

## REVIEW

# Management of Hypertension in Peripheral Arterial Disease: Does the Choice of Drugs Matter?

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*Cardiovascular disease and death are major life-threatening problems in patients with atheromatous peripheral arterial disease (PAD). This review focuses on management of hypertension in the context of cardiovascular risk in patients with PAD. PAD is underdiagnosed and hypertension in PAD is often poorly managed. Current evidence supports a low threshold for blood pressure treatment in PAD and intensive blood pressure control to reduce the high risk of cardiovascular disease and death in patients with PAD. Optimal treatment targets should be <140/85 mmHg, with the lower target of <130/80 mmHg in the presence of diabetes mellitus or chronic renal disease. Class-specific selection of anti-hypertensive treatments in PAD should be based on caution in relation to co-existing renovascular disease and indications and contraindications based on other significant co-morbidity. There is a pressing need for primary end-point studies targeted specifically at patients with PAD. In particular, prospective studies in PAD are needed to obtain evidence for benefits from specific blood pressure classes of treatment as well as the optimal blood pressure treatment target level. These studies should consider impact in PAD of different demographic, risk factor, and co-morbidity profiles.*

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### Introduction

Hypertension is a key risk factor for the development of atheromatous peripheral arterial disease (PAD). In patients presenting with PAD, hypertension is a major associated cardiovascular risk factor, present in up to 55% patients with PAD.<sup>1</sup> Hypertension also increases risk of cardiovascular disease (CVD) complications and mortality in patients with established PAD. Up to 5% of hypertensive patients have been reported to have clinical evidence of peripheral artery disease at presentation, with a marked age-related increase in hypertension associated PAD.<sup>2</sup> The main aim of this review is to consider choice of treatment in the management of hypertension in patients with PAD.

### Level of evidence

A major limitation of the literature on this topic is that the evidence largely derives from sub-groups with PAD studied within major outcome trials for patients with high overall cardiovascular risk factor burden. There are no within treatment class comparisons of effects on PAD-related disease end-points.

### *Why worry about high blood pressure in peripheral arterial disease?*

Peripheral arterial disease is a manifestation of systemic atherosclerosis that is common and often under-diagnosed, and yet is associated with a high risk of death and disabling ischaemic events. Patients with PAD are at risk of blood pressure-attributable progression of the peripheral vascular problems. PAD is also an independent predictor of increased risk of cardiovascular and cerebrovascular death, with high blood pressure a major reversible risk factor.<sup>3,4</sup>

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### *Hypertension and prevalence of PAD*

As for CVD, the major underlying risk factors for PAD are cigarette smoking, hypertension, abnormal lipid profile and diabetes mellitus.<sup>5–7</sup> Untreated hypertension, and treated but uncontrolled hypertension, are important risk factors for PAD, after adjustment for other risk factors, with around a doubling in odds ratio for presence of ABPI [ankle brachial pressure index] evidence of PAD, similar to the impact of previous smoking, diabetes mellitus, or mild renal failure.<sup>6</sup> Systolic blood pressure after multivariate analysis conferred an odds ratio for PAD of 1.3 (CI 1.2–1.5) per 10 mmHg systolic pressure.<sup>7</sup> It is important therefore to consider ABPI monitoring in older hypertensive patients especially those with cardiovascular disease.

### *Hypertension under treated in PAD*

Blood pressure management in PAD tends to be poor. In PARTNERS,<sup>5</sup> hypertension was less often treated in new (84%) and prior PAD (88%) compared to treatment of hypertension in subjects with CVD (95%;  $P < 0.001$ ). This poor management extends to treatment of other cardiovascular risk factors in subjects with PAD.<sup>5</sup>

### *Ethnicity, hypertension and PAD*

The GENOA study<sup>8</sup> reported that in older African-Americans, the prevalence of diabetes, hypertension and clinical PAD was higher and ABPI lower than in non-Hispanic white subjects. African-American ethnicity was a predictor of lower ABPI and clinical PAD after adjusting for age and hypertension. A higher prevalence of PAD in non-Hispanic black men and women, and Mexican-American women than non-Hispanic white men and women was reported in NHANES.<sup>6</sup> Higher risk ethnic groups should be assessed for presence of PAD and particular attention paid to managing cardiovascular risk factors in ethnic groups at higher risk of PAD.

