CLI is a Major Public Health Concern With Prognosis Worse Than Many Types of Cancer

Jihad A. Mustapha, MD, Editor-in-Chief

The Critical Limb Ischemia (CLI) Global Society is a non-profit, patient-centered, advocacy, research, and public awareness professional society formed in 2016. The Society's mission is to improve the quality of life by preventing amputations and death due to CLI. The Society advocates for patients with CLI by collaborating with like-minded organizations that share an interest in CLI to address treatment, outcomes, and medical coding to improve care and prevent amputations for patients with CLI around the world.

On behalf of the Board of Directors of the CLI Global Society, we are honored to launch the first peer-reviewed journal focusing exclusively on CLI. *Journal of Critical Limb Ischemia* will bring to light original research from global experts, emphasizing the important role of the multidisciplinary team devoted to CLI treatment, innovative limb-salvage techniques, and related clinical research. You may ask, with so many journals currently available in the vascular space, why do we need a journal devoted to CLI? While CLI is becoming increasingly prevalent and deadly, CLI awareness and data are still severely lacking. Our focus will be to harness quality data and clinical advances and to disseminate this information in a timely manner to all clinicians involved in the treatment of this complex and debilitating disease.

Despite recent guideline updates on peripheral arterial disease (PAD) and CLI treatment, the standard of care for CLI across the United States is still not uniform. As a result, primary limb amputations occur prior to exploring revascularization options in a large proportion of CLI patients.[1] An estimated 150,000 amputations due to CLI occur annually,[2,3] and primary amputation continues to be first-line therapy for CLI at many healthcare institutions, up to ~20%.[4–9] Surprisingly, of the patients who undergo primary amputation, 73% do not have diagnostic angiography[8] and 54% receive no revascularization attempts prior to the amputation.[9] These statistics underscore that the contemporary management of patients with CLI is still highly variable and inadequate.[4,6,7,9]

When an individual first receives a diagnosis of CLI, the mortality risk is 24% over the first year and 60% over 5 years.[6] Few diseases connote a higher mortality rate. A helpful metric for quantifying the overall mortality burden of a disease is the 5-year incident mortality. That is, among all patients who receive a first-time diagnosis in a year, how many will die over the next 5 years? The annual incidence and 5-year mortality rate for CLI were derived from a Medicare claims analysis undertaken by the CLI Global Society.[4] We compared these values with 22 different malignancies derived from the Cancer Statistics Center of the American Cancer Society.[10]

Because CLI is both common and deadly, more patients die within 5 years of CLI diagnosis than with any type of cancer except for lung cancer. When comparing incident cases of CLI and 22 types of cancer, the diseases responsible for the most deaths over 5 years in the United States are lung cancer (192,000), CLI (58,000), pancreatic cancer (51,000), colorectal cancer (49,000), and liver cancer (35,000).

In a recent study by D. Armstrong, M. Conte, et al, 5-year mortality for people with diabetic foot complications was comparable to cancer. The five-year mortality rate was 46.2% for minor amputations and 56.6% for major amputations. This is compared with 9.0% for breast cancer and 80.0% for lung cancer. Five-year pooled mortality for all reported malignancies is 31.0%.[11]

Overall, the high incidence of CLI in combination with its highly fatal course make this disease an under-recognized major threat to public health. In 2013, the Recalcitrant Cancer Research Act was signed into law by President Barack Obama to develop national strategic plans to address the nation's deadliest cancers. These are defined as those with 5-year mortality rates >50%, and therefore includes cancers of the pancreas, lung, brain, esophagus, liver, ovary, and stomach. This legislation authorizes governmental research agencies to develop a comprehensive plan of action to coordinate prevention, early detection, and treatment research to lower mortality rates associated with these cancers. Unfortunately, no such legislation is pending for CLI, even though the 5-year mortality of CLI is >50%. Therefore, we encourage collaboration to continue raising public and health professional CLI awareness and concerted efforts to designate CLI as a national public health priority in the same manner as the deadliest malignancies. Only with a coordinated and comprehensive national plan to address all aspects of CLI, including diagnosis, treatment, and education of patients and healthcare providers, can the ever-growing impact of this deadly disease be controlled.[12]

Despite a multitude of devices and techniques to revascularize the critically ischemic limb, a paucity of high-quality evidence exists to assist in clinical decision-making. Only the results from the BASIL (Bypass Versus Angioplasty in Severe Ischaemia of the Leg) randomized trial[13] provide guidance, with hope that the

ongoing National Heart, Lung, and Blood Institute-sponsored BEST-CLI (Best Endovascular vs Best Surgical Therapy in Patients with Critical Limb Ischemia) randomized trial will offer modern guidance.[14] Of note, the BASIL trial was published in 2010 and is based on the use of older endovascular technology. A recent study published by the CLI Global Society analyzing Medicare beneficiaries with CLI who were treated with percutaneous transluminal angioplasty, stent placement, atherectomy, or surgical bypass noted only minor differences in mortality (ranging from 49.3%-54.7%) and major amputation rates (ranging from 6.8%-10.8%) over 4 years regardless of revascularization strategy.[15] This highlights the need for the development of new strategies and innovations to care for CLI patients.

