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The Management of Peripheral Arterial Disease (PAD) in Primary Care

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1. Introduction

Peripheral arterial disease (PAD) encompasses a range of non-coronary arterial syndromes that are caused by the altered structure and function of the arteries that supply the brain, visceral organs, and the limbs. Numerous pathophysiological processes can contribute to the creation of stenoses or aneurysms of the non-coronary arterial circulation, but atherosclerosis remains the most common disease process affecting the aorta and its branch arteries. (Hirsch et al., 2006) While "peripheral arterial disease" encompasses disorders affecting arterial beds exclusive of the coronary arteries, this chapter is limited to a review of disease of the lower extremity arteries as these can be easily assessed in the primary care setting.

Vascular disease is the leading cause of death globally (Murray and Lopez, 1997). With an aging global population, this is expected to continue and the burden on healthcare systems from cardiovascular disease is expected to rise. Vascular disease in one arterial territory predicts the presence of disease in other territories (Rothwell, 2000). The risk of a myocardial infarction or death increases significantly after a transient ischemic attack or stroke (Touze et al., 2005). The presence of PAD significantly increases your risk of a vascular event also (Banerjee et al., 2010). Of particular importance is the fact that asymptomatic PAD is a significant predictor of cardiovascular morbidity and mortality (Hooi et al., 2004). These findings demonstrate the systemic nature of cardiovascular disease and the underlying pathophysiology of atherosclerosis. Patients who present with symptoms of single territory arterial disease need to be screened and treated for multiterritory vascular disease.

In a recent observational study, 62% of patients presenting to a vascular outpatient service had symptoms of PAD and more than half of these patients had been managed solely by their primary care physcian (Coveney et al., 2011). This demonstrates the importance for primary care physicans to identify high risk cardiovascular patients and commence appropriate secondary preventative measures. Primary care physicians are best placed to identify and screen high risk vascular patients and to initate and monitor long term secondary preventative measures in these patients.

This book chapter focuses on the importance and significance of screening for PAD in the primary care setting and aims to review existing guidelines for optimising the secondary management of patients with peripheral arterial disease.

A pubmed search to identify recent reviews and articles on the epidemiology, assessment and treatment of peripheral arterial disease using the terms "intermittent claudication", peripheral arterial disease" and "peripheral vascular disease" was performed and existing international guidelines on the management of peripheral arterial disease (Hirsch et al., 2006, Norgren et al., 2007) provide the evidence on which this chapter is based and referenced.

The chapter is divided into different sections which include,

Epidemiology of PAD.
Risk factors for PAD
Diagnosis and assessment of PAD,
Screening for PAD in appropriate patients,
Treatment of PAD
When to refer to a vascular surgeon,
Vascular surgical interventions for PAD.

A summary of the important factors to consider when managing patients with PAD in the primary care setting will be given along with up to date evidence based guidelines.

2. Epidemiology of Peripheral Arterial Disease

Lower extremity PAD affects approximately 8 million men and women in the United States and is associated with significant morbidity and mortality (Hirsch et al., 2001). PAD prevalence increases dramatically with age and disproportionately affects the black ethnic population (Selvin and Erlinger, 2004). As people survive longer with chronic illness, PAD is likely to become increasingly more prevalent. In the general population, only 11% of patients with PAD have the classic symptoms of intermittent claudication (Hirsch et al., 2001). The term claudication is derived from the latin verb claudicare, meaning to limp. Interestingly, the Roman emperor Claudius (AD 41-54) was so named as he limped, most likely due to a birth defect. Classical intermittent claudication describes aching, crampy leg pain brought on by exercise and relieved by rest and is a symptom of leg muscle ischemia due to PAD. Up to 40% of patients with PAD are asymptomatic, while the remaining 50% of patients describe a variety of leg symptoms different from intermittent claudication (McDermott et al., 2001). Non-invasive testing in populations indicates that the true prevalence of PAD is at least five times higher than would be expected based on the reported prevalence of intermittent claudication (Criqui et al., 1997). The Edinburgh artery study (Fowkes et al., 1991), showed that one in five of the middle aged (65-75 years) population of the United Kingdom have evidence of peripheral arterial disease on clinical examination, although only a quarter of them had symptoms. The Rotterdam study (Meijer et al., 1998), demonstrated a 19.1% prevalence of PAD among 7,715 dutch members of the public over 55yrs of age, using the non-invasive ankle-brachial index (ABI), with <0.9 taken as the cut off for diagnosis. A recent french study demonstrated a PAD prevalence of 27.8% when non-invasive ABI screening was performed on 5,679 primary care patients over 55-years old considered at risk (Cacoub et al., 2009).

Patients with PAD have impaired function and quality of life. This is true even for people who do not report leg symptoms. Furthermore, PAD patients, including those who are

asymptomatic, experience significant decline in lower extremity functioning over time (McDermott et al., 2002).

Despite the high prevalence of peripheral arterial disease, the number of people requiring a major amputation is small. A recent german study reported a major amputation rate of only 25.1 per 100,000 population in 2008, down from 27 in 2005. The same study reported an increase in the minor amputation rate due to vascular disease from 47.4 to 53.7 per 100,000 population over the same period from 2005 to 2008 (Moysidis et al., 2011). Among patients with intermittent claudication, there is a 1.0 to 3.3% risk of major amputation over 5 years which increases significantly in diabetic patients (Norgren et al., 2007).

3. Risk factors for PAD

The risk factors for PAD are similar to those for coronary artery disease. Although diabetes and cigarette smoking are particularly strong risk factors for PAD (Criqui et al., 1997), additional risk factors include age and male sex, hypercholesterolemia, hypertension, chronic kidney disease, hyperhomocystinemia, elevated fibrinogen levels, family history of athersclerosis and being of a non-white ethnic background (Norgren et al., 2007).

3.1 Smoking

Smoking is an exceptionally powerful etiologic risk factor for lower extremity PAD (Criqui et al., 1997). Cigarette smoking is a stronger risk factor for PAD than for coronary artery disease (Price et al., 1999). An interesting case-control study (Cole et al., 1993) estimated, using logistic regression analysis to adjust for confounding variables, that 76% of PAD is attributable to smoking. The same study reported the relative risk for PAD in ex-smokers as 7 and in current smokers as 16 when compared to men who had never smoked and the relative risk increased directly with the lifetime number of cigarettes smoked. Among smokers, the risk of developing PAD increases with plasma concentration levels of cotinine, which is a more accurate marker of tobacco exposure, as it takes into account the degree of inhalation per cigarette as well as the amount of cigarettes smoked (Powell et al., 1997).

