

## Seminar

## Peripheral arterial disease

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**Lower extremity peripheral arterial disease (PAD) most frequently presents with pain during ambulation, which is known as “intermittent claudication”. Some relief of symptoms is possible with exercise, pharmacotherapy, and cessation of smoking. The risk of limb-loss is overshadowed by the risk of mortality from coexistent coronary artery and cerebrovascular atherosclerosis. Primary therapy should be directed at treating the generalised atherosclerotic process, managing lipids, blood sugar, and blood pressure. By contrast, the risk of limb-loss becomes substantial when there is pain at rest, ischaemic ulceration, or gangrene. Interventions such as balloon angioplasty, stenting, and surgical revascularisation should be considered in these patients with so-called “critical limb ischaemia”. The choice of the intervention is dependent on the anatomy of the stenotic or occlusive lesion; percutaneous interventions are appropriate when the lesion is focal and short but longer lesions must be treated with surgical revascularisation to achieve acceptable long-term outcome.**

Peripheral arterial disease (PAD) comprises those entities which result in obstruction to blood flow in the arteries, exclusive of the coronary and intracranial vessels. Although the definition of PAD technically includes problems within the extracranial carotid circulation, the upper extremity arteries, and the mesenteric and renal circulation, we will focus on chronic arterial occlusive disease in the arteries to the legs. Intermittent claudication, defined as pain in the muscles of the leg with ambulation, is the earliest and the most frequent presenting symptom in patients with lower extremity PAD. As the disease progresses in severity patients might have pain at rest, most prominent while the legs are elevated in bed at night, and relieved by dependency. Although claudication symptoms are typically localised in the calf or the thigh, “rest pain” is characteristically in the foot. In the late stages of PAD, tissue hypoperfusion progresses to ischaemic ulceration and gangrene, and major amputation is eventually required in more than a third of these patients.<sup>1</sup> Importantly, mortality is closely linked with the presence of rest pain or tissue loss, so-called “critical limb ischaemia”, with a 1-year mortality rate of about 20% in several series.<sup>2,3</sup>

### Epidemiology

Intermittent claudication has been used as a marker of PAD in epidemiological studies to approximate the frequency of lower extremity PAD in a particular patient population. The estimate is dependent, however, on demographic factors of the specific population under study, including age, sex, and geographic area. In addition, the methods used to determine the frequency of intermittent claudication affects the estimate.<sup>4</sup> For instance, studies based on questionnaires tend to overestimate the frequency of PAD with symptoms; patients with complaints that resemble claudication but are unrelated to the vascular system will be erroneously classified as having PAD. Studies that use an objective method of diagnosis, such as measurement of doppler systolic ankle pressures, are most accurate. An “ankle-brachial index” (ABI) can be calculated by dividing the

ankle systolic pressure measured with a blood pressure at the malleolar level by the higher of the two brachial pressures. Defining PAD by an ankle-brachial index of less than 0.95, a frequency of 6.9% was observed in patients aged 45–74 years, only 22% of whom had symptoms.<sup>5</sup> The frequency of intermittent claudication increases dramatically with advancing age, ranging from 0.6% in individuals aged 45–54 years, to 2.5% in those aged 55–64 years, to 8.8% in patients aged 65–74 years.<sup>6</sup> The Rotterdam study, a population-based analysis of 7715 patients, documented a frequency of intermittent claudication ranging from about 1% in those between the ages of 55–60 years to 4.6% in those between the ages of 80 and 85 years.<sup>7</sup> Despite this rather low frequency of intermittent claudication, 16.9% of men and 20.5% of women aged 55 and older had PAD as defined by an ankle-brachial index of less than 0.90 in either leg. This observation confirms that most patients with significant PAD are symptom-free. Although the diagnosis of symptomless PAD has less clinical significance with respect to the lower extremities, it is a strong marker for future cardiovascular events such as myocardial infarction.<sup>8</sup>

A variety of risk factors have been identified for peripheral arterial occlusive disease; risk factors that are almost identical to those of atherosclerotic disease elsewhere. The most important of these are age and sex; atherosclerosis of the lower extremities is more common in elderly individuals and in men. Diabetes mellitus is a most important risk factor for large vessel atherosclerotic occlusive disease. Smoking is also closely linked to PAD, a relation first identified by Erb in 1911, when the risk of intermittent claudication was reported to be three times greater in smokers.<sup>9</sup> The risk of PAD was documented to be twice that in smokers compared with non-smokers in the Framingham study.<sup>10</sup> The increased risk seems correlated with the number of cigarettes smoked,<sup>11</sup> cessation of smoking has been associated with a rapid decrease in the risk for intermittent claudication.<sup>12,13</sup> Hypertension has been linked with an increased risk of peripheral arterial occlusive disease in some studies. The Framingham data documented a 2.5-fold increase in the risk of PAD in men with hypertension and a 3.9-fold increase in women with hypertension.<sup>10</sup> Hyperlipidaemia has been associated with an increased rate of lower extremity occlusive disease. Although some studies have documented total cholesterol concentration as an

