

## Worth an Arm and a Leg: The Critical Importance of Limb Ischemia

Javier A. Valle, MD, MSCS; Stephen W. Waldo, MD

Critical limb ischemia (CLI) represents the final stages of peripheral artery disease, reflecting impairment in tissue perfusion that leads to a threatened limb. The clinical manifestations of this condition may be broad, ranging from rest pain to severe ischemic ulceration or tissue gangrene of the extremities. Unfortunately, this condition is relatively common, with an annual incidence of 3.5 patients per 1000 and a documented age-adjusted prevalence of 1.3% in the United States.<sup>1</sup> More concerning, the incidence of this condition will likely grow because up to 10% of patients with peripheral artery disease are expected to develop CLI over a 5-year period.<sup>2</sup> The primary therapeutic intervention for this condition focuses on urgent revascularization to facilitate tissue salvage, through percutaneous or surgical approaches. The immediate limb salvage rates with revascularization are encouraging, although subsequent morbidity and mortality remain high, with more than one third of these patients experiencing a major adverse cardiovascular event within 3 years of their initial presentation.<sup>3</sup> The need for urgent revascularization during the index presentation and the subsequent risk of adverse events make the treatment of CLI incredibly costly to patients and the healthcare system as a whole.<sup>4,5</sup>

In the article by Mustapha et al in this issue of the *Journal of the American Heart Association (JAHA)*,<sup>6</sup> the authors describe the clinical and financial burden of CLI among

Medicare patients. Using administrative billing codes, the authors identified all Medicare beneficiaries (72 199) treated for this condition in a single calendar year (2011). Procedural codes for endovascular revascularization, surgical revascularization, or amputation were also collected to stratify the clinical outcomes and costs on the basis of the initial treatment strategy. The authors found a similar incidence of CLI in this population as previously reported, with  $\approx 0.3\%$  of the cohort having a new diagnosis during the study period. The clinical outcomes of these patients were poor regardless of initial management strategy, with only 46% survival and 87% freedom from amputation over a 4-year follow-up period. Stratified by clinical presentation, rates of amputation and mortality were proportional to the acuity of presentation, increasing from patients with rest pain to those with ulcerations and highest among patients with gangrene. A propensity-matched cohort was constructed to compare outcomes among the different treatment modalities, with survival found to be comparable among patients undergoing percutaneous or surgical revascularization and significantly lower among those undergoing primary amputation. In addition to the significant personal burden, the financial costs of this condition were also calculated, with a mean expenditure of \$35 700 per patient-year, totaling  $> \$6.5$  billion for the population over the entire study period.

The authors should be commended for bringing additional attention to CLI, and attempting to investigate its clinical outcomes and financial costs across treatment modalities. However, the findings underscore some of the significant challenges in studying this population. CLI remains a broad diagnosis encompassing a wide range of presentations and various stages of limb threat. Billing codes were used to account for these differences, although these entities often have significant clinical overlap that is challenging to codify with administrative data alone. Furthermore, the breadth in presentations can also represent a wide range of anatomic locations for both wounds (ie, focal toe wounds or large forefoot ulcerations) and culprit lesions (ie, isolated femoral occlusions or severe multilevel atherosclerotic disease), requiring differing assessments and therapeutic approaches. The adoption of new billing codes (*International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM]*)

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From the Division of Cardiology, Department of Medicine, University of Colorado, Aurora, CO (J.A.V., S.W.W.); and Division of Cardiology, Department of Medicine, Veterans Affairs Eastern Colorado Health Care System, Denver, CO (J.A.V., S.W.W.).