### **Secondary Hypertension in Patients with Peripheral Arterial Disease**

It is important to identify possible underlying causes so that specific treatment may be targeted against causes of hypertension where identified. Atherosclerotic renal artery stenosis (RAS) is a common underlying cause of hypertension in PAD.<sup>9,10</sup> In a prospective

angiographic study of 629 patients with PAD, hypertension was found in 63% of the patients in the group with renal artery stenosis compared with 41% of controls.<sup>11</sup> There are large differences between studies in prevalence of RAS in PAD. One explanation is that some studies are retrospective. Geographical differences in ethnicity and risk factor burden may contribute, as may definitions of severe RAS, some reports using at least 50% others at least 60% stenosis as threshold definitions. As for other patients with hypertension, patients with PAD may have other secondary causes of hypertension including endocrine problems, such as primary hyperaldosteronism and diabetes mellitus.<sup>12</sup>

### *Renal artery stenosis and PAD*

There is controversy as to whether renal artery imaging should be routinely performed in patients with PAD and hypertension. PAD is an independent predictor of risk of vascular death however it is unclear whether aggressive treatment of patients with PAD and incidental RAS leads to clinical benefits.<sup>13</sup> A pragmatic approach is to image renal arteries in patients with hypertension and more severe PAD, or in patients with PAD and resistant hypertension and/or renal impairment, in particular when there is progressive decline in renal function. The incidence of RAS increases with increasing severity of PAD. After adjustment for age and hypertension, RAS incidence was 4 times greater in patients with 3–4 peripheral arteries affected.<sup>9</sup> Not all RAS is functionally significant. However RAS is a major contributory cause of hypertension in patients with PAD, prevalence dependent on severity of renal artery narrowing. Wachtell *et al.*,<sup>10</sup> using aortography in 100 patients with severe peripheral ischaemia found 81% [25/31] of patients with RAS had hypertension. 13/14 patients (93%) with a renal artery lumen reduction of >50% had hypertension ( $P \leq 0.001$ ) compared with 12/17 (71%) for renal artery lumen diameter reduced by <50%.

### **Lifestyle and Blood Pressure**

Lifestyle measures are effective in preventing development and reducing progression of hypertension.<sup>14</sup> In the absence of specific studies in PAD, it would be pragmatic to advise patients to adopt a multiple life style approach to management of hypertension in the context of overall cardiovascular risk. Reducing sodium intake below 100 mmol/day, combined with the Dietary Approaches to Stopping Hypertension (DASH) diet, is more effective than either approach alone in reducing both onset of hypertension and

blood pressure in patients with milder hypertension.<sup>14</sup> The DASH diet includes increased intake of fruits, vegetables, low-fat dairy foods, potassium, calcium, magnesium, dietary fibre and protein and includes whole grains, poultry, fish, and nuts. It also includes less red meat, sweets, and sugar-containing drinks than a typical Western diet.<sup>14</sup> Long term reduction in dietary salt intake by 30–40 mmol/day in patients with pre-hypertension reduced both blood pressure and cardiovascular events.<sup>15</sup>

#### *Diuretic-based treatment*

Mild distal tubular diuretics in younger and elder populations with uncomplicated hypertension reduce a wide range of CVD endpoints.<sup>16</sup> A thiazide was used within the INVEST Trial (see below) as add-on treatment, with evidence of overall endpoint benefit from intensive blood pressure lowering.<sup>17</sup> In patients taking thiazide treatment it is important to monitor blood glucose, uric acid, potassium and sodium levels to anticipate possible metabolic cardiovascular effects of treatment.

