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Lower Extremity Peripheral Arterial Disease

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1. Introduction

Lower extremity peripheral arterial disease (PAD) is a disorder characterized by atherosclerotic narrowing or occlusion of the lower limb arteries. In addition to its association with impaired mobility and functional status, PAD is a marker of systemic atherosclerosis and is associated with a high incidence of cardiovascular events such as stroke, myocardial infarction (MI) and vascular death.

2. Epidemiology

Eight to 12 million people in United States have PAD (Allison et al. 2007). Only ~10% of patients with PAD have classic intermittent claudication (IC), ~50% have atypical leg symptoms and ~40% are asymptomatic (Hiatt 2001). Its prevalence significantly increases with age; 12 – 20% of those above the age of 65 years suffer from PAD (Ostchega al. 2007). The prevalence of PAD is similar in men and women; however men are more likely to have symptomatic disease (Ness et al. 2000; Aronow et al. 2002; Selvin and Erlinger 2004; Ostchega et al. 2007).

PAD is a polyvascular disease. Sixty to 90% of patients with PAD also have significant coronary artery disease (CAD) and up to 25% have significant carotid artery stenosis (Hertzer et al. 1984; Klop et al. 1991; Valentine et al. 1994; Cheng et al. 1999; McFalls et al. 2004; Steg et al. 2007). In a study at the Cleveland Clinic, all patients undergoing vascular surgery between 1978 and 1981 had coronary angiogram. Only 10% of those patients had normal coronaries and 28% had severe 3 vessel coronary artery disease requiring surgical or catheter based intervention (Hertzer et al. 1984). Patients with PAD have a 3-fold greater 10-year risk (RR, 3.1; 95% CI, 1.9–4.9) of all-cause death and a 6-fold greater risk (RR, 6.6; 95% CI, 2.9–14.9) of cardiovascular (CV)-related death compared to patients without PAD (Criqui et al. 1992). In the REACH registry, by one year , 21% of patients with PAD had developed MI, stroke, cardiovascular death or hospitalization compared with 15% of patients with CAD (Steg et al. 2007).

3. Risk factors for PAD

Risk factors for PAD are similar to those for atherosclerotic disease in other vascular beds with some variation in their individual attributable risks.

3.1 Cigarette smoking

A strong predictor of prevalent PAD and its progression; it also predicts bypass graft and endovascular intervention failure. (Sapoval et al. 1996; Hirsch et al. 2001; Willigendael et al. 2005; Aboyans et al. 2006). Smoking increases the risk of lower extremity peripheral arterial disease by 2- to 6-fold and the risk of intermittent claudication by 3- to 10-fold (Kannel and McGee 1985; Smith et al. 1990; Bowlin et al. 1994; Meijer et al. 1998). 80% of patients with PAD have a smoking history (Smith et al. 1990; Meijer et al. 1998). Interestingly, cigarette smoking is a stronger risk factor for PAD than for CAD with smoker's having a 2 to 3 times greater likelihood of developing PAD than CAD (Hirsch et al. 2001). It is also an independent predictor of the risk for unplanned urgent revascularization of the lower extremities following initial successful treatment (Shamma et al. 2003). With an increasing number of pack years, there is an increase in severity of disease, increased risk of amputation, peripheral graft occlusion and overall mortality.

3.2 Diabetes Mellitus (DM)

The risk of prevalent PAD doubles in the setting of impaired glucose tolerance (Beckman et al. 2002) and increases by 2 to 4 fold in patients with overt diabetes mellitus. PAD presents at an earlier age in diabetics; the prevalence of PAD is ~ 20% in diabetic patients older than 40 years and increases to ~30% among those older than 50 years (Hirsch et al. 2001; 2003). Diabetics tend to have more severe degrees of stenosis and a higher preponderance toward calcification as compared to non-diabetic patients with PAD (Jude et al. 2001). PAD is more likely to remain asymptomatic in diabetics until very advanced. Finally, poor glvcemic control is associated with more rapid PAD progression, increased risk of amputation and mortality (Jude et al. 2001; Beckman et al. 2002).

3.3 Hypertension and dyslipidemia

Although the attributable risk for these factors is less than for DM or smoking, their adverse impact is clear from multiple studies. Uncontrolled higher blood pressures are associated with increased severity of PAD (Ness et al. 2000; Hirsch et al. 2001; Selvin and Erlinger 2004; Ostchega et al. 2007). Elevated total and LDL cholesterol, low HDL cholesterol and hypertriglyceridemia are associated with prevalent PAD (Kannel and Shurtleff 1973; Fowkes et al. 1992; Hiatt et al. 1995; Murabito et al. 2002). The risk of developing PAD increases by 5 – 10% with each 10 mg/dl increase in total cholesterol (Ingolfsson et al. 1994; Murabito et al. 1997).

3.4 Renal insufficiency

Patients with chronic kidney disease (creatinine clearance <60 ml/min) and end stage renal disease have a higher prevalence of IC and low ankle-brachial index (ABI) as compared to patients with normal renal function (O'Hare et al. 2004). They also have a higher prevalence of critical limb ischemia and increased incidence of peri and post operative mortality related to lower extremity revascularization procedures (O'Hare et al. 2003). Potential mechanisms include altered calcium-phosphorus, homocysteine, and lipoprotein (a) metabolism and altered inflammatory and coagulation pathways.