**Correspondence to:** Stephen W. Waldo, MD, 1055 Clermont St, Denver, CO 80238. E-mail: stephen.waldo@va.gov

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will greatly improve the granularity of administrative data, including the laterality and location of lower extremity wounds, although this will require significant time for capture and maturation of the data set before analysis. Finally, residual confounding remains a concern in observational analyses, especially when considering the selection of different treatment modalities. In addition to a lack of granular data on wound severity, there are several patient-level factors that contribute to the selection of endovascular or surgical revascularization, including anatomic measures of peripheral artery disease complexity. These data are not available in administrative data sets and are impossible to adjust for with statistical methods, including the propensity matching used in the present analysis. For example, the costs for those undergoing amputation in this cohort in the year before study were >\$10 000 more than those of their counterparts undergoing endovascular or surgical revascularization, even after adjustment. This significant difference in cost before the index hospitalization suggests preexisting differences in medical complexity that could represent residual confounding when assessing differential outcomes. In addition, prescription of medications for secondary prevention and medication compliance are not easily ascertained from administrative sources, and these unobserved data may influence the observed relationships.

Despite these limitations, the present analysis has significant value. CLI remains a disease entity associated with significant morbidity and mortality in elderly patients, with unacceptably high rates of adverse events despite intervention. Although patients had overall lower rates of amputation than previously reported,<sup>7,8</sup> mortality remains exceedingly high, raising concerns about ongoing gaps in care for these patients after their revascularization. The data also demonstrate the extensive financial burden of this condition, which, if extrapolated beyond the 4-year costs of Medicare patients to the population as a whole, would represent tens of billions of dollars annually. In an era with increasing awareness of healthcare quality and value-based care, any improvement in clinical outcomes could lead to a significant reduction in healthcare expenditures. Finally, 40% of patients in this analysis received a primary treatment strategy other than attempted endovascular or surgical revascularization, and 30% of patients undergoing primary amputation did not carry a diagnosis of gangrene. These findings are surprising given the consensus recommendations for revascularization as the first-line therapy for this condition.<sup>2</sup>

How then to address these findings? First, CLI requires a multidisciplinary assessment and treatment plan, including medical management of the overall atherosclerotic disease burden, ancillary services focused on wound care, and a focused assessment on the options for endovascular or surgical revascularization. Medical therapy, including

antiplatelet agents, angiotensin-converting enzyme inhibitors, and statins, has been demonstrated to reduce adverse events in this vulnerable population.<sup>9–13</sup> Because of this, professional society guidelines have endorsed the use of these agents for all patients with peripheral artery disease and CLI.<sup>14,15</sup> Unfortunately, adherence to these guidelines remains underwhelming, with only 32% of patients with CLI receiving all guideline-recommended medical therapies in some series.<sup>16</sup> Implementation of programs that increase the adoption of guideline-directed medical therapies is needed.

Second, it is important to emphasize that urgent revascularization is imperative to improve outcomes in these patients. Prior data suggest that a substantial number of individuals with CLI do not undergo any revascularization attempt before amputation,<sup>17</sup> confirmed in the present analysis. Education about the importance of revascularization for limb salvage among primary care practitioners and ancillary services, like podiatry, are critical to improve outcomes for this condition. The optimal revascularization modality is more ambiguous, because investigations comparing different revascularization modalities have methodological limitations. Observational analyses comparing endovascular and surgical approaches are hindered by unmeasured confounding, even with optimal adjustment strategies. The most widely cited data for procedural care for this condition stem from a clinical trial that used an outdated definition of the disease entity, and the trial was performed before the current era of antiplatelet and statin therapy.<sup>18</sup> The results of the ongoing National Institutes of Health–sponsored randomized clinical trial assessing mortality and major adverse limb events after endovascular or surgical therapy (BEST-CLI [Best Endovascular Versus Best Surgical Therapy for Patients With Critical Limb Ischemia] trial; <http://www.clinicaltrials.gov>; unique identifier: NCT02060630) will be helpful in determining how best to approach revascularization in these patients.<sup>19</sup> Projected to complete in 2019 with a total enrollment of 2100 patients, the BEST-CLI trial offers the promise of a definitive assessment of the optimal contemporary revascularization modality for CLI. While awaiting these results, it remains important to ensure that as many patients as possible are afforded the opportunity of attempted revascularization regardless of modality.

In summary, these data demonstrate the significant clinical and financial burden that CLI poses to our healthcare system. Considerable efforts are still needed to raise disease awareness and establish data that can guide further medical and procedural management given the critical importance of limb ischemia.

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