Secondary event prevention and risk stratification in patients with stable peripheral arterial disease

Guidelines

summarising clinical guidelines for primary care

MGP Ltd identified a need for clinical guidance in this area and approached Bayer plc for an educational grant to support the development of a working party guideline.

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Secondary event prevention and risk stratification in patients with stable peripheral arterial disease

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Rationale

Cardiovascular disease (CVD) is a leading cause of mortality and morbidity worldwide[1,2] and is associated with a significant cost burden and effect on patient quality of life (QOL).[3] It encompasses coronary artery disease (CAD), stroke/transient ischaemic attack (TIA), and peripheral arterial disease (PAD), and their respective manifestations. Moreover, there is a clear overlap between the three vascular beds of stroke/TIA, CAD, and PAD, and disease in one bed increases the likelihood of disease developing in another (i.e. polyvascular disease).[2,3] Polyvascular disease is associated with an increased risk of vascular death, non-fatal myocardial infarction, non-fatal stroke, and subsequent cardiovascular (CV) events. According to data from the REACH database, individuals with atherothrombosis are likely to have several risk factors for vascular disease including hypertension (~80%) and hypercholesterolaemia (~70%) as well as, to a lesser extent, obesity (26%) and current smokers (14%).[3] Lifestyle modifications and appropriate therapies can reduce the incidence of CVD and vascular events, but these interventions are often underused[4] with many patients failing to achieve their treatment goals.[3,5] As the main risk factors for vascular disease are generally modifiable, improved prevention, identification, and treatment of co-morbidities is likely to improve outcomes for patients as well as reduce costs to society and the health service.[3,5]

PAD is associated with a three to four-fold increased risk of other CVD including myocardial infarction and/or ischaemic stroke even in asymptomatic patients,[6] and most patients with PAD are unlikely to present with obvious symptoms.[7] As PAD progresses, quality of life becomes increasingly impaired due to reduced mobility, pain, and tissue loss from ulceration. Ultimately gangrene can develop and limb amputation may be necessary.[6]

This guideline has been developed to provide guidance for healthcare professionals in primary care on risk stratification and prevention of secondary events in patients with stable PAD. This document provides information on:

- identification of at-risk patients
- interventions to reduce risk
- pharmacological and non-pharmacological treatment options
- when to refer
- monitoring and review.

Box 1: Initial assessment of patients at risk of PAD

- Clinical examination
- Height and weight
- Blood pressure
- Peripheral pulses
- Radial pulse rhythm
- State of the skin (e.g. ulceration, colour, hue, temperature, hair loss, gangrene/necrosis, loss of sensation, evidence of ischaemic change)
- Baseline blood tests (for example, to identify diabetes, impaired glucose tolerance, or chronic kidney disease, as well as assessment of biochemistry and haematology).

Identification of at-risk patients

- PAD may be suspected based on (see Box 1):
  - the presence and severity of limb pain or claudication (cramping/aching pain mainly in the calf, but may be in the buttock, thigh, and rarely the foot; comes on after a degree of exercise and eases with rest; not affected by body position and recurs with the same degree of exercise)
  - critical limb ischaemia
  - examination of the femoral, popliteal, and foot pulses
  - muscle wasting
  - hair loss.

A patient may present for an initial assessment of symptoms suggestive of PAD, for a new condition that is unrelated to PAD and the patient has risk factors for PAD or CVD, or as part of a regular review for a different ongoing condition. These latter consultations provide an ideal opportunity to proactively identify patients with early stage PAD. This is an important consideration as around 60% of patients with PAD will have coexisting disease in another vascular bed[3] and earlier identification and treatment can improve outcomes. Healthcare professionals should be aware that some patients may have symptoms of PAD and have

accepted them without question and are therefore unlikely to mention the symptoms or proactively seek treatment despite interventions being available.

