Grand Rounds

Optimal Management of Peripheral Arterial Disease for the Non-Specialist

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ABSTRACT Peripheral arterial disease (PAD) now affects approximately 20% of adults older than 55 years to an estimated total of 27 million people in the Western World. The aim of this paper is to describe the medical management of PAD for the non-vascular specialist, particularly general practitioners, where PAD has now been included in the Northern Ireland Department of Health's Primary Care Service Framework (Directed Enhanced Service).

KEYWORDS Peripheral Arterial Disease, Epidemiology, Investigation, Treatment.

DEFINITION

Peripheral arterial disease (PAD) is defined by the presence of significant narrowing of arteries distal to the arch of the aorta, most often due to atherosclerosis^{1, 2}. Clinically, PAD most commonly affects the lower limbs as a consequence of arterial narrowing distal to the aortic bifurcation^{1, 2}.

CLINICAL PRESENTATION

PAD is initially asymptomatic. Intermittent Claudication (IC) is defined as reproducible lower extremity muscular pain induced by exercise and relieved by short periods of rest. It is the symptomatic expression of the inability of the lower limb vasculature to maintain adequate tissue perfusion and oxygenation during exertional activity^{2, 3}. Although an ankle-brachial pressure index (ABPI) less than 0.9 suggests arterial disease, only 10% to 30% of such patients will have classic symptoms of IC⁴. *The presence of slight abnormalities in peripheral blood flow does not necessarily result in symptomatic PAD*. Table 1 describes the differential diagnoses of lower limb exertional discomfort.

Critical limb ischaemia is lower extremity arterial occlusive disease of a magnitude that potentially threatens the viability of the limb. Critical ischaemia (CI) is persistent rest pain for a period greater than two weeks duration requiring regular analgesia, with an ankle systolic pressure of less than 50mmHg or toe pressure of less than 30mmHg, with or without associated tissue ulceration or gangrene⁵.

EPIDEMIOLOGY

PAD now affects approximately 20% of adults older than 55 years with an estimated total prevalence of 27 million people in North America and Europe⁶. The peak incidence is 60 new cases per 10,000 persons per year with a prevalence of 8 million people in the United States⁷. In Europe, Hooi *et al* (2001) documented an overall incidence of 1.0 per 1000 people for symptomatic PAD in the Netherlands⁸.

The Framingham study, and others, documented an increasing prevalence of intermittent claudication (IC) with age and a

two-fold male predominance (1.8% for women and 3.6% for men). However, the Edinburgh Artery Study failed to demonstrate any significant difference in PAD between men and women⁹. The risk of PAD increases two- to three-fold for every 10 year increase in age after 40 years¹⁰. More recently, IC was reported to be more common in men, whereas asymptomatic PAD and severe ischaemia were more frequent in women¹.

NATURAL HISTORY OF PERIPHERAL ARTERIAL DISEASE

Between 5% and 10% of individuals with asymptomatic PAD develop IC over 5 years and 75% of such patients will experience symptom stabilisation or improvement over their lifetime without intervention¹¹. This trend occurs despite arteriographic evidence of disease progression in the majority of patients. Symptoms may then deteriorate in the remaining 25%, most commonly in the first year (7-9%), and subsequently at rates of 2% to 3% per year, resulting in an incidence of CI between 0.25 to 0.45 per 1000 people per year³. In the first 5 years following diagnosis, 5% of IC patients will require a therapeutic intervention, while only 2% to 4% will ever require a major amputation¹². The Edinburgh Artery Study demonstrated that 28.8% of IC patients still had pain after 5 years, 8.2% had undergone a vascular surgical revascularization or amputation and that 1.4% developed leg ulceration⁹. Although PAD progression is usually slow and the risk of limb loss is low, approximately 20-25% of symptomatic PAD patients will die from coronary or cerebrovascular events within 5 years^{9, 13}. For this reason, risk factor modification and secondary prevention treatment

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Differential diagnoses for lower limb exertional symptomatology.