3.5 Inflammation

A number of inflammatory markers are associated with prevalent PAD and outcomes among those with PAD. In a meta-analysis, the odds ratio for PAD in patients with increased homocysteine was 6.8 (Boushey et al. 1995). 30-40% of PAD patients have elevated homocysteine levels as compared with 3-5% of the general population (Hajjar 1993). Elevated C – reactive protein and D-dimer are associated with increased cardiovascular mortality in PAD patients (Vidula et al. 2008).

3.6 Age

The Prevalence of PAD increases with age. In the NHANES study, the prevalence of PAD increased significantly with each decade since beyond 40 years (Selvin and Erlinger 2004) (Table 1). In a German epidemiologic study, 21% of the patients above the age of 65 years had symptomatic or asymptomatic PAD yet again demonstrating increased incidence of PAD with age (Diehm et al. 2009).

Age (yrs)	Prevalence of PAD
40 -49	0.9%
50 – 59	2.5%
60 – 69	4.7%
>70	14.5%

Table 1. In the NHANES study, prevalence of PAD increased significantly with age.

3.7 Race/ethnicity

The prevalence of PAD varies by ethnicity and race. Non-hispanic blacks have the highest prevalence, followed by Mexican Americans and non-Hispanic whites, with 19.5%, 15.6% and 11.7% above the age of 60 years having PAD, respectively (Ostchega et al. 2007). It is believed that these relationships are mediated by a genetic predisposition in part secondary to variations in atherogenic and prothrombotic factors (Folsom et al. 1992; Conlan et al. 1993; Gerhard et al. 1999).

4. Clinical presentation

PAD can present in the following forms (Hirsch et al. 2006):

4.1 Intermittent claudication: Exertional symptoms such as muscle pain, cramping, discomfort or fatigue in the legs which resolves with rest of 10 minutes or less. However, these 'classic' symptoms are seen in only 10 % of patients with PAD.

4.2 "Atypical" leg pain: Exertional leg symptoms which may not always resolve with rest or are not consistently reproducible.

4.3 Asymptomatic: 40 % of patients with PAD have no leg symptoms but most will have some other form of functional limitations.

4.4 Acute limb ischemia: A potentially limb threatening syndrome, classically manifest by one of more of the following five "P's" – pain, pulselessness, paralysis, paresthesias and pallor.

4.5 Chronic limb ischemia (also known as 'critical limb ischemia [CLI]): Accounts for 1-2% of all patients with PAD. It presents as rest pain, non-healing ulcers and/or gangrene.

The severity of symptoms usually correlates with degree of stenosis, adequacy of collateral circulation and level of exertion. Location of the discomfort may shed light on the location of stenosis (Table 2).

Lesion location	Site of symptoms
Isolated infra-popliteal	Foot
Popliteal	Calf
Femoral	Calf
Iliac	Calf, thigh possibly impotence
Aorto-iliac	Bilateral calf, thigh, buttock, impotence
Deep femoral artery	Thigh
Internal iliac artery	Buttock and hip, impotence if bilateral disease

Table 2. Level of disease and associated symptoms

5. Natural history of PAD

Over a 5-year period, only 1-2% of claudicants and asymptomatic patients develop CLI. Nevertheless, the overall mortality rate is 15 – 30% (75% of which is cardiovascular) and risk of non-fatal MI or stroke 20% at 5 years. Patients with CLI have much worse outcomes with an annual CV mortality of 25% and annual amputation rate of 25%.

It is noteworthy that the burden of PAD may not correlate with the presence or absence of claudication. Patients who are more physically active are more likely to present with claudication than those who lead a sedentary lifestyle. Patients who are too sedentary to claudicate may present with CLI as their first manifestation of disease.

6. Classification of PAD

The Rutherford and Fontaine classifications (Table 3) are frequently utilized to classify PAD symptom severity.

	Fontaine classification	Rutherford system		
Stage	Clinical	Grade	Category	Clinical
I	Asymptomatic	0	0	Asymptomatic
II a	Mild claudication	I	1	Mild claudication
II b	Moderate – severe claudication	I	2	Moderate claudication
		I	3	Severe claudication
III	Ischemic rest pain	II	4	Ischemic rest pain
IV	Ulceration or gangrene	III	5	Tissue ulceration (minor)
		IV	6	Tissue loss / gangrene

Table 3. Rutherford and Fontaine classification for PAD.

7. Physical exam

A comprehensive vascular history and physical exam is vital in the evaluation and appropriate treatment of patient with PAD or suspected PAD. Current ACC / AHA guidelines recommend a complete vascular exam (class I B) for patients with intermittent claudication (Hirsch et al. 2006).

The key components of physical exam are:

- Bilateral arm blood pressure (to screen for subclavian stenosis/upper extremity PAD)
- Cardiac examination
- Assessment of the abdomen for aortic aneurysmal and stenotic disease
- Thorough Examination of legs and feet
- Pulse
  - Carotid
  - Radial/ulnar
  - Femoral
  - Popliteal
  - Dorsalis pedis (DP)
  - Posterior tibial (PT)

Pulse should be graded on a scale of 0-3. 0=absent, 1=dampened, 2=normal or 3=bounding. If no pulse is palpable on exam, a Doppler exam using a hand-held continuous wave device should be performed. An absent or abnormal PT pulse has a very high specificity for diagnosis of PAD. An absent or abnormal DP is non-specific due to a high prevalence of absent or anomalous DP in the general population.

- It is also vital to asses for vascular bruits (carotid, abdominal, femoral, and popliteal)
- Other characteristics that may be seen in lower extremity PAD:
  - Hair loss
  - Nail hypertrophy
  - Rapid elevation pallor or dependent rubor.
  - Foot examinations should be performed at each visit for patients with PAD to assess for tissue loss (i.e., ulcers or gangrene) as well as for signs of other foot pathology such as callous formation or neuropathy.

