M.G. Davies, M.D., Ph.D., M.B.A.

CRITICAL LIMB ISCHEMIA: ADVANCED MEDICAL THERAPY

Mark G. Davies, M.D., Ph.D., M.B.A.

Methodist DeBakey Heart & Vascular Center, The Methodist Hospital, Houston, Texas

Abstract

Systemic atherosclerosis and its risk factors are present in the majority of patients with critical limb ischemia. Aggressive medical therapy is an immediate and necessary part of the work-up and management of these patients and will involve a multidisciplinary approach. Risk stratification based on a patient's current clinical cardiovascular condition is important in determining the most appropriate and safe intervention and will allow both the patient and physician to make an informed decision regarding risk- and cost-benefits of treatment.

Introduction

Critical limb ischemia (CLI) is a manifestation of peripheral artery disease that significantly impairs blood flow to the lower extremities. The main goal of medical care is to reduce cardiovascular risk on a systemic basis (Table 1).[1, 2] Cardiovascular mortality is very high in this group, with 50-75% of patients succumbing within 5 years. Current recommendations state that all patients with critical limb ischemia must receive antiplatelet therapy, stop smoking, and be screened and treated for hyperlipidemia, hypertension, diabetes, and concomitant cardiac and carotid disease in accordance with national guidelines and community standards (Table 2).

Smoking Cessation — Evidence Level 2A; Grade B

Patients with critical limb ischemia must stop smoking. Smoking exacerbates pre-existing risk factors and has a negative influence on the outcomes of vascular interventions. Unfortunately, the immediacy of critical limb ischemia prevents smoking cessation from having time to work effectively. More than 75% of patients presenting with critical limb ischemia will have tried and failed to quit smoking. Up to 25% of patients will try to follow clinical advice to stop smoking, but more than 75% of them will recommence in less than 3 months.[3] With medical advice alone, approximately 5% of patients will have long-term success in quitting.[4] Nicotine replacement therapies (NRT) such as chewing gum, transdermal patches, nasal sprays, and inhalers are more effective in helping patients stop smoking when placed within a support program. A meta-analysis of trials shows a 1.5- to 2-fold increase in the cessation rate, with nasal spray and inhaled nicotine being the most effective therapies to date.[5] Combining

Nonmodifiable
Increasing age
Male sex
Family history
Modifiable
Raised LDL levels
Low HDL levels
Raised TG levels
Hypertension
Obesity
Smoking
Sedentary lifestyle
Diabetes
Atherogenic diet

Table 1. Risk factors for cardiovascular disease.
LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: triglyceride

Antiplatelet Therapy	
ASA 81 mg	
Lipid Management	
Initiate statin therapy regardless of lipid levels	
Total Cholesterol	<200 mg/dL
LDL	<100 mg/dL
HDL	>60 mg/dL
TG	<150 mg/dL
Blood Pressure Management	
Systolic	<120 mmHg
Diastolic	<80 mmHg
Diabetes Management	
Hb_{A1C}	<7%

Table 2. Optimization of the patient with critical limb ischemia.
ASA: acetylsalicylic acid; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: triglyceride

NRT treatments such as an inhaler with a patch further increases the success rate to nearly 20% at 1 year.[6] Bupropion/amfebutamone (Zyban) is an atypical antidepressant that has recently been approved as a medical therapeutic in smoking cessation. It avoids the hypertensive, cardiac, and other side effects of nicotine replacements. A number of randomized controlled trials (RCTs) have supported the use of bupropion in cigarette smokers with cardiovascular disease. Smoking abstinence rates were reported to be 34%, 27%, and 22% at 3-, 6- and 12-month follow-up as compared with 15%, 11%, and 9%, respectively, with placebo treatment.[7] Trials suggest up to 30% 1-year cessation rates with a dose-related response.[8] The clinical utility of NRT assessed in a Cochrane review[9] demonstrated that all of the commercially available forms of NRT were shown to increase the odds of successfully stopping cigarette smoking by 50–70%. A more recently published Cochrane review[10] examining the use of nicotine receptor partial agonist therapy calculated that the pooled risk ratio for continuous smoking abstinence at 6 months or longer for varenicline (Chantix/Champix) versus placebo was 2.31 (95% CI 2.01–2.66). Varenicline was also shown to be superior to bupropion at 1 year [pooled RR for varenicline vs. bupropion: 1.52 (95% CI 1.22–1.88)]. The goal for the care of these patients should be accessible specialist smokers' clinics, where counseling, education, and support can be combined with appropriate pharmacological treatment.[11] Physician advice on smoking cessation coupled with enrollment in a formal smoking cessation program and access to NRT is associated with an approximately 22% cigarette smoking cessation rate out to 5 years.[12]