Condition	Prevalence	Anatomical Distribution	Character of Pain	Effect of Exercise	Effect of Rest	Effect of Position	Additional Factors
Thigh and Buttock Claudication	Rare	Buttock, hip and thigh	Crampy, aching discomfort	Reproducible onset (same distance for each episode)	Quickly relieved	None	Proximal pulses may be reduced combined with normal distal pulses
Calf Claudication	3% - 5% of the adult population	Calf muscles	Crampy, aching discomfort	Reproducible onset	Quickly relieved	None	May have atypical symptoms on exercise
Foot Claudication	Rare	Foot arch	Severe pain on exercise	Reproducible onset	Quickly relieved	None	Numbness can also be associated with pain
Venous Claudication	Rare	Entire lower limb affected. Worse in calf.	Tight, bursting pain	Occurs after walking	Slow to settle	Elevation enhances recovery	Signs of deep venous congestion and oedema present. May have history of iliofemoral thrombosis
Chronic Compartment Syndrome	Rare	Calf muscles	Tight, bursting pain	Occurs after walking	Very slow to settle	Elevation enhances recovery	Tends to affect heavily muscled athletes
Spinal Stenosis	Common	Buttocks and posterior aspects of lower limb. Often bilateral	Pain and weakness	Occurs with exercise and can mimic claudication	Varies but can have a prolonged recovery time	Lumbar spine flexion eases discomfort	Exacerbated by standing and extending spine
Nerve Root Compression	Common	Radiation of pain down lower limb	Sharp	May be induced by sitting, standing or walking	Often present at rest	Positional change can improve symptoms	History of back pain
Bakers Cyst	Rare	Behind knee down calf	Tenderness and associated swelling	Occurs with exercise	Present at rest	None	Usually a constant discomfort
Hip Arthritis	Common	Lateral aspect hip and thigh	Dull to severe ache	Can occur following a period of exercise	Not relieved quickly	Rest and minimal weight bearing helps	Symptoms can vary. Increased in patients with high BMI
Foot or Ankle Arthritis	Common	Ankle and foot arch	Aching pain	Variable onset following exercise	Not quickly relieved	Rest and minimal weight bearing helps	Variable. Can relate to exercise but present at rest

in PAD patients is as important as in patients with coronary and cerebrovascular disease.

MODIFIABLE RISK FACTORS

Atherosclerosis is a multifactorial disease process associated with the interaction of numerous risk factors. The National Health and Nutrition Examination Survey (1999-2000) analysed 2174 participants over the age of 40 and identified a 4.3% prevalence of PAD based on ABPI < 0.90 in either lower limb¹⁴. Using age and gender adjusted logistic regression analyses, they reported odds ratios for risk factors significantly associated with PAD including current smoking (4.46), black race (2.83), diabetes (2.71), poor kidney function (2.00), hypertension (1.75) and hypercholesterolaemia (1.68).

Smoking: Smokers have a 3 times greater relative risk of developing IC and experience symptoms 10 years earlier

than their non-smoking counterparts³. The Framingham study also showed that smokers are twice as likely to develop PAD as coronary artery disease¹⁵. There is also a dose-dependant relationship between smoking and severity of PAD¹⁶.

Diabetes: Diabetes mellitus is strongly linked to early onset vascular disease, leading to premature cardiovascular events and mortality¹⁵. The Framingham study showed that 20% of IC patients have diabetes and that diabetes increases two- to three-fold the risk of IC. Although most reported studies do not stratify patients according to Type 1 and Type 2 diabetes, patients with both diabetes and IC have a two- to four-fold increased risk of a further cardiovascular event¹⁵. PAD prevalence increases with the duration of diabetes with 15% of diabetic patients affected by PAD at 10 years following diagnosis, rising to 45% at 20 years¹⁷. *Of major concern, Elhadd et al (1999) reported a 25% prevalence of undetected*

TABLE 2

Provisional service descriptions of the Northern Ireland Department of Health's Primary Care Service Framework (Directed Enhanced Service) for the treatment of PAD.

Year	Target Goals
1	 Purchase of equipment for ABPI assessment (doppler, sphygmomanometer). Training of staff to conduct ABPI assessment. Completion of a symptomatic PAD registry.
2	 Completion of appropriate treatment for all symptomatic PAD patients on registry. Commencement of PAD assessment registry for at-risk patients over the age of 50 years who smoke.
3	• Completion of appropriate treatment for all at- risk PAD patients on registry.

PAD in Scottish diabetic patients attending hospital clinics¹⁸. 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 five-year mortality¹⁸. Diabetic ulcers also heal more slowly and are the main cause of non-traumatic lower limb amputation in developed countries accounting for more hospital bed occupancy than any other diabetic complication¹⁹.

Hypertension: Hypertension contributes to atherosclerosis development, particularly in the coronary and cerebral circulations as well as a two- to three-fold increased risk of developing IC¹⁵.

Hypercholesterolaemia: Elevated serum cholesterol, triglyceride and low density lipoproteins (LDL) with reduced high density lipoprotein levels are all implicated as important factors for the progression of atherosclerosis.

Hyperhomocysteinaemia: Elevated homocysteine level may initiate atherosclerosis by modulating cholesterol biosynthesis, thus inducing other cardiovascular risk factors. It is considered an independently graded risk factor for arteriosclerotic vascular disease²⁰.

INVESTIGATION OF PERIPHERAL ARTERIAL DISEASE

Risk Factors: All patients should have a risk factor analysis on their first consultation, particularly smoking and blood pressure measurement. Assessment of haemoglobin, urea and electrolytes to determine baseline renal function as well as fasting serum glucose and lipid profiles should also be performed. Liver function testing should be considered at this stage prior to commencing pharmacological therapy, particularly statins.

