



The Natural History of Intermittent Claudication

Considering atypical presentations of symptomatic peripheral artery disease and the associated major adverse events.

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Intermittent claudication is described as a symptom pattern that includes the development of limb muscular discomfort—commonly described as burning, aching, or heaviness—at a predictable amount of walking that is relieved with a predictable amount of rest (approximately 5–10 minutes of rest). It includes neither pain at rest nor pain with standing. However, this textbook definition describes the minority of patients with symptoms arising from peripheral artery disease (PAD). Only approximately 20% to 30% of patients with known PAD present with classic symptoms of intermittent claudication.¹ Most patients with PAD have atypical or exertional leg symptoms, including leg pain on exertion and rest and atypical leg pain that causes patients to stop walking. Some patients exhibit no exertional leg pain with activity, and others have no exertional leg pain due to inactivity.² Many patients with PAD are asymptomatic, despite having abnormal ankle-brachial indexes (ABIs), because of they makes accommodations for their physical limitation.

Comorbidities that contribute to this varying clinical presentation of PAD have been previously studied. These include diabetes mellitus, neuropathy, intervertebral disc disease, arthritis, and spinal stenosis—all of which may contribute to the walking impairment in these patients. Although impaired perfusion may be the primary abnormality associated with PAD, secondary changes in the skeletal system, mitochondrial dysfunction, denervation, and replacement of myocytes with fatty tissue may also contribute to the ambulatory dysfunction in patients with both typical and atypical PAD leg symptoms. Indeed, patients with leg pain at rest and on exertion have a higher prevalence

of comorbid disease, greater walking impairment, and worse overall function, making clear that atypical presentations may have more adverse implications than standard symptoms.

NATURAL HISTORY OF SYMPTOMATIC PAD

Patients with PAD can experience clinical worsening over time. There are three forms of symptom worsening in the limbs: progressive claudication, development of critical limb ischemia (CLI), and occurrence of acute limb ischemia (ALI).

Claudication

Intermittent claudication can progress with worsening symptoms that become lifestyle limiting if not appropriately treated. Intermittent claudication is a stable or slowly progressive disease. Older data suggest that ambulatory decline is slowly progressive. Aquino et al followed 1,244 claudicants for up to 15 years.³ They reported an average ABI decline rate of 0.014 per year and a decline in self-reported walking distance of 9 yards per year. In a study of patients with claudication and severe reduction in acral blood perfusion (toe pressure \leq 40 mm Hg), two-thirds remained stable over the mean follow-up of 31 months.⁴ McDermott et al followed 676 patients over 2 years, reporting that lower baseline ABI values and PAD with leg pain on exertion and rest were associated with greater mean annual decline in 6-minute walk performance than other clinical presentations. Moreover, a subset of patients with asymptomatic PAD may be associated with the greatest mean annual decline in 6-minute walk performance. These patients were at increased risk for becoming



unable to walk for 6 minutes continuously, suggesting that many of these patients were not walking to avoid pain rather than truly asymptomatic.⁵

In the EUCLID study of 13,885 patients with PAD followed for 30 months, approximately 17% underwent lower extremity revascularization.⁶ This population was mixed such that approximately 8,000 participants underwent previous revascularization and 6,000 did not. Previous revascularization is a risk factor for future revascularization, suggesting that patients without previous intervention will likely have lower revascularization rates. In short, patients with intermittent claudication are largely stable over the acute and intermediate terms. Patients with a history of smoking, diabetes mellitus, other active vascular disease, and previous revascularization likely represent high-risk groups and may have a higher probability of requiring revascularization.

Critical Limb Ischemia

Of the total patient population with PAD, approximately 1% to 2% have chronic CLI.^{7,8} As reported by Aquino et al, among 1,244 patients with claudication, 23% of the cohort developed ischemic ulceration and an additional 7% also developed ischemic rest pain over 10 years of follow-up.³ Major and minor amputations occurred with a cumulative frequency of < 10%. The authors reported that these numbers significantly varied in terms of baseline ABI and the presence or absence of diabetes mellitus. For patients with an ABI > 0.5 and without diabetes, the risk of ischemic ulceration at 10 years was approximately 10%; for participants with both an ABI < 0.5 and diabetes, the risk approached 60%. Diabetes had a greater impact than ABI reductions.