- Patients should be assessed for PAD if they have diabetes, non-healing wounds on the legs or feet; experience unexplained leg pain; are being considered for leg or foot interventions; need to use compression hosiery
- Suspected PAD can be identified by simple questioning and the patient referred for further testing if appropriate:
  - the ankle brachial pressure index test (ABPI) should be assessed when the patient is resting and ideally in a supine position. The systolic blood pressure should be measured in both arms using an appropriately sized cuff as well as in the posterior tibial, dorsalis pedis, and if possible in the peroneal arteries. The index in each leg can be calculated by dividing the highest ankle pressure by the highest arm pressure
- Patients should be questioned about CVD, diabetes, and chest pain as well as the presence of any muscular pains, any leg pain and/or claudication in the calf, thigh, and buttock when walking
- Patients should be assessed for PAD during routine review sessions and a suitable review frequency is annually
- PAD will often co-present with other conditions (chronic kidney disease (CKD), stroke, diabetes, CAD, hypertension) that may increase the risk of an event (see Box 2), especially ones affecting the vascular bed, and asking about PAD can be combined with other assessments
- Individuals with undiagnosed PAD could be identified in the community if awareness of this condition increased:
  - community pharmacists should be familiar with the symptoms of PAD and understand the importance of early identification and treatment as they are well placed to identify PAD, for example, by questioning patients about symptoms when they collect their prescription

Risk reduction

- NICE recommends that all people with PAD receive information, advice, support, and treatment regarding the secondary prevention of CVD in line with published NICE guidance, including:
  - smoking cessation—supported by nicotine replacement therapy (NRT) if required[8,9]
  - weight loss—if needed to achieve a healthy body shape in obese or overweight patients[8,9]
  - healthy diet and lifestyle modifications—including reducing alcohol consumption, if necessary; guidance on diet can be sought from NICE[8,9]
  - optimising glycaemic control—if the patient has diabetes, has impaired glucose tolerance (IGT) or is at risk of type 2 diabetes mellitus
  - prevention and management of high blood pressure

Box 2: Risk stratification in patients with PAD

In patients with PAD, the following factors increase the risk of an event and require more intensive management:
- increasing age
- the number of vascular beds involved
- history of previous events and intervention
- all sequelae/complications such as heart failure
- all concomitant risk factors—hypertension, CAD, diabetes, CKD, Stroke/TIA, obesity, smoking.

CAD=coronary artery disease; CKD=chronic kidney disease; PAD=peripheral arterial disease; TIA=transient ischaemic attack

Secondary prevention of CVD in patients with PAD

Non-pharmacological options

- A structured exercise programme is of paramount importance in reducing the symptoms of PAD[4,10]
- Where available, a 3-month structured and supervised exercise programme is recommended for all patients concurrent to pharmacotherapy:
  - the benefits of this intervention are considerable and need to be clearly explained to patients as it may be difficult to motivate them to participate especially if they are experiencing pain
- The use of lumbar sympathectomy to reduce ischaemic rest pain in PAD has been investigated, but limited data are available to support its use[10,11]

Pharmacological treatment options

Symptom alleviators

- The following treatments can be given to reduce symptoms of PAD and improve walking distance. These treatments should only be trialled after the patient has participated in a structured exercise programme:
  - naftidrofuryl 100–200 mg three times daily is the preferred option;[12] if there is no improvement in symptoms after 3–6 months of treatment with naftidrofuryl, treatment should be discontinued
  - cilostazol ▼ 100 mg twice daily (not recommended by NICE)[12,13]

Antithrombotic therapy

- All patients should receive antithrombotic therapy for prevention of CV events
- Patients with PAD should be offered antithrombotic therapy—potential options include:[10,14,15]
  - clopidogrel 75 mg once daily

  - aspirin 75 mg once daily
  - rivaroxaban▼ 2.5 mg twice daily in combination with aspirin 75 mg once daily
  - warfarin dose sufficient to maintain international normalised ratio (INR) in therapeutic range