3.2 Diabetes

Diabetes mellitus increases the risk of lower extremity PAD by 2- to 4-fold (Criqui et al., 1997) and is present in 12% to 20% of people with lower limb PAD (Hiatt et al., 1995, Beks et al., 1995, Coveney et al., 2011). The risk of developing PAD is proportional to the duration and severity of diabetes (Beks et al., 1995, Katsilambros et al., 1996). In the Framingham Heart Study, diabetes increased the risk of intermittent claudication by 3.5-fold in men and 8.6-fold in women (Kannel and McGee, 1985). The risk of developing critical limb ischemia is also greater in diabetic patients than in non-diabetic patients (Bowers et al., 1993, McDaniel and Cronenwett, 1989). Diabetic patients with lower extremity PAD are 7- to 15-fold more likely to undergo a major amputation than non-diabetics with lower extremity PAD (Dormandy and Murray, 1991, McDaniel and Cronenwett, 1989, Most and Sinnock, 1983).

3.3 Dyslipideamia

As seen with coronary artery disease, lipid abnormalities that are associated with lower extremity PAD include elevated total and low-density lipoprotein (LDL) cholestrol, decreased

high-density lipoprotein (HDL) cholestrol, and hypertriglyceridemia (Fowkes et al., 1992, Kannel and Shurtleff, 1973, Murabito et al., 2002, Hiatt et al., 1995). In the Framingham study, a fasting cholestrol level greater than 7 mmol/L (270mg/dL) was associated with a doubling of the incidence of intermittent claudication, but the ratio of total to HDL cholesterol was the best predictor of occurrence of PAD. The risk of developing lower extremity PAD increases by approximately 5% to 10% for each 10 mg/dL rise in total cholestrol (Newman et al., 1993, Ingolfsson et al., 1994, Murabito et al., 1997). It has also been suggested that cigarette smoking may synergistically enhance the effects of hypercholestroleamia.

3.4 Hypertension

Hypertension which has a longstanding association with coronary artery disease and cerebrovascular disease, is also associated with PAD but to a weaker extent (Criqui et al., 1997, Murabito et al., 1997, Novo et al., 1992, Hooi et al., 1998). In some, but not all epidemiological studies, hypertension increased the risk of developing PAD (Fowkes et al., 1992, Smith et al., 1990, Murabito et al., 1997, Reunanen et al., 1982). In the Framingham Heart Study, hypertension increased the risk of intermittent claudication 2.5-fold in men and 4-fold in women, and the risk was proportional to the severity of the hypertension. (Murabito et al., 1997)

3.5 Hyperhomocysteineamia

Elevated levels of homocysteine are associated with a 2- to 3-fold increased risk for developing atherosclerotic arterial disease (Boushey et al., 1995, Graham et al., 1997). Approximately 30% to 40% of patients with lower extremity PAD have high levels of homocysteine (Taylor et al., 1991). Hyperhomocysteineamia is prevalent in both the elderly and younger patients with lower extremity PAD and appears to increase the risk of progression of their PAD. Approximately 25% of patients with intermittent claudication have plasma homocysteine levels exceeding the 95th percentile (Molgaard et al., 1992).

Homocysteine metabolism is influenced by nutritional factors. Supplementation with B-vitamins, especially folate, reduces plasma homocysteine levels. Multiple trials based on the hypothesis that folate supplementation would reduce homocysteine levels and lead to a reduction in cardiovascular risk have failed to show any beneficial results (Lonn, 2008, Toole et al., 2004, Song et al., 2009). Therefore, B-vitamin supplementation cannot currently be recommended for the prevention of CVD events and there is no role for the routine screening for elevated homocysteine levels.

Despite the convincing epidemiological evidence linking high homocysteine levels with atherothrombotic disease, it is possible that hyperhomocysteineamia is not a common primary cause of the atherothrombotic disorder in the general population, but rather a marker of systemic or endothelial oxidant stress that is a major mediator of these disorders (Hoffman, 2011).

4. The presentation of Peripheral Arterial Disease

Clinically PAD has been recognised since as early as 1831 and the disease spectrum varies from asymptomatic PAD to gangrene and critical limb ischemia requiring amputation. Two

separate classification systems based on symptoms and clinical measures are commonly used to classify the severity of PAD. These are the Fontaine classification system and the more recently developed Rutherford classification system (Norgren et al., 2007). (Tables 1&2).

Fontaine Stages

Stage	Symptoms
I	Asymptomatic
II	Intermittent claudication
IIa	Pain-free, claudication walking >200m
IIb	Pain-free, claudication walking <200m
III	Rest / Nocturnal pain
IV	Necrosis / Gangrene

Table 1. Fontaine stages of peripheral arterial disease (adapted from TASC II guidelines)

Rutherford Classification

Grade	Category	Clinical Description
0	0	Asymptomatic
I	1	Mild claudication
	2	Moderate claudication
	3	Severe claudication
II	4	Ischemic rest pain
	5	Minor tissue loss; nonhealing ulcer, focal gangrene with diffuse pedal oedema
III	6	Major tissue loss extending above transmetatarsal level; foot no longer salvageable

Table 2. Rutherford classification of peripheral arterial disease (adapted from TASC II guidelines)

4.1 Intermittent claudication

The majority of patients with PAD have limited exercise performance and walking ability. As a consequence, PAD is associated with reduced physical functioning which impacts on

quality of life. While a large proportion of patients are asymptomatic from their PAD, (emphasising the importance of screening for the disease, discussed below), the most common symptom among patients is intermittent claudication. The classical symptom of intermittent claudication is muscle discomfort in the lower limb reproducibly brought on by exercise and relieved by rest within 10 minutes. Patients may describe a cramping muscle pain, ache or muscle fatigue brought on by exertion, most commonly localised to the calf, that is relieved by rest. Symptoms may also affect the thigh or buttock when the arterial lesion is more proximal, such as in iliac disease. Patients with intermittent claudication have normal blood flow at rest and therefore have no limb symptoms. However, on exercising the oxygen demand of the leg muscles increases, necessitating increased blood flow. Occlusive lesions in the arterial supply of the leg muscles limits this increase in blood flow, resulting in a mismatch between oxygen supply and muscle metabolic demand that leads to the symptoms of claudication.