#### *Beta-blockers*

Although beta-blockers would be expected to worsen PAD by reducing muscle blood flow, there is no clear evidence of long-term disadvantage of beta-blocker treatment in PAD and some evidence that patients with concomitant coronary artery disease have better cardiovascular outcomes when treated with a beta-blocker. A meta-analysis of randomised controlled trials in PAD treated with beta-blockers reported no significant worsening of intermittent claudication or walking distance.<sup>18</sup> However when combined, atenolol and nifedipine reduced maximum walking distance by 9%, indicating the importance of context of beta-blocker treatment.<sup>19</sup> A capillary microscopy study<sup>20</sup> reported no microcirculatory or symptom differences between measurements obtained before and during withdrawal of beta-blocking therapy, and again 2 weeks after re-introduction of beta-blocker treatment in patients with intermittent claudication or ischaemic rest pain and mild-moderate hypertension. Beta-blocking drugs appear to be cardioprotective in patients with PAD however evidence is largely from observational or unblinded randomised studies. Polde-mans *et al*<sup>21</sup> studied patients with abnormal stress echocardiography who were undergoing elective abdominal aortic or infra-inguinal arterial reconstruction. Patients were randomised to receive standard care alone or with the addition of bisoprolol treatment to

beta-blockade with bisoprolol. Adding bisoprolol reduced cardiac death or myocardial infarction after surgery [0.30 (95% CI: 0.11–0.83)]. However the design was open and beta-blockade was prescribed for cardio-protection, not hypertension. A separate prospective observational study<sup>22</sup> reported that, in the survivors of myocardial infarction, patients with intermittent claudication not treated with beta-blockers had 3-fold mortality excess versus those receiving beta-blockers. There is clinical interest in potential advantages of beta-blockers such as nebivolol or carvedilol with the additional property of vasodilation mediated by nitric oxide release or anti-oxidant properties.<sup>23</sup> Double-blind, randomised controlled studies are needed to find to whether this additional mechanism confers end-point benefits over other types of beta-blocker in patients with PAD. It is unclear whether cardio-protection applies to beta-blockade targeted at hypertension in PAD, beyond that conferred by other blood pressure-lowering treatments.

Although there are concerns about new onset of diabetes mellitus with beta-blocker treatment,<sup>24</sup> it is currently recommended that beta-blockers should not be withdrawn in patients with compelling indications for beta-blockade, e.g. myocardial infarction or angina.<sup>25</sup> If blood pressure therapy is initiated with a beta-blocker and a second drug is required, BHS/NICE guidelines<sup>25</sup> recommend adding a calcium-channel blocker rather than a thiazide-type diuretic to reduce the patient's risk of developing diabetes. When a beta-blocker is withdrawn, the dose should be reduced gradually to avoid a rapid increase in sympathetic drive.<sup>25</sup>

#### **Calcium Channel Blocker [CCB] Treatment**

Major options are dihydropyridines, which vasodilate and increase renal sodium and water excretion and the cardioselective CCBs diltiazem and phenylalkalamine verapamil, which vasodilate, and reduce cardiac output by reducing heart rate and force of cardiac contraction. In the VALUE Trial the primary outcomes were cardiac morbidity and mortality<sup>26</sup> with a primary intention to assess response to treatment with the angiotensin receptor blocker valsartan compared to the dihydropyridine CCB amlodipine in the subgroup of patients with PAD. There was no difference in composite cardiac outcome in the 1052 PAD patients treated with valsartan and 1062 patients treated with amlodipine.<sup>26</sup> The Invest Trial (International Trandolapril Study) included 2699 PAD patients.<sup>17</sup> The ACE inhibitor trandolapril and diuretic hydrochlorothiazide were added to verapamil sustained release ( $n = 1345$ ) or beta-blocker (atenolol-based) initial