- Clopidogrel is preferred to aspirin for secondary prevention of CVD in PAD based on data from the CAPRIE study[16]

- There is evidence that rivaroxaban and aspirin is an option for patients at increased risk of CVD[17] because of vascular disease in two or more vascular beds, poor glycaemic control, and/or diabetes (ongoing monitoring is needed because of the increased risk of bleeding episodes)

- If the patient is already receiving treatment with warfarin, this can be continued rather than switching the patient's prescription to clopidogrel (ongoing monitoring is needed because of the increased risk of bleeding episodes)

- If the patient has atrial fibrillation (paroxysmal, persistent, or permanent), treatment with warfarin or a direct-acting oral anticoagulant (dose according to product license) is recommended

Statins

- All patients should receive statin therapy for prevention of CV events

- Treatment with high intensity statins can reduce the level of low-density lipoprotein cholesterol by >40% and has been shown to have a beneficial effect on mortality and morbidity due to CVD.[9] Options include:[9,14]
  - atorvastatin 20–80 mg once daily
  - rosuvastatin (if atorvastatin is not tolerated) initially at 5 mg and titrated up to 20 mg once daily

- If the patient is not able to tolerate atorvastatin or is unwilling to take high-intensity statins, alternative approaches to lowering the patient's lipid profile may be necessary. These could include:
  - withdrawing statin treatment for 2 months and then re-introducing atorvastatin at 50% of the initial dose
  - switching to rosuvastatin (if atorvastatin is not tolerated) initially at 5 mg and titrated up to 20 mg once daily
  - or switching to a medium or low intensity statin

- The community pharmacist may be able to support statin adherence as this treatment will need to be taken for life

- There is no outcome evidence to support the use of other lipid-lowering agents or vitamin supplementation[9]

ACE inhibitors

- While not generally recommended for use in PAD, angiotensin-converting enzyme (ACE) inhibitors should be prescribed if a patient with PAD also has hypertension and/or diabetes. Treatment should be titrated up until a good response is achieved

- In the absence of co-morbid hypertension and/or diabetes, the use of ACE inhibitors in PAD remains controversial. Data from a meta-analysis of four randomised controlled trials showed modest improvements in pain-free walking distance associated with use of ACE inhibitors[7,18]

Beta-blockers

- The evidence to support the long-term use of beta-blockers in vascular disease is low and they are a relative contraindication in patients with severe PAD

- A vasodilating beta-blocker may be an option in patients who require one for other indications and have PAD

Practicalities of managing stable PAD over the long term

- Treatment of PAD may need to be adapted if disease progression occurs and/or if related conditions develop, such as poor glycaemic control, diabetes, and/or CKD

- Regular review of patients with PAD or at risk of developing this condition can be performed by a number of healthcare professionals (e.g., GP, pharmacist, new medicines service) and should be conducted annually:
  - is the person being reviewed for other conditions or treatments? If so, consider grouping individual reviews together as most patients will have polyvascular disease
  - blood samples for analyses including full blood count (FBC), estimated glomerular filtration rate (eGFR), thyroid stimulating hormone (TSH), and lipid profile
  - electrocardiography (ECG)
  - blood pressure
  - height and weight
  - heart rhythm
  - review modifiable risk factors
  - symptom assessment to monitor progression
  - adherence to treatment including non-pharmacological and/or pharmacological interventions; a community pharmacist can provide support if adherence is likely to be an issue
  - consider peripheral factors with potential to impact on behavioural change associated with long-term conditions, such as socioeconomic status, family/peer pressure, personal circumstances, depression, patient's perception of side-effects, readiness/motivation to change, depression, availability of services
    - consider undertaking a brief motivational interview

- Box 3 summarises key points to cover during ongoing and annual surveillance of patients with PAD

