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TITLE

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ABSTRACT

Peripheral arterial disease (PAD) is one of the most frequent manifestations of atherosclerosis and is associated with atherosclerosis in the coronary and carotid arteries, leading to a highly increased incidence of cardiovascular events. Major risk factors of PAD are similar to those that lead to atherosclerosis in other vascular beds. However, there are differences in the power of individual risk factors in the different vascular territories. Cigarette smoking and diabetes mellitus represent the greatest risks of PAD. For prevention of the progression of PAD and accompanying cardiovascular events similar preventative measures are used as in coronary artery disease (CAD). However, recent data indicate that there are some differences in the efficacy of drugs used in the prevention of atherothrombotic events in PAD. Antiplatelet treatment is indicated in virtually all patients with PAD. In spite of the absence of hard evidence- based data on the long term efficacy of aspirin, it is still considered as a first line treatment and clopidogrel as an effective alternative. The new antiplatelet drugs

ticagrelol and prasugrel also represent promising options for treatment of PAD. Statin therapy is indicated to achieve the target low density lipoprotein cholesterol level of ≤ 2.5 mmol/L (100 mg/dL) and there is emerging evidence that lower levels are more effective. Statins may also improve walking capacity. Antihypertensive treatment is indicated to achieve the goal blood pressure (<140/90 mmHg). All classes of antihypertensive drugs including beta-blockers are acceptable for treatment of hypertension in patients with PAD. Diabetic patients with PAD should reduce their glycosylated haemoglobin to ≤ 7.0%. As PAD patients represent the group with the highest risk of atherothrombotic events, these patients need the most intensive treatment and elimination of risk factors of atherosclerosis. These measures should be as comprehensive as those in patients with established coronary and cerebrovascular disease.

Key words: Peripheral arterial disease, PAD, Atherosclerosis, Risk factors, Management.

TEXT

INTRODUCTION

Arterial atherosclerotic disease of the lower limbs (PAD) represents one of the most frequent manifestations of atherosclerosis. It affects 4-12% of people aged 55-70 years, and the prevalence

increases with age.[1] The Framingham study showed that the incidence of intermittent claudication (IC) in men increases from 0.4 per 1,000 aged 35-45 years to 0.6 per 1,000 aged 65 years and older.[2] The incidence in women is about half than that in men, but becomes more similar at older ages. Smoking and DM represent the most serious risk factors for PAD. Arterial occlusive disease of the lower limbs is a relatively benign condition of the legs in that only 2 out of 100 patients with IC lose their legs within 5 years. It is quite the opposite as a risk indicator for ischemic coronary and cerebrovascular disease.[3] However, because of accompanying coronary artery and cerebrovascular disease patients with PAD, are at increased risk of cardiovascular mortality.[4] The mortality rate, mainly from coronary and cerebrovascular events, is 3-4 times greater than in age and sex matched controls without claudication[1] Therefore, patients with PAD are at high risk of multifocal atherosclerosis and require more intensive management of risk factors of atherosclerosis.

PAD AS AN INDICATOR OF SYSTEMIC ATHEROSCLEROSIS AND ITS RELATION TO CORONARY ARTERY DISEASE AND CEREBROVASCULAR DISEASE

Peripheral arterial disease (PAD) is only one of the manifestations of atherosclerosis and is often associated with coronary artery disease (CAD) and cerebrovascular disease.[5] Therefore, atherosclerosis should be considered to be a systemic disease, and if found in one vascular bed, it is very probable that another is also involved.[6] Half of the patients with PAD have concomitant CAD, which may seriously affect their prognosis.[7-10] Patients with concomitant PAD harbour more extensive and calcified coronary atherosclerosis and more rapid disease progression which are likely to contribute to adverse cardiovascular outcomes.[11, 12] Therefore PAD is an indicator of systemic and progressive atherosclerosis.[7-9, 13] The management of PAD should therefore not be restricted to the peripheral circulation but should include measures to manage and decrease the systemic atherosclerotic burden of the patient.

Indeed, the presence of PAD in patients with other manifestations of cardiovascular disease (CVD) identifies a population at increased risk of complications at the time of their acute coronary and/or cerebrovascular event over the long-term. Therefore, patients with CAD and cerebrovascular disease who have associated PAD represent a population in which secondary prevention of cardiovascular events should be addressed aggressively.[14] In patients with previous coronary or cerebrovascular events, PAD occurs with a much higher prevalence than usually estimated. It has been suggested that screening for PAD is justified and that it should be carried out in these patients in order to modify their lifestyle and introduce a more intensive medical intervention.[15]

A recent meta-analysis showed that PAD is an independent predictor of worse outcomes in patients already at high risk after myocardial infarction because of left ventricular systolic dysfunction, heart failure or both.[16] Therefore, these patients represent an important group for intensive implementation of secondary preventive therapies and an important target for PAD screening, considering that detection of subclinical PAD by ankle brachial pressure index (ABI) in patients with stable CAD provides additional risk information for long-term mortality.[17] Similarly, the presence of CAD adds insight into the development of PAD complications; indeed, the severity of CAD increases the risk of adverse cardiac events and the amputation rate of the lower extremity in patients with PAD.[8] It has been shown that the long-term prognosis of patients with PAD who undergo surgery is significantly worse than in patients with CAD.[18] Patients who underwent peripheral vascular surgery received less cardiac medication (beta-blockers, statins, angiotensin-converting enzyme inhibitors, aspirin, nitrates, and calcium antagonists) than CAD patients, and cerebro-cardiovascular events were the major cause of late postoperative death (46%).

Regarding cerebrovascular disease, a recent study showed that the prevalence of cerebral infarction was markedly higher in patients with PAD than in controls, indicating that PAD is a meaningful risk factor of cerebrovascular disease.[19] This suggests that recognizing the presence of cerebrovascular disease may be important for proper management of patients with PAD, as well as recognizing the presence of PAD in patients with stroke. It has been shown that in patients with stroke or transient ischemic attack (TIA), asymptomatic PAD is independently associated with recurrent vascular events and stroke.[20]

In conclusion there is a definite and strong correlation between PAD, CAD and cerebrovascular disease. A thorough evaluation to recognize disease affecting all vascular territories, which leads to effective secondary prevention, will reduce future coronary and cerebrovascular events in these high-risk patients.[21]

RISK FACTORS OF PAD: ARE THEY DIFFERENT FROM OTHER ATHEROSCLEROTIC DISEASES?