treatment ( $n = 1354$ ). Achieving a pressure  $<140$  systolic or  $<90$  diastolic reduced adverse cardiovascular outcomes [Hazard Ratio (HR): 0.82 or 0.70]. Combining trandolapril with verapamil was associated with fewer adverse outcomes than beta-blocker based strategy [HR 0.79]. The inverse relationship between ABPI and cardiovascular events was lost in subjects undergoing intensive blood pressure treatment, suggesting that the expected greater cardiovascular risk associated with a lower ABPI is avoidable when blood pressure is intensively lowered.<sup>17</sup> The ABCD study included patients with PAD associated with Type II diabetes. It reported a major benefit from tight vs. usual BP control, irrespective of whether control was achieved with a CCB (nisoldipine) or an ACEi (enalapril). However the PAD sub-group was not powered to allow comparison of independent effects of nisoldipine or enalapril on cardiovascular outcomes.<sup>27</sup>

### ACE Inhibitor (ACEi) Treatment

The HOPE trial (Heart Outcomes Protection Evaluation Study) is important in having a predefined PAD hypothesis.<sup>28</sup> Patients with PAD were followed for 4.5 years. 4051 of 9297 patients had PAD evidence based on  $ABPI < 0.9$ , 1725 had clinical features of PAD. The primary endpoint of death from vascular causes or nonfatal myocardial infarction or non-fatal stroke was reduced by ACEi treatment with ramipril 10 mg/day to 14.1% [placebo 17.7%]. Ramipril benefits were about two-fold for low ABPI vs.  $ABPI > 0.9$  (50/1000 events prevented: vs. 24/1000 events prevented). A prospective observational study noted that ACEi-based PAD treatment was associated with reduced renal failure progression;<sup>4</sup> since this was not a randomised study, results should be treated with caution. Effects of ACEi and angiotensin receptor blockers may lead to clinical benefits independent of blood pressure lowering. These effects include attenuating the pleiotropic effects of angiotensin II such as stimulation of oxidant stress, cardiovascular fibrosis, vascular and cardiac muscle hypertrophy.<sup>29</sup> However, 24 hour ambulatory blood pressure monitoring suggested blood pressure decrease with ramipril could have explained cardiovascular benefits. HOPE raises the question about target blood pressure in PAD, as many patients in HOPE had blood pressure below the conventional hypertensive range.<sup>28</sup> In significant renal artery stenosis (RAS), blood flow within the affected kidney or kidneys is critically dependent on local levels of angiotensin II. In RAS, blocking the synthesis of angiotensin II by inhibiting the enzyme ACE or blocking the action of angiotensin II at the

receptor by using angiotensin type I receptor blocker risks may cause significant renal impairment, risk of heart failure and renal failure.<sup>30</sup> The Utrecht group noted a rise of  $>20\%$  in creatinine in all patients with bilateral RAS [ $n = 52$ ] given ACEi treatment, after a delay from  $<4$  days in 26 patients and  $<2$  weeks in 31 patients.<sup>30</sup> The authors suggest that controlled exposure to ACEi is safe in the setting of suspected severe RAS, as no acute renal failure occurred and creatinine always recovered on stopping treatment. However in 12 patients, plasma creatinine only increased after diuretic treatment was added to improve blood pressure control.<sup>31</sup> Furthermore renal failure may develop in bilateral RAS within 36 hr of ACEi treatment and renal function may not recover.<sup>31</sup> Thus it is critically important in PAD that before using ACEi or Angiotensin Receptor Blocker treatment (ARB: see below), significant RAS is excluded and renal function monitored regularly.