When the prevalence of PAD in population based studies diagnosed using an ABI <0.9 is compared to the prevalence of intermittent claudication using questionnaires, it becomes apparent that only about 25% of patients with PAD complain of intermittent claudication. Of further relevance is the fact that between 10% and 50% of patients with intermittent claudication have never consulted a doctor about their symptoms, considering it a normal part of the aging process (Norgren et al., 2007). This highlights further the need for primary care physicians to actively seek out patients that would benefit from secondary preventative treatment.

Peripheral arterial disease patients without typical claudication symptoms commonly have walking limitations that may be associated with atypical or no limb symptoms (McDermott et al., 2001). It should also be noted that patients with PAD commonly have multiple co-morbidities that may restrict their exercise capacity (musculoskeletal disease, pulmonary disease, congestive heart failure) and prevent sufficient activity to produce limb symptoms. So patients with severe PAD might not necessarily complain of intermittent claudication. Equally patients who complain of apparent symptoms of intermittent claudication may not have PAD, as some conditions can mimic the symptoms of intermittent claudication such as nerve root compression, compartment syndrome, arthritis, spinal stenosis and venous claudication.

4.2 Rest pain

As seen from tables 1&2, as PAD progresses clinically, patients start to develop rest pain. Classically, patients describe being woken at night by severe pain in their leg, which forces them to sit up and hang the leg out over the edge of the bed for relief. The pain is similar to intermittent claudication, except the arterial disease has progressed to a stage where exercise is no longer required to precipitate a lack of sufficient blood supply to the leg muscles. Increased ambient heat while in bed, diverts available blood away from muscles to superficial skin in order to maintain normal body temperature. Lying horizontal in bed also reduces the orthostatic pressure that contributes to the intra arterial pressure in the blood vessels of the leg, reducing leg perfusion further. Hanging the legs out of the warm bed, cools them down and makes them more dependent, resulting in increased blood flow to the muscles and some relief from the symptoms.

4.3 Tissue loss and impaired healing.

Occasionally patients present with a chronic leg ulcer or wounds that simply refuse to heal as a consequence of poor peripheral blood supply secondary to PAD. Diabetic patients are particularly at risk, due to their increased risk of infection and impaired healing due to known immunological dysfunction and the presence of peripheral neuropathy contributing to foot trauma. Prevention of foot trauma is an essential part of diabetic management and the use of appropriate footwear and access to podiatry services are important elements of the secondary prevention of amputation in diabetics. Trauma to a diabetic foot such as that seen in figure 1B, can lead to a cascade of events resulting ultimately in a below knee amputation.

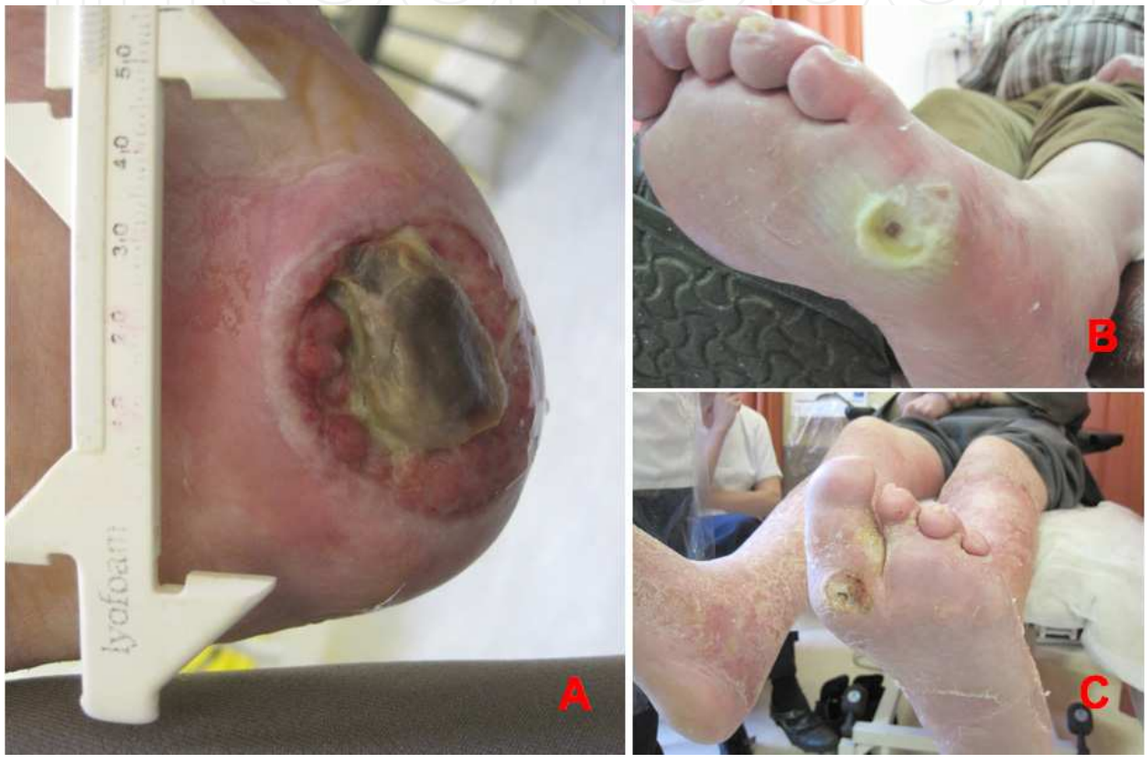

Fig. 1. A. Chronic arterial ulcer on heal, B. Trauma to a diabetic foot, C. Chronic arterial ulcer on patient with previous 2nd toe amputation.

Recognition of PAD in patients with chronic tissue loss is essential so as to expediate appropriate referral to teritary centres for potential revascularisation procedures. Often the aim of revascularisation procedures is to ensure adequate healing after an inevidable amputation.