Traditional risk factors are similar to those that lead to atherosclerosis in the carotid, coronary and other vascular beds. Major risk factors for PAD include cigarette smoking, DM, advanced age, dyslipidemia and arterial hypertension.[22, 23] Non-traditional risk factors include race, chronic renal disease, elevated levels of inflammatory markers such as C-reactive protein and hypercoagulable states. Among traditional risk factors cigarette smoking and DM represent the greatest risk of PAD,[24] while for CAD, hyperlipidemia (elevated LDL) is probably the most important and for cerebrovascular disease arterial hypertension represents one of the most powerful risk factors.

Cigarette smoking is the most important modifiable risk factor for the development of PAD. Smoking increases the risk of PAD approximately four-fold for each decade, with an apparent dose-response relationship between pack-year history and PAD risk.[25] Compared to non-smokers, smokers with PAD have lower survival rates, are more likely to progress to critical

limb ischemia (CLI) and are twice as likely to progress to amputation.[26] The association between smoking and PAD is about twice as strong as that between smoking and coronary artery disease.

Diabetes mellitus carries a 1.5-fold to 4-fold increased risk of developing symptomatic or asymptomatic PAD. It is also responsible for early mortality among individuals with PAD; the prevalence and extent of PAD increases with the age of the individual and the duration and severity of DM. Diabetes is a stronger risk factor of PAD in women than in men. The seriousness of PAD appears to be related to glycemic control. There is a 28% increase of PAD for every per cent of glycosylated hemoglobin.[27] Diabetes is most strongly associated with occlusive disease in the tibial arteries. Diabetic PAD patients are more likely to develop small vessel disease. Therefore, they have a higher risk of ischemic ulceration and gangrene, which is one of the reasons why DM is the most common cause of amputation.[28]

The prevalence of PAD increases with *age.* The prevalence of PAD (abnormal ABI) is about 2 - 3% in individuals aged 50 years or less compared to 20% in those aged more than 75 years.[29] However, younger patients tend to have poorer overall long-term outcomes, including a higher amputation rate.

Hyperlipidemia represents a weaker risk factor of PAD. In the Framingham heart study an elevated total cholesterol level was associated with a two-fold increased risk of IC. However, in the Atherosclerosis Risk in Community (ARIC) study and the Edinburgh Artery Study only elevated triglyceride levels were associated with PAD.[24, 30]

Most epidemiological studies have also shown an association between *arterial hypertension* and PAD, with hypertension being present in as many as 50 – 92% of patients with PAD. The Framingham study demonstrated a 2.5 - 4-fold increase in the development of IC in patients with hypertension.[2]

CLINICAL PRESENTATION

A detailed history should enable a diagnosis of PAD to be made in most patients. A thorough examination should then confirm the presence of PAD and also indicate the extension and level of arterial occlusion. Patients with peripheral arterial disease have a wide range of symptoms from none at all to disabling IC. The majority of PAD patients are asymptomatic or present with atypical symptoms.[31] Intermittent claudication is generally a clear symptom. The patient describes pain in the muscles of the leg on walking a certain distance, with the distance being constant at a particular walking pace (symptom onset will be at a shorter distance for walking uphill or more rapidly). The calf muscles are most commonly affected, but pain may be experienced in the buttock, hip, thigh, leg and feet, depending on the level and extent of the arterial occlusion. Buttock pain on walking together with impotence is typical of the Leriche syndrome, with absent femoral pulses due to aorto-iliac occlusion.

Patients with critical limb ischaemia (CLI) are readily identifiable by the characteristic symptoms and signs which are associated with advanced PAD. Rest pain occurs at night when the leg is elevated. It is typically a severe pain in the foot and toes which initially occurs with leg elevation (at night) and is relieved by leg dependency.

Clinical signs of the Bürger's test are elevation pallor followed by dependent rubor, often with delayed refill of superficial veins. Tissue loss occurs with progressive CLI. Ischemic ulceration is painful and typically develops over pressure points (lateral malleolus, 5th metatarsal, and heel) and the distal parts of the foot, tips of toes or in between toes. With further progression of CLI, there will be more extensive tissue necrosis presenting as gangrene, generally affecting the toes initially, with subsequent spread into the forefoot. Additional signs to look for on inspection of the lower extremities are loss of hair, brittle nails and evidence of healed or active ischemic ulceration.

Abdominal examination should assess the presence of aneurysm, bruits and other pathologies. If femoral, popliteal and pedal pulses are all present and normal, significant PAD is unlikely.

Neurogenic claudication, associated with lumbar spondylosis and lumbar canal stenosis, may be symptomatically similar and even identical to vascular claudication. There is usually a clue in the history which points to neurogenic claudication, such as leg pain occurring not only on walking, but also sometimes on sitting, standing, or on first arising. Nevertheless, it may be difficult at times to distinguish neurogenic from vascular claudication on the basis of history, and may require an exercise treadmill test in the vascular laboratory for accurate diagnosis.

DIAGNOSTIC PROCEDURES

Both invasive and non-invasive diagnostic procedures are used. Most frequently used non-invasive screening tests include measurement of the ankle brachial pressure index (ABI) and ultrasound. Invasive (various arteriographic procedures) are indicated only in patients in whom a revascularization procedure is planned.

Ankle brachial pressure index (ABI).

Measuring the ABI is easy, inexpensive, and non-invasive and should be part of the physical examination of patients with suspected PAD. It is expressed by dividing the systolic blood pressure measured at the ankle by the highest brachial artery systolic pressure. A portable Doppler device and standard arm blood pressure cuff are sufficient to perform the measurements. A normal ABI is 1.0 or slightly above. A figure of 0.9 (or lower) is generally accepted as indicative of the presence of obstructive arterial disease in the limb. Information obtained by ABI recordings is not of the all or none type; the increasing severity of the vascular obstruction is accompanied by a progressive decrease in the index. Thus an ABI between 0.7 and 0.9 is indicative of a mild stenosis, while an ABI of lower than 0.5 indicates a severe stenosis. In the case of the presence of an arterial ulcer,

the chances of spontaneous healing or by medical means can be estimated by measuring the systolic pressure at the ankle: below 50 mmHg, there rarely is spontaneous healing, even with the best possible medical therapy; in diabetic patients, even higher figures (like 80 mmHg) are needed to allow for successful healing of the ulcer. The ABI is simple to perform and has good sensitivity and specificity, estimated respectively at 79% and 96%. The sensitivity can be slightly improved by measuring ABI after a short exercise (e.g. walking on the treadmill).