8. Screening for asymptomatic patients

In the PAD Awareness, Risk and Treatment: New Resources for Survival (PARTNERS) study, 6979 patients aged ≥ 70 years or aged 50-69 years with a history of cigarette smoking or diabetes were screened with ABI's (Hirsch et al. 2001). PAD (defined as an ABI of ≤ 0.90) was diagnosed in 29% of this cohort. This diagnosis would have been missed in 85% to 90% had physicians relied solely on patients presenting with intermittent claudication (Hirsch et al. 2001). Even patients with IC infrequently report this symptom as they attribute it to the normal aging process (Dormandy and Rutherford 2000). A German epidemiologic study which included 6880 patients > 65 years of age reported that 21% of these patients had asymptomatic or symptomatic PAD (Diehm et al. 2009). Given that up to 50% of patients with PAD may be asymptomatic, it is critical that these high risk patients are identified so that appropriate interventions may be initiated to prevent the associated morbidity and mortality. ACC /AHA guidelines recommend screening ABI's among high risk patients (class IC) defined as individuals with 1 or more of the following: exertional leg symptoms, non-healing wounds, age 65 years and older, or 50 years and older with a history of smoking or diabetes (Rooke et al. 2011).

The ADA also recommends that any diabetic patient above the age of 50 years who has a normal ABI should have ABI's repeated every 5 years (American Diabetic Association 2003).

9. Diagnostic evaluation

It is necessary to differentiate claudication from other conditions causing leg pain when evaluating patients with PAD. Patients may have an abnormal ABI and present with leg pain unrelated to PAD. Claudication may be confused with pseudoclaudication resulting from spinal stenosis, nerve compression syndromes, arthritic pain or venous claudication. Certain clinical features help differentiate these conditions Questionnaires have also been frequently used for identifying, monitoring, assessing severity of PAD and treatment success. The Rose claudication questionnaire is a simple screening tool for claudication which can be administered by asking 2 simple questions; "Do you get pain in either leg when you walk?" and "Does the pain go away when you stop walking?" If the answer to both the question is yes then the like hood for PAD is 95% (Rose 1962). There is an updated version of the World Health Organization Rose Questionnaire and also the Edinburgh Claudication Questionnaire which are used to diagnose PAD and the Walking Impairment Questionnaire, the Peripheral Artery Questionnaire and the Medical Outcomes Study 36-Item Short Form Health Survey are used to assess severity of PAD and assess response to therapy (Criqui al. 1985; Leng and Fowkes 1992; Criqui et al. 1996; Spertus et al. 2004).

10. Diagnostic tests

Physiological studies such as the ABI, segmental limb pressures, or pulse-volume waveform analysis can help identify functional limb perfusion abnormalities. Imaging methods, such as duplex ultrasonography, CT angiography (CTA) and magnetic resonance angiography (MRA) provide detailed anatomical, but less frequently functional information on limb perfusion. Diagnostic modalities and respective clinical indications appear in Table 4.

10.1 Ankle-Brachial Index

ABI measurement is the universally accepted standard for the initial diagnostic evaluation of patients with suspected PAD and for high risk asymptomatic patients (Hirsch, Haskal et al. 2006; Mohler and Giri 2008; Rooke et al. 2011). It is simple, reliable, extremely sensitive (79 - 95%) and specific (96-100%) and can be performed in a primary care office in < 15 minutes (Fowkes 1988; Lijmer et al. 1996). The ABI is calculated by measuring the systolic blood pressure in each arm (brachial artery) and ankle (dorsalis pedis and posterior tibial arteries) using a hand held Doppler device in a patient who has been resting in the supine position for 10 minutes. The right ABI = higher right ankle pressure/higher pressure in either arm; the left ABI = higher left ankle pressure/higher pressure in either arm. An ABI ≤ 0.90 suggests PAD with ≥ 50% stenosis in at least one artery. (Fowkes 1988; Lijmer, Hunink et al. 1996).

Based on publication of the results of the Ankle Brachial Index Collaboration, a normal ABI range is defined as between 1.00 to 1.40, and abnormal values continue to be defined as those ≤0.90. ABI values of 0.91 to 0.99 are considered "borderline" and values ≥1.40 indicates noncompressible arteries (Fowkes, Murray et al. 2008; Rooke, Hirsch et al. 2011).

In addition to its diagnostic utility, the ABI also provides important prognostic and functional information. The relative risk of mortality increases by 3.1% with a decrease of 0.50 in ABI. Sikkink et al followed 150 patients who were >40 years of age and had ABI< 0.90 and found that the cumulative survival at 5 years was 63% for patients with an ABI of < 0.50, 71% for patients with an ABI of 0.50 to 0.69, and 91% for those with an ABI of ≥ 0.70

(Sikkink et al. 1997). McDermott and colleagues found that poor functional outcomes were associated with lower ABI's (McDermott et al. 2002). Interestingly, functional outcomes did not correlate with leg symptoms, again confirming that leg symptoms are a poor marker for identifying PAD severity.

Resting ABI may be insensitive for detecting aorto-iliac occlusive disease. ABI after exercise should be performed in these patients if PAD is suspected. If resting values in patients with intermittent claudication are normal, then ABI should be repeated after exercise. Incompressible arteries (e.g., elderly, diabetes, renal failure) may yield falsely normal or elevated ABI measurements. Toe- brachial index (TBI) measurement or pulse volume recording measurements should be performed in these patients as they are more accurate in this setting(Rooke et al. 2011).