Vascular Flow Investigation: An assessment of peripheral blood flow ranges from non-invasive ankle-brachial pressure index, arterial duplex, computerised tomography and magnetic resonance imaging to conventional transfermoral angiography.

Ankle-Brachial Pressure Index (ABPI) is derived from the brachial, posterior tibial and dorsalis pedis artery systolic pressures which are measured using cuff occlusion by a sphygmomanometer and Doppler ultrasound (Figure 1). A resting ABPI of <0.90 indicates a haemodynamically significant arterial stenosis and is most often used as a haemodynamic definition of PAD. An ABPI <0.5 would suggest moderate to severe claudication while an ABPI <0.3 is suggestive of impending critical ischaemia. An ABPI < 0.90is also 95% sensitive in detecting arteriogram-positive lesions in symptomatic individuals². Calcification and inability to compress the arteries secondary to diabetes or renal insufficiency may result in a false elevation of ABPI > 1.4 in some cases². In these patients, arterial duplex at multiple sites in the lower limb may identify a haemodynamically significant lesion². Significant disease may also be demonstrated by the characteristics of the actual Doppler waveforms which range from normal triphasic waveforms to atherosclerotic biphasic and monophasic patterns which occur distal to 50% and >70%stenoses respectively.



Fig 1. Ankle-brachial index – Doppler assessment of dorsalis pedis which is measured using cuff occlusion by a sphygmomanometer and Doppler ultrasound (Super Dopplex[®] II Huntleigh Healthcare, UK).

The Trans-Atlantic Inter-Society Consensus Document on Management of Peripheral Arterial Disease (TASC) II guidelines recommend that ABPI measurements should be performed in all patients between the age of 50-69 with a cardiovascular risk factor, who have exertional leg symptoms, who are over the age of 70 regardless of their risk-factor status and in all patients with a Framingham risk score of 10-20% (Framingham risk score is based on patient gender, age, blood pressure, total cholesterol and HDL levels and presence of smoking and diabetes)².

Magnetic resonance angiography (MRA) is a relatively safe modality offering three-dimensional images of the abdomen, pelvis and lower extremities (**Figure 2**). The use of techniques to minimise venous contamination have improved the accuracy compared to invasive angiography²¹. Although gadolinium-based contrast agents administered during MRA scanning may be associated with a lower risk of renal dysfunction when compared to iodinated contrast media, nephrogenic systemic fibrosis has now been reported which can lead to severe disability and even death through the induction of skin, muscle and organ fibrosis in patients with background renal impairment.



Fig 2. Magnetic Resonance Angiogram (MRA) of the peripheral arterial system extending from the abdominal aorta to the pedal vessels which demonstrated bilateral popliteal artery occlusion with surrounding collateralization (Inset figure is patients preoperative transfemoral angiogram demonstrating bilateral popliteal artery occlusion).

Multidetector Computerised Tomography Angiography yields rapid high quality imaging (Figure 3)²². Major limitations include iodinated contrast and radiation exposure combined with the requirement for careful interpretation during automated digital subtraction due to the presence of arterial wall calcification which has a Hounsfield unit value close to arterially opacified blood.

Transarterial Angiography assessing the infrarenal vasculature remains the "gold standard" arterial imaging test, with concurrent therapeutic intervention potential (Figure 2). However, complications can arise as a consequence of the arterial puncture or from administration of the contrast material².

Vascular Function Assessment: includes both a subjective assessment of quality of life combined with quantitative walking distances on a treadmill.

Quality of Life is an important outcome measure for interventions based on global and specific measures²³. Generic health questionnaires such as the Short Form-36 (SF-36)



Fig 3. Computerised tomography angiogram of the peripheral arterial system demonstrating proximal disease of both lower limbs extending from the external iliac to the superficial femoral arteries.

evaluate QoL through measurement of physical, social and emotional dimensions of health. However, they are less sensitive in detecting subtle but clinically important treatment differences²⁴. Disease-specific QoL instruments for patients with PAD include the Walking Impairment Questionnaire (WIQ) and the VascuQoL Questionnaire^{23, 25}.







Fig 5. Belfast Health and Social Care Trust Referral Pathway for patients with intermittent claudication.



Fig 6. Belfast Health and Social Care Trust Referral Pathway for patients with critical ischaemia.



Figure 7. Belfast Health and Social Care Trust Referral Pathway for patients with diabetes and renal failure.

Treadmill Testing provides an objective measure of walking capacity, performed on calibrated treadmill machines at a constant speed of 2mph (3.2 kph) and gradient of $10\%^{2, 26}$. The time of onset of claudication pain is called the initial claudication distance (ICD) or claudication onset time (COT). The maximal walking performance before the patient stops due to pain is called the absolute claudication or maximal walking distance (ACD or MWD)²⁷. Claudication patients have reduced walking capacities, with a 50% to 60% reduction in peak treadmill performance, compared to agematched healthy controls. A therapeutic intervention which results in a greater than 25% increase in both ICD and ACD is considered significant²⁸.