5. Diagnosis and assessment of peripheral arterial disease

As with any clinical condition or disease, a full history and thorough physical examination is the cornerstone of making the correct diagnosis. Patients with risk factors for PAD, limb symptoms on exertion or reduced limb function should undergo a vascular history to evaluate for symptoms of claudication or other limb symptoms that limit walking ability. They should also undergo a vascular examination evaluating their peripheral pulses.

A comprehensive physical examination in a suspected PAD patient should assess the circulatory system as a whole. Key components of the general examine include blood pressure measurement in both arms, assessment of cardiac rate and rhythm, assessment for cardiac murmurs and palpation of abdomen for an abdominal aortic aneurysm (although non-palpation of one does not exclude an anuerysm). Close inspection of the feet should be performed examining closely for signs of PAD, which might include, non-healing ulcers, muscle atrophy, hair loss, hypertrophied slow growing nails, reduced temperature, pallor or reactive hypereamia. A peripheral vascular examination also requires palpation of the radial, ulnar, brachial, carotid, femoral, popliteal, dorsalis pedis and posterior tibial artery pulses. A small number of healthy adults will have an absent doralis pedis due to anatomical variation. An especially prominent pulse at the femoral or popliteal artery should raise suspicion for an aneursym. It is important to compare the pulses of both legs and correlate any abnormalities with leg symptoms to determine lateralisation of disease. Absent pedal pulses tends to over-diagnose PAD, whereas using the symptom of classical intermittent claudication for diagnosing patients tends to underdiagnose PAD (Criqui et al., 1985). Palpable pedal pulses on examination have a negative predictive value of over 90% that may rule out the diagnosis of PAD in many cases.

Patients with a history or examination suggestive of PAD should proceed to objective testing including ankle-brachial index (ABI) measurement. The ABI which is the ratio of systolic blood pressure at the ankle to the arm, is used in the diagnosis of peripheral arterial disease. A low ABI is associated with concomitant coronary and cerebrovascular disease. The lower the ABI, the greater the increase in cardiovascular risk; however, even those with modest, asymptomatic reductions in the ABI (0.8 to 1.0) appear to be at increased risk of cardiovascular disease (Newman et al., 1993). A meta-analysis of 16 cohort studies of healthy individuals, demonstrated a 10-year risk of a major coronary event in men with an ABI < 0.90 or less to be 27% compared to 9% in those with a normal range 1.11 to 1.40 (Fowkes et al., 2008). This highlights the main benefit of diagnosing PAD is not to treat the symptoms of PAD , but is instead to initiate the secondary preventative measures against systemic arterial disease and prolong patient survival. The ABI can also be used to assess the progression of existing PAD.

The gold standard method of diagnosing PAD is angiography. While this has the benefit of also offering the possibilty of intervention in the form of angioplasty, it is an invasive test not without risk. It also requires significant expertise and resources. Patients with PAD should be on an antiplatelet as disccused later and are therefore at increased risk of bleeding from their arterial puncture site. Vascular surgeons are not uncommonly asked to repair iatrogenic trauma of the common femoral artery after angiography. A metaanalysis of over 30 randomised control trials looking at the efficacy of vascular closure devices found a 0.7% rate of vascular surgical intervention after diagnostic angiography, with no significant difference in vascular complications found between patients treated with vascular closure devices and manual compression (Biancari et al., 2010). Bleeding, heamatoma formation, pseudoaneurysm formation, arterial stenosis and embolic complications are all potential complications of angiography that my require vascular surgical intervention. Advances in the quality of CT scanners have made CT angiography a reasonable alternative to formal diagnostic angiograms, thus eliminating the complications of arterial access but the potential side effects of intravenous contrast, including allergy and nephrotoxicity remain.

Some patients with PAD will have non-compressible arteries due to calcified atherosclerotic vessels resulting in falsely high ankle blood pressures. This is particularly prevalent in diabetic patients. Caution should be taken in interpreting ABI measurements in such patients, which may have an ABI > 1.4. Alternative non-invasive objective tests should be used to assess these patients. Transcutaneous oxygen saturation levels is one alternative non-invasive method for assessing PAD. Others include toe systolic pressures, pulse volume recordings or duplex ultrasound. Unfortunately, these tests generally require referral to a specialised vascular laboratory.

A proportion of patients diagnosed with PAD will have underlying undiagnosed diabetes. It is therefore important to screen newly diagnosed PAD patients for diabetes. PAD is more aggressive in diabetic patients compared to non-diabetics, with the need for amputation five- to ten-times higher. This is contributed to by sensory neuropathy and decreased resistance to infection. Based on these observations, the American Diabetes Association recommends PAD screening with an ABI every 5 years in all diabetic patients(2003).

6. Screening for PAD

The principles of health screening were well documented by the World health Organisation (WHO) in a document published in 1968 (Wilson and Jungner, 1968). The document outlined ten important principles when initiating screening for disease which remain as relevant today as in 1968 and are summarised below in table 3. The adherence of screening for PAD to each of these ten principles requires further elaboration.

Health Screening Principles
1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

Table 3. Health Screening Principles (Wilson and Jungner, 1968)

Regarding the first principle that "the condition sought should be an important health problem", is evident from epidemiological studies already discussed which estimate a prevalence of PAD to be around 20% in the over 55 at risk population. The risk of a person

with claudication progressing to critical limb ischemia and requiring major amputation is low (1%-3.3% over 5 years). However the risk of death in patients diagnosed with PAD is high (5-10% a year) mainly from coronary and cerebrovascular events, representing 3-4 times the risk to an age and sex matched population without PAD. So while the symptoms of PAD may not represent a major health problem on their own, the fact that PAD is an indirect measurement of a patient's cardiovascular disease which is the greatest killer in the world today, makes PAD a very important health problem.

Patients diagnosed with PAD, can be initated on secondary preventative treatment for their cardiovascular disease. There are multiple accepted treatments for patients identified as being at increased cardiovascular risk, which have been shown to improve surival and reduce morbidity. These treatments include life-style, medical and surgical interventions which will be discussed later in the chapter. By initiating secondary preventative measures earlier in these increased risk cardiovascular patients, their overall survival is lengthened and their cardiovascular morbidity reduced.