Besides helping in the diagnosis of PAD and estimating the degree of arterial perfusion, the ABI can assist in estimating the long term cardiovascular morbidity and mortality of PAD patients. There is a linear inverse correlation between the decrease in ABI and the risk of developing a cardiovascular event. Such a correlation holds true even after adjusting for the major Framingham risk factors. Recently it was also shown that an elevated ABI ($\geq$ 1.3) predicts a worsened prognosis. A falsely elevated ABI is likely due to increased arterial stiffness and non-compressibility due to vessel wall calcification, which is part of the atherosclerotic disease process, and is linked to increased risk. The true relationship between cardiovascular risk and ABI, therefore, is the shape of a U-shaped curve.[31]

The confounding condition of a falsely elevated ABI or severe hardening of the vascular wall making the arteries incompressible is often observed in diabetic patients. This is because the ankle vessels can resist compression pressures above 250 mmHg. Such hardening may also result in misleading “normal” values or a higher “abnormal” value by increasing the figures in patients who have in reality low perfusion pressure. In such cases, alternative perfusion studies need to be performed. These include direct pulse volume recordings and wave form analysis of arterial segments and toe pressure measurements. When the calf arteries are incompressible the level at which a pedal Doppler disappears on elevation of the foot may be taken as a crude measure of ankle arterial pressure (the Jonathan Beard pole test).[32] In this test the food is raised alongside a

calibrated pole marked in mmHg (0.73 mmHg=1 cmH_2O). The pole test is useful only in severe ischemia as it is not possible to raise the foot high enough to measure normal pressures.

The prognostic value of the ABI has recently been criticized on the grounds that the information given by the technique does not improve on the prognostic input coming from standardized risk scores. However, these studies did not deny the strength of the correlation between ABI and risk; they only put the results in relation to the input of risk scores by themselves and raised doubt about the necessity of having both risk scores and ABI. However, in contrast to various risk scores which estimate the statistical probability that a member of a certain population will develop atherosclerosis, the pathological ABI identifies the individual subject in whom the atherosclerotic process is ongoing.

The role of colour flow duplex scanning (CFDS) in identification of PAD

The need for imaging to supplement patient history and physical examination depends upon the clinical scenario and the urgency of the condition. Peripheral arterial disease traditionally has been investigated by arteriography which was considered to be the gold standard. It does, however, suffer from a low but consistently reported complication rate of injury (dissection, embolization, false aneurysm),[33, 34] contrast agent reactions and can be unreliable in depicting the degree of stenosis accurately, particularly if the plaque is eccentric. It provides information about the vessel lumen and whilst some inferences can be made about the arterial wall depending on the outline of the stenosis, it does not provide direct information about velocities, plaque thickness, consistency or asymmetry.

Over the past two decades, such is the improvement in non-catheter techniques, that led to an increased acceptance of duplex arterial scanning alone, from diagnosis to the decision making process.[35-37] Duplex scanning has become an extremely useful diagnostic modality, not only because

of its non-invasive nature, low cost, and patient acceptance, but also due to its ability to acquire both anatomical and morphological information and combine it with a hemodynamic assessment of the lesion, thereby providing a more complete anatomical and functional picture.

The role of duplex scanning in peripheral arterial disease fulfils several purposes where it:

- Confirms the presence or absence of disease;
- Identifies the level and severity of occlusive disease;
- Identifies run-off arteries suitable for use in distal reconstructions;
- Allows for planning further management of the patient;
- Allows for monitoring bypass grafts.

In addition, duplex scanning has an important role to play in the acute surgical admissions unit, where acute arterial occlusions can be rapidly located, identified and treated or other pathologies such as aneurysms, diagnosed.

Confirms or excludes disease

In some cases, particularly in younger patients who present with claudication in the absence of demonstrable disease, there may well be other causes such as popliteal entrapment. Diabetics who have rigid calcified arteries may have normal or even elevated ankle-brachial indices because the compression cuff fails to occlude the artery, resulting in false ABI readings in the presence of significant disease. In all these cases duplex can confirm the diagnosis of PAD.

CFDS identifies the level and severity of occlusive disease

Whilst a patient may have a clear cut clinical diagnosis of PAD, it can sometimes be difficult to relate the extent of the disease to the severity of the symptoms. This situation may occur when there are general medical or orthopaedic problems such as spinal claudication. A normal CFDS study will then be able to confirm the possibility of a differential diagnosis. In addition duplex imaging allows an objective assessment of the severity of the disease and this can then be used as a baseline against

which symptoms can be compared and the subsequent progression of the disease process monitored.

CFDS identifies run-off arteries suitable for use in distal reconstructions

The primary objective of duplex imaging before an infrainguinal bypass is to select arterial segments for placement of proximal and distal anastomoses. Ideally such sites should be non-diseased arteries without calcifications consistent with the available length of a venous or prosthetic conduit and easily accessed during surgery. In the process of selecting such sites, clinical suspicion of arterial obstruction, and the location and extent of occlusions and stenoses need to be confirmed and quantified.

CFDS allows for planning further management of the patient

Many studies have examined the imaging methods available for planning leg revascularization. However, duplex can be performed successfully and can contribute in a variety of situations. Short segment occlusions or isolated stenosis amenable to percutaneous endovascular treatment, can both be identified by duplex. The questions remains whether patients with less severe disease should undergo operative intervention. Patients with severe disease can be taken to the operating room, where inflow can be evaluated by ultrasound images and pressure measurements. For the outflow, if ultrasound fails to demonstrate a distal site for bypass, arteriography should be performed as a preoperative or intraoperative study before considering bypass or amputation. Pemberton and London concluded that arteriography should no longer be the standard for imaging peripheral arteries and that future studies should concentrate on the efficacy of duplex scanning in guiding clinical decisions.[38]

CFDS allows for monitoring bypass grafts

It is well established that an important cause of early infrainguinal graft failure is the development of asymptomatic graft-related stenoses that progress to occlusion. It is certainly well accepted that

duplex studies represent a more accurate method for localizing and assessing such lesions, more sensitively than relying on ABI.[39] If a graft stenosis is suspected, ultrasound imaging can guide whether angioplasty or surgery is required before occlusion/thrombosis occurs.[40]

Duplex scanning has achieved an established and continually expanding role in the management of PAD. Its routine use in patient evaluation allows rapid and safe assessment of a wide spectrum of lower limb vascular conditions. The diagnostic accuracy of lower limb duplex scanning is similar to contrast angiography and superior to MRA for defining arterial anatomy in patients undergoing revascularization. With the ever increasing endovascular therapies available, duplex arterial testing is ideally suited to identify lesions appropriate for percutanous transluminal angioplasty (PTA) and then monitor procedural adequacy.

