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# Anti-hypertensive treatment in peripheral artery disease

Costas Tsioufis[1], Ioannis Andrikou[1], Gerasimos Siasos[1], Konstantinos Filis[2] and Dimitrios Tousoulis[1]

Peripheral artery disease (PAD) affects more than 200 million people worldwide. Hypertension has been related to increased risk of PAD. The treatment of elevated blood pressure (BP) in these patients is indicated to lower the cardiovascular risk with a BP goal of less than 130/80 mmHg. Although there is no evidence that one class of antihypertensive medication or strategy is superior for BP lowering in PAD, the use of renin-angiotensin-system (RAS) inhibitors can be effective to reduce the cardiovascular risk. Beta-blockers (BBs) are not contraindicated. In the presence of carotid atherosclerosis, calcium-channel blockers (CCBs) and angiotensin-converting-enzyme inhibitors are recommended. In fibromuscular dysplasia the treatment of choice is percutaneous renal angioplasty. In renal artery disease optimal medical therapy includes RAS inhibitors, CCBs, BBs and diuretics.

**Addresses**
[1] First Cardiology Clinic, Medical School, National and Kapodistrian University of Athens, Hippokration Hospital, Athens, Greece
[2] First Department of Propaedeutic Surgery, University of Athens Medical School, Hippocration Hospital, Athens, Greece

Corresponding author: Tsioufis, Costas (ktsioufis@hippocratio.gr)

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## Introduction

Peripheral artery disease (PAD) affects >8 million Americans [1••] and more than 200 million people worldwide [2]. Coronary heart disease and/or cerebrovascular disease are present in >50% of patients with PAD [3]. Besides, atherosclerosis is the pathophysiological background of PAD and these subjects are often considered as patients with polyvascular disease, although completely asymptomatic in many cases. Beyond this, PAD patients have increased risk for cardiovascular events [4]. In most epidemiological studies, hypertension has been related to increased risk of PAD, with systolic blood pressure (SBP) showing a more constant association, most likely because of stiffening of the large arteries [5,6,7••]. According to a recent prospective study hypertension was the only component of metabolic syndrome independently associated with incident PAD [8]. In this article, we will review data on antihypertensive treatment in PAD, including carotid and renal artery disease.

## Antihypertensive drug classes in PAD

Recent AHA/ACC Guidelines on the management of patients with lower extremity PAD recommend that treatment of elevated blood pressure (BP) is indicated to lower the risk of cardiovascular events in patients with hypertension and PAD [1••]. However, the idea that higher BP levels could result in improved limb perfusion is confusing and raises concerns about antihypertensive therapy [1••,9•]. On the other hand, the recent SPRINT trial has suggested that even more aggressive targets (<120/80 mmHg) may be appropriate in patients at high cardiovascular risk [10••], and PAD patients convey an increased risk. However, according to the post hoc analysis of INVEST, a randomized clinical trial (RCT), which included hypertensives with concomitant PAD and coronary artery disease ($n = 2699$) followed for a mean of 2.7 years, the primary outcome, all-cause death, nonfatal myocardial infarction or stroke, occurred least frequently among patients treated to an average SBP of 135–145 mmHg and an average diastolic BP of 60–90 mmHg. There was a J-shape relationship between SBP and the outcome [11]. There was no difference between two types of medication strategies (verapamil ± trandolapril vs. atenolol ± hydrochlorothiazide). Therefore, up to now, ESC guidelines suggest that target BP should be ≤140/90 mmHg,except in patients with diabetes, for whom a diastolic BP ≤85 mmHg is considered safe [12,13••]. In patients with lower extremity artery disease, this is mainly based on data from the INVEST study [11]. However, latest AHA guidelines on management of hypertension, incorporating the results of SPRINT trial, recommend a BP target <130/80 mmHg for adults with increased cardiovascular risk, like patients with PAD [14••].

In HOPE study 9297 high-risk patients (≥55 years old, mean entry BP 139/79) with evidence of vascular disease or diabetes plus another cardiovascular risk factor, without heart failure, were randomized to receive ramipril or matching placebo for a period of five years [15]. Ramipril significantly reduced the rates of death, myocardial infarction and stroke. It is noteworthy that ramipril was found to be also beneficial in the subgroup of patients with PAD and the efficacy was similar in patients with symptomatic