Administration of Antiplatelet Agents — Evidence Level 1A; Grade A

There is a direct clinical benefit of antiplatelet therapy for primary cardiovascular prevention; however, there is currently no convincing data showing a delay or reduction of the progression of lower limb disease.[13] The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial demonstrated that the combined risk of death from vascular causes, myocardial infarction (MI), and stroke was significantly lower with clopidogrel (75 mg/day) compared with aspirin (325 mg/day),[14] and these benefits were most pronounced in patients with peripheral arterial disease (PAD). The Antithrombotic Trialists' Collaboration meta-analysis found a 23% reduction in serious vascular events within 42 trials.[15] However, there was no significant reduction of cardiovascular events in patients with PAD. In a subsequent analysis, which included study data on various antiplatelet drugs such as aspirin, clopidogrel, ticlopidine, dipyridamole, and picotamide, the group reported a 23% risk reduction of cardiovascular events in patients with PAD.[16] Low-dose aspirin (75–325 mg) is as effective as higher doses in PAD patients.[17] However, higher doses of aspirin will result in increased bleeding rates,[18] and very low doses (<75 mg) are not effective.[17] The daily dose of clopidogrel for secondary prevention in PAD patients is 75 mg. Ticlopidine reduces the risk for myocardial infarction, stroke, and vascular death,[19] but its clinical utility is limited by its potential side effects, such as neutropenia and thrombocytopenia.

Two RCTs analyzed whether or not antiplatelet therapy may improve patency rates subsequent to lower limb endovascular therapy. In the first study,[20] a total of 199 patients undergoing angioplasty of the femoropopliteal segment were randomized to three groups: dipyridamole (75 mg) plus aspirin (330 mg), dipyridamole (75 mg) plus aspirin (100 mg), or placebo. Patients from both dipyridamole arms showed higher patency rates as compared to those on placebo. In the second study,[21] of patients randomized to placebo or aspirin (50 mg) plus dipyridamole (400 mg) after peripheral vascular angioplasty, there were no significant differences in primary patency. The CASPAR (Coronary Artery Spasm in Patients With Acute Coronary Syndrome) study randomized a total of 425 patients undergoing below-the-knee bypass grafting to either aspirin (75–100 mg/day) alone or aspirin (75–100 mg/day) plus clopidogrel (75 mg/day).[22] The combination of clopidogrel plus aspirin did not improve lower limb or systemic outcomes. However, compared to aspirin alone, dual antiplatelet therapy was associated with a lower rate of a composite of index-graft occlusion or revascularization, above-ankle amputation of the affected limb, or death, without increasing bleeding risks. Four studies have analyzed whether a high dose (90–1000 mg) of aspirin is more potent in inhibiting re-occlusions subsequent to endovascular therapy.[23-25] Six months after the intervention, these studies showed no benefit of high-dose aspirin, whereas the rates of gastrointestinal side effects increased with higher doses. The CAMPER (Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularization) study was designed to evaluate the combined administration of aspirin and clopidogrel in patients undergoing endovascular revascularization of the femoropopliteal arteries, but the study was closed early due to low enrollment.