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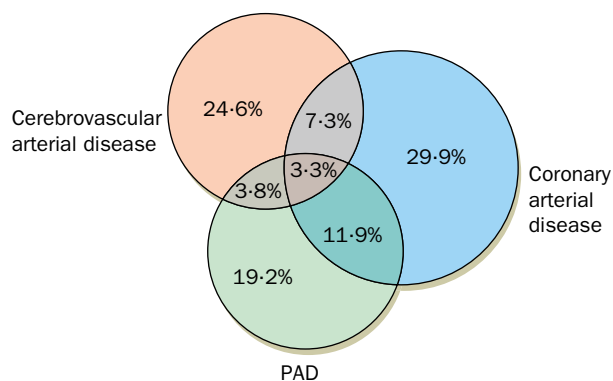


Figure 1: Frequency of disease with symptoms in the three organ systems and their overlap, from the CAPRIE trial

important independent risk factor,<sup>14,15</sup> others have suggested that the ratio of high density to total cholesterol is perhaps a better predictor.<sup>16</sup> Hypertriglyceridaemia<sup>17</sup> and lipoprotein (a)<sup>18</sup> have been shown to be independently associated with lower extremity PAD. Homocysteine has also been implicated in atherogenesis; hyperhomocysteinaemia can be shown in 30% of patients with premature PAD.<sup>19</sup> There is a more substantial relation between hyperhomocysteinaemia and peripheral atherosclerosis compared with atherosclerosis in the coronary bed (odds ratio 6.8 *vs* 1.6, respectively). And an increased fibrinogen concentration<sup>20</sup> and an increased haematocrit<sup>21</sup> have been associated with an increased risk of peripheral atherosclerosis. The concurrence of a multiplicity of risk factors in a single patient dramatically increases the risk for PAD. In the Basle longitudinal study<sup>22</sup> the relative risk for PAD increased from 2.3 to 3.3 to 6.3 in individuals who had one, two, or three of the risk factors, respectively: smoking, diabetes, and systolic hypertension. The Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial tabulated the frequency of comorbid problems in patients with claudication.<sup>23</sup> In this study of almost 20 000 patients with atherosclerotic disease in the peripheral, coronary, or cerebrovascular beds, about a third had intermittent claudication as their primary presenting symptom (figure 1). Men outnumbered women by a ratio of almost 3:1. Comorbid risk factors were present in a large number of patients entered into the trial; cigarette smoking (current 38%, former 53%), hypertension (51%), and hypercholesterolaemia (45%) were most frequent. The generalised nature of atherosclerosis was well shown by the CAPRIE data; 41.1% of patients with PAD had concurrent coronary artery or cerebrovascular disease, and 8.6% had disease in all three beds.

The natural history of lower extremity PAD has been assessed in a variety of studies, both with regard to progression of disease in the leg as well as long-term morbidity from concurrent generalised atherosclerotic disease. With respect to the legs, claudication symptoms are surprisingly benign; the risk of limb loss is overshadowed by the risk of morbid cardiovascular events and death (figure 2).<sup>24</sup> Although arteriographic progression of atherosclerotic disease may be documented in 63% of patients after 5 years,<sup>22</sup> Bloor's classic study of 1961 documented a rate of major amputation of only 7% after 5 years and 12% after 10 years of follow-up.<sup>25</sup> More recent data corroborate the finding that limb-loss is a fairly rare event in patients with intermittent claudication, with a 5-year risk of major amputation of only 2%.<sup>26</sup> By contrast, limb-loss is much more frequent once symptoms

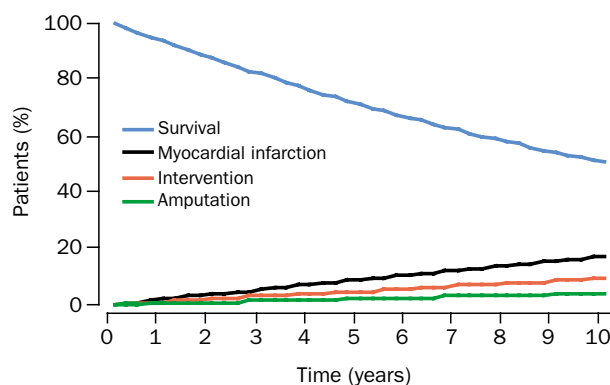


Figure 2: Survival, myocardial infarction, surgical or percutaneous revascularisation, and major amputation over 10 years of follow-up in patients initially presenting with intermittent claudication

