Treatment of Infrapopliteal Disease in Critical Limb Ischemia

Beyond Angioplasty

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Revascularization for critical limb ischemia (CLI), the most advanced form of peripheral artery disease, is the only treatment that has shown to reduce amputations. Indeed, all societal guidelines have given a class I indication for revascularization in patients with CLI. However, individuals with CLI frequently present with multilevel disease where >70% have some degree of infrapopliteal involvement, and these lesions are typically occluded and long. Although there have been significant advances in the femoropopliteal segment with drug-eluting stents (DES) and drug-coated balloons, some progress has been made for the treatment of infrapopliteal disease. Yet, the rates of amputation and mortality continue to decline in patients with CLI, whereas surgical bypass has significantly decreased. Given the paucity of advances for infrapopliteal disease, Mustapha et al, in this issue of Circulation: Cardiovascular Interventions, examined the current state of angioplasty for the treatment of infrapopliteal disease through conducting a meta-analysis and a systematic review of all studies from 2005 to 2015.

The authors analyzed 52 contemporary studies of 6769 patients with ≈9400 infrapopliteal atherosclerotic lesions in patients with CLI (97%). They found a technical success rate of 91% with a 63% primary patency. Rates of major amputation (15%) and all-cause mortality (15%) were also similar to those of Romiti et al, previously published in 2008. The authors concluded that there were suboptimal short- and long-term clinical outcomes with angioplasty in patients with CLI.

The authors should be congratulated for conducting this contemporary analysis of patients with CLI undergoing angioplasty alone. However, as indicated by the investigators, the robustness of this meta-analysis is markedly limited because of the incompleteness and heterogeneity of patient and lesion characteristics, reported outcomes, and their definitions across individual daughter studies. The majority of the studies were from a single center (83%), some had a sample size as small as 15 patients, and many were retrospective. Indeed, there is no explanation for the differential report for major amputations among the prospective studies (6.2%) compared with 18.6% with retrospective analyses. In addition, only 28 of the 52 studies reported Rutherford class, only 10 studies reported the presence of calcifications; furthermore, there was no mention of the inflow disease status or medication use, both of which may impact clinical outcomes.

More importantly, only 19 studies reported primary patency using inconsistent definitions, and only 7 studies reported all outcomes. There was also significant publication bias with some outcomes (revascularization and major amputation) and persistent inconsistencies for all 1-year outcomes with high $I^2$ scores. Many other limitations are present; for example, there are no data on operator experience, wound size, presence of infection, and perfusion assessment. Furthermore, important information on the angiosome, number of tibial vessels treated, and pedal arch patency is missing.

The study also has surprising results that cannot be explained. For example, lesion length, calcification, and occlusive status were not associated with primary patency or revascularization. Furthermore, short and less calcified lesions were associated with higher mortality. Collectively, these findings highlight the limitations and validity of some of the previous studies.

Given the extensive limitations listed above, what does the current study teach us? First, we have an obligation to our patients and to our field to conduct more rigorous, scientifically sound, and comparative studies. To do this, we need to establish a wound classification system that can be applied across multiple studies so that valid comparative analyses can be conducted. The recent wound, ischemia, and foot infection classification is a step forward but has many limitations. For example, the current societal guideline recommendations for ankle-brachial index to assess perfusion, which is also used by the wound, ischemia, and foot infection classification, are only accurate in 6% of the patients. Second, better tools are needed to assess the quality of angioplasty at the time of procedure. This is especially relevant to the infrapopliteal vessels where angioplasty without stenting is the primary treatment. Frequently, patients are treated with undersized balloons with significant dissections and residual stenoses. Invasive tools such as intravascular ultrasound for proper vessel sizing and fractional flow reserve to help identify hemodynamically significant postangioplasty lesions may improve outcomes in these patients. Third, the role of adjunctive therapies such as atherectomy in this patient population must be clarified. Although prospective registries have shown promising
safety and efficacy data, to date, there are no randomized trials proving the added benefit of atherectomy to angioplasty in treating infrapopliteal disease. Fourth, we must identify better methods to assess short- and long-term patency in infrapopliteal lesions. Hemodynamic assessment, pre- and postprocedure and in follow-up, is one approach to monitor perfusion status after intervention; however, current tools to assess perfusion have many limitations. Other invasive tools such as duplex ultrasound, computed tomographic angiography, and magnetic resonance angiography can be useful but are also limited because of calcific shadowing in tibial vessels, patient size, renal toxicity, radiation exposure, and high cost. Importantly, these tools are not widely available and most require special expertise. Fifth, we agree with the authors’ conclusions of suboptimal results with angioplasty with low primary patency and high rates of major amputation. However, we think that although amputation is an important end point, it fails to capture rates of wound healing, time to ambulation, and quality of life, important end points that directly affect our patients and may provide additional information regarding the efficacy or lack thereof of angioplasty for the treatment of infrapopliteal disease in patients with CLI.

Another important limitation of the current study is the lack of comparative data on provisional utilization of bare-metal and DES in the proximal infrapopliteal arteries. Three randomized clinical trials have compared DES with either bare-metal stents or angioplasty alone for infrapopliteal disease. Overall, DES had higher patency, reduced reintervention, reduced amputation, and improved event-free survival over angioplasty or bare-metal stents; however, Many of these patients had claudication alone. It would have been interesting to know the rates of technical success, primary patency, and major amputation in patients undergoing infrapopliteal angioplasty with provisional DES placement.

Although technological advances for treating infrapopliteal disease have been limited, many technical ones have been made. These include the retrograde tibiopetal access to improve technical success. Furthermore, with more flexible balloons, pedal arch angioplasty is now possible (Figure). Finally, we now have better understanding of the importance of proper balloon sizing, prolonged inflation, and acute luminal gain to improve and maintain short- and long-term patency. Collectively, there is room for improvement despite the limited number of tools that are currently available for treating infrapopliteal disease.

The study by Mustapha et al also highlights the importance of a personalized approach in treating complex patients with CLI. Not all patients with CLI and infrapopliteal disease should undergo an endovascular approach. Important factors such as patient and lesion characteristics, wound size, availability of venous conduits, and target vessel with foot runoff should be considered. Beyond this, CLI requires a multidisciplinary approach in dedicated centers with experienced operators.

Management of CLI continues to evolve with decreasing numbers of open bypass, but yet there is a sustained decrease in the rates of amputation and mortality. This is despite an increase in the prevalence of comorbidities such as diabetes mellitus, chronic kidney disease, and obesity. Beyond better tools and techniques, many other challenges remain. These include proper reimbursement for treating complex lesions and patients, underutilization of revascularization in patients undergoing amputation, and continued disparities in revascularization and amputation among blacks and those of lower socioeconomic status. Although better procedural techniques are important, without a comprehensive approach that involves the patient, physician, institutions, and payers, our results will remain suboptimal.

**Disclosures**

None.
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References


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