Of the 5,845 patients with known PAD in the TRA2°P-TIMI 50 trial, 16% underwent at least one peripheral revascularization over a median time of 2.5 years. More than half (55%) of the procedures were for worsening claudication, followed by 24% for CLI, 16% for ALI, and 4% for asymptomatic severe stenosis.⁹ These data suggest a worsening rate of claudication symptoms of approximately 4% per year and just 1% to 2% per year for CLI,⁹ which is similar to the data from more than a decade earlier by Aquino et al.³

The presence of microvascular disease is reported to be a significant factor in amputation risk. In a cohort of 125,674 veterans, the presence of microvascular disease increased the risk of amputation over 9 years from 14- to 23-fold in patients with PAD.¹⁰ These hazards were true in the presence or absence of diabetes mellitus, smoking, hypertension, and renal disease.

Acute Limb Ischemia

Recently, the risk of ALI has become clearer in patients with PAD. In the TRA2°P-TIMI 50 trial, 1.3% of patients with symptomatic PAD developed ALI annually.¹¹ The frequency of ALI was similar to amputation in the trial. Similar rates of ALI were noted in the COMPASS and FOURIER trials.^{12,13} Predictors of ALI include previous revascularization, smoking, and lower ABI. The risk of ALI was reduced in these trials by vorapaxar and evolocumab.

ADVERSE EVENTS

Major Adverse Limb Events

Several trials have examined a broad set of outcomes in patients with symptomatic PAD. At 2.5-year follow-up in FOURIER, 2.6% of patients with symptomatic PAD but no previous myocardial infarction (MI) or stroke who were treated with placebo developed major adverse limb events (MALEs), 1.8% had ALI or major amputation, and peripheral revascularization was performed in 12.3%. Furthermore, in patients with PAD who were treated evolocumab, 1.3% experienced MALEs. The COMPASS investigators reported that the combination of ALI, chronic limb ischemia, and major vascular amputation occurred in 3.4% of participants with symptomatic PAD and 0.9% of participants with asymptomatic PAD over 23 months of follow-up.¹² This rate was significantly reduced in symptomatic patients with rivaroxaban. Similarly, vorapaxar reduced the need for endovascular and surgical revascularization and the occurrence of ALI in patients with symptomatic PAD.^{9,12} There are no other prospectively studied therapies that reduce the rates of MALEs and amputation.

Major Adverse Cardiovascular Events

The presence of symptomatic PAD is also associated with an increased risk of MI, stroke, and death. Among a large cohort of veterans, PAD was associated with a 30% mortality rate over 10 years of follow-up¹⁴ and a 5.8% annual incidence of death, acute MI, and coronary revascularization.¹⁰ Similar event rates have been reported by Diehm et al in the getABI study.¹⁵ In this cohort of 6,880 patients who were prospectively screened by ABI, the annual incidence of death was 4.6% and 3.5% for combined MI, coronary revascularization, and cardiovascular death among patients with PAD. Event rates were higher in patients with symptomatic disease compared to those without symptoms, and both groups had significantly higher event rates than participants without PAD.

In the EUCLID trial, patients with PAD could be recruited based on a diagnostic ABI or previous revascularization.



Patients who had undergone previous revascularization were more likely to develop MI during follow-up. However, the primary composite endpoint of cardiovascular death, MI, or ischemic stroke over a median 30-month follow-up did not differ statistically among patients who were enrolled based on previous revascularization versus ABI (11.4% vs 9.9%, respectively).⁶

The most recent multispecialty PAD guidelines were published in 2016.¹⁶ As of that edition, standard medical therapy for symptomatic PAD includes aspirin or clopidogrel monotherapy, statin therapy, blood pressure control (including the use of an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker), and smoking cessation. The guidelines were published before reports and FDA approval for rivaroxaban and evolocumab for those with PAD.

CONCLUSION

The natural history of intermittent claudication is beset by both limb morbidity and cardiovascular morbidity and mortality. The symptom complex of claudication, for most patients, slowly and progressively declines over time. Markers of adverse limb prognosis include diabetes mellitus, severe PAD as measured by low ABI, polyvascular disease, microvascular disease, and continued smoking. As with manifestations of atherosclerosis in other vascular beds, the rates of MI, stroke, and death are significantly increased compared to patients without PAD. Guideline-directed therapies should be applied to reduce these adverse event rates. ■

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