### Angiotensin Receptor Blockers (ARBs)

Selective blockade of the Type 2 receptor for angiotensin II inhibits angiotensin II mediated vasoconstriction, aldosterone secretion, cardiovascular hypertrophy and fibrosis and salt and water retention. The VALUE study included specified sub-group analyses of the primary endpoint according to history of peripheral artery disease.<sup>26</sup> The primary outcome measure of cardiac morbidity and mortality was not significantly different between the ARB valsartan ( $n = 1052$ ) and CCB amlodipine-based PAD treatment groups (1062), although blood pressure reductions and myocardial infarction incidence were significantly lower in the amlodipine-based regimen.<sup>26</sup>

#### *Alpha-blocker treatment*

There is currently no primary endpoint data in PAD populations with alpha blocker-based treatment. However alpha blockers may be of practical benefit in patients who have benign prostatic hypertrophy by reducing symptoms and deferring need for surgery. Furthermore, long-acting alpha blockers are a pragmatically recognised agent as 4th line (step 4) treatment in the 2006 BHS/NICE Guidelines where treatment based on CCB, ACEi and diuretic is insufficient to achieve blood pressure control.<sup>25</sup>

#### *Intensive vs. usual management of raised blood pressure*

There is concern that critical blood pressure reduction may cause end-organ ischaemia by decreasing

perfusion distal to occlusive atheromatous vascular disease. Two studies suggest that intensive blood pressure-lowering reduces high cardiovascular risk in PAD, in the INVEST Trial [see above;<sup>17</sup>], by adding ACEi and thiazide to prior treatment based on the CCB verapamil or the beta-blocker atenolol; in ABCD,<sup>27</sup> for Type 2 diabetes, by adding the CCB nisoldipine or ACEi enalapril [see CCB section above].

*Compelling indications for class-specific selection of anti-hypertensive agents*

**a) Impact of cardiovascular risk factors**

There is little primary evidence on interaction between blood pressure lowering treatment and cardiovascular risk factors in patients with PAD. Thiazide diuretics and beta-adrenergic blockers may adversely affect lipid profile.<sup>24</sup> However, thiazide associated increase in lipid levels is dose-related and less of an issue with modern use of low dose diuretics e.g. bendroflumethazide 2.5 mg or equivalent. Furthermore, the relative risk from mild lipid profile abnormalities appears greatly outweighed by the reduction in cardiovascular end-points from anti-hypertensive treatment with thiazides or beta-adrenergic blockers in younger patients and for thiazide-based treatment for hypertensive patients at least up to the age of 80.<sup>16,32</sup> Beta-adrenergic blockers predispose to development of diabetes mellitus and limit awareness of diabetic symptoms.<sup>24</sup>

**b) Impact of co-morbidity on choice of treatment (Table 1)**

The impact of co-morbidity on choice of treatment may be to provide a specific additional indication for treatment, for example cardio-protection from ACEi or beta-blockade following acute myocardial infarction, and value of alpha-adrenergic blockade to reduce symptoms of benign prostatic hypertrophy.<sup>24</sup>

Co-morbidity may also suggest contra-indications in view of potential adverse effects. Renal artery stenosis should be excluded before exposure of patients to potential risks of renal impairment if given a renin system blocker (including beta-blocker, ACEi, ARB or renin inhibition). Dihydropyridine CCBs should be used with caution in patients with benign prostatic hypertrophy as the resulting increase in urine flow may increase symptoms of nocturia and polyuria.<sup>33</sup> Beta-blockers exacerbate airways disease in patients with asthma or chronic obstructive lung disease and should therefore be avoided in these disorders. Other contra-indications or cautions for beta-blockers include: avoidance in patients with heart block or on drug treatment which predisposes to heart block; caution in diabetes mellitus in view of risk of masking symptoms of hypoglycaemia; avoidance in acute heart failure and caution in established heart failure.<sup>24,25</sup>

*National treatment guidelines*

There are to date no specific national recommendations for choice of blood pressure therapy in peripheral arterial disease patients with hypertension. However, it is widely accepted that existing guidelines should be used to help to provide the best possible medical care to patients with PAD. For example, for the USA, this is based on a 7th revision of JNC guidelines and for the UK in 2006, Scottish SIGN guidelines<sup>34</sup> and joint guidelines of the British Hypertension Society and National Institute of Clinical Healthcare Excellence (NICE).<sup>24,25</sup> Other relevant guidelines include those for Type 2 diabetes associated with hypertension [UK:NICE, 2002;<sup>35</sup>]. A further relevant UK guideline entitled "Early identification and management of adults with chronic kidney disease in primary and secondary care" is due for completion in September 2008. The latest BHS/NICE hypertension guideline<sup>25</sup> states that persistent raised

