FOCUS ON PERIPHERAL ARTERIAL DISEASE

"The identification and appropriate management of this often unidentified, high risk patient group, represents a significant opportunity in general practice to improve survival and reduce the risk of heart attack and stroke."1

Summary
Peripheral arterial disease (PAD), a manifestation of systemic atherosclerosis, most commonly presents in the lower limbs, but also serves as an indicator for atherosclerotic disease at other vascular sites. Patients with PAD have an increased risk of coronary and cerebrovascular events including myocardial infarction, stroke and death. Up to 30% die within 5 years of presenting to their doctor with symptoms, mostly from cardiovascular disease.1 The defining symptom of PAD, intermittent claudication, is evident in only a minority of patients, while the majority will remain asymptomatic throughout their lifetime, leading to this condition frequently going undetected. Early diagnosis and secondary prevention in primary care are paramount to effective treatment of PAD. Evidence suggests, however, that there is currently a lack of awareness regarding PAD in clinical practice and in the general public, leading to underdiagnosis and undertreatment.1,3

Atherosclerosis
Atherosclerosis in the peripheral arteries is a chronic, slowly developing condition causing narrowing of the femoral and popliteal, subclavian, carotid, iliac and renal arteries. Depending on the degree of narrowing at each vascular site, a range of severity of symptoms may develop, while the majority of patients remain asymptomatic throughout their lifetime. Occasionally acute events occur, often associated with thrombosis and/or embolism and/or occlusion of a major artery.4

The most important implication of PAD in terms of morbidity and mortality is that PAD serves as an indicator for atherosclerotic disease at other vascular sites, and is associated with an increased risk of coronary and cerebrovascular events including myocardial infarction, stroke and death.1

Prevalence
The occurrence of PAD is strongly age related; uncommon before 50 years, rising steeply at older ages.4 The risk of PAD increases two- to three-fold for every 10 year increase in age after 40 years.5 PAD is frequently reported in the literature to affect approximately 20% of adults older than 55 years, although estimates of the prevalence of PAD vary widely.6

Worldwide, the estimated prevalence in high-income countries ranged from 5.3% for individuals 45 to 49 years of age, to 18.6% for individuals 85 to 89 years old for data collected in 2000 to 2010. The incidence of PAD reportedly increased significantly over the preceding decade (13.1%) which may be attributable to factors such as population ageing and diabetes.7

Prevalence rates between men and women are inconsistent; some studies report a two-fold male predominance, while others fail to demonstrate any significant difference in PAD between the two sexes.5-8 Intermittent claudication may be more common in men, whereas asymptomatic PAD and severe ischaemia may occur more frequently in women.6

Awareness
Despite its prevalence, PAD remains relatively poorly publicised compared to other life-threatening conditions such as myocardial infarction, stroke and cancer. A number of population based studies have shown a low level of awareness and knowledge of PAD amongst both doctors and the general public.1,3,9

A recent survey conducted to assess the awareness of PAD among patients attending a tertiary vascular clinic for management of PAD in Ireland indicates that the level of knowledge of this disease and strategies for secondary prevention is low. However, it does show increased health awareness between those at their first visit to the vascular clinic and those who were return patients, indicating that education by a medical professional can affect patients understanding of the disease.3

Compared to other patient groups, this patient cohort generally has poor interaction with modern educational tools such as the internet, and in general make little effort to seek further information. Since a high number of patients report getting their information from their GP, it suggests that primary care represents an important gateway for educating this patient group on PAD and secondary prevention.3
Clinical presentation
PAD has several different presentations, categorised according to the Fontaine or Rutherford classifications (see table 1). Even with a similar extent and level of disease progression, symptoms and their severity may vary from one patient to another.4

Intermittent claudication is the most typical symptom of PAD. However, only 10% to 30% of patients present with intermittent claudication, and the majority are asymptomatic or have atypical symptoms, even with advanced disease.4,6

Claudication is characterised by cramping, or tightness in the calf, thigh or buttock, brought on by exercise and relieved by rest. Calf claudication is by far the most common symptom but some patients may describe buttock claudication and impotence due to severe aortoiliac disease.1

Many patients dismiss their symptoms as the normal effects of ageing, and do not seek medical attention until they become severely disabled. Doctors who rely on classic intermittent claudication alone to detect PAD will miss approximately 85% to 90% of patients who are asymptomatic.1

Other symptoms of PAD may include:10
• Leg numbness or weakness
• Hair loss or slower hair growth on legs and feet
• Brittle, slow-growing toenails
• Ulcers on legs and feet which do not heal
• Changing skin colour on legs, turning pale or bluish
• Coldness in lower leg or foot
• Shiny skin
• Muscles in legs may shrink
• No pulse or a weak pulse in legs and feet
• Erectile dysfunction in men