10.2 Segmental Pressure Examination (SPE) and Pulse Volume Recordings (PVR)

SPE is a physiological test helpful in identifying location of individual arterial stenoses. It is performed by placing blood pressure cuffs at the upper thigh, the lower thigh, the upper calf and the lower calf above the ankle. Systolic blood pressure measurements are obtained at all these sites and both brachial arteries. A difference of ≥ 20 mm Hg between two adjacent segments is considered physiologically significant. For example, a significant pressure gradient between left upper thigh cuff and left lower thigh cuff would indicate a physiologically significant stenosis in the left superficial femoral artery. As with the ABI, pressures may be elevated or uninterpretable in patients with non-compressible vessels. Pulse volume recordings are performed by measuring volume changes in the limb along with segmental pressure recordings (Darling et al. 1972). Segmental pressure examination when performed with pulse volume recordings has an overall accuracy of 90 – 95% in assessing the location and severity of arterial stenosis (Symes et al. 1984).

10.3 Duplex ultrasound

It is recommended by ACC / AHA guidelines (Class I) for routine surveillance after femoral-popliteal or femoral-tibial pedal bypass with a venous conduit (Hirsch et al. 2006).

The 2011 ACC/AHA guidelines recommend that segmental pressures, Doppler waveform analysis, pulse volume recordings, or ABI with duplex ultrasonography (or some combination of these methods) to document the presence and location of PAD in the lower extremity can be used (Rooke et al. 2011). In general, imaging studies are reserved for patients with PAD in whom revascularization is planned, for bypass graft or percutaneous vascular intervention surveillance or for cases in which the diagnosis of PAD or etiology of PAD is unclear such as arterial aneurysm, fibromuscular dysplasia, entrapment syndrome or vasculitis. Imaging studies are also used to diagnose PAD in patients with non-compressible vessels such as those with ABI > 1.3.

Physiological testing such as ABI and PVR are adequate for asymptomatic patients. For symptomatics (claudication or pseudoclaudication) ABI and PVR with or without exercise, duplex or dopler ultrasound are utilised. CTA, MRA or duplex / doppler ultrasound are usually used for patients considered for revascularization as well as for post endovascular interventions and follow ups as well as for post vein graft follow ups.

11. Management of Peripheral Arterial Disease

Guidelines for the management of PAD have been published by

a. American college of Cardiology / American Heart Association which was a Collaborative Report from the American Association for Vascular Surgery/ Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines
b. Scottish Intercollegiate Guidelines Network (SIGN), and
c. Trans-Atlantic Inter-Society Consensus (TASC) II (Dormandy and Rutherford 2000; Hirsch et al. 2006; Network 2006; Norgren et al. 2007).

Each of these guidelines focuses on management of PAD as a two-tiered process. First and foremost, they recommend cardiovascular risk reduction through vascular risk factor modification and antiplatelet therapy and second, symptom-guided therapy including supervised exercise, pharmacological interventions and revascularization procedures, when needed.

11.1 Cardiovascular risk factor modification

11.1.1 Smoking cessation

Patients with PAD should be referred to a formal smoking cessation program including pharmacotherapy when appropriate. A Cochrane review of 20 prospective cohort studies showed that smoking cessation is associated with a 36% risk reduction in cardiovascular events in patients with known atherosclerotic disease (Critchley and Capewell 2004) and is recommended by all three guidelines(Dormandy and Rutherford 2000; Hirsch et al. 2006; Network 2006; Norgren et al. 2007; Rooke et al. 2011); Smoking cessation is achieved in approximately 5% of patients with physician encouragement and advice along with regular follow-ups and as compared to 0.1% without physician intervention at 1 year (Law and Tang 1995). Success rates are higher with interventions such as nicotine replacement, bupropion or varenicline. When compared with usual care, formal smoking cessation program which consisted of a strong physician message and 12 two-hour group sessions, using behavior modification and nicotine gum had a higher success rate at 5 years (22% vs. 5%) (Anthonisen et al. 2005). Abstinence rates with bupropion at 3-, 6- and 12- month follow up are 34%, 27% and 22% respectively, compared with 15%, 11% and 9%, for placebo(Tonstad et al. 2003). A combination of bupropion and nicotine replacement is superior to nicotine replacement alone, however but has similar in efficacy to only monotherapy with bupropion (Jorenby et al. 1999). Varenicline has been proven effective in smokers with cardiovascular disease including those with PAD. Rigotti et al conducted a multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of varenicline (12 weeks treatment) with placebo showed a continuous abstinence rate was higher for varenicline than placebo during weeks 9 through 12 (47.0% versus 13.9%;) and weeks 9 through 52 (19.2% versus 7.2%). The varenicline and placebo groups did not differ significantly in cardiovascular mortality, all-cause mortality, cardiovascular events, or serious adverse events. (Rigotti et al. 2010). Another RCT compared varenicline vs. bupropion vs placebo showed varenicline was more efficacious than bupropion or placebo in short term (9-12 weeks) (43.9% vs. 29.8% vs. 17.6)% as well as long term period 9 – 52 weeks) (23% vs. 14.6% vs. 10.3%) (Jorenby et al. 2006).