TREATMENT OF PERIPHERAL ARTERIAL DISEASE

Treatment of PAD aims to improve longer-term cardiovascular outcomes through risk factor modification combined with antiplatelet and lipid lowering primary medical therapy whilst attenuation of lower limb symptomatology is mediated through walking specific pharmacological agents, endovascular or surgical interventions. The Vascular and Endovascular Units from the Belfast Health and Social Care Trust have issued PAD referral pathways to assist nonvascular practitioners in their management of such patients (**Figures 4-7**).

CONSERVATIVE

Dietary therapy has beneficial effects on the occurrence and progression of atherosclerosis²⁹. The National Cholesterol Education Program III (NCEP) report recommends a tiered dietary approach to weight reduction, with the further addition of cholesterol lowering agents if required²⁹.

Smokers should be strongly advised to stop through physician advice, group counselling sessions and nicotine replacement². Smoking cessation reduces the severity of claudication and the risk of developing rest pain³⁰.

Exercise significantly improves maximum walking time and overall walking ability in stable IC patients. The absolute or peak walking distance can be improved by more than 100% with a greater effect identified in longer-term programmes³¹. 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 patients³². Exercise programmes deliver better outcomes when supervised by hospital based-departments compared to home based-programmes and if the mean duration is greater than 2

months³¹. Badger *et al* (2007) also commented on the efficacy of a supervised exercise programme, which led to further improvements in walking distance after lower limb arterial bypass surgery.

MEDICAL

PAD medical therapies include systemic cardiovascular or walking specific therapies.

Systemic Cardiovascular Therapies

Antiplatelet Therapy: Antiplatelets delay the rate of PAD progression, reduce the need for intervention and the rate of graft failure following revascularisation procedures³³. More importantly a meta-analysis of 195 placebo-controlled trials of antiplatelet therapy demonstrated a reduced cardiovascular death risk of approximately 25% in high risk patients including those with symptomatic PAD³³. The Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial reported a 8.7% relative risk reduction for MI, stroke or cardiovascular death when clopidogrel (75mg/day) was compared to aspirin (325mg/day) in high-risk patients³⁴. Aspirin (75mg) is therefore indicated in all patients with PAD while Clopidogrel (75mg) should be considered for higher risk patients particularly those with severe cardiac disease and diabetes. Other antiplatelet therapies including picotamide, triflusal and ketaserin have not been reported to be superior to aspirin for preventing systematic complications in PAD patients³³.

Lipid Lowering Therapy: Statins are clearly efficacious in cholesterol homeostasis with additional cardiovascular benefits which include a 20% relative risk reduction of stroke, MI, vascular death and revascularisation procedures in PAD patients with increased baseline cholesterol levels³⁵. 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 patients with carotid artery stenosis^{36, 37}. Current guidelines for lipid control state that symptomatic PAD patients should have their LDL lowered to <2.59 mmol/ with a target for further reduction down to <1.81 mmol/l in patients with concomitant vascular disease elsewhere². In conjunction with dietary modification, statins are the primary pharmacological agent with fibrates and/or niacin reserved for patients with abnormalities in triglyceride and HDL profiles.

Antihypertensives: Control of hypertension in PAD patients reduces cardiovascular co-morbidities over the medium to longer-term period³⁸. All PAD patients with hypertension should have blood pressure controlled to <140/90 mmHg or <130/80 mmHg if they also have diabetes or renal insufficiency. Thiazides and angiotensin converting enzyme inhibitors are the initial antihypertensive agents to reduce the risk of cardiovascular disease². Angiotensin-converting enzyme inhibitors, in hypertensive patients with PAD, may also improve walking distances without a change in ABPI measurements³⁹. Although β -blockers do not affect IC distance and are not actually contraindicated in PAD, a cautious approach is advocated for more severely affected PAD patients⁴⁰.

WALKING SPECIFIC THERAPIES

Traditional PAD vasodilators such as naftidrofuryl and

pentoxifylline have largely been superseded by cilostazol whereas other arterial vasodilators such as α -blockers, papaverine, nylidrin and nifedipine are not clinically efficacious in PAD^{41,42}.

Cilostazol: Cilostazol (Pletal[®] - 100mg twice a day orally) has antiplatelet, antithrombotic, vasodilatory, antimitogenic and cardiogenic properties⁴³. A meta-analysis showed a significant increase of 67% vs. 40% in ICD and 50% vs. 21% for ACD for oral cilostazol 100mg and placebo respectively²⁷. A further meta-analysis from the Cochrane Peripheral Vascular Diseases Group confirmed cilostazol's efficacy on ICD and ACD in patients with stable, moderate to severe IC⁴⁴. Thompson *et al* (2002) and Regensteiner *et al* (2002) have also reported improvements in quality of life with cilostazol therapy as assessed by the SF-36 and Walking Impairment Questionnaires^{25, 27}.