Assumptions include a 6.8% annual risk of mortality,<sup>29,35</sup> a 2.0% risk of myocardial infarction,<sup>23</sup> a 1.0% risk of intervention,<sup>25</sup> and a 0.4% risk of amputation.<sup>25</sup>

of rest pain or tissue loss become evident (critical limb ischaemia). In a prospective study from Italy, the risk of major amputation was 12.2% after only 3 months in patients with rest pain or ischaemic ulceration.<sup>27</sup> The risk of limb-loss is increased further when patients continue to smoke,<sup>28</sup> and in patients with diabetes.<sup>22</sup>

The long-term prospects for patients with lower extremity PAD must be considered in the context of coexistent generalised atherosclerosis. In a study from the Cleveland Clinic, some degree of coronary atherosclerosis was present in 90% of patients undergoing routine coronary angiography before elective peripheral vascular surgery and 28% of the patients had severe, three-vessel coronary disease.<sup>29</sup> Long-term survival in patients with lower extremity PAD is greatly diminished as a result of atherosclerotic complications in the coronary and cerebrovascular beds. In the classic study of Criqui, even symptom-free patients with peripheral atherosclerosis had a risk of mortality that exceeded that of the population without disease,<sup>8</sup> a finding substantiated by other studies.<sup>30</sup> Mortality risk was incrementally higher in patients with PAD with symptoms and was further increased in patients with severe disease. The cause of death in patients with PAD, however, is rarely a direct result of the lower extremity arterial disease itself. About 55% of patients die from complications related to coronary artery disease, 10% from complications of cerebrovascular disease, and 25% die of non-vascular causes.<sup>26</sup> Less than 10% die from vascular events, most commonly a ruptured aortic aneurysm.

### Pathophysiology

The pathogenesis of lower extremity PAD is best considered through a study of atherogenesis in general. Atherogenesis is most efficiently described through consideration of three stages, initiation of the lesion, progression of the lesion, and plaque complications.<sup>31</sup> The first stage involves the recruitment of mononuclear leucocytes to the intimal layer of the vessel wall. This inflammatory process is dependent on at least two groups of adhesion molecules. The first group, the selectins, is involved in the transient deposition of leucocytes on the endothelium. Endothelial cells overlying the atheromatous lesions express P-selectin. The second group of leucocyte adhesion molecules comprises an assemblage of immunoglobulins that are responsible for more sustained

adherence of the leucocytes to the endothelium. Most notable in this regard is vascular cell adhesion molecule-1 (VCAM-1), present on the endothelial cells and responsible for binding of monocytes and lymphocytes.<sup>32</sup> After leucocyte adherence, chemoattractant chemokines potentiate migration of the cells into the intima. Although the steps in initiation of the early atheromatous plaque have been fairly well elucidated, a more basic question relating to the factors responsible for the focal increase in expression of adhesion molecules and cytokines remain ill defined. Clearly, however, oxidised lipoproteins are important in this process.<sup>33</sup> In addition, perturbations in local haemodynamics have also been implicated in the potentiation of adhesion molecule expression.<sup>34</sup> Finally, expression of adhesion molecules important in early atherogenesis can be downregulated as well. Nitric oxide has been shown to reduce leucocyte adhesion to endothelium,<sup>35</sup> in addition to its vasodilator actions. At the transcriptional level, nitric oxide interferes with the nuclear factor-kappa B signalling pathway, inhibiting VCAM-1 gene expression in endothelial cells. Normal laminar blood flow augments endothelial nitric oxide synthase, increasing local nitric oxide concentrations and potentiating its anti-inflammatory and vasodilator actions. By contrast, turbulent flow, for example, as occurs at sites of arterial branching, attenuates nitric-oxide-mediated anti-inflammatory activity. Once the leucocytes have migrated into the intima through diapedesis, they accumulate lipids and assume a foamy histologic appearance. These foam cells comprise the earliest grossly recognisable stage of atherogenesis, the fatty streak. Although the fatty streak is reversible, increasing accumulation of foam cells in the intima transforms the fatty streak into a more advanced plaque. The plaque becomes increasingly more fibrous as smooth muscle cells accumulate within the lesion and elaborate extracellular macromolecules that form a fibrous matrix. Calcium accumulates in the progressing atheroma with vascular smooth muscle cell expression of proteins that are involved in osteogenesis.