11.1.2 Diabetes Mellitus

Approximately 20-30% in patients with DM have PAD (Marso and Hiatt 2006). The severity of PAD in this cohort correlates with the duration and severity of DM (Selvin et al. 2004; Wattanakit et al. 2005). With every 1% increase in glycosylated hemoglobin levels, the risk of PAD increases by 28% (Selvin et al. 2004)and risk of intermittent claudication by 3.5- and 8.6-fold in men and women, respectively (Kannel and McGee 1985). DM may also lead to peripheral neuropathy and decreased resistance to infection, which increases the risk of infected foot ulcers. Patients with DM are at a higher risk of amputation and have reduced primary patency after revascularization as compared to non-diabetics (Bild et al. 1989; DeRubertis et al. 2008). The UKPDS study showed that the overall microvascular complication rate decreased by 25% by lowering blood glucose levels in type 2 diabetes with intensive therapy, which achieved a median HbA_{1c} of 7.0% compared with conventional therapy with a median HbA_{1c} of 7.9%. No significant effect on cardiovascular complications was observed. A non-significant ($p = 0.052$) 16% reduction in the risk of combined fatal or nonfatal myocardial infarction and sudden death was observed (UKPDS 1998).

The American Diabetic Association recommends maintaining hemoglobin A1c below 7% to reduce microvascular events (ADA 2010). This recommendation is endorsed by all three PAD guidelines. The ADA also recommends comprehensive foot care including proper footwear, regular podiatric foot and nail care, daily foot inspection, skin cleansing, and use of topical moisturizing creams (ADA 2010).

11.1.3 Dyslipidemia

The Heart Protection Study (HPS) randomized 20,536 high-risk patients to 40 mg/d of simvastatin or placebo, including 6,748 patients with PAD. PAD patients taking statins had a 25% cardiovascular risk reduction at 5 years independent of baseline LDL level (HPS 2002). Statin use is also associated with reduction in the risk of new or worsening claudication (Pedersen, Kjekshus et al. 1998). A RCT comparing high dose atorvastatin (80 mg) vs. placebo irrespective of baseline LDL cholesterol showed that high dose atorvastatin improves pain-free walking distance and community-based physical activity in patients with intermittent claudication, however there was no change noted in the maximal walking time. This beneficial effect was noted over statins cardiovascular risk reduction benefits. (Mohler, Hiatt et al. 2003).

The AHA / ACC and TASC 2 guidelines recommend the following for dyslipidemia management in patients with PAD (Dormandy and Rutherford 2000; Smith et al. 2001; Hirsch et al. 2006; Norgren, Hiatt et al. 2007).

- All patients should have low-density lipoprotein (LDL)- cholesterol <2.59 mmol/L (<100 mg/dL).
- In patients with PAD and a history of vascular disease in other beds (e.g. coronary artery disease) it is reasonable to lower LDL cholesterol levels to <1.81 mmol/L (<70 mg/dL).
- In patients with elevated triglyceride levels where the LDL cannot be accurately calculated, the LDL level should be directly measured and treated to the above targets. Alternatively, the non-HDL (high-density lipoprotein) cholesterol level can be calculated with a goal of <3.36 mmol/L (<130 mg/dL), and in high risk patients <2.59 mmol/L (<100 mg/Dl).
- Dietary modification should be the initial intervention to control abnormal lipid levels [B].

- In symptomatic PAD patients, statins should be the primary agents to lower LDL cholesterol levels to reduce the risk of cardiovascular events [A].

The SIGN guidelines recommend statins for patients with PAD and total cholesterol level > 3.5 mmol/l (63 mg/dl) (Network 2006).

The ACC/AHA and TASC II guidelines also recommended considering niacin / fibrates for raising HDL cholesterol and lowering triglycerides in patients with PAD who have abnormalities in these lipid fractions. Recently, the randomized trial, AIM – HIGH, failed to reduce the incidence of cardiovascular events among patients with CAD at 3 years and was terminated prematurely, raising questions about the benefit of niacin in patients with atherosclerotic vascular disease (http://www.aimhigh-heart.com/ 2011).

11.1.4 Management of hypertension

Blood pressure lowering by any pharmacological means reduces cardiovascular risk (Chobanian et al. 2003); however angiotensin converting enzyme inhibitors (ACEI) have benefit in patients with PAD beyond their effect on lowering blood pressure. The Heart Outcomes Prevention Evaluation (HOPE) study showed a 22% reduction in risk of MI, stroke, or vascular death in patients randomized to ramipril compared to placebo, independent of the blood pressure–lowering effect (Yusuf et al. 2000). Although once thought to worsen claudication, the safety of beta blockers, has been demonstrated in a meta-analysis of 11 trials of patients with PAD (Radack and Deck 1991); these agents are of benefit of patients with CAD, particularly among those with a history of prior myocardial infarction.

11.1.5 Anti-platelet therapy

11.1.5.1 Aspirin

Aspirin was initially recommended mainly based on a sub-group analysis of a Antithrombotic Trialists' Collaboration meta-analysis which is a meta-analysis of 42 RCT's published in 2002 which showed that anti-platelet therapy (primarily aspirin) reduced cardiovascular events by 23% in patients with symptomatic PAD including patients with IC (23%), those with peripheral grafts (22%) and those undergoing peripheral angioplasty (29%) (2002). However, this study had a lot of heterogeneity in selection criteria and different antiplatelet drugs used at different doses. Also the benefit of aspirin in asymptomatic PAD wasn't in this meta-analysis. A more recent meta-analysis of 18 RCT's including 5,269 patients with PAD, aspirin therapy alone or in combination with dipyridamole led to a non-significant 12% reduction in the primary end point of cardiovascular events(Berger et al. 2009). Two large RCT evaluated the benefit of aspirin in patients with asymptomatic PAD and found no benefit (Belch et al. 2008; Fowkes et al. 2010). However, both of these RCT's had populations with asymptomatic PAD with very mild decrease in ABI and characterized as mild PAD in general. In the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial enrolled patients with ABI <0.99 and the Aspirin for Asymptomatic Atherosclerosis trial enrolled patient with ABI ≤0.95 which calculated by using the lower pedal pressure at the ankle. In standard clinical practice and guidelines, ABI is calculated using the higher pedal pressure (Belch et al. 2008; Fowkes et al. 2010). Hence, both of these studies had significant limitations in design and enrollment and no change in recommendation regarding anti-platelet therapy in this cohort have occurred (Belch et al. 2008; Fowkes et al. 2010).