Whilst the role of duplex scanning has been recognized as a preprocedural diagnostic imaging tool for detecting and grading the degree of occlusive disease of the lower limbs, the ultimate purpose is to establish the appropriate therapeutic strategy, either surgical or endovascular, for the PAD patient.

PREVENTION AND NON-INVASIVE TREATMENT OF PAD

General principles of prevention of atherosclerosis

Primary prevention of atherosclerosis-related CVDs refers to behaviours and pharmacologic intervention that may alter or delay the onset of disease, thereby reducing the absolute risk and leading to a more favourable health outcome. **Secondary prevention** involves the same procedures for reducing the progression of disease and recurrent events. A sharp distinction between primary and secondary prevention of CVD may be unrealistic, in part due to how we define “primary” prevention.[41] It is possible to detect early disease, which is often asymptomatic.

These patients may benefit from aggressive medical risk factor medication, whereas the asymptomatic disease-free patient will not.

Within the framework of primary CVD prevention, two main approaches are identified: the *population strategy*[42] and the *high-risk individual approach.*[43] The two strategies are certainly *complementary* to each other.

Population strategy in the primary prevention of cardiovascular diseases

The population strategy aims at reducing CVD incidence at the population level through lifestyle and environmental changes targeted at the population at large. This strategy is primarily achieved by establishing ad-hoc policies and community interventions.

The first step is to stress the extent and importance of CVD at the population level as a whole and in its at-risk subgroups. The implementation of broadly-based prevention programmes should include the highest possible number of different organizations whose missions concern CVD prevention. The strategic model of the population approach should be designed to reduce behavioural risk factors. Such a model should include methods for monitoring, education and advice, the provision of health care services and the appropriate legislation/policies in various social circumstances, as well as an appropriate organizational partnership.[44]

High-risk individual approach in the primary prevention of cardiovascular diseases.

Historically, the traditional guidelines on CVD prevention were focused on the assessment of different major risk states, mainly smoking, high blood pressure and high blood cholesterol, with an emphasis on the treatment of individual factors.

In clinical practice we deal with the individual patient(s) and not only with one or more risk factors. The simultaneous effects of several risk factors can have a synergistic detrimental effect. This

creates the conceptual basis for understanding CVD risk and its intervention.[45] As lifestyle and CVD risk factors differ among ethnicities, cultures, genders and age groups, an accurate risk assessment model is the critical first step for guiding appropriate use of testing, lifestyle counselling resources, and preventive medications.

In accordance with most modern CVD prevention guidelines, the individual should be assessed for the total absolute CVD risk based on risk factors and the presence of disease states known to increase CVD risk (e.g. DM, chronic renal disease, and/or markedly raised individual major CVD risk factors, such as age, gender, smoking status, blood pressure, blood cholesterol, etc.).[41, 45-49]

According to the most recent joint European CVD prevention guidelines.[41] decisions on the type and intensity of intervention(s) are based upon one of four major groups, according to their estimated (calculated) level of absolute total CVD risk:

Very high risk:

- Documented CVD of any type including PAD
- Diabetes with one or more risk factors or end organ damage.
- Severe chronic renal disease.
- A calculated absolute risk according to different risk charts of >10% score, or >40% Framingham score.

High risk:

- Markedly elevated single risk factors (dyslipidemia, severe hypertension).
- Diabetes without risk factors or end organ damage.
- Moderate chronic renal disease.
- A calculated risk according to different risk charts of 5-10% SCORE, or 20-40% Framingham score.

Moderate risk:

- A calculated risk according to risk charts of 1-5% SCORE, or of 10-20% Framingham score.
- Many middle-aged subjects belong to this category.

Low risk:

- A calculated risk according to risk charts <1% SCORE and/or <10% Framingham score, and free of any qualifiers that would put them at moderate risk.

Measures for prevention of PAD

Antiplatelet drugs for prevention of PAD

The use of any treatment for primary prevention specifically refers to that treatment's effectiveness in avoiding serious events prior to the patient developing clinically evident PAD. Most patients with asymptomatic PAD are identified on the basis of a physical examination revealing diminished or absent pulses, confirmed by an ankle-brachial index (ABI) < 0.90. The prognosis of patients with PAD is predominantly based on their increased risk of cardiovascular ischaemic events due to concomitant CAD and cerebrovascular disease.[50-52] Prior guidelines have recommended platelet inhibiting agents in patients with asymptomatic PAD.[53, 54] These recommendations derived from extrapolation based on the increased risk of developing PAD, observed in the years prior to the use of statins, ACE inhibitors, and the more effective use of antihypertensive drugs in the at-risk patients. Additionally, the observation that long-term aspirin use has been associated with a decrease in cancer mortality[55] was considered by the committees writing prior guidelines.[54]

The Antithrombotic Trialists' Collaboration study[56] showed a significant reduction in cardiovascular events in symptomatic patients with PAD who were randomized to platelet inhibition versus placebo. However, two trials randomizing patients with asymptomatic PAD to aspirin versus placebo showed no benefit in those receiving aspirin.[57] One needs to be cautious as to whether the

patients in these two trials can be generalized to all asymptomatic patients detected by most physicians since the definition of PAD varied in these two studies. The Prevention Of Progression of Asymptomatic Diabetic Arterial Disease (POPADAD) study enrolled subjects with an ABI ≤ 0.99, whereas the Aspirin for Asymptomatic Atherosclerosis trial enrolled patients with an ABI of ≤ 0.95. Furthermore, Fowkes et al. calculated the ABI using the lower of the two pedal pressures at the ankle.[58] Both of these studies may not be generalizable to the entire asymptomatic PAD population and may underestimate the true cardiovascular risk.