Administration of Statins — Evidence Level 1A; Grade B

Increased concentrations of each of the lipid components — cholesterol, low-density lipoprotein (LDL), triglyceride, and lipoprotein (a) — have been shown to be independent factors for acceleration of critical limb ischemia and contribute to an elevated cardiovascular risk.[26] In the Heart Protection Study,[27] all-cause mortality and cardiac death were significantly reduced by administration of statins, irrespective of the patients' cholesterol concentration, with a 22% reduction in major vascular events in patients with PAD. In the 4S study (Scandinavian Simvastatin Survival Study),[28] the risks for mortality, stroke, and intermittent claudication were significantly reduced. In the PREVENT III study of CLI patients undergoing lower-extremity bypass grafting,[29] statin use was associated with a significant reduction of 1-year mortality in a propensity score adjusted model. In a Cochrane review of 18 RCTs (10,049 participants), statins were shown to have a beneficial effect on the incidence of total cardiovascular events, primarily due to an overall reduction in coronary events (OR [odds ratio]: 0.8; 95% CI 0.7–0.9).[30] Statins may also prevent plaque instability and thrombosis due to their pleiotropic effects, such as improvement of endothelial function, reduction of inflammation, and stabilization of atherosclerotic plaques.[31] Current recommendations for managing lipid disorders in PAD are to achieve an LDL cholesterol level of <100 mg/dL and to treat the pattern of increased triglyceride and low high-density lipoprotein (HDL).[32, 33] Perioperative statin treatment in statin-naïve patients reduces atrial fibrillation, myocardial infarction, and duration of hospital stay.[34]

Control of Arterial Blood Pressure — Evidence Level 1A; Grade B

Control of blood pressure remains an important intervention for cardiovascular primary prevention and has been established as one of the principal improvements in stroke reduction. Arterial hypertension is a major independent risk factor for lower-extremity

occlusive disease. Current hypertension guidelines advocate aggressive treatment of elevated blood pressure in patients with atherosclerosis. Current treatment goals of antihypertensive therapy are arterial blood pressures of <140/90 mmHg. Moreover, blood pressure should be <130/80 mmHg if the patient has diabetes or renal insufficiency.[35] While there are many individual and combination agents for blood pressure control, there is only evidence for angiotensin-converting enzyme (ACE) inhibitors and beta blockers. The specific benefit of ramipril, an ACE inhibitor, in PAD patients was shown in the HOPE (Heart Outcomes Prevention Evaluation) study.[36] The subgroup of PAD patients randomized to rampril experienced a 22% risk reduction in the composite endpoints of myocardial infarction, stroke, or cardiovascular death. Interestingly, this clinical benefit was independent of lowering blood pressure. However, it must be kept in mind that this study was not carried out exclusively in CLI patients. Based on results from initial studies with nonselective beta blockers such as propranolol, use of beta-adrenergic blocking drugs have previously been discouraged in PAD patients due to their potential to reduce cardiac output and prevent beta-2-receptor-mediated skeletal muscle vasodilation.[37] Two meta-analyses of studies involving patients with mild and moderate lower-limb ischemia did not confirm that beta blockers were associated with exacerbation of PAD symptoms.[38, 39] As a result of these trials, the introduction of beta-1 specific medications, and the proven general cardiovascular benefit of beta blockers, beta blockers are now commonly prescribed for the treatment of arterial hypertension in PAD patients. The clinical value of administering perioperative beta blockers remains controversial. Use of beta blockers was shown to be associated with significant reductions of perioperative myocardial ischemia and infarction in various surgical settings.[40] In the POISE (PeriOperative Ischemic Evaluation) study,[41] the primary endpoint — a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal cardiac arrest — was more frequently observed in the beta-blocker cohort (5.8%) as compared to the placebo group (6.9%). However, while fewer patients in the metoprolol group experienced myocardial infarction (4.2% vs. 5.7%), both mortality (3.1% vs. 2.3%) and stroke (1.0% vs. 0.5%) rates were higher in the metoprolol-treated group compared to the placebo group. The dose of beta blockers in the POISE trial was higher compared to doses used in earlier studies.[42] In patients undergoing vascular surgery or major amputation, with low to intermediate cardiac risk, preoperative targeted beta blockade alone is more effective in preventing cardiac morbidity than selective cardiac stress testing and nontargeted beta blockade.[43] Beta blockers are still recommended to reduce perioperative events.[44]