Box 3: Ongoing annual surveillance in patients with PAD

- Atorvastatin 80 mg once daily or rosuvastatin initially at 5 mg and titrated up to 20 mg
- Clopidogrel 75 mg once daily
- Systolic blood pressure aim for <130 mmHg
- Consider ACE inhibitor especially in patients with high blood pressure and/or T2DM
- Seek other evidence of cardiovascular disease, checking glycated haemoglobin, and asking direct questions about chest pain, palpitations, or orthopnoea
- If symptoms are deteriorating, review patient management according to algorithm

ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; PAD=peripheral arterial disease; T2DM=type 2 diabetes mellitus

Red flags and when to refer patients

Urgent referral

- Patients with signs of acute limb ischaemia require urgent referral; symptoms include:
  - pain
  - pallor
  - pulseless
  - perishing cold
  - paraesthesia
  - paralysis

- Patients with signs of critical limb ischaemia require urgent referral; symptoms include:
  - ulceration
  - gangrene
  - rest pain (usually pain in the foot when the legs are elevated, particulary at night)

Note: Ensure there are no signs or symptoms indicative of stroke/TIA. If necessary, consider administering the FAST test (facial drooping, arm weakness, speech difficulties, and time to call the emergency services)

Referral to secondary care for assessment

The decision on whether to refer a patient to secondary care should be based upon an assessment of the patient's QOL and whether they have complied with the structured exercise programme, made the suggested lifestyle changes, and have adhered to the prescribed medications. Together these measures should be able to control symptoms and improve QOL for most patients and often the risk from surgical intervention outweighs its benefits.

- Patients who present with the following or who have these conditions identified during an unrelated consultation should be referred to secondary care for assessment:
  - ischaemic rest pain
  - nocturnal pain
  - reduced claudication walking distance
  - tissue loss or minor injuries that may trigger critical limb ischaemia
  - foot wound that fails to heal
  - arterial ulceration over pressure areas (note: a venous or arterial ulcer over a pressure area may indicate arterial insufficiency or complication)
  - gangrene and/or tissue loss

Treatment pathway in primary care

The algorithm in Figure 1 summarises the treatment pathway for the management of PAD.

Summary

PAD is associated with a three to four-fold increased risk of developing other cardiovascular conditions, including some that are life-threatening. While PAD can be identified in some patients, most will not realise that they are affected by this insidious condition. In addition, others may have symptoms they have accepted and are unlikely to mention them to healthcare professionals or seek treatment.

PAD can be diagnosed in primary care by questioning the patient about cardiovascular co-morbidities and risk factors as well as the presence of any muscular pains, any leg pain and/or claudication in the calf, thigh, and buttock when walking. This assessment can be conducted if the patient presents with symptoms or proactively during other routine reviews as PAD will often co-present with other conditions, especially ones affecting the vascular bed.

Once a diagnosis of PAD has been made, the patient should participate in a 3-month structured and supervised exercise programme as well as receiving treatment for any co-morbid cardiovascular conditions and active management of cardiovascular risk factors through lifestyle changes. After the patient has completed the exercise programme, they should be re-assessed and prescribed naftidrofuryl 100–200 mg three times daily for 3-months if their QOL has not improved with exercise. Patients should receive antithrombotic and statin therapy for prevention of CV events.

Patients should be reviewed annually to monitor symptoms and assess quality of life. Most patients can improve their QOL or at least maintain this with these approaches and, while surgical intervention is an option, often the risk outweighs the benefits.

