Effective Vascular Therapeutics for Critical Limb Ischemia
A Role for Registry-Based Clinical Investigation

Alan T. Hirsch, MD; Sue Duval, PhD

Critical Limb Ischemia as a Public Health Crisis
Peripheral artery disease (PAD) is one of the most common cardiovascular diseases and is associated with high short-term morbidity and mortality. It is the primary cause of lower extremity amputation throughout the world and is a powerful marker of advanced systemic atherosclerosis. Chronic critical limb ischemia (CLI) represents the most advanced clinical manifestation of PAD and is defined by the presence of ischemic rest pain, nonhealing wounds, or tissue loss (gangrene). CLI does not represent a single pathophysiologic process (ie, progressive leg arterial atherosclerosis), but is caused by multiple pathogenetic mechanisms, including native artery atherosclerosis, cardioembolic events, inflammatory arteritides (eg, thromboangiitis obliterans), hypercoagulable states, or leg bypass graft failure.

The current CLI knowledge base is considerably less established than for other major cardiovascular syndromes. There has indeed been a paucity of well-designed strategy of care randomized controlled trials. Current challenges include very slow recruitment of CLI subjects, incomplete knowledge regarding CLI natural history, relatively few novel interventions that might lower limb or systemic ischemic event rates, and inadequate funding to support investigations. The relative rarity of CLI randomized controlled trials is strikingly adverse to PAD knowledge growth. An alternative approach to CLI investigation could utilize large CLI disease registries. Such cardiovascular disease registries have provided major knowledge advances for common cardiovascular diseases, such as acute coronary syndromes, ST segment elevation myocardial infarction, or after percutaneous coronary intervention. Registries have also long played a central role in the study of cardiovascular syndromes. Successful registries accomplish this by inclusion of a large, representative sample, with complete baseline and outcome data collection, and with adequate lengths of clinical follow-up.

Registries as a PAD Research Tool
Registries have also long played a central role in the study of PAD and CLI. Endovascular outcomes have been evaluated in multicenter regional outcomes registries. The early success of peripheral angioplasty to treat infrapopliteal stenoses in patients with CLI was reported using a registry approach. The durability of atherectomy to treat leg arterial stenoses lesions was reported from the TALON registry. The benefit of polytetrafluoroethylene covered stents to improve long superficial femoral artery stenoses was confirmed by registry study. Single-center registries have reported the benefits of sirolimus drug-eluting stents for infrapopliteal stenoses in patients with CLI. A 7-center registry design was used to report the benefits of catheter-based plaque excision in individuals with CLI. Such registries have usually represented small case series, and invariably report consistent coding in administrative billing databases. Yet, it has been estimated that CLI prevalence is approximately 150 to 300/100,000 based on a few noncontemporary surveys that were mostly conducted between 1985 and 2000. Although there is some evidence that US-based CLI cases and amputation may be declining, the health economic burden of CLI remains very high. These costs are increased by the high rates of cardiovascular and limb ischemic events. The increased use of endovascular therapies (EVT) is a major contributor to the rising national burden of PAD-related costs.

The current incidence and prevalence of CLI, and thus the public health impact of this syndrome, is incompletely defined. Population-based study of this syndrome is hampered by the inability of field surveys to measure incident cases, use of varying CLI definitions, and due to the lack of consistent coding in administrative billing databases. Yet, it has been estimated that CLI prevalence is approximately 150 to 300/100,000 based on a few noncontemporary surveys that were mostly conducted between 1985 and 2000. Although there is some evidence that US-based CLI cases and amputation may be declining, the health economic burden of CLI remains very high. These costs are increased by the high rates of cardiovascular and limb ischemic events. The increased use of endovascular therapies (EVT) is a major contributor to the rising national burden of PAD-related costs.

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high procedural success rates (defined by angiographic or duplex ultrasound criteria) $>95\%$ at short, 6 month or 1 year, follow-up periods. It seems likely, but is unknown, if major reporting bias has occurred by the nonpublication of endovascular registries (case series) in which results were not so impressive. However, many of these endovascular registries are characterized by small cohorts (thus not providing reliable point estimates and confidence intervals to define systemic or limb adverse event rates realistically), highly selective subject recruitment, limited duration or completeness of follow-up, inadequate recording of cardiac events, or lack of a control group. Thus, these registries offer poorer data quality compared with that derived from larger population studies.$^{21}$

