



When “No Options” is No Longer an Option: Moving the Needle Forward in Advanced Stage Critical Limb Ischemia

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Despite significant advances in the diagnosis and treatment of peripheral arterial disease (PAD), the incidence remains remarkably high and increasing worldwide.¹ In part, this is due to the fact that the clinical course and management of PAD remains understudied and underfunded in comparison with cardiovascular and cerebrovascular conditions. The individual-level and population-level economic burden of PAD and critical limb ischemia mandates further understanding, as the cost of care is approaching nearly \$6.1 billion in the United States alone.² Notably, the vast majority of costs are incurred by patients with advanced stage disease, in particular, critical limb ischemia with tissue loss. Although peripheral vascular revascularization rates have increased in the past decade, both due to refinement in technique and the development of new technology, amputation rates remain high.³ Amputation is one of the most morbid and fatal sequelae of cardiovascular disease, with an immediate impact on quality of life and prognosis on par with the most advanced cancers.⁴

The current study⁵ curates and centralizes a significant amount of work that sheds light on the overall dismal clinical course of patients with Rutherford category 5 and 6 PAD and “no options” for revascularization. In this meta-analysis, Ghare et al⁵ compiled 32 studies of more than 1400 Rutherford^{4,6,7} patients that examine outcomes after they were deemed to have no revascularization options, making this the largest single piece of work examining this patient population. The primary endpoint evaluated was amputation-free survival (AFS) at either 6 or 12 months. The authors found that AFS increased significantly after 2003 at both 6- and 12-month intervals (48.3% vs 68.3% after 2003 and 47.3% vs 57.2% after 2003, respectively), but remained similar between 2003-2010 and 2010-present, potentially reflecting an initial stepwise improvement in medical or interventional therapy that has now plateaued. After risk adjustment accounting for the slightly lower risk of Rutherford category 4 patients included in some studies, the investigators found an AFS rate of 42.0% at 6 months and 33.3% at 12 months. The study overall demonstrates that among patients with severe disease who have progressed past medical management and traditional revascularization options, we still have a long way to go to make a meaningful impact on reducing amputation rates and improving survival.

A key tenet that arises from this study is the necessity for early detection and intensive medical management, as this is likely the single most effective way to reduce the burden of not only amputations, but PAD as an entity. While the most effective known interventions are lifestyle changes (ie, smoking cessation, exercise therapy, and comorbidity management) and aggressive medical management with statins and antiplatelets, there remain significant barriers to achieving these goals, especially in regard to patient awareness.^{6,7} The lack of support for routine ankle-brachial index screening of high-risk patients has remained a major obstacle to improving the opportunity to implement early preventative measures for those at risk of PAD and amputation.⁸ This recommendation against screening contradicts supportive randomized trial data.⁹ Furthermore, our efforts at optimizing medical and lifestyle therapies among those with known PAD have been met with marginal success. For instance, in patients with diagnosed PAD who remain smokers, only 35% of patients receive counseling or medication. In addition, among all patients diagnosed with PAD, as few as 33% are taking statins despite the well-known benefits of these therapies.¹⁰ In addition to appropriate pharmacologic management, supervised exercise therapy is well established at improving symptoms of stable PAD and cardiovascular conditioning, yet many physicians have never referred patients to a supervised exercise program and nearly a third of physicians surveyed did not know whether CMS reimburses for exercise therapy.^{6,11} This has resulted in dismal utilization, as highlighted by a recent assessment of Medicare data demonstrating that only 1.3% of insured patients diagnosed with claudication were enrolled in supervised exercise therapy.¹²

On the other end of the spectrum, the population of patients deemed to have no revascularization options is continuing to shrink. Multidisciplinary, standardized strategies to approach limb care for patients deemed to have no-option critical limb ischemia have resulted in improvements in 1-year limb-salvage rates.¹³ Furthermore, novel techniques to improve limb flow have provided additional opportunities for these patients to delay or avoid amputation. In particular, the recent re-emergence of deep vein arterialization has created a treatment opportunity for many patients traditionally deemed to have no revascularization options. The LimFlow device, which arterializes the peroneal vein at the tibioperoneal trunk, has yielded amputation-free

survival rates of 83% at 6 months and 67% at 24 months in patients with Rutherford categories 5 and 6 disease, as well as achieving complete wound healing in 73% of all treated patients.¹⁴ As this procedure continues to be refined, it has the opportunity to make a substantial impact on limb-salvage rates.

As we progress through this next decade, it is critical that we invest in preventative care, foster the implementation of multidisciplinary and multidimensional therapeutic strategies into routine PAD practice, and promote the development of new technologies for revascularization in order to improve the long-term outcomes for this complex patient population. With time and investment, we may be able to retire the term “no option” and finally move the needle forward on reducing amputations.

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