The evidence supporting the use of platelet inhibitors for primary prevention in patients with PAD is weak. However, PAD patients are known to have increased cardiovascular risk compared to patients without PAD. Integration of other cardiovascular risk factors when evaluating patients with asymptomatic disease appears appropriate for selecting PAD patients likely to benefit from platelet inhibitors for primary prophylaxis.[59]

The results of investigations of the efficacy of antiplatelet drugs in secondary prevention of PAD are also equivocal. A meta-analysis comprising 287 studies compared the efficacy of antiplatelet therapy in high-risk patients with vascular diseases, including lower extremity PAD.[56] Among those patients with PAD treated with antiplatelet therapy, there was a 23% relative risk reduction ($P < .004$) of adverse cardiovascular events, including myocardial infarction, stroke, or vascular death. Similar benefits were observed in patients with IC, those having peripheral PTA, and those having a peripheral bypass graft. However, only one third of the patients included were treated with aspirin at different dosages.

A meta-analysis of randomized trials of the efficacy of aspirin for the prevention of cardiovascular events in patients with PAD investigated the effect of aspirin on cardiovascular event rates in patients with PAD only.[60] The analysis included 18 prospective randomized trials of aspirin therapy with or without dipyridamole. The results of this meta-analysis demonstrated that for patients with

PAD, aspirin therapy alone or in combination with dipyridamole did not significantly decrease the primary endpoints of cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death). Only a significant reduction in non-fatal stroke was observed. However, in spite of contradictory results aspirin remains the first line antiplatelet drug in secondary prevention of PAD. The recommendations below use the Grade and level of evidence as described by Guyatt et al.[61]

Recommendation 1: For patients with asymptomatic PAD, and at least one additional risk factor, 75-100 mg aspirin daily is suggested over no aspirin therapy (Grade 2, Level of Evidence C).

Comment: If aspirin is taken for a decade or more, there will be a slight reduction in overall mortality. In asymptomatic PAD patients, the reduction in myocardial infarction and stroke is likely to be offset by an increase in major bleeding unless the asymptomatic PAD patients have additional high-risk factors.

Recommendation 2: Antiplatelet therapy is indicated to reduce the risk of myocardial infarction, stroke, or death in individuals with symptomatic atherosclerotic PAD (Grade 1, Level of evidence A).

Comment: The Antithrombotic Trialists' Collaboration meta-analysis showed that antiplatelet drugs reduce the incidence of vascular death, myocardial infarction and stroke by 23%.

Smoking cessation. Observational studies have shown that the risk of death, myocardial infarction and amputation is substantially greater and patency rates of lower extremity angioplasty and open surgical revascularization are lower in subjects with PAD who continue to smoke, than in those who stop smoking.[62, 63] It was also shown that walking distance is greater in patients who stop smoking than in current smokers.[64] Further, smoking cessation is associated with a rapid decline in the

incidence of claudication, which equates to that of non-smokers after 1 year of smoking cessation.[65] Smokers should be advised to stop smoking and be offered smoking cessation programmes. Nicotine replacement therapy and bupropion or varenicline can facilitate cessation.[66] With pharmacological interventions smoking cessation rates of approximately 30% are achieved in the general population of smokers.[67] Varenicline, a nicotine receptor partial antagonist, has been shown to be superior in comparison to nicotine replacement and bupropion.[68] Tobacco cessation programmes are particularly important in individuals with thromboangiitis obliterans, because tobacco may be causative in the pathogenesis of this syndrome.

Recommendation: All patients who smoke should be advised to stop smoking (Grade 1, Level of evidence B).

Comment: Smoking is one of the most important risk factors for PAD and smoking increases the risk of the disease two to six-fold.

Statins. The use of statins in PAD is an actual issue and has been frequently addressed. As the presence of PAD is strongly correlated with the presence of other manifestations of atherosclerosis, statin therapy in patients with PAD could theoretically improve morbidity and mortality from cardiovascular disease (CVD), without directly affecting the peripheral arteries. The Scandinavian simvastatin survival study (4S) showed a reduction of 38% in the incidence of new or worsening symptoms of IC among patients receiving simvastatin during a 5.4 year follow-up.[69] The heart protection study found a 16% relative reduction in the incidence of a first peripheral vascular event, independent of baseline LDL.[70]

Studies looking into stabilization or regression of atherosclerotic plaque found a consistent positive relationship with statin therapy.[71] Furthermore, carotid intima–media thickness significantly improved after 8 weeks of low doses of atorvastatin (20 mg).[72]

The Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol 6-HDL and LDL Treatment Strategies in atherosclerosis

(ARBITER-6 HALTS) study showed that the addition of niacin to statin therapy, compared to ezetimibe plus statin therapy resulted in significant regression of carotid intima–media thickness;[73, 74] On the other hand, the recently released results of the AIM-HIGH trial showed no additional benefit in reducing cardiovascular morbidity and mortality for patients who received niacin.[75]

Regarding improvement in walking distance, some papers that examined this issue prospectively in patients with IC found a modest, though significant improvement in treadmill time when a statin (simvastatin or atorvastatin) was added.[76]

A retrospective study by McDermott et al. found that in nearly 400 patients with IC, the use of statins was independently associated with a modestly superior 6-min walk performance compared with non-use of statins.[77] This relationship was present regardless of serum cholesterol levels, supporting the hypothesis that the benefits of statins go beyond their lipid-lowering properties. Several investigations during recent decades have demonstrated that statins can improve endothelial function, stabilize the atherosclerotic plaque and decrease vascular inflammation[78] probably explaining the improved exercise capacity shown previously.

A recent exhaustive report from the ACCF/AHA on the management of patients with PAD strongly recommends treatment with statins for cardiovascular risk reduction.[79]

A better understanding of the interaction between endothelial dysfunction, inflammation, hyperglycemia, dyslipidemia and the individual's exercise capacity may ultimately result in a more rational use of statins for PAD.

Recommendation: Patients with PAD should have LDL cholesterol levels < 2.5 mmol/L (< 100 mg/dL) (Grade 1, Level of evidence B).

In patients with atherosclerosis involving other vascular beds or at very high risk of ischemic events more aggressive LDL – cholesterol lowering to < 1.75 mmol/L (<70 mg per dL) is needed (Grade 1, Level of evidence B).

