



# Revascularization for Claudication and Subsequent Chronic Limb-Threatening Ischemia: Separating Association From Causation

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*On Behalf of the CLI Global Society Publications Committee*

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## Introduction

A recent, widely cited publication by Alabi et al<sup>1</sup> evaluated progression to chronic limb-threatening ischemia (CLTI) after index revascularization for claudication as well as differential risks based on ethnoracial and sex identification. We have significant concerns related to the overarching conclusions of this study, prompting us to more deeply evaluate the issue of progression to CLTI.

The study from Alabi et al reported that in 10,012 patients undergoing lower extremity revascularization for claudication from the Medicare-linked Vascular Quality Initiative procedural registry from 2016 to 2019, the risk of developing CLTI within 180 days after revascularization was 5.4% for men and 6.5% for women. Rates were highest in Black women (11.8%), Hispanic men (8.8%), and Black men (7.2%).

Alabi et al demonstrate an important association between revascularization for claudication and subsequent CLTI, but their study cannot establish that revascularization causes progression. The observed association may reflect misclassification, confounding by indication, higher-risk anatomy, early treatment failure, inequitable care, or genuine procedure-related harm in selected subgroups.

## Are We Doing Harm to Patients by Treating Claudication Invasively?

Restoring blood flow when coupled with optimal medical/exercise therapy intuitively should prevent the development of CLTI. In fact, when discussing claudication, the topic of progression to CLTI is not well established; it is frequently argued that treating claudication can be associated with progression of disease. Evidence from carotid and coronary disease illustrates that preventive revascularization can improve selected outcomes in carefully

defined anatomical and physiological settings.<sup>2,3</sup> However, the results of these alternative vascular bed treatments cannot be directly transferred to lower extremity claudication, where the primary benefit is symptom and functional improvement rather than prevention of limb loss.

Is there a scientific rationale for the “paradox” that restoring blood flow could lead to progression of CLTI? A thought experiment could yield potential mechanisms: (1) angioplasty of a vessel without accompanying drug-eluting devices can stimulate neointimal hyperplasia, leading to restenosis or occlusion; (2) invasive vascular procedures could increase inflammation, triggering progressive atherosclerotic disease; (3) loss of collateral flow from index intervention could raise the risk should reocclusion occur; and (4) procedural complications or embolization during the index procedure could lead to acute or chronic limb ischemia.

While acknowledging these potential mechanisms, we feel that treatment of claudication leading to CLTI progression is much more nuanced than implied by Alabi et al and seek to highlight issues with the design and subsequent conclusions drawn from the study. To be clear, we are not challenging the assertion that disparities based on sex and race or ethnicity exist. Multiple studies have shown that these disparities are significant problems in the U.S. health care system with groups such as women, Hispanic patients, and Black patients having limited access to high-quality care.<sup>4-6</sup> We take issue with the more basic conclusion of the study that in all-comers, treatment of claudication is associated with more rapid development of CLTI.

## Concerns Related to the Recent Publication From Alabi, et al

First, the study blends claudication and CLTI as points along a single disease spectrum. Claudication and CLTI are fundamentally different clinical entities with distinct pathogenesis.<sup>7</sup> Claudication

results from flow-limiting stenosis in the setting of stable atherosclerotic plaque, with a benign natural history and low amputation risk. CLTI involves severe multivessel, multilevel disease usually involving the tibial vessels compounded by microvascular dysfunction, neuropathy, and an inflammatory milieu that is absent in most claudicants. The Global Vascular Guidelines explicitly recognize CLTI as a distinct disease state requiring separate staging and treatment paradigms.<sup>7</sup> Treating progression to CLTI after a claudication intervention as a uniform outcome mixes natural history with procedure-related complications and conflates disease categories that demand different management.