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Conflicts of interest

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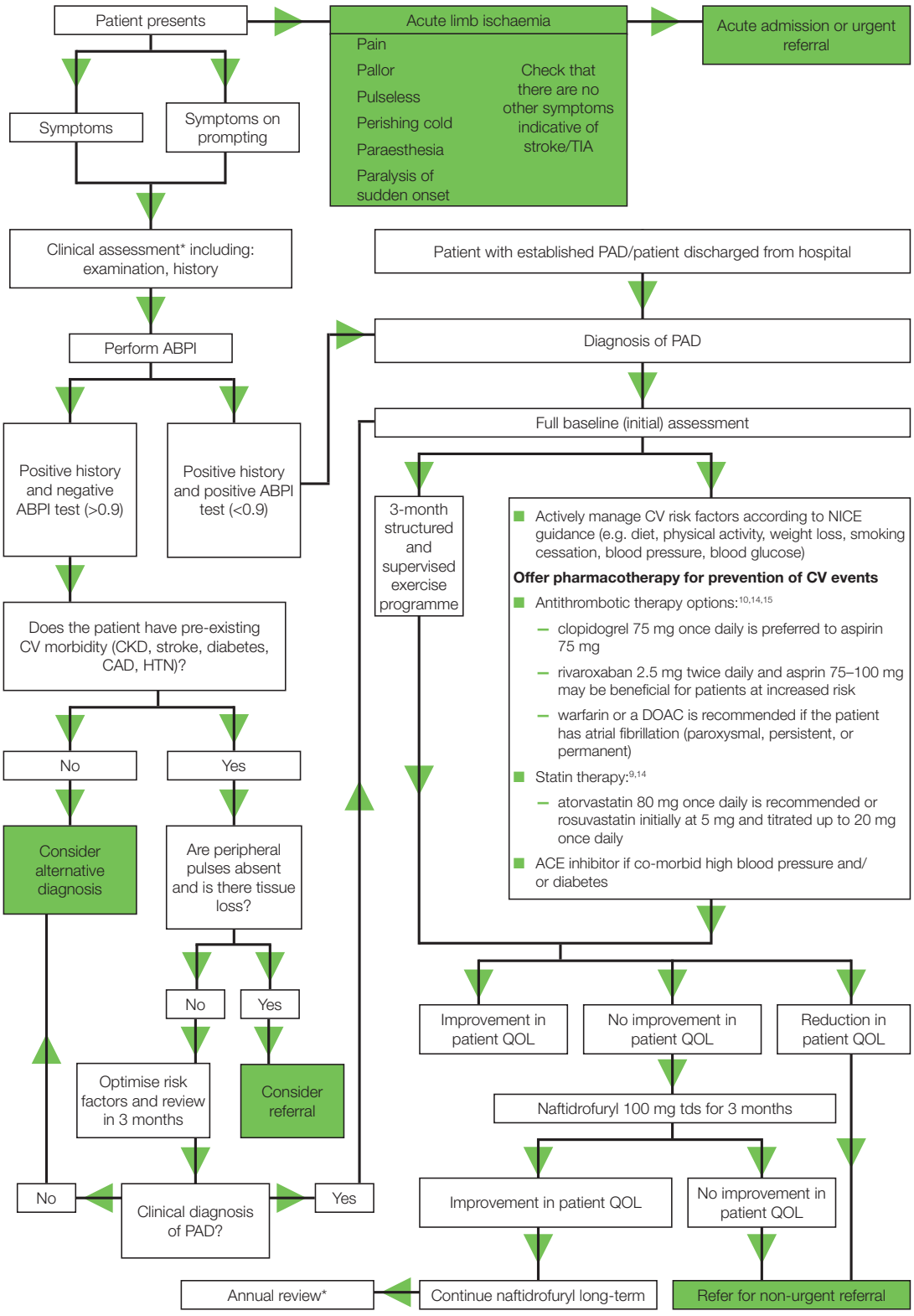
Figure 1: Treatment algorithm for stable PAD



* The annual review can be specifically for PAD or may be conducted as part of a review for a separate condition.

ABPI=ankle brachial pressure index; ACE=angiotensin-converting enzyme; CAD=coronary artery disease; CKD=chronic kidney disease; CV=cardiovascular; CVD=cardiovascular disease; DOAC=direct-acting oral anticoagulant; HTN=hypertension; PAD=peripheral arterial disease; QOL=quality of life; tds=three times a day; TIA=transient ischaemic attack.

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