Intensive Intervention for Diabetes — Evidence Level 5; Grade D

Diabetes mellitus is independently associated with the development of PAD and its progression to CLI. It has also shown to be an independent risk factor for amputation and increased complications in CLI patients. In the STENO-2 study, 160 diabetics were randomly assigned to either intensified or conventional therapy (i.e., control of blood glucose, statins, antithrombotic therapy, blood pressure control). On follow-up, intensive therapy was associated with significantly reduced risks of all-cause death and cardiovascular death.[45] In the United Kingdom Prospective Diabetes Study,[46] intensified therapy was associated with risk reductions for microvascular disease, myocardial infarction, and death from any cause as well as for any diabetes-related endpoint. In contrast, in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial,[47] rates of microvascular complications, but not macrovascular complications or cardiovascular deaths, were improved by

Criteria		
• High-Risk Surgery:		1 Pt
• Coronary Artery Disease:		1 Pt
• Congestive Heart Failure:		1 Pt
• Cerebrovascular Disease:		1 Pt
• Diabetes Mellitus on Insulin:		1 Pt
• Serum Creatinine >2 mg/dL:		1 Pt
Scoring		
• Points 0: Class I	**Very Low**	(0.4% complications)
• Points 1: Class II	**Low**	(0.9% complications)
• Points 2: Class III	**Moderate**	(6.6% complications)
• Points 3: Class IV	**High**	(>11% complications)
Type: High-Risk Surgery (Cardiac Risk >5%)		
1. Emergency surgery (especially over age 75 years)		
2. Cardiac procedures		
3. Aortic or other major vascular procedures		
4. Peripheral arterial vascular procedures		
5. Prolonged surgery anticipated (>2 hours)		
• Anticipated large fluid shift or blood loss		
• Examples: Whipple Procedure, major spinal surgery		
Type: Intermediate-Risk Surgery (Cardiac Risk 1–5%)		
1. Orthopedic surgery		
2. Urologic surgery		
3. Uncomplicated abdominal or thoracic surgery		
4. Uncomplicated head and neck surgery		
5. Carotid endarterectomy		
6. Prostate surgery		
Type: Low-Risk Surgery (Category I, Cardiac Risk <1%)		
1. Endoscopy		
2. Bronchoscopy		
3. Hysteroscopy		
4. Cystoscopy		
5. Dermatologic procedures (skin and subcutaneous tissue)		
6. Breast biopsy or other breast surgery		
7. Ophthalmologic procedures (e.g., cataract resection)		

Table 3. Revised Cardiac Risk Index.

intensive diabetes therapy during a follow-up of 5 years. Moreover, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study[48] was prematurely stopped after 3.4 years due to increased mortality in the intensively treated group, although by that time the rates of nonfatal myocardial infarction and stroke were lower in that group. At 5 years follow-up, the use of intensive therapy for the prior 3.7 years reduced 5-year nonfatal myocardial infarctions but increased 5-year mortality. The benefits of tight diabetes control on functional lower-limb outcomes such as limb salvage or freedom from repeated revascularization in CLI patients has not been determined.

Treatment of Coronary Artery Disease

Routine treatment with beta blockers before vascular surgery is recommended. (Evidence Level 1b; Grade B).

Routine coronary revascularization before vascular surgery is not recommended. (Evidence Level 1b; Grade B).