Second, the use of Rutherford 4 ischemic rest pain as an outcome variable as part of the ICD-10 CLTI definition is problematic due to its highly subjective nature. In this cohort, amputation was rare, so using the endpoint of amputation in isolation substantially reduces statistical power and misses clinically important progression that results in rest pain, tissue loss, repeated intervention, hospitalization, or severe quality-of-life deterioration. The ideal endpoint should distinguish true clinical progression from coding transitions and capture both limb threat and patient-centered harm. A composite of objectively confirmed CLTI, tissue loss, major adverse limb events, amputation, and death, with separate reporting of quality-of-life and functional outcomes, would be more informative than either a claims code or amputation alone.

Furthermore, the question of whether some of the study patients were actually Rutherford 4 CLTI at the time of index procedure and may have been misclassified in the Vascular Quality Initiative database is a real concern. About 8% of the cohort underwent index tibial intervention, which is usually reserved for the treatment of CLTI. Patients undergoing index tibial intervention should have been analyzed separately, with prespecified sensitivity analyses excluding tibial-only and femoropopliteal-plus-tibial procedures. A 2025 Medicare-linked registry study found higher 3-year conversion to CLTI after infrapopliteal intervention than after isolated femoropopliteal intervention (33.3% vs 23.8%, adjusted hazard ratio 1.39). Amputation was also higher after infrapopliteal intervention.<sup>8</sup> These patients may have had more extensive or advanced peripheral artery disease (PAD) than the coded procedural indication suggested.

Third, a central methodological issue is that the study lacks a non-revascularized comparator. Without one, the study cannot establish whether the procedure increased risk relative to medical therapy and exercise. Randomized evidence does not demonstrate that revascularization reduces progression to CLTI, nor does it establish that revascularization increases it. It does, however, suggest that invasive treatment leads to more repeat procedures and should therefore be reserved for patients with substantial, persistent functional limitations.<sup>9</sup>

Fourth, the data window (2016-2019) is now 7 to 10 years old. Guideline-directed medical therapy has evolved substantially,

most notably with the VOYAGER PAD trial, which showed that rivaroxaban 2.5 mg twice daily plus aspirin reduces major adverse limb events after revascularization.<sup>10</sup> The treatment-era lag limits the study's external validity. Modern studies should examine whether outcomes differ with current antithrombotic therapy, lipid-lowering strategies, access to structured exercise, device technology, and present-day appropriateness criteria.<sup>11</sup>

Finally, in patients with intermittent claudication, early identification of PAD does not necessarily translate into improved clinical outcomes, particularly when the disease remains clinically stable and does not progress to CLTI. As with lead-time bias, earlier recognition of PAD may lengthen the observed interval between diagnosis and an adverse event without necessarily altering the underlying natural history of the disease or reducing morbidity. However, it remains unclear whether patients presenting with claudication who ultimately progress to CLTI represent an early stage of the same disease process or a distinct phenotype with additional, poorly understood biological or clinical triggers. The specific factors that precipitate the transition from asymptomatic to symptomatic PAD to CLTI remain incompletely defined. Indeed, the severity of anatomic disease does not always correlate with clinical presentation: some patients with extensive and technically challenging PAD remain asymptomatic, whereas others with relatively limited or anatomically straightforward lesions may develop tissue loss or arterial wounds. This apparent disconnect between anatomic disease burden and clinical manifestation highlights the complex and multifactorial nature of CLTI. This also underscores the limitations of relying solely on early anatomic diagnosis to predict subsequent limb-related outcomes.

## Conclusion

Alabi et al identify an important association between revascularization for claudication and subsequent diagnosis of CLTI, particularly among Black women. The observational design, claims-based outcome definition, absence of a non-revascularized comparator, and heterogeneous procedural cohort do not establish that revascularization causes progression. The association may reflect confounding by indication, unrecognized advanced disease, procedure-related failure, differences in access and follow-up, or a combination of these factors.

Claudication and CLTI are distinct clinical syndromes within the spectrum of PAD. Revascularization for claudication should therefore be reserved for patients with substantial functional limitations despite guideline-directed medical therapy and structured exercise, with careful attention to anatomy, procedural durability, and the potential harms of repeat intervention. Future studies should focus not simply on whether claudication should be treated, but on which patients benefit, which procedures may cause harm, and how equitable care can reduce progression and limb loss.

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