**Table 1. Impact of co-morbidity on selection of blood pressure-lowering treatment**

	Thiazide	Potassium-sparing diuretic	Beta-blocker	CCB dihydropyridine	CCB diltiazem or verapamil	ACE inhibitor or angiotensin receptor blocker or renin inhibitor	Alpha blocker
Asthma or COPD			Avoid				
Renal artery stenosis		Caution: hyper-kalaemia risk				Avoid: renal failure risk	
Renal failure		Caution: hyper-kalaemia risk				Caution: exclude renal artery stenosis	
Diabetes mellitus	Caution		Caution				
Benign prostatic hypertrophy				Caution			Preferred
Ischaemic heart disease			Preferred				
Heart failure			Caution		Avoid	Preferred	
Heart block			Avoid		Avoid		

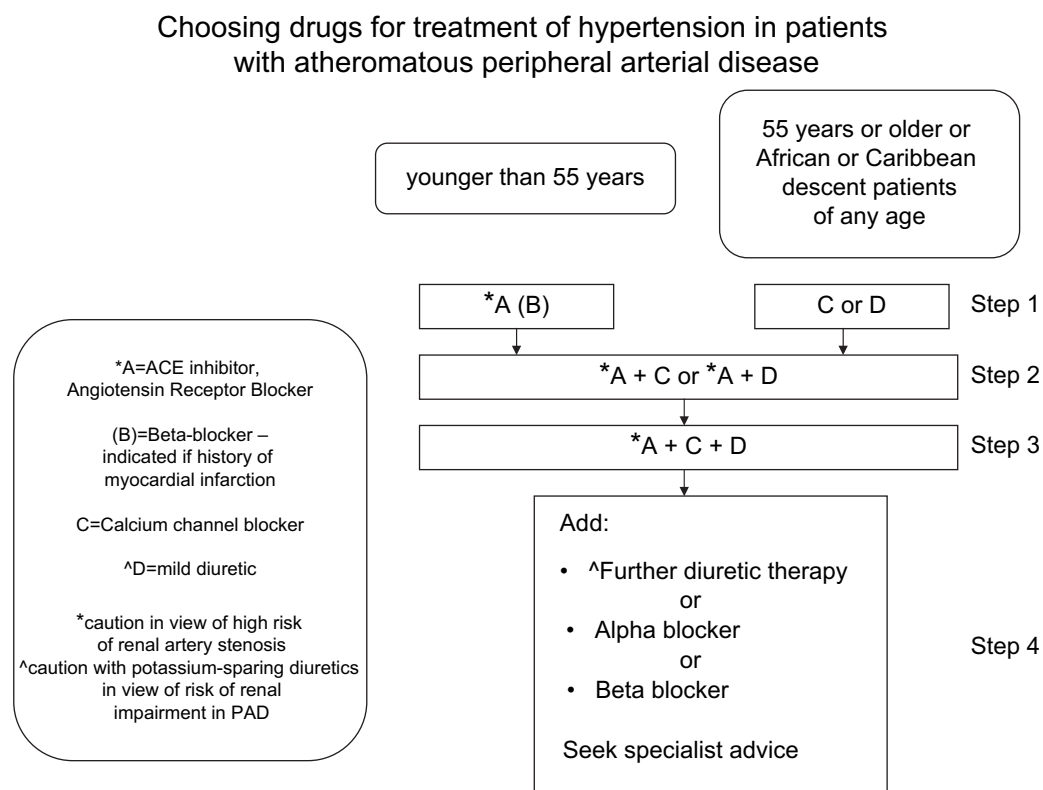
CCB: calcium channel blocker. ACE: angiotensin converting enzyme. COPD: chronic obstructive pulmonary disease.