Patients with CLI have a high prevalence of coronary artery disease (CAD), which strongly increases the risk of cardiac mortality and morbidity.[49] Therefore, all PAD patients should be considered at high risk for clinically significant ischemic heart disease, for which guidelines exist.[50, 51] Cardiac risk is related to urgency, extent, type, and duration of the planned intervention. Patients should be evaluated for evidence of CAD and can be risk stratified. Treatment decisions should be based on current practice guidelines.[44] Cardiac assessment scores may be useful in patients being considered for peripheral revascularization (Table 3). Patients with stable CAD should be managed according to the severity of their symptoms and comorbid conditions. Patients with unstable symptoms (such as acute coronary syndrome or congestive heart failure) or a high cardiac risk assessment score will need optimization; this may include possible coronary revascularization prior to intervention and/or re-examining the magnitude of the intervention.[42] However, the Coronary Artery Revascularization Prophylaxis (CARP) trial, which studied patients with peripheral vascular disease who were considered high risk for perioperative complications and had significant CAD, demonstrated that coronary revascularization did not reduce perioperative MI or overall mortality.[52] There was a delay between coronary revascularization and the planned vascular surgery, which in CLI patients may be counterproductive. The results of CARP suggest that pre-emptive coronary revascularization prior to urgent peripheral vascular surgery should not normally be pursued. In most patients, perioperative use of beta-adrenergic blocking agents is associated with reduced cardiovascular risks of surgery. Recent studies have shown that beta-adrenergic blockade with bisoprolol significantly decreases the risk for cardiovascular events during vascular surgery and afterwards.[53, 54] However, starting beta-blockers shortly before surgery as in the POISE study has not proven to be beneficial in terms of mortality and stroke.[41]

Carotid Artery Disease

The prevalence of carotid artery disease in patients with PAD is 10–30%, and there are no specific data for CLI. Since PAD patients have an increased risk of stroke, it might be reasonable to screen those patients for carotid artery disease routinely. In the SMART study,[55] the prevalence of internal carotid artery (ICA) stenosis 70% or greater was low in patients with risk factors for atherosclerosis only (1.8–2.3%), intermediate in patients with angina pectoris or MI (3.1%), and highest in patients with PAD (12.5%) or abdominal aortic aneurysm (AAA) (8.8%). In patients with PAD, selecting those ages 55 years and older increased the prevalence of ICA stenosis to 21.8%. Selecting patients with lower diastolic blood pressure (<83 mmHg) increased the prevalence of ICA stenosis to 17.9%. In patients with both advanced age and lower diastolic blood pressure, the prevalence of ICA stenosis increased to 34.7%. Further evaluation and consideration for revascularization should be based on current guidelines.[56] One must keep in mind that CLI patients with limited life expectancy will hardly benefit from carotid endarterectomy or stenting for asymptomatic carotid disease.

Renal Artery Disease

Patients with PAD are at an increased risk for renovascular hypertension. The management of patients with atherosclerotic renal artery disease and PAD is focused on preserving renal function and controlling hypertension. Patients with hypertension should be assessed by renovascular ultrasound imaging. In the presence of significant renal artery stenosis, treatment should be based on current guidelines.[57-61]

Aortic Aneurysm Disease

The prevalence of aneurysms in patients with CLI is 12%.[62] In patients with PAD, an aneurysm is present in 11–14% of men and 6% of women for a total prevalence of 4–9%.[63, 64] Only 1.5% of the patients will have a large AAA (>5 cm). The prevalence significantly increases with age, with the highest in men over 75 years of age. Patients with tibial disease have a significantly higher prevalence of AAA than those with aortoiliac or femoropopliteal disease.[64] Aortic screening for AAA in patients with CLI will detect aneurysms of 4.0 cm or greater in 3.2% of the entire population and in 8.8% of male smokers over age 65 years. The best predictors for detecting an AAA were male gender, advanced age (>65 years), and a history of smoking.[65] In the SMART study,[55] the prevalence of an AAA 3 cm or larger is low in patients with risk factors for atherosclerosis only (0.4–1.6%), intermediate in patients with angina pectoris or MI (2.6%), and highest in patients with PAD (6.5%) or transient ischemic attack (TIA), stroke, or ICA stenosis (6.5%). Selecting patients with advanced age increased the prevalence of AAA 3 cm or larger to 9.6%. In patients with TIA, stroke, or ICA stenosis, selecting those with advanced age increased the prevalence of AAA 3 cm or larger to 8.2%. Selecting patients with taller stature (>169 cm) increased the prevalence of AAA 3 cm or larger to 9.3%. In patients with advanced age and taller stature, the prevalence of AAA 3 cm or larger increased to 13.1%.

Conclusion

In patients presenting with CLI, immediate advanced medical therapy will have a perioperative and long-term benefit on their risk of perioperative mortality and morbidity. Aggressive compliance with the current guidelines should be undertaken once a patient with CLI is identified.

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