-up were contacted via telephone to determine survival and amputation data, with only 7 patients lost to follow-up. Limited data exist regarding long-term follow-up of this complex patient population and lack of compliance may be a predictor of poorer outcomes. Future analysis regarding the outcomes of the patients who return for follow-up vs those who do not is warranted.

Important concomitant PAD registries exist; however, none are exclusively devoted to the study of EVTs among subjects with advanced PAD and CLI for 3 consecutive years. BMC2 is focused on both coronary and peripheral interventions, and follows subjects for only 6 months. The ACC-PVI registry includes all patients with PAD, as well as patients undergoing carotid artery stenting and carotid endarterectomy. VQI encompasses a large surgical focus including carotid stenting, endarterectomy, abdominal aortic aneurysm (AAA) repair, bypass, endovascular aortic repair (EVAR), and PVI. XLPAD includes PAD patients of all Rutherford categories and follows for 12 months. LIBERTY 360 includes Rutherford 2-6 PAD subjects, but does not include patients being treated for in-stent restenosis, and data collection is capped at 1200 patients. The OLIVE registry focused solely on 314 Japanese CLI patients.[27]

LIMITATIONS

Data were collected prospectively and all requested information was not always available. Data were included as appropriate for descriptive analysis. In addition, invasive and non-invasive imaging was analyzed and reported; however, adjudication is not currently built into the protocol. For future inquiries, alternate solutions will be implemented.

As previously discussed, a race and ethnicity bias is present as the data are currently mostly based on white, non-Hispanic individuals. Referral bias may also be present, as subjects with symptomatic advanced PAD and CLI may be more likely to be assessed at one of the participating institutions. Asymptomatic or undiagnosed subjects have not been included and may have different characteristics from symptomatic subjects. Not including undiagnosed subjects also limits the ability to determine the true prevalence of CLI. Lack of 12-month follow-up may also limit the amount of information able to be extracted. For future publications, phone follow-up may be implemented for subjects unable to return to the institution.

As the registry matures, more centers will be activated and a larger number of subjects will be enrolled. This change will reduce bias and make findings more generalizable.

CONCLUSION

Analysis of the first 328 patients confirms previously published data on demographics, showing that CLI

most frequently affects white males who are Medicare beneficiaries. Our interim analysis also confirms the limitations that currently accepted non-invasive modalities have in the accurate identification of CLI patients. Improved AFS rates may point to increased awareness and earlier detection of CLI, with more aggressive treatment that incorporate adjuvant therapies beside balloon angioplasty. The study of more patients and a longer follow-up will allow us to derive further knowledge on the diagnostic and therapeutic tools used to treat complex CLI subjects.■

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