The third and final stage of atherogenesis, the formation of a complicated or "unstable" plaque, is initiated by exposure of subintimal thrombogenic substances to the blood stream. The blood is protected from the lipid-laden atherosclerotic core by a "fibrous cap" in an uncomplicated plaque. There are two characteristics that determine whether a plaque will be stable or unstable. The first variable is simply the thickness of the fibrous plaque.<sup>36</sup> The second factor is the amount of collagen present in the fibrous cap. Systemic factors have been implicated as determinants of plaque stability.<sup>30</sup> Inflammation, mediated through the attraction of activated T cells to the atheroma, may inhibit smooth muscle cell synthesis of collagen, weakening the fibrous cap. The finding of T lymphocyte accumulation at sites of plaque rupture is circumstantial testimony to this hypothesis.<sup>37</sup> Metalloproteinases are produced and released by macrophages within the atheroma, digesting collagen fibrils of the fibrous cap. Similarly, elastin can be degraded by cathepsin S and K secreted by macrophages present within the plaque, as well as by metalloproteinase.<sup>38</sup> Finally, a paucity of smooth muscle cells may occur by apoptosis, accentuated by inflammatory cytokines within the atheroma,<sup>39</sup> further diminishing the potential to maintain the collagen component of the fibrous cap. *Chlamydia pneumoniae* has also been implicated as an aetiologic factor in atherosclerosis, with infection of the cellular components of arterial plaque.<sup>40</sup> Although such infection can be shown experimentally to

be associated with an increased expression of procoagulant proteins and chemoattractant activity,<sup>41</sup> the precise role of *C pneumoniae* remains undefined.

Proaggregatory substances in the subintima are exposed when the fibrous cap is disrupted. Tissue factor is perhaps the most important subintimal element involved in initiation of the coagulation cascade. Platelets, however, play a most important role under the high shear-rate conditions present in arteries. A monolayer of platelets adheres to subintimal collagen fibrils through glycoprotein Ia/IIa receptors present in the platelet membrane and to exposed von Willebrand factor through platelet membrane glycoprotein Ib receptors. Next, platelets undergo the release reaction, secreting a variety of antagonists including thrombin, serotonin, adenosine diphosphate, and thromboxane A<sub>2</sub>. As the platelets undergo structural changes, flattening and forming pseudopodia, increasing numbers of glycoprotein IIb/IIIa receptor molecules are activated on the platelet surface. Fibrinogen in the blood stream acts as a bridge between two platelets, binding to the glycoprotein IIb/IIIa receptors of adjacent platelets. A matrix of platelets and fibrinogen molecules forms a platelet plug, which can progress in one of two ways. First, if the platelet clump is firmly attached to the vessel wall, it can continue to build in size until the lumen is completely obstructed with platelet-rich thrombus. In other cases, however, the platelet clump may be less firmly attached to the wall or the blood flow may be rapid enough that shear forces detach the clump before it occludes the vessel. In these cases, platelet-rich emboli flow downstream to lodge in peripheral vessels and cause clinical events such as stroke, amaurosis fugax, and digital ischaemia.

### Diagnosis

The diagnosis of peripheral arterial occlusive disease begins with an accurate history. Intermittent claudication must be differentiated from lower extremity pain occurring as a result of non-vascular aetiologies. True claudication begins after a reproducible length of ambulation and resolves within a few minutes after the patient stops walking, even if he or she remains standing. By contrast, pain from impingement on the nervous structures as a result of spinal stenosis does not resolve after cessation of ambulation and, in fact, might be worsened by long periods of sitting or standing. The location of the pain is the key to the site of arterial occlusion; calf claudication is typically a result of disease in the superficial femoral artery, while hip, thigh, and buttock claudication occurs with narrowing of the aorta and iliac arteries.

An efficient means of objectively documenting the presence and severity of lower extremity PAD is the measurement of the doppler ABI, more widely used in North America than Europe. Normally, the ABI is greater than 1.0. The index is decreased to 0.50–0.90 in patients with claudication and to lower levels in patients with pain at rest or tissue-loss (figure 3).<sup>42,43</sup> The ABI may be normal in some patients with mild arterial narrowing; treadmill exercise has been used in these cases to increase the sensitivity of the test. Patients with diabetes mellitus or renal failure may have calcific lower leg arteries, rendering them incompressible and causing a falsely raised ABI; in these cases a toe brachial pressure index can be measured and is more predictive of substantial arterial disease.<sup>44</sup> Transcutaneous oxygen tension has also been used to assess the severity of peripheral arterial occlusion,<sup>45</sup> as well as to predict the most appropriate level of amputation.<sup>46</sup>

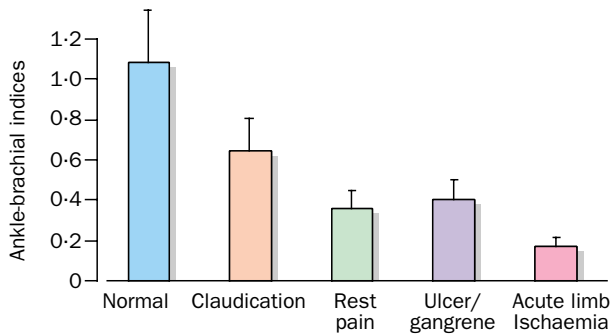


Figure 3: Representative ankle-brachial indices in various patient symptom categories