Cilostazol is contraindicated in congestive heart failure, haemostatic disorders or active bleeding. Although cilostazol does not alter coagulation parameters, caution is advised with initial clinical monitoring of patients on antiplatelet and warfarin therapy as well as its use in patients with moderate renal or hepatic dysfunction. Cilostazol is associated with a high frequency of side effects, particularly headache, diarrhoea and palpitations due to vasodilatory properties, occurring in up to 32% of patients^{27,45}. However, most of these effects are reported to settle within 6 weeks^{45,46}.

Naftidrofuryl: Naftidrofuryl (Praxilene[®]) has vasodilatory effects, improving tissue oxygenation and muscle metabolism². In a meta-analysis of 888 patients with IC, naftidrofuryl increased pain-free walking distance by 26% compared to placebo⁴⁷. Patients with IC who have a poor quality of life may be considered for treatment with naftidrofuryl^{2, 48}.

Pentoxifylline: Pentoxifylline (Trental[®]) produces doserelated haemorrheologic effects, lowers blood viscosity and improves erythrocyte flexibility. Although pentoxifylline is associated with modest increases in walking distance over placebo, the overall clinical efficacy is unclear. It is no longer recommended for use in PAD patients^{2, 48}.

Inositol and Cinnarizine: Inositol nicotinate causes vasodilation, lysis of fibrin, a mild hypolipidaemic effect and inhibition of oxidative metabolism in hypoxic tissues. Cinnarizine acts via antagonism of vasoconstrictive substances such as noradrenaline, serotonin and angiotensin⁴⁹. Although trials for these agents suggested efficacy by improving walking distances, their overall methodology was poor and have not shown clear evidence of benefit over placebo⁴⁸.

Alternative Peripheral Vasodilators and Treatments: Ticlodipine and ginkgo biloba special extract (Egb 761) significantly increase pain-free walking distance^{50, 51}. Assessment of angiogenic stimulation of new collateral channels by growth factors, autologous bone marrow cells and transcription factor gene therapy modalities are currently being evaluated⁵²⁻⁵⁴. Although dietary supplementation with B-vitamins and / or folate has been shown to lower homocysteine levels, high-level evidence for beneficial effects in PAD patients in terms of preventing cardiovascular events is lacking and such therapy is not recommended⁵⁵.

THERAPEUTIC INTERVENTION

Revascularisation should be considered in patients with critical limb ischaemia or severely debilitating claudication symptoms that persist despite maximal medical treatment. Although operative arterial bypass appears to have a better long term patency, the risks of surgery are significantly greater when compared to endovascular interventions in terms of mortality, major morbidity and return to the normal activities of daily living.

Endovascular

The technical success of percutaneous transluminal angioplasty (PTA) and/or stenting for proximal lesions in the iliac artery exceeds 90% with reported variations between 80% and 100% depending on the presence of either long or focal stenotic iliac lesions respectively². Five year primary patency rates range between 64% and 75% for all cases with a higher rates of 79% reported for claudicants^{2, 56, 57}.

Endovascular treatment of infrainguinal disease is also associated with a low morbidity and mortality with a technical and clinical success rate of PTA for femoropopliteal stenoses exceeding 95%². However, longer term outcomes are lower compared to proximal iliac interventions with 5 year patency rates of 55% (range 52-62%) and 42% (range 33-51%) for femoropopliteal stenoses and occlusions respectively².

Although PTA improves symptomatology and median ACD at 6-months in patients with mild to moderate claudication, longer term benefits are limited with no significant difference in walking distances or quality of life at 2 or 6 years post-PTA⁵⁸. Independent risk factors for re-stenosis include the disease severity (claudication vs. critical ischaemia), the actual length of the stenosed / occluded segment and the quality of the distal outflow (run-off) vessels.

Surgical

Surgical intervention is indicated for critical limb ischaemia where the primary goal is to relieve pain, encourage ulcer healing, prevent limb loss and improve patient function, quality of life and survival². Surgical intervention may also be considered in intermittent claudication in patients with proximal lesions or deteriorating symptomatology despite best medical therapy and endovascular intervention. Although surgical procedures improve medium to long-term outcome rates compared to endovascular intervention, they carry a higher early post-procedural complication rate^{2, 59, 60}.

An aortobifemoral arterial bypass is usually recommended for diffuse aortoiliac disease with limb-based patency rates for patients with claudication of 91.0% and 86.8% at 5 and 10 years, respectively, as compared with 87.5% and 81.8% for patients with critical limb ischemia⁵⁹. In higher risk patients with medical co-morbidities, extra-anatomical bypass modalities include femoro-femoral or axillo-femoral arterial conduits. However, these routes have a lower success rate with 5 year patency rates between 51% and 75%². Infrainguinal arterial bypass requires uncompromised inflow at the proximal anastomosis, preferably to a native artery rather than graft. A satisfactory distal run-off vessel is the most important determinant of longer-term patency which ranges between 35% for prosthetic material to 60% for vein grafts over 5 years².