blood pressure with existing cardiovascular disease should be treated, when after measurement at 2 separate visits systolic, diastolic or both are above 140/90 mmHg. The aim should be to reduce blood pressure to an optimum target of below 140/85 mmHg. Treatment should be based on lifestyle advice (see above). In non-black patients, Step 1 treatment should be with an ACE inhibitor if less than 55 years old, with a calcium channel blocker or thiazide-type diuretic used if the patient is >55 years old, or for a black patient of any age.<sup>25</sup> Where additional treatment is needed, appropriate add on treatments should be used (see algorithm: Fig. 1). This may help to explain the difference in outcomes in the INVEST study,<sup>17</sup> as a CCB (and not a beta-blocker) combined with an ACE inhibitor is the rational combination for effective blood pressure lowering.<sup>24,25</sup> The Type 2 diabetes and hypertension guidelines suggest that optimal blood pressure treatment target is below 130/80 mmHg. In the presence of microalbuminuria, treatment with an ACE inhibitor is recommended for combined cardiovascular and renal protection.<sup>35</sup>

### Conclusions and strategy

Blood pressure treatment in PAD reduces cardiovascular morbidity and mortality. Intensive blood pressure reduction provides significantly greater cardiovascular risk reduction than usual blood pressure management. The HOPE trial suggests that lowering blood pressure below conventional treatment thresholds in patients with PAD is also effective in reducing cardiovascular risk.<sup>28</sup> There is no clear level 1 evidence [low bias prospective randomised control trial evidence,<sup>36</sup>] that specific classes of treatment are to be preferred in the absence of contra-indications or pressing indications because of co-morbidity [see above]. For intensive blood pressure reduction, benefits appear similar for dihydropyridine or ACE-inhibitor based regimes.<sup>27</sup>

There is a pressing need for primary end-point studies targeted specifically at patients with PAD, to obtain evidence for blood pressure class and level related benefits for PAD in general and for PAD with specific risk factor, demographic and co-morbidity profiles. This will help to support development



**Fig. 1.** Algorithm for blood pressure management in patients with atheromatous peripheral artery disease (PAD). Adapted from British Hypertension Society/NICE Guidelines.<sup>25</sup> ACE inhibitors and ARBs should be used with caution if clinically significant renovascular disease is suspected. At Step 4, potassium sparing diuretics should be used with caution in view of the increased risk of renal impairment in patients with PAD.

of evidence-based international guidelines on medical management in PAD,<sup>35,37</sup> with implementation supported by PAD networks and effective Registries.<sup>5,38</sup>

**Text Box 1.** General cardiovascular risk factor burden

- This is poorly managed in peripheral arterial disease.
- It is important to reduce blood pressure in the context of overall cardiovascular risk to make sure other risk factors are identified and treated including hyperlipidaemia, smoking, poor diabetic control and the need for effective anti-platelet treatment.
- For the latter it is important to consider risk of GI bleed or intra-cerebral haemorrhage.
- Aspirin and other anti-platelet treatment should be used with caution in a patient whose blood pressure is not well-controlled.

**Text Box 2.** Renal artery stenosis

- Renal artery stenosis is common in patients with PAD.
- clues include:
  - increased severity of peripheral arterial disease
  - concomitant cardiovascular disease, for example in the carotid or coronary circulation
  - refractory hypertension
  - impaired renal function. In patients with RAS there is a major risk of acute renal impairment or complete loss of renal function if a patient is treated with an angiotensin converting enzyme inhibitor or an angiotensin receptor antagonist.

**Text Box 3.** Other causes of hypertension

- Consider other causes of hypertension in patients with PAD e.g. endocrine hypertension and intrinsic renal disease.
- High serum sodium and low serum potassium indicate the need to exclude primary hyperaldosteronism (Conn's syndrome).

- Hypercalcaemia may be missed because serum calcium is no longer routinely measured in 'routine' blood samples. Clues include unexplained nocturia, abdominal pains, joint symptoms and confusion.
- Raised creatinine may be due to renal disorders other than renovascular disease.

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