11.1.5.2 Clopidogrel

In a post hoc subgroup analysis of 6,452 PAD patients in The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, the incidence of stroke, MI, or vascular death was reduced by 24% among those randomized to clopidogrel compared to aspirin monotherapy (1996).

Dual antiplatelets therapy (DAPT) with aspirin and clopidogrel was not more effective than aspirin monotherapy in the Clopidogrel for High Atherothrombotic Risk and Ischemia Stabilization, Management and Avoidance (CHARISMA) study (Bhatt et al. 2006). However, post hoc analysis of the CHARISMA study revealed that DAPT was superior to aspirin monotherapy among patients with known symptomatic PAD at the time of enrollment (Bhatt et al. 2007). The combination of antiplatelet and anticoagulant therapy was evaluated in The Warfarin Anti-platelet Vascular Evaluation (WAVE) trial. This study found no incremental benefit of vitamin K antagonists when added to anti-platelet therapy for the prevention of cardiovascular events in patients with PAD (Anand et al. 2007). In fact, patients randomized to the combination of antiplatelet and anticoagulant therapy had an increase in life-threatening bleeding when compared with those randomized to anti-platelet therapy alone.

In general, all three PAD guidelines recommend antiplatelet therapy for PAD patients. Selection of an antiplatelet regimen (aspirin or clopidogrel or both or other antiplatelet medications) for the PAD patient should be individualized on the basis of tolerance and other clinical characteristics (i.e., bleeding risk) along with cost and guidance from regulatory agencies. (Dormandy and Rutherford 2000; Hirsch et al. 2006; Network 2006; Rooke et al. 2011). ACC / AHA guidelines strongly recommend antiplatelet therapy to reduce the risk of MI, stroke, and vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia (class IA). They feel that antiplatelet therapy can be useful to reduce the risk of MI, stroke, or vascular death in asymptomatic individuals with an ABI less than or equal to 0.90 (Class IIa C), however do not strongly recommend it given lack of definite evidence of any benefit (Rooke et al. 2011).

11.2 Medical therapy for claudication

11.2.1 Supervised exercise program

Many patients with PAD have severely impaired functional capacity, which leads to decreased quality of life (McDermott et al. 2004). A meta-analysis of 21 studies showed that patients with IC who underwent exercise training improved mean walking time by 180% and maximal walking time by 120% (Gardner and Poehlman 1995). Supervised treadmill exercises programs are also are more effective than lower extremity resistance training (McDermott et al. 2009). However, due to lack of reimbursement access to this important therapeutic intervention has been limited. In a Cochrane review of 8 RCT's evaluating supervised and unsupervised exercise among 319 participants with IC, statistically significant and clinically relevant improvements in maximal treadmill

walking distance occurred with supervised compared with non-supervised exercise therapy during 12 weeks to 12 months of follow up (Bendermacher et al. 2006). Unsupervised therapy may be less effective than supervised therapy due to lack of motivation, compliance with recommended exercise, lack of progression of workload in the absence of professional supervision and concern for personal safety to advance the moderate claudication discomfort severity.

11.2.2 Pharmacological agents

Cilastozol is an FDA-approved medication for the management of IC. It is a reversible phosphodiesterase inhibitor whose exact mechanism of benefit is unclear. It inhibits platelet aggregation, thrombin formation, and vascular smooth muscle proliferation and acts as a vasodilator. It also increases HDL and lowers TG levels. In an analysis of 9 RCT's of cilastazol at dose of 100 mg BID, cilostazol showed a 50.7% improvement from baseline maximal walking distance compared to placebo (24.3%) (Pande et al. 2010). A Cochrane review found similar benefit (Robless et al. 2008). Given the increased incidence of sudden cardiac death with other phosphodiesterase inhibitors (e.g., milrinone), cilostazol is contraindicated in patients with heart failure and/ or ejection fraction less than 40% (Packer et al. 1991). The ACC/AHA guidelines have given cilostazol a grade IA recommendation for patients with intermittent claudication in the absence of heart failure.

Pentoxifylline is a methylxanthine derivative that decreases blood viscosity and has hemorheologic (improves erythrocyte and leukocyte deformability), anti-inflammatory, and antiproliferative effects. Its anti-claudication effect has been inconsistent. A study randomizing 698 patients with IC to cilostazol, pentoxifylline or placebo did not observe any difference between pentoxifylline and placebo (Dawson et al. 2000). ACC/AHA guidelines recommend using pentoxifylline as an alternative in patients who cannot tolerate cilostazol or in whom cilostazol is contraindicated.