IMPLICATIONS FOR NORTHERN IRELAND

General Practitioners in Northern Ireland participate in the Quality and Outcomes Framework which incentivises a number of activities to enhance patient outcomes. The Department of Health is currently drafting a Cardiovascular Service Framework including a care pathway from prevention, promotion, protection of health and wellbeing, to appropriate assessment, diagnosis, treatment and care provision, rehabilitation and end of life care based on evidence from established sources such as the National Institute of Clinical Excellence. The Northern Ireland Department of Health's Primary Care Service Framework (Directed Enhanced Service) is now developing standards which will cover risk assessment for those patients who have a high risk of or who have PAD⁶¹.

Provisional service descriptions as described in **Table 2** suggest the initial training of staff members in the assessment of PAD and the development of two disease registers to account for all patients with PAD followed by a second phase to incorporate patients greater than 50 years of age at risk of peripheral and cardiovascular disease particularly those who smoke. Finally, treatment protocols should then be implemented for patients on both registries⁶¹.

CONCLUSION

Peripheral arterial disease (PAD) now affects approximately 20% of adults older than 55 years. However, less than 30% of patients diagnosed with PAD based on the ankle-brachial index will have classic symptoms of IC. Asymptomatic and patients able to walk greater than 100 yards should be initially managed in the community with risk factor modification, peripheral arterial examination combined with the calculation of ankle-brachial indices. All patients should be considered for antiplatelet and lipid lowering therapies. Diabetic patients should also receive foot care advice. Symptomatic patients able to walk further than 100 yards require walkingspecific medication such as cilostazol for a period of three months. Tertiary referral should be reserved for refractory symptomatology despite maximal conservative management in the community and short distance claudication (<100 yards). Critical limb ischaemia warrants urgent referral.

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REFERENCES

- Sigvant B, Wiberg-Hedman K, Bergqvist D, Rolandsson O, Andersson B, Persson E, *et al.* A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences. *J Vasc Surg.* 2007;45(6):1185-91.
- Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, *et al.* Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg.* 2007;33 (Suppl 1): S1-75.
- Schmieder FA, Comerota AJ. Intermittent claudication: magnitude of the problem, patient evaluation, and therapeutic strategies. *Amer J Cardiol.* 2001;87(12A): 3D-13D.
- McDermott MM. The magnitude of the problem of peripheral arterial disease: epidemiology and clinical significance. *Cleve Clin J Med.* 2006;**73 (Suppl 4)**: S2-7.
- 5. Second European Consensus Document on chronic critical leg ischaemia. *Eur J Vasc Surg.* 1992;6 (Supp A): 1-32.