Contemporary CLI clinical care pathways rely on prompt establishment of adequate antegrade flow. Due, in part, to the reports of increasing rates of success in achieving PAD patency rates, documented via registry studies, there is now international consensus that an endovascular first approach is appropriate for patients whose anatomy permits such revascularization, justified by the lower short-term morbidity compared with open surgical procedures. Yet, recent evidence-based care guidelines recognize that for individuals with CLI whose survival is anticipated to be $>2$ years, open surgical bypass may provide a superior outcome.$^{22}$

The OLIVE CLI Registry

In this issue of *Circulation: Cardiovascular Interventions*, the study by Iida et al provides another contemporary dataset that implies high benefit from application of endovascular techniques to patients with CLI due to infrainguinal PAD.$^{23}$ This study demonstrates that straight line patency and increased foot perfusion may be achieved using current endovascular techniques within a highly selected population with multisegmental PAD, with an associated improvement in ambulatory status and lower amputation rate.

In this study, 314 elderly Japanese patients with CLI and major comorbidities received endovascular revascularization to achieve a high amputation-free survival (AFS) rate of $74\%$ at 1 year, with low major adverse coronary events and major adverse limb events rates of 2.2 and 1.9%, respectively. This superb result was achieved at the cost of a 34% rate of use of a second invasive endovascular procedure, at unknown health economic cost. The authors suggest that these results are comparable or superior to what might be achieved via open surgical care strategies, but these patients were selected on the basis of being endovascular candidates and the efficacy and risk of a surgical approach was not tested, obviating any reliable conclusion by historical comparison.

Although these CLI registry outcomes data are impressive, readers should be cautious in extrapolating the results to broader populations. First, this study population is ethnically different from European, South American, or North American CLI populations. This Japanese cohort has a much lower body mass index, surprisingly low documented dyslipidemia for an elderly CLI cohort (41%), and an extremely high prevalence of end-stage renal disease (ESRD). Fully, half of the CLI population in this registry was dialysis-dependent, and this fact alone distinguishes the cohort from nearly any other CLI case series. The impact of diagnostic, endovascular, and surgical PAD therapies in chronic kidney disease cohorts has largely remained an area free from investigation.$^{24}$

The registry population received high usage of cilostazol, a medication approved for use to improve claudication symptoms, but not to improve CLI outcomes. The use of evidence-based medicine risk-reduction therapies was poor (eg, statin use of 26%). Blood pressure, lipid values, measures of glycemic control, and adequacy of dialysis are not described.

The registry is characterized by several other limitations. The entry criteria included a requirement that subjects had to be available for follow-up for 1 year after EVT. Patients lost because of anticipated poor follow-up are often characterized by worsened comorbid conditions, poor social support, and other factors that would be anticipated to affect CLI outcomes adversely (such as AFS). Entry criteria also mandate that subject life expectancy be $>1$ year. Yet, most individuals within a cohort with such a high rate of ESRD, dialysis, and concomitant CLI would not be anticipated to be alive after 1 year.

The authors state that 760 patients, beyond those in the registry, were treated with only EVT. Was this the total number of individuals with infraringuinal anatomic CLI who were provided care at the 19 participating Japanese hospitals during the registry’s enrollment period? This would define the study eligible population. The authors have not defined the fraction of the eligible population who were then enrolled (the enrollment fraction). The reader, thus, cannot know how significantly selection bias may have altered the characteristics of the final study cohort. We do know that 16.5 subjects were enrolled per hospital for 18 months, representing <1 subject per month per hospital.

As noted above, CLI is defined by symptoms and objective confirmation of foot ischemia. The authors use an unusual approach to the measurement and reporting of foot perfusion. The mean entry ankle-brachial index value was 0.70, which is high for any CLI cohort. As well, 19% of their subjects have an ankle-brachial index $>0.90$. These values might be anticipated by the high rate of dialysis-dependent ESRD, which is associated with noncompressible pedal arteries. Yet, current guideline-based CLI diagnostic algorithms suggest next-step use of absolute toe pressures (and toe-brachial index) to confirm the CLI diagnoses.$^{1}$ When pedal pressures are not reliable, toe perfusion values in a cohort can be compared with other CLI series. The pedal and toe pressures (not the ankle-brachial index or toe-brachial index) represent the troponin value of acute foot ischemia, serve as the best objective biomarker of ischemia, and are easily performed in multicenter clinical sites. These values are reproducible and predict both systemic and limb outcomes.

The authors document foot hypoperfusion via use of the noninvasive skin perfusion pressure (SPP) measurement, as an alternative method to measure distal foot perfusion. The postprocedure SPP measurement did show improvement, but the authors offer categorical reporting of changes in SPP, not absolute SPP values. Reporting of absolute pedal, toe, or skin pressures represents the internationally recognized reporting standard for CLI outcomes.