11.2.3 Revascularization

Revascularization is only appropriate for symptomatic patients and should not be undertaken as prophylactic therapy for an asymptomatic limb (Hirsch et al. 2006). Revascularization is indicated in patients' with acute limb ischemia (ALI), CLI and among those with lifestyle- or vocation-limiting claudication who have failed a trial of medical therapy or who have highly favorable anatomy for endovascular therapy such as focal aorto-iliac disease (Hirsch et al. 2006) . Data comparing medical therapy with either endovascular or surgical therapy are scant. The ongoing Claudication: exercise vs endoluminal revascularization (CLEVER) trial is comparing medical therapy alone vs. medical therapy + supervised exercise vs. medical therapy + endovascular therapy (Murphy et al. 2008).

Endovascular therapy is currently the preferred mode of revascularization in cases where anatomy is more favorable (e.g., aorto-iliac disease). Endovascular therapy is less invasive, is associated with fewer complications and with shorter hospital stay as compared to bypass procedures. The durability of endovascular or surgical procedures depends on a number of factors including anatomic location (aorto-iliac revascularization whether open surgical or endovascular has superior long term outcomes compared with infra-inguinal

revascularization), lesion characteristics, technical features (e.g., angioplasty alone vs. angioplasty + stent, type of surgical conduit used for surgical bypass). Hybrid procedures are performed for multi-level in an effort to minimize the overall operative risk of the revascularization (e.g., iliac artery stenting followed by femoral-popliteal bypass). Open surgical revascularization (e.g., bypass or endarterectomy) is typically reserved for endovascular failures or anatomy not likely to respond to an endovascular attempt.

12. Summary of the guideline recommendations for PAD

In table 4 we outline the grade A level of recommendation for PAD by TASC II guidelines. In table 5 we outline the class I recommendations by American College of Cardiology and American Heart association for PAD. Finally in table 6 we outline the differences in recommendations between the TASC II and American College of Cardiology /American Heart association guidelines for management of PAD.

TASC II grade A level of recommendation for peripheral arterial disease
All patients who smoke should receive a program of physician advice, group counseling sessions and nicotine replacement
Cessation rates can be enhanced by the addition of antidepressant drug therapy (bupropion) and nicotine replacement
All symptomatic PAD patients should have their LDL-cholesterol lowered to <2.59 mmol/L (<100 mg/dL)
In symptomatic PAD patients, statins should be the primary agents to lower LDL cholesterol levels to reduce the risk of cardiovascular events
All patients with hypertension should have blood pressure controlled to <140/90 mm Hg or <130/80 mm Hg if they also have diabetes or renal insufficiency
The Joint National Committee (JNC VII) and European guidelines for the management of hypertension in PAD should be followed
Beta-adrenergic blocking drugs are not contraindicated in PAD
All symptomatic patients with or without a history of other cardiovascular disease should be prescribed an antiplatelet drug long-term to reduce the risk of cardiovascular morbidity and mortality
Aspirin/ASA is effective in patients with PAD who also have clinical evidence of other forms of cardiovascular disease (coronary or carotid)
Routine coronary revascularization in preparation for vascular surgery is not recommended
When there are no contraindications, beta-adrenergic blockers should be given perioperatively to patients with peripheral artery disease undergoing vascular surgery in order to decrease cardiac morbidity and mortality
Supervised exercise should be made available as part of the initial treatment for all patients with peripheral artery disease
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. Exercise sessions are typically conducted three times a week for 3 months
A 3- to 6-month course of cilostazol should be first-line pharmacotherapy for the relief of claudication symptoms, as evidence shows both an improvement in treadmill exercise performance and in quality of life
Naftidrofuryl (Not available in United States of America) can also be considered for treatment of claudication symptoms
CLI patients should have aggressive modification of their cardiovascular risk factors
Antiplatelet therapy should be started preoperatively and continued as adjuvant pharmacotherapy after an endovascular or surgical procedure. Unless subsequently contraindicated, this should be continued indefinitely

Table 4. This table outlines TASC II grade A level of recommendation for peripheral arterial disease