- Hankey GJ, Norman PE, Eikelboom JW. Medical treatment of peripheral arterial disease. *JAMA*. 2006;295(5):547-53.
- Hiatt WR, Nehler MR. Peripheral arterial disease. *Adv Int Med.* 2001;47: 89-110.
- Hooi JD, Kester AD, Stoffers HE, Overdijk MM, van Ree JW, Knottnerus JA. Incidence of and risk factors for asymptomatic peripheral arterial occlusive disease: a longitudinal study. *Am J Epidemiol.* 2001;**153(7)**: 666-72.
- Leng GC, Lee AJ, Fowkes FG, Whiteman M, Dunbar J, Housley E, *et al.* Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. *In J Epidemiol.* 1996;**25(6)**: 1172-81.
- Hiatt WR. Pharmacologic therapy for peripheral arterial disease and claudication. J Vasc Surg, 2002;36(6): 1283-91.
- Hooi JD, Stoffers HE, Knottnerus JA, van Ree JW. The prognosis of non-critical limb ischaemia: a systematic review of population-based evidence. *Br J Gen Pract*, 1999;49(438): 49-55.
- Dormandy J, Heeck L, Vig S. Predictors of early disease in the lower limbs. *Semin Vasc Surg.* 1999;12(2):109-17.
- Hooi JD, Kester AD, Stoffers HE, Rinkens PE, Knottnerus JA, van Ree JW. Asymptomatic peripheral arterial occlusive disease predicted cardiovascular morbidity and mortality in a 7-year follow-up study. J Clin Epidemiol. 2004;57(3):294-300.
- Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation*. 2004;**110(6)**:738-43.
- Murabito JM, D'Agostino RB, Silbershatz H, Wilson WF. Intermittent claudication. A risk profile from The Framingham Heart Study. *Circulation*. 1997;96(1): 44-9.
- Willigendael EM, Teijink JA, Bartelink ML, Kuiken BW, Boiten J, Moll FL, et al. Influence of smoking on incidence and prevalence of peripheral arterial disease. J Vasc Surg. 2004;40(6):1158-65.
- Kreines K, Johnson E, Albrink M, Knatterud GL, Levin ME, Lewitan A, *et al.* The course of peripheral vascular disease in non-insulindependent diabetes. *Diabetes Care.* 1985;8(3):235-43.
- Elhadd T, Robb R, Jung R, Stonebridge P, Belch J. Pilot study of prevalence of asymptomatic peripheral arterial occlusive disease in patients with diabetes attending a hospital clinic. *Pract Diabetes Int.* 1999;**16(6)**:163-6.
- Caputo GM, Cavanagh PR, Ulbrecht JS, Gibbons GW, Karchmer AW. Assessment and management of foot disease in patients with diabetes. *New Eng J Med.* 1994;331(13):854-60.
- Sharma M, Rai SK, Tiwari M, Chandra R. Effect of hyperhomocysteinemia on cardiovascular risk factors and initiation of atherosclerosis in Wistar rats. *Eur J Pharmacol.* 2007;574(1):49-60.
- Koelemay MJ, Legemate DA, Reekers JA, Koedam NA, Balm R, Jacobs MJ. Interobserver variation in interpretation of arteriography and management of severe lower leg arterial disease. *Eur J Vasc Endovasc Surg.* 2001;**21(5)**:417-22.
- Ota H, Takase K, Igarashi K, Chiba Y, Haga K, Saito H, et al. MDCT compared with digital subtraction angiography for assessment of lower extremity arterial occlusive disease: importance of reviewing cross-sectional images. AJR Am J Roentgenol. 2004;182(1): 201-209.
- Morgan MB, Crayford T, Murrin B, Fraser SC. Developing the Vascular Quality of Life Questionnaire: a new disease-specific quality of life measure for use in lower limb ischemia. *J Vasc Surg.* 2001;33(4):679-87.
- 24. Mehta T, Venkata Subramaniam A, Chetter I, McCollum P. Disease-

specific quality of life assessment in intermittent claudication: review. *Eur J Vasc Endovasc Surg.* 2003;**25(3)**:202-8.

- Regensteiner JG, Ware JE, Jr., McCarthy WJ, Zhang P, Forbes WP, et al. Effect of cilostazol on treadmill walking, community-based walking ability, and health-related quality of life in patients with intermittent claudication due to peripheral arterial disease: meta-analysis of six randomized controlled trials. JAm Geriatr Soc. 2002;50(12):1939-46.
- Badger SA, Soong CV, O'Donnell ME, Boreham CA, McGuigan KE. Benefits of a supervised exercise program after lower limb bypass surgery. *Vasc Endovascul Surg.* 2007;41(1):27-32.
- Thompson PD, Zimet R, Forbes WP, Zhang P. Meta-analysis of results from eight randomized, placebo-controlled trials on the effect of cilostazol on patients with intermittent claudication. *Am J Cardiol.* 2002;90(12):1314-9.
- Hiatt WR, Hirsch AT, Regensteiner JG, Brass EP. Clinical trials for claudication. Assessment of exercise performance, functional status, and clinical end points. Vascular Clinical Trialists. *Circulation*. 1995;**92(3)**: 614-21.
- 29. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;**285(19)**: 2486-97.
- Stead LF, Bergson G, Lancaster T. Physician advice for smoking cessation. *Cochrane Database of Systematic Reviews (Online)*. 2008(2): CD000165.
- Ernst E, Fialka V. A review of the clinical effectiveness of exercise therapy for intermittent claudication. *Arch Int Med.* 1993;153(20):2357-60.
- Lord SR, Lloyd DG, Nirui M, Raymond J, Williams P, Stewart RA. The effect of exercise on gait patterns in older women: a randomized controlled trial. *J Gerontol A Biol Sci Med Sci.* 1996;**51(2)**: M64-70.
- Antithrombotic Trialist's Collaboration Collaborative meta-analysis of randomised trials of antiplatelet therapy for the prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;**324(7329)**:71-86.
- CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348(9038):1329-39.
- 35. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of Cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002;**360(9326)**:7-22.
- 36. Mohler ER 3rd, Hiatt WR, Creager MA. Cholesterol reduction with atorvastatin improves walking distance in patients with peripheral arterial disease. *Circulation* 2003;**108**(12):1481-6.
- Reid JA, Wolsley C, Lau LL, Hannon RJ, Lee B, Young IS, *et al.* The effect of pravastatin on intima media thickness of the carotid artery in patients with normal cholesterol. *Eur J Vasc Endovasc Surg.* 2005;**30(5)**:464-8.
- Yusef S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study (HOPES) Investigators. N Eng J Med. 2000;342:145-53.
- Lip GY, Makin AJ. Treatment of hypertension in peripheral arterial disease. *Cochrane Database Systematic Reviews (Online)* 2009(4): CD003075.
- 40. Radack K, Deck C. Beta-adrenergic blocker therapy does not worsen intermittent claudication in subjects with peripheral arterial disease.