Comment: Statins reduce the risk of mortality, cardiovascular events and stroke in patients with PAD, with or without CAD.

Drugs for symptomatic treatment of PAD

Vasoactive substances

The pharmacotherapy of IC has been controversial. Numerous previously recommended vasoactive drugs were reconsidered and found to be without sufficient evidence of efficacy.[21]

Drugs with evidence obtained from randomized controlled trials are generally not accepted. They are often disqualified by the low difference of the mean improved walking distance in comparison with placebo.[21] But in this case it is questionable to discuss them as a parameter, because the statistical evaluation of clinical tests is different and based on comparison of paired values obtained before and after treatment. However, clinical use of vasoactive drugs is not so disappointing or ineffective. Patients successfully treated by these substances never express their condition in terms of mean prolongation of walking distance in comparison with placebo and many of them are satisfied and without walking limitations. Recently diagnosed patients especially respond well to vasoactive drugs. In our experience only 20-30% of patients with IC are indicated later for revascularization because of the insufficient effect of pharmacotherapy. Of course, pharmacotherapy has practically no chance of success in patients with long-lasting IC, after repeated revascularization and reocclusion, or in those without the possibility of any intervention and with exhausted functional reserves.

The list of currently recommended drugs is rather short. At present, according to consensual documents and guidelines,[21, 80-84] there are only two drugs with proof of efficacy; cilostazol and naftidrofuryl. Cilostazol is an inhibitor of phosphodiesterase type 3, with two main actions, inhibition

of platelet aggregation and vasodilation. A meta-analysis of randomized controlled trials involving more than 1,751 patients confirmed improvement of walking distance after cilostazol.[85]

In a controlled study comparing cilostazol to pentoxifylline, cilostazol was effective while the second substance was not different from placebo.[86]

In spite of its leading position in the guidelines, cilostazol is not distributed in all countries.[21] Another accepted treatment supported by recommendations is naftidrofuryl.[83] This substance is a 5-hydroxytryptamine type 2 antagonist with main effects on muscle metabolism and erythrocyte and platelet aggregation. In a meta-analysis of this Cochrane database systematic review, including more than 1200 patients, naftidrofuryl was found to be statistically and clinically effective in improving walking distance in the six months after initiation of therapy at a dosage 200 mg of taken three times a day.

Drugs classified as not recommended are more numerous, as a result of insufficient evidence of their clinical utility in claudication. Many previously used and recommended treatments are at present not supported by international consensus: these include pentoxifylline, isovolemic hemodilution, antithrombotic agents, L-arginine, ketanserin, oral prostaglandins, buflomedil, defibrotide, vitamin E, chelation therapy, omega-3 fatty acid, and ginkgo-biloba.[21] Also most arteriolar vasodilators (alpha-blockers, direct-acting vasodilators, beta-2-adrenergic agonists, calcium channel blockers) have been shown to lack clinical efficacy. However, encouraging results supporting their clinical utility were obtained with respect to angiotensin-converting enzyme inhibitors[84] and lipid lowering drugs.[77] Further studies are necessary to determine the clinical benefits of their administration in this respect.

Recommendation: In patients with IC with symptoms affecting life style activity symptomatic treatment with drugs may be considered (Grade 2, Level of evidence A).

Comment: Several drugs were claimed to increase walking distance in patients with IC. However, objective documentation of such an effect is limited for cilostazol and naftidrofuryl.

Physical training

Effects and indications

Physical training is universally recognized as the most efficacious means for improving walking capacity in patients with PAD. Combined with risk factor modification and pharmacological treatment, it offers the possibility of changing the clinical course of PAD.[87]

The goals of comprehensive prevention strategies including exercise are threefold:

1) to reduce limb symptoms;

2) to improve general exercise capacity and prevent or lessen physical disability;

3) to decrease the occurrence of cardiovascular events.

The benefits and possible mechanisms include improvements in endothelial function, skeletal muscle metabolism and blood viscosity. Exercise training may also improve leg blood flow and oxygen delivery, but the observed changes are inconsistent and not generally correlated with the training response. In addition to hemodynamic and metabolic mechanisms, improved biomechanics of walking also contribute to increased walking ability by decreasing the oxygen requirements to sustain a given level of constant load exercise.[88]

Many studies have also documented an improvement in general physical capability with a reduction in heart rate, respiration and oxygen consumption with the same work load. Patients acquire the capacity to walk for longer distance and duration at higher speeds.[89, 90]

The optimal exercise programme for improving walking ability in persons with PAD includes intermittent walking to near-maximal pain during a regimen of at least 6 months.[91] Exercise training markedly improves walking ability in PAD patients with IC, while strength training is less effective

than treadmill walking.[92] The utility and efficacy of physical training has been confirmed by several systematic reviews.[93]

The improvement in walking capacity is independent of the presence of associated risk factors such as smoking, DM and other concomitant pathologies.[94-96] Smoking adversely affects exercise capacity in PAD patients, whereas the presence of CAD, DM and other medical problems has a relatively minor impact on exercise capacity.[97] However, smokers with IC are prime candidates for exercise rehabilitation because their relatively low baseline physical function does not impair their ability to regain lost functional independence to levels similar to nonsmoking patients with PAD.[96] Recent evidence demonstrates the benefits of exercise training even among those patients with PAD who do not have claudication. While all studies showed exercise-related improvements of physical capacity, in clinical practice the use of physical training in patients with IC remains low, and with very high variability in the degree of benefit.

How intensive should training be to prevent harmful effects?

Exercise protocols have great variability and they are often unclear concerning the working load. This leads to controversy and confusion regarding the rehabilitation of IC patients. The crucial point is *when* and *at what work load* should exercise be stopped during a single training session.