Certain Class I recommendations for the Identification and Management of Peripheral artery Disease (PAD) by American Heart Association and American College of Cardiology with level of evidence (LOE)
All Patients with Peripheral Arterial Disease: 1. Smoking cessation, lipid lowering, and diabetes and hypertension treatment according to current national treatment guidelines are recommended for individuals with lower extremity peripheral arterial disease. (LOE: B) 2. -Blockers are effective antihypertensive agents and are not contraindicated in patients with PAD (LOE – A) 3. All Diabetic patients with PAD should properly care for their feet, and all skin lesions and ulcerations should be urgently addressed (LOE – B) 4. For patients who smoke, comprehensive smoking cessation, including behavior modification therapy, nicotine replacement, and/or bupropion should be strongly encouraged (LOE – B) 5. All patients with PAD should be treated with statins to achieve target LDL ≤ 100 mg/dl (LOE–B) 6. Antiplatelet therapy is indicated to reduce the risk of MI, stroke, and vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization or prior amputation for lower extremity ischemia (LOE:A) Asymptomatic patients: 1. A history of walking impairment, claudication, ischemic rest pain, and/or nonhealing wounds is recommended as a required component of a standard ROS for adults 50 years and older who have atherosclerosis risk factors and for adults 65 years and older. (LOE: C) 2. Individuals with asymptomatic lower extremity peripheral arterial disease should be identified by examination and/or measurement of the ABI so that therapeutic interventions known to diminish their increased risk of MI, stroke, and death may be offered. (LOE: B) 3. Antiplatelet therapy is indicated for individuals with asymptomatic lower extremity peripheral arterial disease to reduce the risk of adverse cardiovascular ischemic events. (LOE: C) Patients with intermittent claudication: 1. Patients should undergo a vascular physical examination, including measurement of the ABI. *(LOE: B)* 2. ABI should be measured after exercise if the resting index is normal. *(LOE: B)* 3. Patients should have significant functional impairment with a reasonable likelihood of symptomatic improvement and absence of other disease that would comparably limit exercise even if the claudication was improved before undergoing an evaluation for revascularization. *(LOE: C)* 4. Patients should be offered the option of endovascular or surgical therapies should: (a) be provided information regarding supervised claudication exercise therapy and pharmacotherapy; (b) receive comprehensive risk factor modification and antiplatelet therapy; (c) have a significant disability, either being unable to perform normal work or having serious impairment of other activities important to the patient; and (d) have lower extremity peripheral arterial disease lesion anatomy such that the revascularization procedure would have low risk and a high probability of initial and long-term success. *(LOE: C)* Critical Limb Ischemia: 1. Patients should undergo expedited evaluation and treatment of factors that are known to increase the risk of amputation. (LOE: C) 2. Patients in whom open surgical repair is anticipated should undergo assessment of cardiovascular risk. (LOE: B) 3. Patients with a prior history of CLI or who have undergone successful treatment for CLI should be evaluated at least twice annually by a vascular specialist owing to the relatively high incidence of recurrence. (LOE: C) 4. Patients at risk of CLI should undergo regular inspection of the feet. (LOE: B) 5. Patients should be evaluated for aneurysmal disease. (LOE: B) 6. Systemic antibiotics should be initiated promptly in patients with CLI, skin ulcerations, and evidence of limb infection. (LOE: B) 7. Patients with CLI and skin breakdown should be referred to healthcare providers with specialized expertise in wound care. (LOE: B) 8. Patients who develop acute limb symptoms represent potential vascular emergencies and should be assessed immediately and treated by a specialist competent in treating vascular disease. (LOE: C) 9. Patients should receive verbal and written instructions regarding self-surveillance for potential recurrence. (LOE: C) Acute Limb Ischemia: Patients with acute limb ischemia and a salvageable extremity should undergo an emergent evaluation that defines the anatomic level of occlusion and that leads to prompt endovascular or surgical revascularization. *(LOE: B)*

Table 5. This table outlines Class I recommendations for the Identification and Management of Peripheral artery Disease (PAD) by American Heart Association and American College of Cardiology with level of evidence (LOE)

Comparison of ACC/AHA and TASC II guidelines
Evidence grading systems: Both the ACC/AHA and the TASC II guidelines utilize the ABC system of recommendation grading. The ACC/AHA guidelines provide further information by using an additional classification (Class I, II, IIa,IIb and III) for each of the examined procedures/treatments.
Diabetes therapy: Both guidelines suggest aggressive control of glycosylated hemoglobin (HbA_{1c}) in patients with diabetes to a target of <7.0%. Additionally, the TASC II guidelines indicate that, optimally, HbA_{1c} should be as close to 6% as possible.
Claudication: The guidelines recommend different agents as second-line alternatives to cilostazol in patients with claudication – the ACC/AHA recommends pentoxyfylline and the TASC II guidelines recommend naftidrofuryl (not available in USA).
Hypertension: The ACC/AHA guidelines provide no indication as to the initial pharmacotherapeutic strategy to be utilized as antihypertensive medication in patients with PAD. In contrast, the TASC II guidelines advocate the use of either thiazide diuretics or angiotensin-converting enzyme (ACE) inhibitors as first-line blood pressure lowering therapy.
Lipid-lowering therapy: The TASC II guidelines recommend that the initial strategy for reducing lipid levels should focus on the use of dietary modifications whilst the ACC/AHA guidelines recommend the use of statins as first-line therapy for lipid level reduction.
In summary, there is little difference between the guidelines in terms of recommendations for clinical practice (Mohler and Giri 2008)

Table 6. This table outlines the main differences between the ACC/AHA PAD guidelines and TASC II guidelines are summarized in this table

13. Conclusions

PAD is a common disease, present in more than 8 million Americans and is associated with a relatively high risk of cardiovascular events. Nevertheless, it remains under-recognized by healthcare providers and patients alike. Increased awareness, earlier identification of the disease and aggressive medical therapy and vascular risk factor modification would reduce the likelihood of fatal and non-fatal cardiovascular events and improve overall functional status and quality of life.

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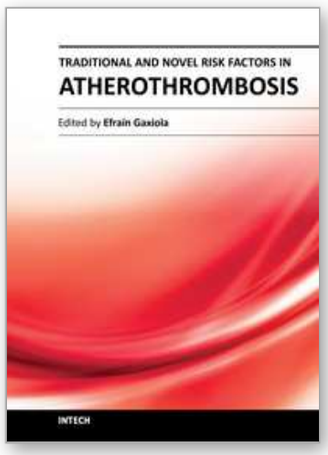
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Traditional and Novel Risk Factors in Atherothrombosis
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Atherothrombosis has reached pandemic proportions worldwide. It is the underlying condition that results in events leading to myocardial infarction, ischemic stroke and vascular death. As such, it is the leading cause of death worldwide manifested mainly as cardiovascular/cerebrovascular death. The complex and intimate relationship between atherothrombosis and traditional and novel risk factors is discussed in the following chapters of Traditional and Novel Risk Factors in Atherothrombosis - from basic science to clinical and therapeutic concerns. Beginning with pathology and pathophysiology of atherothrombosis, plaque rupture/disruption, this book continues with molecular, biochemical, inflammatory, cellular aspects and finally analyzes several aspects of clinical pharmacology.

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