Vertical bars represent standard deviations.<sup>41,96</sup>

The anatomic level of the arterial stenoses can be predicted from palpation of pulses in the femoral, popliteal, and ankle regions. For example, patients with disease confined to the superficial femoral artery will have a normal femoral pulse but no palpable popliteal or ankle pulses below, whereas patients with aortoiliac disease will have absent femoral pulses as well. Doppler segmental pressures are also useful in defining the level of involvement; a drop in pressure of 30 mm Hg or more between two segments predicts arterial occlusion between the two levels. For example, a superficial femoral arterial occlusion would be suggested in a patient with a systolic pressure of 120 mm Hg at the proximal thigh pressure cuff and 90 mm Hg at the above knee cuff. It should be noted that the practice of measuring doppler segmental pressures is rarely used in Europe, despite widespread use in North America.

Contrast arteriography remains the gold standard with which all other tests must be compared. Even today, standard arteriography is the most accurate test for all but the occasional patient with such slow flow in the tibial or foot vessels that digital subtraction imaging fails to show a patent artery. Arteriography is, however, a semi-invasive modality and as such its use should be confined to those patients for whom a surgical or percutaneous intervention is contemplated. Patients with borderline renal function might have contrast-induced nephrotoxicity, and in this subgroup the use of alternate contrast agents such as gadolinium or carbon dioxide have been used.

Duplex ultrasound has been used in some centres to define the anatomic extent of PAD. Although duplex has been useful in documenting the patency of a single arterial segment, such as a stented superficial femoral artery or a bypass graft, assessment of the entire lower extremity arterial tree remains imprecise and its adequacy as the sole diagnostic modality for planning a percutaneous or open surgical intervention remains controversial.<sup>47</sup> Magnetic resonance angiography is increasingly being used in patients with PAD. When gadolinium is used as a magnetic resonance contrast agent, the specificity and sensitivity of the test exceeds that of duplex ultrasonography and approaches the accuracy of standard arteriography.<sup>48</sup> Today, magnetic resonance angiography is widely used in patients with chronic renal insufficiency to limit the dye load. With future improvements in hardware and software technology, it is likely that magnetic resonance angiography will effectively replace conventional diagnostic arteriography such that arterial cannulation will be reserved solely for percutaneous interventional therapies.

**Preventative measures directed at decreasing the long-term systemic complications in patients with lower extremity arterial occlusive disease**

- |                            |  |
|----------------------------|--|
| Pharmacologic intervention | Antihyperlipidaemic pharmacotherapy<br>Antiplatelet therapy<br>Treatment of hyperhomocysteinaemia<br>Blood sugar control<br>Antihypertensive therapy |
| Life-style modifications   | Regular exercise programme<br>Smoking cessation<br>Weight loss programme   |

**Treatment**

*General principles*

The management of patients with lower extremity PAD is two-pronged, addressing the risk factors important in the progression of generalised atherosclerosis first (panel), followed by interventions such as pharmacotherapy, endovascular therapy, or surgery to remedy the lower extremity symptoms (figure 4). Patients should undergo basic haematologic and metabolic laboratory assessment, including complete blood and platelet counts, fasting glucose or haemoglobin A1c, blood urea nitrogen, and creatinine concentrations, urinalysis, and fasting lipid profile. Although it is not cost-efficient to screen patients with PAD for the wide variety of hypercoagulable syndromes, patients with repeated failure of revascularisation procedures or young individuals with accelerated atherosclerosis should undergo testing for diseases such as the antiphospholipid syndrome and hyperhomocysteinaemia. Patients should be instructed to abstain completely from tobacco use and can be offered pharmacologic or behavioural interventions to assist in this task. They should begin a regular exercise programme. Lipids, blood pressure, and blood sugar should be brought under control, although admittedly the evidence for this recommendation is based on inferences from published reports of coronary artery disease and the relation between these factors and the progression of peripheral atherosclerosis is not as great as the link between smoking and peripheral disease.<sup>17</sup> An antiplatelet agent should be administered, usually aspirin.<sup>49</sup> Although the CAPRIE study documented a small clinical benefit with clopidogrel over aspirin, with an 8.7% relative risk reduction in the occurrence of the stroke, myocardial infarction, or vascular death,<sup>23</sup> the use of this agent has been limited by a large cost disadvantage when compared