The literature reports two different opinions, which can be summarized as follows: use an aerobic load and stop exercise before claudication pain; or, reach (or exceed) the pain threshold because ischemic hypoxia is the most potent vasodilator stimulus to increase the blood flow and muscle perfusion. These different opinions and proposals result in a variety of protocols being adopted and heterogeneity of results (as reported by the two main relevant meta-analyses showing an improvement in walking capacity between 70% and 230%.[98, 99]

The majority of papers and guidelines suggest encouraging exercise *to near-maximal pain* [88] and the TASC 2nd Consensus Document indicates that pain during exercise is predictive of the best results.[21] On the other hand, several aspects conflict with the concept of walking near maximal pain. First of all it should be recalled that it has never been demonstrated that physical training increases local arterial inflow. In contrast, it has been demonstrated that walking capacity increases significantly without resting blood being changed.[100] [101]

Secondly, we should note that maximal exercise worsens most microcirculatory parameters. It has long been known that hematocrit, fibrinogen, blood viscosity and erythrocyte deformability worsen significantly during maximal exercise in trained athletes, while submaximal exercise does not induce clinically and statistically significant improvement.[100] More recent studies have confirmed these data, showing that maximal exercise worsens endothelial function,[102] increasing the levels of free radicals,[103] the expression of leukocyte adhesion molecules,[104] and inflammatory activation.[105-107] Moreover, in patients with severe claudication, markers of inflammation increase during maximal exercise and during the recovery phase,[108]

A recent study reported that maximal exercise increased the expression of proangiogenic marrow-derived progenitor cells (PPCs). However, training (walking until moderate claudication pain) attenuates this expression profile of PPCs. These observations suggest that physical training remains the treatment of choice in patients with IC.[109]

Physical training in patients with IC should use only aerobic exercise, without reaching *near maximal pain*. Further, it is advisable to suggest endurance exercise and a moderate workload, between 60% and 70% of the absolute claudication distance.[110] In fact, despite the definition of near maximal pain, if we look carefully at individual papers, we find that patients are encouraged to walk up to the onset of mild or moderate pain intensity. In Hiatt's protocol, the patient walks up to the appearance of mild to moderate pain and then rests until the pain subsides.[111] The TASC 2nd

consensus document, despite the general statements first mentioned, also recommends that the patient stops exercise at the appearance of mild to moderate pain, always avoiding excessive fatigue and discomfort.[21]

Finally, to definitively refute the theory of overstated hypoxia, Gardner et al. recently demonstrated the lack of difference in outcomes on adopting a training programme with either a high (80% of the walking capacity) or low (40%) intensity.[112] All these data clearly indicate that the best workload in training of patients with IC should be aerobic and submaximal. For this reason, the c*onsensus document on the management of IC* of the Central European Vascular Forum[92, 113] proposed the use of a protocol providing a workload with a single well-defined fraction of training (60-70% of maximum walking capacity measured during the test) which is near maximal pain, but without reaching claudication pain.

Supervised versus non-supervised physical training

Supervised exercise programmes markedly improve walking ability in PAD patients with IC, and have been recommended as first line therapy for treatment of claudication.[114] Besides walking ability, it improves peak oxygen consumption, and the quality of life. A training regimen based on treadmill walking produces better functional outcomes when compared with strength training.[90, 93]

A meta-analysis performed in 1995 that included uncontrolled trials suggested the clinical efficacy of exercise in ameliorating claudication symptoms, indicating that supervised exercise increased pain-free walking distance by 180%.[90]

A rigorous systematic Cochrane review, including only controlled clinical trials encompassing 22 studies with over 1200 participants, compared supervised exercise programmes with usual care in the treatment of IC and concluded that supervised exercise training was superior to non-supervised exercise.[93]

Another review in 2010 confirmed that supervised programmes are superior to unsupervised ones, with significant increases in peak walking time and pain-free walking.[115] The differences between supervised and unsupervised training may be related to better patient adherence and the greater intensity of treadmill exercise compared to normal walking.

A randomized controlled trial compared supervised treadmill training to strength exercises and usual care.[91] Both treadmill and strength exercise training improved physical functioning-associated quality of life measures. However, these good results were not associated with a change in daily physical activity as measured by an accelerometer. Perhaps additional behavioural interventions are needed to attain such increases.

Similar results were shown in the CLEVER study, in which the peak walking time was higher in supervised exercise patients than in those revascularized by stenting.[116] The latter, however, showed a better performance in daily walking. The reason for this behaviour might be a different perception of the two treatments by the patient. Training might have felt like a chronic treatment which is repeated over time, and the slow improvement over time not appreciated while stenting may have been perceived as more definitive and conclusive, with an immediate appreciation of improved ambulation (although not sustained).

Considering all the available data, the consensus document on the management of IC of the Central European Vascular Forum[92, 113] in accordance with the American College of Cardiology/American Heart Association 2005 practice guidelines for the management of patients with PAD,[117] suggests for patients with mild IC the simple advice to walk independently for at least thirty minutes a day, reserving the supervised training programme for patients with moderate or severe IC. After the supervised training programme, walking capacity should be checked every month by the patient himself, consulting with the specialist in case of worsening.

A supported home exercise programme (exercise diaries, weekly phone calls) may provide an acceptable alternative for many patients for whom the financial and time demands of attendance at highly supervised, hospital-based programme may preclude participation. A highly structured home programme resulted in improved functional capacity and quality of life benefits, although these were less than in those following supervised hospital-based exercise.[118] Among patients with PAD, self-directed walking exercise performed at least 3 times weekly is associated with significantly less functional decline during the subsequent year.[87] In any case, it is advisable that a home programme is preceded by serial supervised training to learn how to walk in the most useful way in relation to their disability, following the style utilized at the hospital.

Recommendation: In patients with PAD, particularly in those with IC, supervised exercise therapy is indicated (Grade 1, Level of evidence A). Non-supervised exercise therapy is indicated when supervised therapy is not available (Grade 1, Level of evidence C).

Comment: In patients with PAD physical therapy is effective in improving symptoms and increasing exercise capacity. Supervised exercise therapy is more effective than non-supervised.