The ankle-brachial index measurement is a non-invasive accurate test that can be performed in an office setting, by a family physican, general practitioner or trained nurse practitioner. The accepted threshold for the diagnosis of PAD on ABI is 0.90. (Hirsch et al., 2006, Norgren et al., 2007). Studies comparing the ABI threshold of 0.90 to invasive angiography have demonstrated a sensitivity of 89-95% and a specificity of 99-100% in diagnosing PAD (Fowkes, 1988, Feigelson et al., 1994). The mean time required among 1,219 french general practioners performing 5,679 ABI measurements in their own practices was 11.5 minutes (Cacoub et al., 2009). This represents a very acceptable time demand for both the patient and physician for a non-invasive test that is harmless and costs nothing (excluding the intial capital cost of the hand held doppler), yet can yield accurate diagnostic results that impact significantly on patient management.

Recommendations for ankle-brachial index (ABI) screening
An ABI should be measured in :
1. All patients with exertional leg symptoms.
2. All patients aged 50-69 and have a cardiovascular risk factor (particularly diabetes or smoking).
3. All patients age ≥ 70 years, regardless of risk factors status.
4. All patients with a Framingham risk score 10%-20%

Table 4. At risk patients who should undergo ABI screening (TASC II guidelines, 2007).

A large proportion of patients with PAD confirmed by an ABI< 0.9 are asymptomatic from their disease, however they have a significantly increased risk of cardiovascular morbidity and mortality (Hooi et al., 2004) as seen in symptomatic patients. The use of questionnaires as used in some screening programs in the past rely on patients having symptoms and would be of little use in identifying PAD in asymptomatic patients. It is these asymptomatic patients who stand to benefit most from screening with ABI measurement and general practioners are best placed to perform this screening for several reasons. Firstly, due to their indepth knowledge of their patients, they are able to appropriately select at risk patients for screening, which should include those listed in table 4 below. Evidence from the recent eurpoean PANDORA study looking at the prevalence of asymptomatic PAD using ABI<0.9, found that many PAD diagnosed patients failed to meet the screening requirements for ABI testing, which may lead to a broadening of the screening criteria to include more patients (Sanna et al., 2011).

Patients may benefit from opportunistic screening performed on patients who present for other reasons to their general practitioner. Those patients found to have PAD are best managed initially by their doctor in the community, who can monitor their progress in relation to lifestyle interventions and medication side effects. Finally, screening by their general practitioner is more convenient and cost effective for the patient and also reserves secondary and teritary referral centres for the more symptomatic and complex vascular cases.

7. Treatment for peripheral arterial disease

The treatment of peripheral arterial disease has two goals. The first, is to improve the patient's function and reduce their local symptoms, by minimising progression of their disease towards critical limb ischemia and reduce the need for amputation. The second goal is to reduce their overall increased risk of cardiovascular death or morbidity, most commonly due to a coronary or cerebrovascular event. Initial management of patients diagnosed with PAD should consist of modification of vascular risk factors and implementation of best medical treatment with the expectation that this will prolong life, reduce morbidity and improve functional status. A sufficient time should elapse before assessing the success of initial medical treatment before referring for endovascular or surgical intervention. Most patients' symptoms improve sufficiently that further invasive treatment is no longer needed (Leng et al., 1996). In those that do require surgical or endovascular intervention, the success and durability of their intervention is improved if best medical treatment has already been initiated and adherred to (Whyman et al., 1997).

7.1 Smoking cessation

Smoking is the single most important modifiable risk factor in PAD. Complete and permanent cessation of smoking is by far the single most important factor determining the outcome of patients with PAD. While this sounds like an easy intervention, it is very difficult to achieve, as most patients with PAD are life-long smokers and have failed on many occasions in the past to quit.

In middle aged smokers with reduced pulmonary function, physician advice to stop smoking, coupled with a formal cessation program and nicotine replacement was associated with a 22% cessation rate at 5 years, compared with only 5% cessation in the usual care

group (Anthonisen et al., 2005). The same study showed a significant survival advantage for the interventional group after 14 years follow up. Nicotine replacement can be delivered via multiple methods, including gum, patches, and inhaler devices.

The use of the antidepressant bupropion in patients with cardiovascular disease to improve the cessation rate of smoking has been supported in a number of randomised trials, with one study demonstrating 3-, 6- and 12-month abstinence rates of 34%, 27% and 22%, respectively, compared with 15%, 11% and 9% respectively, with placebo treatment (Tonstad et al., 2003). Nicotine replacement therapy in combination with bupropion has been shown to be more effective than either treatment alone. There is also some evidence that group therapy increases the rate of smoking cessation and is comparable to intensive individual therapy, which is often impractical due to limited resources (Stead and Lancaster, 2000).

The practical approach as advocated in the TASC II guidelines is to encourage physician advice at every patient visit, combined with behaviour modification, nicotine replacement and bupropion treatment in order to achieve the best cessation rates. These are summarised in table 5 below.

Recommendations for smoking cessation
1. All patients who smoke should be strongly and repeatedly advised to stop smoking. 2. All patients who smoke should receive a program of physician advice, group counseling sessions, and nicotine replacement. 3. Cessation rates can be enhanced by addition of antidepressant drug therapy (bupropion) and nicotine replacement.

Table 5. Smoking cessation recommendations (TASC II guidelines).

Smoking cessation does not necessarily improve the symptoms of intermittent claudication, with improved walking distance seen in only some patients. However, smoking cessation is associated with a reduced risk of cardiovascular events and a reduced risk of amputation. Those patients that do undergo bypass surgery have a three-fold increased risk of graft failure with continued smoking which reduces to that of non-smokers with smoking cessation (Willigendael et al., 2005). These significant findings make smoking cessation a pre-requisite for any semi-elective or elective bypass surgery.

7.2 Exercise programs

In patients with intermittent claudication, supervised exercise programs have demonstrated clinical benefit in improving exercise performance (Stewart et al., 2002). It is likely that

asymptomatic patients with PAD also benefit form exercise. In one prospective study, supervised exercise conducted for 3 months or longer, led to a clear increase in threadmill exercise performance and reduced the severity of claudication pain during exercise (Hiatt et al., 1994). There are multiple biological mechanisms underlying this clinical improvement, including the formation of collateral vessels and increased blood flow, changes in the microcirculation and endothelial function, changes in muscle metabolism and oxygen extraction, walking economy and systemic benefits of exercise including weight loss and improved cardiac function (Stewart et al., 2002).