A meta-analysis of randomized controlled trials. *Arch Int Med.* 1991;**151(9)**:1769-76.

- Liu Y, Shakur Y, Yoshitake M, Kambayashi Ji J. Cilostazol (pletal): a dual inhibitor of cyclic nucleotide phosphodiesterase type 3 and adenosine uptake. *Cardiovasc Drug Rev.* 2001;**19(4)**:369-86.
- Dean SM. Pharmacologic treatment for intermittent claudication. Vasc Med. 2002;7(4):301-9.
- 43. Chapman TM, Goa KL. Cilostazol: a review of its use in intermittent claudication. *Am J Cardiovasc Drugs*. 2003;**3(2)**: 117-38.
- Robless P, Mikhailidis DP, Stansby GP. Cilostazol for peripheral arterial disease. *Cochrane Database of Systematic Reviews (Online)* 2008(1): CD003748.
- O'Donnell ME, Badger SA, Sharif MA, Young IS, Lee B, Soong CV. The vascular and biochemical effects of cilostazol in patients with peripheral arterial disease. *J Vasc Surg.* 2009;49(5):1226-34.
- O'Donnell ME, Badger SA, Sharif MA, Makar RR, Young IS, Lee B, et al. The vascular and biochemical effects of cilostazol in diabetic patients with peripheral arterial disease. Vasc Endovascular Surg. 2009;43(2):132-43.
- Lehert P, Comte S, Gamand S, Brown TM. Naftidrofuryl in intermittent claudication: a retrospective analysis. *J Cardiovasc Pharmacol* 1994;23(Suppl 3): S48-52.
- Scottish Collegiate Guidelines Network (SIGN) Diagnosis and Management of Peripheral Arterial Disease - A National Clinical Guideline. Edinburgh: SIGN; 2006. Available online from: http:// www.sign.ac.uk/pdf/sign89.pdf. Last accessed November 2010.
- Van Neuten JM, Janssen PA. Effect of cinnarizine on peripheral circulation in dogs. *Eur J Pharmacol.* 1972;17(1): 103-6.
- Balsano F, Coccheri S, Libretti A, Nenci GG, Catalano M, Fortunato G, *et al.* Ticlopidine in the treatment of intermittent claudication: a 21-month double-blind trial. *J Lab Clin Med.* 1989;114(1):84-91.
- Horsch S, Walther C. Ginkgo biloba special extract EGb 761 in the treatment of peripheral arterial occlusive disease (PAOD)--a review based on randomized, controlled studies. *Int J Clin Pharmacol Ther*: 2004;42(2):63-72.

- Lederman RJ, Mendelsohn FO, Anderson RD, Saucedo JF, Tenaglia AN, Hermiller JB, *et al.* Therapeutic angiogenesis with recombinant fibroblast growth factor-2 for intermittent claudication (the TRAFFIC study): a randomised trial. *Lancet.* 2002;**359(9323)**:2053-8.
- Tateishi-Yuyama E, Matsubara H, Murohara T, Ikeda U, Shintani S, Masaki H, *et al.* Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. *Lancet.* 2002;**360(9331)**: 427-35.
- 54. Rajagopalan S, Olin J, Deitcher S, Pieczek A, Laird J, Grossman PM, *et al.* Use of a constitutively active hypoxia-inducible factorlalpha transgene as a therapeutic strategy in no-option critical limb ischemia patients: phase I dose-escalation experience. *Circulation.* 2007;115(10): 1234-43.
- Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. New England J Med. 2006;354(15):1567-77.
- Becker GJ, Katzen BT, Dake MD. Noncoronary angioplasty. Radiology. 1989;170(3 Pt 2): 921-40.
- Rutherford R, Durham J. Percutaneous balloon angioplasty for arteriosclerosis obliterans: long term results. In: Yao J, Pearce W, editors. *Techniques in Vascular Surgery*, Philadelphia: Saunders; 1992. p. 329-45.
- Fowkes G, Gillespie IN. Angioplasty (versus non surgical management) for intermittent claudication. *Cochrane Database of Systematic Reviews (Online)* 1998(2): CD000017.
- de Vries SO, Hunink MG. Results of aortic bifurcation: a metaanalysis. J Vasc Surg. 1997;26(4):558-69.
- 60. Bachoo P. Peripheral arterial disease. Clin Evid. 2004(12):144-58.
- 61. Department of Health, Social Services and Public Safety, Northern Ireland. The primary medical services (direct enhanced services) directions (Northern Ireland) 2008. Belfast: DHSS; 2008. Available online from: http://www.dhsspsni.gov.uk/specification_on_the_ primary_medical_services_des_directions_ni_2008.pdf