Critical limb ischaemia is the most severe clinical manifestation of PAD and is defined in patients who present with lower extremity ischaemic rest pain, skin ulceration, or gangrene. In these individuals, the untreated natural history of severe PAD would lead to major limb amputation within 6 months.11

Patients with critical limb ischaemia usually present with limb pain at rest, with or without trophic skin changes or tissue loss. The discomfort is often worse when the patient is supine and may lessen when the limb is maintained in the dependent position. Arterial ulcers are usually extremely painful; they are frequently secondary to local trauma. When pain is absent, peripheral neuropathy should be considered. Ulcers are often complicated by local infection and inflammation.4,11

The risk of a person with claudication progressing to critical limb ischaemia and needing amputation is low (<1% per year). However the risk of death mainly from coronary and cerebrovascular events, is high at 5% to 10% per year.1

Further examination of the cardiovascular system may disclose signs of subclavian or cervical (both carotid and vertebral) bruits, abdominal aneurysm, cardiac murmurs, arrhythmia, or other conditions that might affect patient health.1

The presence of PAD whether symptomatic or asymptomatic, is associated with grave prognostic implications. Up to 30% of patients die within 5 years of presenting to their doctor with intermittent claudication, with cardiovascular disease accounting for up to 75% of deaths.1

Table 1. Clinical staging of lower extremity PAD4

<table>
<thead>
<tr>
<th>Fontaine classification</th>
<th>Rutherford classification</th>
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<tbody>
<tr>
<td>Stage</td>
<td>Symptoms</td>
</tr>
<tr>
<td>I</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>II</td>
<td>Intermittent claudication</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Ischaemic rest pain</td>
</tr>
<tr>
<td>IV</td>
<td>Ulceration or gangrene</td>
</tr>
</tbody>
</table>

Prognosis
Five-year natural history of patients presenting to their doctor with intermittent claudication:12
• 50% will improve, 25% will stabilise and 25% will worsen. Of those who worsen, 20% (5% of total) will need intervention and 8% (2% of total) will need a major limb amputation.
• 5-10% will have a non-fatal cardiovascular event.
• 30% will die: cardiac 16%, cerebral 4%, other vascular 3%, non-vascular 7%.
• 55-60% will survive with no cardiovascular event.

The prognosis following amputation is poor. Two years following a below-knee amputation, 30% are dead, 15% have an above-knee amputation, 15% have a contralateral amputation, and only 40% have full mobility.4
**Risk factors**

Risk factors for PAD include:
- Smoking*
- Diabetes*
- Hypertension
- Hyperlipidaemia
- Hyperhomocysteinaemia
- Elevated plasma fibrinogen
- Age

*Account for over half the attributable risk of PAD

**Diagnosis**

Techniques used to diagnose PAD should include:
- Medical history
- Physical examination
- Diagnostic tests (including the ankle-brachial index)

**Ankle-brachial index**

The recommended assessment strategy for PAD is the ankle-brachial index (ABI). Measurement of the ABI enables lower limb systolic blood pressures to be compared with normal brachial blood pressure. It is a simple, reliable, non-invasive and inexpensive test to diagnose PAD in primary care (a maternity Doppler device is not suitable for measurement).

Additionally, the ABI is useful in assessing the severity and progression of PAD (see table 2). The ABI is helpful in stratifying the risk of mortality in PAD patients. The lower the ABI, the greater the risk of serious cardiovascular events.

**Table 2. Interpretation of ABI measurement**

<table>
<thead>
<tr>
<th>ABI value*</th>
<th>Interpretation</th>
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<tbody>
<tr>
<td>&gt;1.3</td>
<td>Incompressible/calcified arteries</td>
</tr>
<tr>
<td>1.0 - 1.29</td>
<td>Normal (suggests no blockage)</td>
</tr>
<tr>
<td>0.91 - 0.99</td>
<td>Borderline (equivocal)</td>
</tr>
<tr>
<td>0.41–0.90</td>
<td>Mild-moderate PAD</td>
</tr>
<tr>
<td>&lt;0.40</td>
<td>Severe PAD</td>
</tr>
</tbody>
</table>

*cut-off points vary slightly in the literature - some papers suggest >1.4 for incompressible/calcified arteries or <0.5 for severe PAD.

The ABI may not be accurate in individuals in whom systolic blood pressure cannot be abolished by inflation of an air-filled blood pressure cuff. Incompressible/calcified arteries are often observed in patients with diabetes, end-stage renal disease and the very elderly. Importantly, a substantial proportion of patients with an elevated ABI actually do have occlusive artery disease. Patients with either severely stenotic or totally occluded iliofemoral arteries may also have a normal ABI value at rest if sufficient collaterals are present. Thus, for patients in whom symptoms strongly suggest lower extremity PAD, the presence of a normal or high ABI should not be presumed to rule out this diagnosis, and an alternative diagnostic test (e.g., toe-brachial pressure, Doppler waveform analysis, pulse volume recording, exercise ABI test, or duplex ultrasound) should be performed.