Exercise sessions should be held three times per week, beginning with 30 minute sessions and then increasing to one-hour sessions. During each session, threadmill exercise is performed at a speed and grade that induces claudication within 3-5 minutes. The patient should continue to walk through the onset of claudication pain until it reaches moderate intensity and then stop until claudication resolves, after which exercise is resumed and the cycle repeated. The sessions are gradually increased to one hour duration as the patient becomes more comfortable with the exercise sessions, while avoiding excessive fatigue or leg discomfort. The speed or grade of the threadmill is increased as longer durations are required to induce claudication symptoms. An additional goal of the exercise program is to increase patient walking speed up to the normal 4.8 km/h from the average PAD patient walking speed of 2.4-3.2 km/h. This exercise prescription has been adapted from the TASC II guidelines (Norgren et al., 2007) and is summarised in table 6 below.

Exercise therapy in intermittent claudication
1. Supervised exercise should be made available as part of the initial treatment for all patients with PAD.
2. The most effective programs employ treadmill or track walking that is of sufficient intensity to bring on claudication, followed by rest, over the course of a 30-60 minute session.
3. Exercise sessions should typically be conducted three times a week for a minimum of three months.

Table 6. Exercise therapy for intermittent claudication (TASC II, 2007).

The benefits of an exercise program not only improve the patient's functional walking capacity, but also offer other benefits including improved overall cardiorespiratory function, a reduction in body weight, better lipid and glycemic profiles and lower blood pressure.

Unfortunately, there are some contraindications to participation in an effective exercise program. Some patients are unable to participate due to musculoskeletal disease, poor cardiac function or neurological impairment. Caution should be taken to ensure appropriate footwear for diabetic patients who are at increased risk of foot lesions due to peripheral neuropathy. The major limitation of exercise rehabilitation is the lack of availability of supervised settings to refer patients. Despite the proven benefits of exercise therapy, some patients lack the self motivation to persist with the program to maintain this benefit.

7.3 Optimising medical management of PAD patients

The medical optimisation of patients with peripheral arterial disease focuses primarily on reduction of cardiovascular risk. The goal of optimising medical therapy is to tackle each of the known cardiovascular risk factors and achieve specific targets with appropriate medical therapy. All patients with PAD commenced on secondary prevention of cardiovascular risk should be prescribed an antiplatelet, have a target LDL<2.59mmol/L and a blood pressure <140/90 mmHg. Diabetic patients have stricter targets, LDL< 1.81mmol/L and blood pressure <130/80 mmHg and have a taret HbA1c < 7.0% (Norgren et al., 2007). The medical therapy to achieve these targets are discussed below.

7.3.1 Antiplatelet therapy

The use of antiplatelets in arteriopathic patients is well established. The benefits of antiplatelets are best described in a meta-analysis of 129 RCCT published by the antiplatelet trialist's collaboration in the BMJ (1994a). The meta-analysis included >100,000 patients and demonstrated a 25% decrease in MI, stroke and death in arteriopathic patients on low dose prolonged antiplatelet treatment. Since this publication, the prescription of antiplatelet therapy has increased significantly, as is demonstrated in a recent study showing more than 96% of patients on some form of antiplatelet or anticoagulant therapy (Coveney et al., 2011). Antiplatelets are further indicated in PAD as they greatly reduce the risk of arterial or vascular graft occlusion (1994b). The use of the anticoagulant warfarin, is not indicated in PAD patients unless there is an increased risk of embolic events secondary to the presence of atrial fibrillation. However, the use of wafarin did deter the co-prescribing of an antiplatelet due to the increased risk of bleeding complications with only 3 of 17 patients on warfarin recieving aspirin also. (Coveney et al., 2011)

7.3.2 Lipid lowering therapy

Dietary modification should be the initial intervention to control abnormal lipid levels. All arteriopathic patients should be prescribed HMG CoA reductase inhibitors (statins). Arteriopathic patients should be aggressively treated with a lipid lowering therapy even if their baseline cholesterol levels are normal (2002b). LDL cholesterol should be the primary target of cholesterol lowering therapy as a 1% reduction in LDL levels reduces the relative risk of a major cardiovascular event by 1% over a five year period, independent of age, gender and baseline levels (Grundy et al., 2004). Statin therapy typically dropped LDL levels by 30-40% in all of the treatment arms of the major clinical trials (Shepherd et al., 2002, Sever et al., 2003, 1994c, 2002a, 2002b). The doses used are comparable to current clinical doses, representing a significant risk reduction benefit when used in arteriopathic patients. The

Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) was a multicentre RCCT of Pravastatin use in 5,800 patients with vascular disease (Shepherd et al., 2002). Mortality from coronary artery disease fell by 24% in the pravastatin group. While the risk for stroke was unaffected, the hazard ratio for transient ischemic attacks was 0.75 in the treatment group compared to placebo. As well as improving overall survival, statins improve symptoms of PAD through pleiotropic effects, thought to be mediated through a reduction in endothelial dysfunction, plaque stabilisation and anti-inflammatory effects (Kinlay, 2005, Faggiotto and Paoletti, 1999). The Scandinavian Simvastatin Survival Study found a 38% decrease in "new or worsening claudication" over a 5.4 yr period in 4,444 patients treated with simvastatin (1994c). This further supports the use of statins in vascular patients.

7.3.3 Antihypertensive therapy

Hypertension is associated with a two- to three-fold increased risk for PAD. As mentioned above, hypertension guidelines support the aggressive treatment of blood pressure in patients with atherosclerotic PAD. In this high risk group, the TASC II recommendations set a target blood pressure of <140/90 mmHg, and <130/80 mmHg if the patient has diabetes or renal insufficiency. Achieving these blood pressure targets are more important than the choice of antihypertensive medication. Fortunately there are several effective antihypertensive medications available, including thiazide diuretics, ACE-inhibitors, angiotension receptor blockers, calcium channel blockers and Beta-adrenergic blocking drugs. Often more than one antihypertensive agent is required to achieve target blood pressure. Several of these antihypertensive agents provide additional benefits to the antihypertensive effects and should therefore be considered.