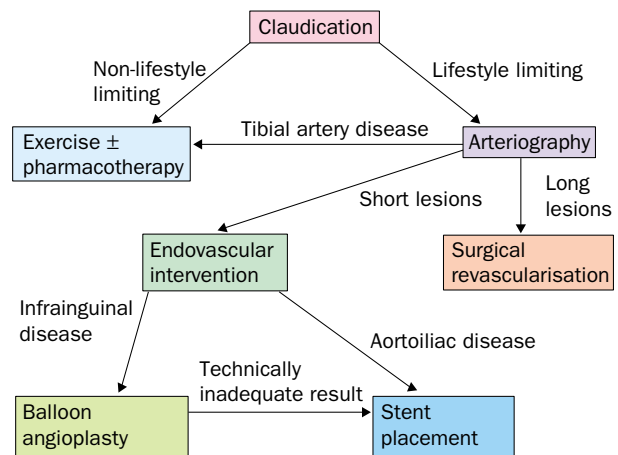


Figure 4: Algorithm for managing the patient with intermittent claudication



with aspirin. Clopidogrel is a very reasonable substitute antiplatelet agent, however, in patients who are intolerant to aspirin.

#### Pharmacotherapy

Treatment of the patient's lower extremity symptoms should be chosen on the basis of the severity of the symptoms. Invasive intervention for symptomless disease is never appropriate, but the presence of even symptomless disease should serve as a marker of generalised atherosclerosis and therapy should be directed at primary prevention of the systemic complications such as myocardial infarction and stroke. Similarly, patients with mild or moderate claudication symptoms are best treated with conservative measures such as the institution of an exercise programme. Pharmacotherapy for intermittent claudication can be added as adjunctive treatment to improve walking, although no agent has provided sufficient efficacy to gain widespread acceptance. While significant differences in such endpoints as treadmill walking distance can be shown in clinical trials, the lack of robust clinical impact has limited the widespread use of these agents. Moreover, the use of pharmacotherapy for claudication varies from country to country, with a high rate of use in France and a fairly low rate in the USA.

Pentoxifylline, through its actions on red cell deformability, lowering of fibrinogen, and mild platelet antiaggregatory effects, has conferred mild benefits over placebo in several studies.<sup>50,51</sup> Naftidrofuryl, a serotonin antagonist, and buflomedil, an  $\alpha_1$  and  $\alpha_2$  adrenolytic agent have been shown to improve walking distance in several randomised trials, but its use remains controversial and the drug is universally licensed for this indication.<sup>52-54</sup> Cilostazol, a phosphodiesterase inhibitor with antiplatelet and vasodilator effects, is probably the most promising agent presently available. Cilostazol was associated with significant increases in walking distance as well as quality of life in a double-blind, randomised trial.<sup>55</sup> Side-effects include headache and diarrhoea, and the agent should not be given to patients with diminished cardiac reserve.

Although patients with chronic limb-threatening ischaemia are best served with surgical revascularisation, pharmacotherapy can be considered when, for whatever reason, a surgical procedure is impossible. Long-term (several weeks), intermittent intravenous infusion of prostanoids, such as prostaglandin E<sub>1</sub> or more stable prostacyclin analogues such as iloprost have been shown to reduce rest pain<sup>56</sup> and heal ischaemic ulcerations<sup>57</sup> in masked, placebo-controlled trials, but results have not been consistent. Probably the newest therapy, gene-induced angiogenesis with vascular endothelial growth factor, for example, holds potential to improve collateral vessel development.<sup>58</sup> Preliminary uncontrolled investigation of intramuscular vascular endothelial growth factor gene transfer stimulated the formation of new vessels angiographically, improved the ABI, relieved rest pain, and healed ischaemic ulcers in patients with endstage PAD.<sup>59</sup> Lower extremity oedema from enhanced vascular permeability seemed to be the only untoward effect of vascular endothelial growth factor administration,<sup>60</sup> but gene therapy holds the theoretical potential to induce the growth of malignant cells concurrent with therapeutic angiogenesis.<sup>61</sup> The beneficial results of the early gene therapy studies must be corroborated by subsequent controlled studies before widespread use can be recommended.

Hyperbaric oxygen has been used in patients with non-healing ulcers who, for whatever reason, are not

candidates for revascularisation. In a randomised study of 70 patients with diabetes and ischaemic foot ulcers, Faglia and colleagues documented a decreased rate of amputation.<sup>62</sup> The use of hyperbaric oxygen is expensive, however, and results at many institutions have been equivocal.<sup>63,64</sup>

