Contemporary Outcomes of Endovascular Intervention for Critical Limb Ischemia

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KEYWORDS

• Critical limb ischemia • Peripheral arterial disease • Revascularization

KEY POINTS

- Critical limb ischemia (CLI) remains an important cause of significant morbidity and mortality.
- Although limited randomized data are available, an endovascular first approach seems an acceptable alternative to open surgery, especially in patients with high risk of morbidity and mortality in the perioperative setting.
- Specific outcomes in the CLI population vary among trials related to a variety of endovascular therapies, patient populations, and inconsistent administration and reporting of adjunctive wound care.
- Newer therapeutic options for endovascular therapies, such as atherectomy devices and drug-coated balloons (DCBs), may improve procedural outcomes and durability but remain to be rigorously studied in the CLI population.

INTRODUCTION

It is estimated that more than 200 million people worldwide have lower extremity peripheral arterial disease (PAD).[1] Although the economic impact of symptomatic PAD is substantial, the morbidity and mortality in patients with CLI highlight the importance of this disease process. Modern data suggest that amputation rates of 35% to 67% persist in CLI patients.[2] The mortality after a first lower extremity amputation is estimated to be 25% at 30 days and 50% at 1 year.[3] The cause of death in the majority of these patients is related to cardiovascular causes — and as such CLI represents a potent marker for future cardiovascular risk.[4] Concordant with this statement are the recent data related to CLI admissions from the National Inpatient Sample, which demonstrated a steady decrease over the past decade in amputation rates in this population with a much less robust decline in mortality.[5]

TREATMENT STRATEGIES FOR CRITICAL LIMB ISCHEMIA

Given that CLI represents a marker for systemic vascular and often multisystem organ dysfunction (eg, renal disease, diabetes, and obesity), a 2-pronged approach addressing both limb salvage and the underlying medical comorbidities is obligatory. Although this review focuses on revascularization — specifically, the outcomes of endovascular therapy — the importance of medical therapy for reduction of future cardiovascular events should not be ignored. With regard to limb salvage, treatment of CLI is aimed at improving peripheral arterial perfusion via timely

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revascularization coupled with adjunctive wound care.

Antiplatelet Therapy

In patients with symptomatic PAD, antiplatelet therapy with aspirin alone or clopidogrel alone remains a class I recommendation.[6] Antiplatelet therapy confers a 22% odds reduction for cardiovascular events, including myocardial infarction, stroke, and vascular death.[7] Some data highlight the uncertainty in this field, however: a meta-analysis of 18 randomized controlled trials with more than 5200 patients did not find a statistically significant reduction in the primary endpoint of cardiovascular death, MI, and stroke.[8] Specific agents remain an active area of interest with clopidogrel demonstrated superior to aspirin in cardiovascular risk reduction in a population of patients with systemic atherosclerotic vascular disease, including symptomatic PAD.[9] Ticagrelor, a reversible inhibitor of P2Y12, was not shown superior to clopidogrel for the reduction of cardiovascular events in patients with symptomatic PAD.[10]

Vorapaxar is a novel antiplatelet agent that antagonizes the protease-activated receptor (PAR-1). By inhibition of PAR-1, thrombin-mediated platelet aggregation is inhibited. This receptor is also present on vascular endothelium and smooth muscle, where its mechanism of action result in mitogenicity.[11] Vorapaxar was found to reduce the incidence of cardiovascular death or ischemic events when added to a background of aspirin and thienopyrdine or warfarin in patients with a history of myocardial infarction, stroke, or peripheral vascular disease. There was an increased risk of bleeding, however, especially in patients with a history of stroke.[12] A prespecified PAD cohort containing more than 3500 patients with a history of intermittent claudication and ankle-brachial index less than 0.85 or previous revascularization for limb ischemia was also analyzed with respect to a composite endpoint of MI, stroke, and cardiovascular death and secondary endpoints of acute limb ischemia, peripheral revascularization (urgent and elective), and urgent hospitalization for vascular cause of an ischemic nature.[13] Vorapaxar did not reduce the risk of cardiovascular death, MI, or stroke in patients with PAD; however, vorapaxar significantly reduced acute limb ischemia and peripheral revascularization. These benefits were accompanied by a higher risk of bleeding. In the 2016 American Heart Association/American College of Cardiology Guideline on the Management of Patients with Lower Extremity Peripheral Artery Disease, vorapaxar has a class IIB (level of evidence B-R) indication for the medical management of PAD.[6]

Statin Therapy

In the Heart Protection Study, which included 6748 patients with PAD, 40 mg of simvastatin daily reduced the rate of first major vascular event by 22% relative to placebo.[14] Kumbhani and colleagues[15] showed that statin use in patients with PAD reduced 4-year adverse limb-related events (worsening claudication, new CLI, new lower extremity revascularization, and new ischemic amputation) compared with no statin use.

Angiotensin-converting Enzyme Inhibition

Angiotensin-converting enzyme inhibitors are currently a class IIA recommendation in the management of patients with PAD.[6] In patients who were normotensive at the time of enrollment, 4051 patients with PAD treated with ramipril experiences a 25% reduced risk of MI, stroke, or vascular death.[16]

Smoking Cessation

Perhaps the most critical intervention in the management of PAD is tobacco cessation counseling. Observational studies suggest that smoking cessation is associated with lower rates of cardiovascular ischemic events, limb-related events, bypass graft failure, amputation, and death in patients with PAD.[6,17–20]

Revascularization

The choice of revascularization approach has important implications in selecting endpoints and outcomes when performing trials for CLI patients. In the coronary literature, selecting between medical therapy, surgical bypass, or percutaneous coronary revascularization for individual patients has remained a moving target — with approximately 3 decades of randomized clinical trials. In contrast, there is a paucity of data to guide therapy in CLI. Prior to the development of endovascular techniques, open surgical approaches dominated the treatment of CLI. Limitations of surgery have centered on perioperative morbidity and mortality in a sick population and anatomic challenges related to adequate graft conduits, inadequate distal targets, and poor outflow. In part due to reduced procedural morbidity and mortality, endovascular techniques have become the first-line approach to CLI revascularization, with a marked temporal decline in surgical procedures.[5] This shift has been related to decreasing rates of major amputations in the United States — however, whether this relationship is causative or associative remains a point of uncertainty.

The early experience with balloon angioplasty compared with surgical revascularization in the