The use of beta-blockers is well established in coronary artery disease. A meta-analysis of 82 RCCTs incorporating >54,000 patients demonstrated the effect of beta-blockade in long-term secondary prevention after myocardial infarction with a proven reduction in mortality (Freemantle et al., 1999). Carotid artery disease, peripheral vascular disease and abdominal aortic aneurysms are termed coronary risk equivalents as they represent a comparable increased risk of developing new coronary events equivalent to patients with established coronary artery disease (>20% over 10 years). Patients with coronary risk equivalents should have the same target blood pressure as patients with coronary artery disease (2002c). The achievement of optimal blood pressure control appears more important than the antihypertensive agent used in overall risk reduction in patients without established coronary artery disease. One prospective observational study (Feringa et al., 2006), demonstrated a hazard ratio of 0.68 for patients with PAD receiving beta-blockers. In this study of 2,420 patients, beta-blockers were the second most benefical drug after statins in reducing long-term mortality.

Unfounded fears have existed with regard to the use of beta-blockers in patients with intermittent claudication. A recent Cochrane review of 6 RCCTs of beta-blocker vs. placebo in PAD showed no statistically significant worsening effect of beta-blockers on maximum walking distance, claudication distance, calf blood flow or skin temperature (Paravastu et al., 2008). An earlier meta-analysis of 11 RCCTs again showed no evidence of adverse effects on walking capacity or symptoms of intermittent claudication in patients with mild to moderate PAD (Feringa et al., 2006). Both of these publications support the use of beta-blockers in patients with coronary artery disease and PAD.

Angiotensin Converting Enzyme (ACE) inhibitors act on the renin-angiotensin-aldosterone system by inhibiting the ACE-mediated conversion of angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor. Within the kidneys, angiotensin II preferentially constricts the efferent arterioles leading to increased perfusion pressure in the glomeruli. It is a drop in this glomerular filtration pressure that initially stimulates renin release. Angiotensin II also stimulates the adrenal cortex to release aldosterone which causes retention of sodium and excretion of potassium in the kidneys which leads to increased water retention, blood volume and consequentially blood pressure. It also stimulates the release of anti-diuretic hormone from the posterior pituitary which again increases water retention and increases blood pressure. By blocking the conversion of angiotensin I to angiotensin II with ACE-inhibitors, antihypertensive effects are achieved.

However ACE–inhibitors have been shown to reduce the cardiovascular morbidity and mortality rates in patients with peripheral vascular disease by 25% regardless of the presence or absence of hypertension. This was demonstrated eloquently in the HOPE trial, a multicentre international RCCT with > 9,000 high risk vascular patients assigned to either a placebo group or a ramipril (10mg) group (Yusuf et al., 2000). In fact, the beneficial effects of ramipril were so evident that the trial was concluded after only 2yrs instead of the initially planned 4.5 years. The 2006 AHA/ACC guidelines state that it is reasonable to treat patients with peripheral vascular disease with ACE-inhibitors to reduce the risk of adverse cardiovascular events. As well as reducing mortality, a small double blind placebo controlled trial published by Ahimastos in 2006 demonstrated that ACE-inhibitors improve the symptoms of peripheral vascular disease, increasing walking time by >200%, although the patient numbers were small and patients with hypertension and diabetes were excluded (Ahimastos et al., 2006). Data from the same cohort of patients suggested that this improvement was due to reduced arterial wall stiffness caused by ACE-inhibitors in the treatment group (Ahimastos et al., 2008). Like Statins, ACE-inhibitors have pleiotropic vascular protective effects including plaque stabilisation, improved vasomotor dysfunction and many biochemical mechanisms including inhibition of platelet adhesion and aggregation, inhibition of platelet derived growth factor, endothelin, and stimulation of endothelial relaxation via stimulation of nitric oxide and prostacyclin (Faggiotto and Paoletti, 1999).

7.3.4 Glyceamic control

Diabetes increases the risk of PAD approximately three- to four-fold, the risk of claudication two-fold, and the risk of amputation five- to ten-fold. Studies of both type 1 and type 2 diabetic patients have demonstrated that aggressive blood-glucose lowering reduces the risk of microvascular complications, particularly retinopathy and nephropathy. However these findings have not be replicated in PAD, primarily because the studies have not been powered to examine the PAD endpoints (Norgren et al., 2007). The current American Diabetes Association guidelines recommend a HbA1c <7.0%. However its unclear whether achieving this goal will effectively protect the peripheral circulation or prevent amputation.

7.3.5 Adjuvant therapy

Cilostazol has been shown to significantly increase (35- 109%) walking distance in people with claudication in several large double blind placebo controlled randomized trials (Money

et al., 1998, Elam et al., 1998). The precise role of cilostazol remains to be defined, but a trial of the drug is probably indicated in patients who have unacceptable symptoms despite three to six months of adherence to best medical treatment. No convincing evidence supports treatment with other drugs or vitamins.

8. When to refer to a vascular surgeon?

One of the principle roles of a general practitioner is to act as a gatekeeper to more resource intensive expert care available in teritary referral centres. General practitioners become skilled at recognising the signs and symptoms of serious pathology and referring patients with appropriate urgency. An indept knowledge of a patient's social, family and medical history helps to facilitate this important responsibility on general practitioners.

Due to the high prevalence of PAD, many PAD patients need to be diagnosed and treated by their general practitioner and never meet a vascular surgeon. Referral patterns vary considerably depending on local circumstances, such as the availability of teritary referral centres and the duration of vascular outpatient waiting lists.

If the primary care team is not confident of making the diagnosis, lacks the resources necessary to institute and monitor best medical treatment, or is concerned that the symptoms may have an unusual cause, then it is reasonable to make a referral to a vascular surgical service. Equally, if a patient has unacceptable symptoms despite a reasonable trial of, and adherence to, best medical treatment, then expert vascular surgical assessment and advice is appropriate. Patients who have a weak or absent femoral pulse should be sent to a vascular surgeon for further investigation of aortoiliac disease.