In conclusion, despite advancing technologies available to treat CLI, we clearly have a long journey ahead of us on behalf of our patients. We are pleased to be able to provide a forum for original CLI work that will be reviewed by multidisciplinary, international CLI experts who understand the complex nature of CLI. The Editorial Board of *Journal of Critical Limb Ischemia* comprises physicians from across the globe who understand the difficulty and complexity of gathering CLI data. They are vascular surgeons, interventional cardiologists and radiologists, podiatrists, angiologists, and wound care experts. These experts are well aware of the reality of the advanced and complex nature of CLI disease with high 5-year mortality. Because of this, we believe that CLI trials should be modeled after diseases that have a high mortality rate over a short period of time. We must be able to capture the true nature of the disease and its impact on patients affected by it. If we continue to model CLI studies under the conventional nature of vascular disease in general we will never be able to achieve meaningful and convincing data to change the course of therapy. We desperately need new technologies to treat CLI to reduce the incidence of unnecessary amputations occurring in the United States and throughout the world. We clearly can, and must, do better. Our patients are demanding progress.

References

1. Mustapha JA, Saab FA, Martinsen BJ, et al. Digital subtraction angiography prior to an amputation for critical limb ischemia (CLI): an expert recommendation statement from the CLI Global Society to optimize limb salvage. *J Endovasc Ther.* 2020 May 29 (Epub ahead of print).
2. Hirsch AT, Duval S. The global pandemic of peripheral artery disease. *Lancet.* 2013;382:1329-1340.
3. Li Y, Burrows NR, Gregg EW, et al. Declining rates of hospitalization for nontraumatic lower-extremity amputation in the diabetic population aged 40 years or older; U.S., 1988-2008. *Diabetes Care.* 2012;35:273-277.
4. Mustapha JA, Katzen BT, Neville RF, Lookstein RA, Zeller T, Miller LE, Jaff MR. Determinants of long-term outcomes and costs in the management of critical limb ischemia: a population-based cohort study. *J Am Heart Assoc.* 2018;7:e009724.
5. Abu Dabrh AM, Steffen MW, Undavalli C, et al. The natural history of untreated severe or critical limb ischemia. *J Vasc Surg.* 2015;62:1642-1651.e3.
6. Mustapha JA, Katzen BT, Neville RF, Lookstein RA, Zeller T, Miller LE, Jaff MR. Disease burden and clinical outcomes following initial diagnosis of critical limb ischemia in the Medicare population. *JACC Cardiovasc Interv.* 2018;11:1011-1012.
7. Valle JA, Waldo SW. Worth an arm and a leg: the critical importance of limb ischemia. *J Am Heart Assoc.* 2018;7:e010093.
8. Henry AJ, Hevelone ND, Belkin M, et al. Socioeconomic and hospital-related predictors of amputation for critical limb ischemia. *J Vasc Surg.* 2011;53:330-339.e1.
9. Goodney PP, Travis LL, Nallamothu BK, et al. Variation in the use of lower extremity vascular procedures for critical limb ischemia. *Circ Cardiovasc Qual Outcomes.* 2012;5:94-102.
10. American Cancer Society. Cancer statistics center. Available at https://cancerstatisticscenter.cancer.org/?_ga=2.39975970.1231753458.1537645337-1450708034.1537467257#!/. Accessed February 18, 2018.
11. Armstrong DG, Swerdlow MA, Armstrong AA, Conte MS, Padula WV, Bus SA. Five year mortality and direct costs of care for people with diabetic foot complications are comparable to cancer. *J Foot Ankle Res.* 2020;13:16.
12. Mustapha JA, Katzen BT, Neville RF, et al. Critical limb ischemia: a threat to life and limb. *Endovascular Today.* 2019:18(5).
13. Bradbury AW, Adam DJ, Bell J, et al; BASIL trial participants. Bypass versus angioplasty in severe ischaemia of the leg (BASIL) trial: a survival prediction model to facilitate clinical decision making. *J Vasc Surg.* 2010;51:52S-68S.
14. Menard MT, Farber A, Assmann SF, et al. Design and rationale of the best endovascular versus best surgical therapy for patients with critical limb ischemia (BEST-CLI) trial. *J Am Heart Assoc.* 2016;5:e003219.
15. Mustapha JA, Katzen BT, Neville RF, et al. Propensity score-adjusted comparison of long-term outcomes among revascularization strategies for critical limb ischemia. *Circ Cardiovasc Interv.* 2019;12:e008097. Epub 2019 Sep 9.

Address for correspondence: Jihad A. Mustapha, MD, Advanced Cardiac and Vascular Amputation Prevention Centers, 1525 E. Beltline Ave. NE, Suite 101, Grand Rapids, MI 49525. Email: jmustapha@acvcenters.com