**Targeted ABI screening**

Targeted screening of PAD is recommended by all professional vascular societies in order to increase the frequency of diagnosis, improve the use of appropriate medical therapies, and consequently reduce cardiovascular morbidity and mortality rates.

In the context of identifying a high risk population, the ACC/AHA practice guidelines recommend that persons who should be considered for ABI screening include:
- Age less than 50 years with diabetes and one other atherosclerosis risk factor (smoking, dyslipidemia, hypertension, or hyperhomocysteinemia)
- Age 50 to 69 years and history of smoking or diabetes
- All patients aged 70 years and older
- Leg symptoms with exertion (suggestive of claudication) or ischaemic rest pain
- Abnormal lower extremity pulse examination
- Known atherosclerotic coronary, carotid, or renal artery disease

The Irish Heart Foundation Council on PAD also recommends that the following routine investigations should be performed - full blood count, urea and creatinine, fasting blood glucose, and fasting lipid profile.

Additional optional parameters include - HbA1c, serum fibrinogen, serum homocysteine, high sensitivity C reactive protein and an ESR.

**Secondary prevention for PAD**

Lifestyle modification, including exercise and smoking cessation, combined with pharmacologic therapy to manage risk factors have been shown effective in reducing cardiovascular risks in patients with PAD.

**Exercise**

Exercise significantly improves maximum walking time and overall walking ability in stable intermittent claudication patients. Exercise has been reported as more effective than angioplasty or antiplatelet therapy for improving walking
time and quality of life, but remains similar to surgical treatment. Exercise also improves gait patterns in non-surgical patients. Patients should be clearly advised of the benefits of exercise for overall cardiovascular health.

**Smoking cessation**

Cigarette smoking is associated with a marked increased risk for peripheral atherosclerosis. The number of pack years is associated with disease severity, an increased risk of amputation, peripheral graft occlusion, and mortality. Pharmacologic therapy, including nicotine replacement and anti-depressants, can assist in smoking cessation.

**Treatment of diabetes**

Diabetes is strongly linked to early onset vascular disease, leading to premature cardiovascular events and mortality. There is a more rapid progression in diabetic patients with an 11 times higher rate of major lower limb amputation compared to non-diabetics and a doubling of the 5-year mortality. Diabetic ulcers also heal more slowly and are the main cause of non-traumatic lower limb amputation.

**Anti-platelet therapy**

Anti-platelets delay the rate of PAD progression, reduce the need for intervention and the rate of graft failure following revascularisation procedures. The CAPRIE trial reported a 8.7% relative risk reduction for myocardial infarction, stroke or cardiovascular death when clopidogrel was compared to aspirin in high-risk patients. Apirin is indicated in all patients with PAD while clopidogrel should be considered for higher risk patients particularly those with severe cardiac disease and diabetes.

**Statin therapy**

The Heart Protection Study demonstrated that in patients with PAD, aggressive LDL cholesterol-lowering therapy with a statin was associated with a reduction in cardiovascular events of about 25%. Statins have been reported to reduce the incidence of new onset intermittent claudication whilst improving pain-free walking distances as well as reducing intimal-media thickness in carotid artery stenosis.

**Antihypertensives**

Hypertension is an independent risk factor for PAD that is associated with a 2- to 3-fold increase. The angiotensin-converting-enzyme (ACE) system plays an important role in the pathogenesis and progression of atherosclerosis, and ACE-inhibitors are useful for reducing the risk of cardiovascular events in clinical and subclinical PAD.

It is recommended that all patients with PAD should be on anti-platelets, lipid-lowering therapy and anti-hypertensives as appropriate.

**Indications for referral to a vascular surgeon**

Patients with absent pulses and/or other indications of peripheral ischaemia require referral to a vascular surgeon. Urgent referral by telephone should be undertaken for patients with critical limb ischaemia (rest pain, ulceration, or gangrene).

Surgery is indicated in all patients with critical limb ischaemia and in patients with severe lifestyle limiting claudication. Critical limb ischaemia is a serious threat to the limb and usually warrants revascularisation or amputation.

Referral may also be considered if:
- Not confident about the diagnosis
- Concern that the symptoms may have an unusual cause
- Patients present with claudication significantly affecting their quality of life
- Patient preference

**Surgical and endovascular interventions**

Surgery is only considered in patients in whom smoking cessation has been successful and in whom the full range of secondary prevention is employed.

Currently the procedures available include angioplasty (with or without stenting), bypass surgery, endarterectomy, or a combination of all of these procedures and is dependent on patient and lesion characteristics.

**References:**