Patients with critical limb ischaemia should be referred urgently to a vascular surgical service. These will include patients with rest pain, gangrene and ulceration. Patients with a clinically suspected abdominal aortic aneurysm or a carotid territory transient ischemic attack should also be referred on an urgent basis to a vascular service.

9. Vascular surgical interventions for PAD

Despite best medical management approximately 25% of patients with intermittent claudication will suffer a deterioration in their PAD. Many of these patient will require a re-vascularisation procedure to improve their symptoms and prolong the functional use of their leg. Unfortunately, even with the current available re-vascularisation procedures, patients with severe PAD may ultimately require amputation for relief of symptoms and to prevent death from sepsis. In general the risk of surgery outweighs the benefit, except in cases of critical limb ischeamia, where the limb is at risk. Intermittent claudication is generally not an indication for re-vascularisation.

Re-vascularisation procedures can be classified into endovascular procedures and open surgical procedures. Often a combination of both are utilised and close co-operation between interventional radiologists and vascular surgeons is essential. Complete smoking cessation and best medical therapy are essential to maximise the durability of any re-vascularisation procedure.

Endovascular procedures use balloon angioplasty to dilate discrete arterial stenoses, typically seen in the superficial femoral artery. It necessitates arterial puncture at the femoral artery, which is not without its risks as discussed with diagnostic angiography. An example of a successful angioplasty is shown below in figure 2. Placement of endovascular stents is also feasible in larger calibre arteries, which in practice implies suprainguinal arteries.

Open surgical interventions include endarterectomy which involves opening up the diseased artery and removing the atherosclerotic plaque to restore blood flow. With severe long segement disease a bypass procedure can be performed, such as a femoral-popliteal bypass for an occluded superfical femoral artery or an aorto-bifemoral bypass for occlusive iliac disease. Endogenous graft material is significantly more superior to exogenous synthetic grafts with significantly better 5 year patency rates. The long saphenous vein or cephalic vein are the most commonly used vessels for endogenous grafts.

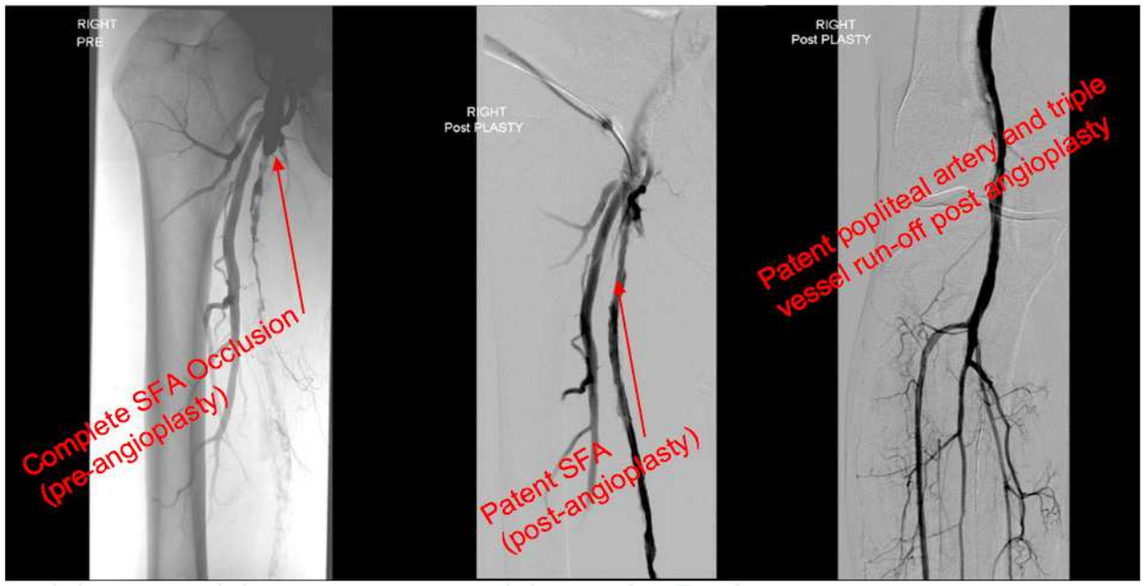

Fig. 2. Successful 5mm subintimal balloon angioplasty of an occluded superficial femoral artery of a 65 yr old male.

10. Summary

The prevalence of PAD is increasing with an aging global population. PAD is a marker of systemic atherosclerotic disease. Patients diagnosed early with PAD can be initiated on appropriate secondary preventative meaures to reduce the significantly increased cardiovascular risk associated with PAD, as well as preventing progression of their PAD. More than two thirds of patients with PAD are asymptomatic, which highlights the major role primary care physicians can play in identifying, screening and diagnosing patients with PAD. Optimal secondary preventative treatment for PAD, requires complete smoking cessation, a supervised exercise program, cholesterol reduction, antihypertensive therapy, tight glyceamic control (in diabetics) and antiplatelet therapy.

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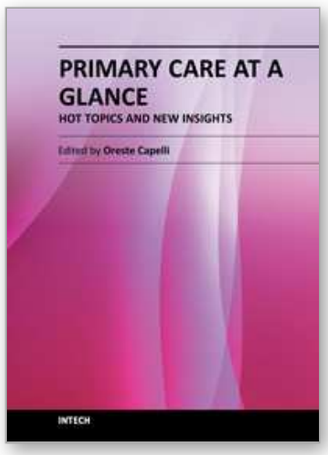

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"Both among scientists and clinical practitioners, some find it easier to rely upon trivial explanations, while others never stop looking for answers". With these surprising words, Augusto Murri, an Italian master in clinical medicine, reminds us that medical practice should be a continuous journey towards knowledge and the quality of care. The book brings together contributions by over 50 authors from many countries, all around the world, from Europe to Africa, from Asia to Australia, from North to South America. Different cultures are presented together, from those with advanced technologies to those of intangible spirituality, but they are all connected by five professional attributes, that in the 1978 the Institute of Medicine (IOM)1 stated as essentials of practicing good Primary Care: accessibility, comprehensiveness, coordination, continuity and accountability. The content of the book is organized according to these 5 attributes, to give the reader an international overview of hot topics and new insights in Primary Care, all around the world.

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