Pharmacotherapy attains great importance in patients with acute limb ischaemia occurring as a result of in situ native artery thrombosis or thrombosis of a bypass graft. Early heparin anticoagulation may limit the propagation of thrombus and prevent clinical deterioration, although there is little objective data on which to base this practice.<sup>65</sup> Retrospective studies suggest that heparin decreases the risk of recurrent embolisation in patients with embolic occlusions and most surgeons continue heparin therapy through the perioperative period, until the patient can be adequately anticoagulated with oral agents.<sup>66,67</sup> Thrombolytic agents are of value in patients with acute limb ischaemia, and some studies have suggested that their use reduces the high rate of morbidity and mortality associated with immediate surgical intervention.<sup>68,69</sup> Although thrombolytic therapy does not uniformly obviate the need for an endovascular or open surgical procedure to correct the underlying causative lesion, initial use of these agents as initial therapy allows one to defer the more invasive modalities to the elective setting.<sup>70</sup>

#### Surgical procedures for PAD

Surgical revascularisation is unquestioned as appropriate therapy for patients with chronic critical limb ischaemia, directed at the prevention of limb-loss and its accompanying disability. By contrast, surgical intervention is rarely indicated in patients with intermittent claudication alone, since the risk of major amputation is exceedingly low. Only in the occasional patient whose symptoms interfere with the patient's lifestyle or performance of an occupation will the benefits of surgical revascularisation outweigh the risks. There are two basic choices when surgery is considered for chronic lower extremity disease, endarterectomy and bypass grafting. Endarterectomy is an acceptable option when truly localised disease is present, for example, narrowing of the aorta and common iliac arteries alone.<sup>71</sup> Otherwise, patency rates are unsatisfactory and bypass grafting is more appropriate. The traditional operation for aortoiliac occlusive disease is an aortofemoral bypass, performed with a prosthetic graft due to the large diameter of the vessels. Infrainguinal bypass procedures are best done with autogenous vein grafts, although the results of prosthetic bypasses are acceptable if the graft does not cross the knee joint.<sup>72</sup> The results of bypass procedures are correlated with the level of the disease; aortofemoral reconstructions are associated with higher patency rates than infrainguinal procedures. Nevertheless, with a non-diseased saphenous vein of adequate caliber the long-term patency rate of bypass to even the infrapopliteal (crural) vessels is quite satisfactory, about 70–80% at 5 years irrespective of whether the vein is reversed or left in situ with the valves disrupted.<sup>73,74</sup> Considering the quite dismal results of percutaneous angioplasty and stenting for disease in the crural arteries, autogenous vein bypass to the distal vessels should be judged as first line therapy in patients with limb-threatening ischaemia and distal disease.<sup>74</sup>

The use of antithrombotic therapy is advisable in conjunction with certain peripheral vascular surgical procedures. Systemic anticoagulation with heparin is almost always used during the intraoperative cross-clamp period in patients undergoing lower extremity arterial

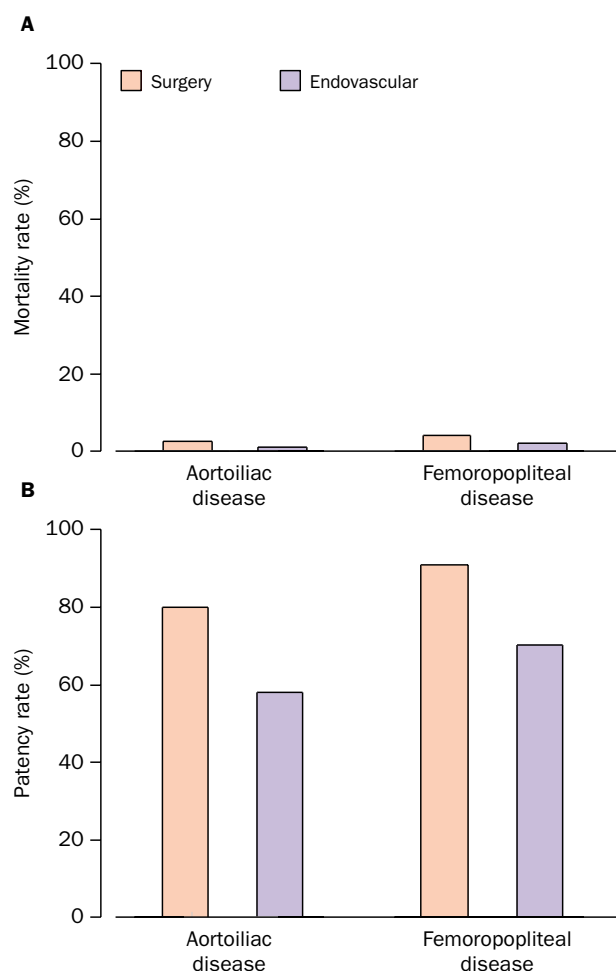


Figure 5: **Periprocedural mortality rates and 3-year patency rates in patients undergoing percutaneous angioplasty/stenting or surgical revascularisation.**<sup>25</sup>