Conservative treatment for Critical limb ischemia (CLI)

Critical limb ischemia (CLI) is the most advanced stage of PAD of the lower limbs. It is clinically defined as the presence of continuous rest pain for at least two consecutive weeks with or without ulcers and gangrene[21, 117, 119] Limb revascularization is the first treatment option that reduces limb amputations and the mortality of CLI patients.[119] Despite progress in revascularization (endovascular, surgery, hybrid) and anesthesiological procedures, today there are still some patients who are considered poor candidates for revascularization.[120, 121] In these patients conservative treatment could be the preferred option. Currently conservative treatment consists of a multidrug therapy such as analgesic medications, antiplatelet drugs (aspirin, ticlopidine, and clopidogrel),

atherosclerotic risk factor modification, wound treatment and intermittent pneumatic compression.[122-125]

Prostanoid infusions have shown beneficial effects on the microcirculation, and were used since the 1990s for limb salvage of non-revascularizable CLI patients.[126-129] Recently studies have shown that prostanoids failed to reach a significant limb salvage rate, providing only some benefits for CLI patients such as pain reduction and improvement of ischemic skin lesions.[130] However, prostanoids have remained the only specific drugs for the treatment of CLI, because gene therapy has not achieved good results in reducing amputations.[131, 132] and cell therapy needs more robust results.[133] Other types of non-pharmacological conservative treatment such as spinal cord stimulation and hyperbaric oxygen therapy, despite being used in selected patients with good results, have not shown significant benefit.[21, 117, 119]

Accurate screening of patients is an important factor in reducing the number of amputations and deaths associated with conservative treatment. A vascular surgeon, interventional radiologist and angiologist, after accurate examination of non-invasive and particularly invasive imaging studies (selective limb angiography) and multi-disciplinary clinical discussions, should careful assess the indication for conservative treatment.[123] Conservative treatment of CLI should not be performed for CLI patients who present with severe and unrecoverable skin lesions that need an immediate limb amputation. [21, 119] Conservative treatment should be performed in vascular centres that can offer the patients prompt bed availability and all the possibilities of immediate limb revascularization in case of CLI worsening.[123] Usually patients amenable to conservative treatment need repeated infusion of prostanoids during a span of a year. Pain scale, wound treatments and transcutaneous pressure of oxygen (TcpO2) assessments should be performed to monitor the patient. Continuous clinical surveillance should be available with on-call service. If rest pain persists without relief or worsens, limb revascularization should be reconsidered.[123]

Recommendation: In patients with CLI, revascularization is indicated whenever feasible. If revascularization is not possible, prostanoids, antiplatelets and wound treatment is indicated (Grade 2, Level of evidence B).

Comment: In patients with CLI unsuitable for revascularization the only drugs with some positive results are prostanoids. All other procedures are symptomatic.

The management of diabetic patients with PAD; are there some peculiarities?

Diabetic patients are at high risk of PAD characterized by symptoms of IC or CLI. PAD increases the risk of heart attack and stroke. An estimated 1 out of every 3 people with DM over the age of 50 has PAD.[134] Treatment of PAD in diabetic patients focuses on reducing symptoms and preventing further progression of the disease. Modification of lifestyle and effective management of established risk factors such as smoking (*smokers should be advised to stop smoking and be offered a smoking cessation programme such as nicotine replacement therapy, bupropion or varenicline*), dyslipidemia (*LDL cholesterol should be lowered to < 100 mg/dL, and optimally < 70 mg/dL*), hyperglycemia (*HbA1c level should be kept < 6,5%*) and hypertension (*blood pressure should be controlled to <140/90 mmHg*) to retard the progression of the disease and reduce cardiovascular events in these patients.[135] In most cases, lifestyle changes, exercise and claudication medications (*Cilostazol*) and statins are enough to slow the progression or even reverse the symptoms of PAD. The most effective treatment for PAD is regular physical activity: a programme of supervised exercise training is recommended. Newer risk factors such as insulin resistance, hyperfibrinogenemia, hyperhomocysteinemia and low-grade inflammation have been identified, but the advantages of modifying these novel factors in diabetic patients with PAD have yet to be proven.[3, 134] Intensive management of DM, including platelet aggregation control, decreases vascular complications over the long term. (Grade 1; Level of evidence A).[135] It

is noteworthy that the latest ATC meta-analysis of randomized control trials of aspirin therapy involving patients with DM and PAD demonstrated no benefit of aspirin in reducing cardiovascular events.[136] The new anti-platelet drugs prasugrel, ticagrelor and picotamide seem to be more effective than aspirin in PAD patients, particularly in diabetic patients with PAD.[137] Outcomes after revascularization procedures such as PTA and surgical bypasses in DM patients are poorer, with increased perioperative morbidity and mortality compared with that in non-diabetic patients. Amputation rates are higher due to the distal nature of the disease. Surgical intervention for moderate or severe infections is likely to decrease the risk of major amputation (Grade 2; Level of evidence B).[3] Therapeutic angiogenesis, on the other hand, represents a promising therapeutic adjunct in the management of PAD in these patients.[134] Efforts towards increasing awareness and intensive treatment of risk factors will help to reduce morbidity and mortality in diabetic patients with PAD.[138]

Recommendation 1: Patients with PAD and DM should have an annual screening with measurement of ABI (Grade 2, Level of evidence C).

It is recommended that all patients with PAD and DM who smoke be advised to stop smoking (Grade 2, Level of evidence A).

Recommendation 2: Patients with PAD and DM should have LDL-C lowered to 1.8 mmol/L (< 70 mg/dL) or by ≥ 50% when the target level cannot be reached (Grade 1, Level of evidence B).

Recommendation 3: Patients with PAD and DM should have their blood pressure controlled to < 140/90 mmHg (Grade 2, Level of evidence 1).

Recommendation 4: Antiplatelet therapy is recommended in all patients with symptomatic PAD and DM without contraindications (Grade 1, Level of evidence A).

AWARENESS AND UNDERTREATMENT OF PAD

In spite of the above, PAD is highly prevalent and carries a significant risk of morbidity and mortality. However, it is yet substantially under-diagnosed and undertreated.[139] As it was shown in the PAD Awareness Risk, and Treatment: New Resources for Survival (PARTNERS) program[140] less than 50% of physicians were aware of diagnosis of PAD of their patients. Also risk factors of atherosclerosis; hypertension, hyperlipidaemia and others were in PAD patients less frequently treated as in coronary patients. Antiplatelet medications were prescribed less often with new (53%) and prior PAD (54%) only than in those with other atherosclerotic disease (71%). The National health and nutrition examinations survey (NHANES) reported that 68% of patients with PAD had LDL cholesterol above target level (100 mg/dL or 2.5 mmol/L), and 46% had systolic blood pressure < 140 mmHg; 69.5% were not taking statins, 75.1% PAD patients were not taking ACE inhibitors and 61% of this group were not taking any antiplatelet agent.[141] Therefore, nationwide programs are needed to increase public and healthcare providers awareness about PAD and its association with other cardiovascular disease. These programs should improve detection and diagnosis of PAD, to educate patients and physicians, particularly primary care providers to share information on prevention and available treatment option.

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