The authors present an unusual triad of factors that predict adverse AFS, including low body mass index, heart failure, and wound infection. Predictors of AFS in an ESRD cohort
would not, pre hoc, be anticipated to be similar to a non-ESRD, free-living CLI population. Using the PREVENT III CLI dataset, Schanzer et al demonstrated that dialysis (heart rate [HR], 2.81; \( P<0.0001 \)), tissue loss (HR, 2.22; \( P=0.0004 \)), age \( \geq 75 \) (HR, 1.64; \( P=0.001 \)), hematocrit \( \leq 30 \) (HR, 1.61; \( P=0.012 \)), and advanced coronary artery disease (HR, 1.41; \( P=0.021 \)) were significant predictors for AFS in a multivariable model. In the Olive registry, the best predictor of AFS was low body mass index, perhaps identifying subjects with the most adverse nutritional status.

The reported beneficial endovascular outcomes are impressive. The cohort had only a 7% 1-year rate of major amputation, but there is no report of minor amputations, which usually occur at a comparable rate (thus, the true amputation rate could be double that reported). The 1-year mortality in the OLIVE CLI cohort of 17% is frankly amazing: one-year mortality for an aged dialysis-dependent ESRD population is the OLIVE CLI cohort of 17% is known to be at least 25% (without PAD), or as high as 50% when PAD and gangrene are present.26,27 Why did these patients survive?

This article raises additional questions that might help guide future CLI registry design. The authors did not report major relevant disease outcome modifiers (e.g., blood pressure, low density lipoprotein, blood sugar, use of risk-reduction medications, social support). The authors did not report adjudicated cardiovascular disease outcomes (nonfatal myocardial infarction or stroke, cardiovascular disease hospitalization, or coronary procedures). In the absence of data collected on known disease modifiers or morbid outcomes, these data cannot be used to provide a reliable outcome-prediction model.

In summary, this article provides readers with an optimistic view of what might be achieved in real-world practice via current application of endovascular technology in patients with infragenicular CLI. AFS can be relatively high. This bodes well for patients with access to such clinical care tools.

The Future: High Quality CLI Registries

When registries are well designed, they can be highly informative. Achievement of a large, inclusive CLI cohort is not likely when subject entry is constrained to enrollment only from endovascular laboratories or from one cardiovascular specialty. Data collection should include all known and putative effect modifiers to key disease outcomes, beyond patency (including biological, anatomic, device-based, sociodemographic, and pharmacological factors). Sites must proactively collect all relevant outcome events, and a fraction of events should be reviewed and adjudicated for accuracy. CLI is a complex disease, and improvement of AFS is a key clinical goal. But, other measures of morbidity and cost associated with achieving a high AFS must also be measured; thus, such registries must use a reliable tool to measure functional status and quality of life. As such, future investigators will be poised to design better CLI-specific randomized controlled trials and observational studies.

The CLI Challenge and Hope

Why, thus far, have we relied on small, single-center, or limited multicenter registries to assess the determinants of quality outcomes for patients with CLI? A paucity of resources has been devoted to creation of a more robust CLI knowledge base by a fragmented set of stakeholders. We have achieved superb short-term patency outcomes that are the result of incremental endovascular advances, but these successes do not alter CLI incidence, the societal burden, and do not lower health care costs. The provision of endovascular (or PAD open surgical) procedures alone—divorced from access to high-quality podiatric and wound care, access to prevention-focused vascular specialists, and without access to rehabilitation medicine skills—cannot provide an adequate palliative approach, nor one that is population-scalable or sustainable at current costs.

The knowledge gaps are large. No prior clinical trial or registry has provided reliable data on how CLI might be prevented in vulnerable populations. It is not known whether any medical therapies alter rates of heart attack, stroke, death, or amputation in CLI patients. More reliable operational definitions of CLI (as in patients with chronic kidney disease) are needed for application in clinical trials and clinical care. There is no CLI population surveillance or significant investment in observational or interventional CLI clinical research. The null public health hypothesis (“Can intervention ‘X’ lower the incidence of CLI or improve AFS?”) is sustained by the null dataset available.

Yet, modeling the hard work completed by the OLIVE investigators, national health agencies, cardiovascular research sponsors, and health outcomes agencies could best serve the CLI public health challenge, if a national CLI scientific strategic plan were created. Invasive EVT is part of the answer, but is not the whole answer to the challenge of CLI. Cardiovascular public health challenges have never been resolved with nitinol alone. Population-based disease prevention and control require an expanded CLI science base, if we are to devise and deploy the most effective vascular therapies (EVT).

Disclosures

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References

Hirsch and Duval

Effective Vascular Therapies


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