A: Mortality rate. B: Patency rate.

reconstructive procedures. Antiplatelet agents have been studied in patients with peripheral bypass grafts, and the general recommendation is for aspirin in patients undergoing placement of prosthetic infrainguinal bypass grafts to improve graft patency and reduce the risk of myocardial infarction and stroke.<sup>75</sup> The addition of warfarin should be considered in patients thought to be at high risk for graft thrombosis.<sup>76</sup> The Dutch multicentre randomised trial of oral anticoagulation or aspirin in

2690 patients undergoing infrainguinal revascularisation suggested that oral anticoagulation improves vein graft patency, whereas aspirin improves the results in patients with prosthetic grafts.<sup>77</sup>

#### Endovascular interventions

Percutaneous catheter interventions to treat occlusive lesions of the lower extremities, first described by Dotter and Judkins in 1964,<sup>78</sup> are attractive alternatives to open surgical procedures such as bypass and endarterectomy. Procedural indications have been liberalised as compared with those for surgical procedures, arguing that the minimally invasive nature of percutaneous modalities warrants broadened application. Nevertheless, although devices and results have improved over time, the long-term patency of percutaneous interventions remains inferior to open surgical techniques (figure 5). Moreover, the use of primary stenting has never been proved to be advantageous when compared with the placement of a stent only after an inadequate balloon dilatation alone.<sup>79,80</sup>

Proponents of endovascular therapy cite two contentions to justify continued use of these modalities; first, the decrement in durability is offset by the less invasive nature of endovascular interventions and resultant decreased morbidity, and second, it is infrequent for a patient to have clinical or angiographic worsening upon failure of an endovascular intervention; interventions can be repeatedly done after they fail. In a meta-analysis of 2116 patients who underwent aortoiliac percutaneous balloon angioplasty and stent placement, the 30-day mortality rate was less than 1%.<sup>79</sup> The patency of percutaneous balloon angioplasty and stenting for aortoiliac stenoses averages 86% at 3 years, falling to 62% when aortoiliac occlusions are treated.<sup>80</sup> The results of infrainguinal percutaneous balloon angioplasty and stenting are not as good, with 3-year patency rates below 60% (table).<sup>81-91</sup> Thus, available data would suggest that long-term durability is greater with surgical revascularisation compared with endovascular therapy, but periprocedural complications are lower when percutaneous modalities are used. The risk-benefit ratio associated with endovascular versus open surgical revascularisation is a question that can only be answered by well-designed comparative clinical trials. In patients with anatomically appropriate lesions, however, most practitioners use endovascular interventions preferentially; a practice based on the presumption of lower risks to the patient.

Treatment of patients presenting with acute limb ischaemia was formerly relegated to open surgical revascularisation. Such an approach was associated with a

Arterial segment	Primary author	Limbs	Primary patency rate		Major complication rate
			1 year	3 year	
<b>Aortoiliac (stenoses)</b>	Tetteroo <sup>86</sup>	149	89%	..	0
	Vorwerk <sup>87</sup>	118	97%	86%	3.4%
	Martin <sup>88</sup>	163	81%	..	4.3%
	Henry <sup>89</sup>	184	94%	86%	1.0%
	Murphy <sup>90</sup>	99	78%	53%	7.6%
<b>Aortoiliac (occlusions)</b>	Vorwerk <sup>80</sup>	127	68%	62%	5.8%
<b>Femoropopliteal (all)</b>	Matsi <sup>91</sup>	140	47%	42%	4.0%
	Murray <sup>92</sup>	44	86%	53%	5.0%
	Henry <sup>89</sup>	126	81%	72%	1.0%
	Martin <sup>88</sup>	96	61%	..	17.0%
	Strecke <sup>93</sup>	80	76%	48%	8.8%
	Gray <sup>94</sup>	58	22%	..	12.0%
	Bray <sup>95</sup>	57	79%	..	..
White <sup>96</sup>	32	75%	..	..	

#### Results of balloon angioplasty and stenting treatment of aortoiliac and infrainguinal disease in selected studies published after 1993

high rate of complications, including major amputation and death.<sup>63,92</sup> Today, many centres use intra-arterial thrombolytic therapy as the initial intervention, infusing thrombolytic agents directly into the occluding thrombus. Agents such as urokinase,<sup>93</sup> alteplase,<sup>94</sup> and reteplase<sup>95</sup> provide a less invasive means of restoring adequate arterial perfusion, addressing the unmasked culprit lesion responsive for the occlusion with an endovascular or open surgical procedure done on an elective basis after adequate patient preparation. A strategy of initial thrombolysis, reserving definitive remediation of the culprit lesion until the patient is adequately prepared, might underlie a decreased rate of complications in patients with severe limb ischaemia.<sup>96</sup>

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