PAD disease and asymptomatic low ankle-brachial index (ABI) [16]. The use of angiotensin receptor blockers (ARBs) as an alternative to angiotensin converting enzyme inhibitors (ACEIs) was examined in ONTARGET, which compared telmisartan, ramipril and combination therapy in patients with cardiovascular disease, including PAD, and/or diabetes mellitus. All 3 treatments had similar cardiovascular event rates with higher rates of adverse events in the combination-therapy group. The interesting finding was that the efficacy of telmisartan was similar in the subgroup of 3468 PAD patients [17]. In a recent study including patients on maintenance dialysis, ARBs significantly attenuated the risk of PAD requiring angioplasty [18•]. In another prospective observational cohort study with 2420 PAD patients (age ~64 years, eight years median follow-up), ACEIs and beta-blockers (BBs) were associated with reduction in long-term mortality in patients with PAD, whereas calcium channel blockers (CCBs) and diuretics were not [19]. Also, a recent retrospective study in 464 patients with critical limb ischemia (CLI) who underwent diagnostic angiography or endovascular intervention showed that ACEIs/ARBs use is associated with lower major adverse cardiovascular events and mortality, but there was no effect on limb-related outcomes [20]. On the other hand, in subgroup analysis of patients with clinical PAD of VALUE trial ($n$ = 2114), there was no difference in the incidence of composite cardiac endpoint with valsartan and amlodipine-based treatments, despite a greater BP reduction in the amlodipine group [21]. Similarly, in ALLHAT, 33357 participants aged ≥55 years, with hypertension and at least another one risk factor were randomly assigned to receive chlorthalidone, amlodipine or lisinopril. After a mean follow-up of 4.9 years, there was no difference between treatments regarding the primary outcome of combined fatal or nonfatal myocardial infarction [22]. Moreover, in 830 participants with specified secondary outcome of lower extremity PAD events during the randomized phase of ALLHAT, neither amlodipine nor lisinopril showed superiority over chlorthalidone in reducing clinically advanced PAD risk [23••]. Recent guidelines mention that there is no evidence that one class of antihypertensive medication or strategy is superior for BP lowering in PAD [1••,24]. However, although the benefits of ACEIs on walking distance are uncertain [25], the use of ACEIs or ARBs can be effective to reduce the risk of cardiovascular ischemic events in patients with PAD [1••,13••]. It is worth mentioning that a recent study revealed the underuse of cardiovascular prevention medication, including ACEIs/ARBs in patients with PAD in the United States from 2005 through 2012 [26•].

Regarding patients with PAD and diabetes the optimal glucose level control is of special importance [13••]. Although all BP-lowering drugs are effective in those patients, ACEIs and ARBs are preferred as first-line antihypertensive therapy, as there is evidence provided by randomized trials including diabetic patients with PAD, such as HOPE and ONTARGET, and recent meta-analyses that these agents have some greater cardiovascular preventive action [13••,27]. Renin-angiotensin-system (RAS) blockers are the only drug class for which evidence is available of a significant reduction of diabetic end-stage renal disease risk in comparison with placebo [27].

Subjects with PAD are patients with polyvascular disease, at increased cardiovascular risk, often with many comorbidities, obliged to take many drugs, including antihypertensives, antithrombotics and lipid-lowering drugs. The condition of polypharmacy results in poor adherence in the prescribed medication. Fixed-dose combination therapy can decrease the risk of medication non-compliance, which translates into better clinical outcomes. Diuretics, BBs, CCBs, ACEIs and ARBs are all suitable for antihypertensive treatment in PAD, as monotherapy or in different combinations [13••]. According to the abovementioned results combination therapy should primarily include ACEIs or ARBs.

## Beta-blockers in PAD

The role of BBs in PAD has been a matter of debate so far. It has been hypothesized that the decrease of cardiac output and the upregulation of alpha adrenergic drive due to blockage of the beta-2-dependent vasodilating effect result in peripheral hemodynamic consequences such as vasoconstriction, increasing limb ischemia and worsening the symptoms of intermittent claudication (IC) [6]. Thus, the use of BBs is considered to be relatively contraindicated in patients with PAD, although these patients suffer frequently from concomitant ischemic heart disease and the use of BB is warranted. In this setting, NORMA Trial, a RCT, that randomized 128 patients with IC and hypertension to receive nebivolol or metoprolol, has shown that BB therapy was well tolerated during an almost 1-year treatment period [28]. Both drugs were equally effective in lowering BP. Absolute claudication distance improved significantly in both patient groups ($p < 0.05$ for both), with no difference across treatments. A significant increase of initial claudication distance, that is the first pain when walking on the treadmill, was found in the nebivolol group, which is especially important in everyday life because patients most often stop when claudication pain starts [6]. Thus, the vasodilator properties of agents such as nebivolol could be helpful in case of decreased muscle blood flow, as in PAD patients while walking. Moreover, the study showed that beta-blockade increased significantly the ABI [29]. The authors conclude that the use of BBs in these hypertensive patients appears to be safe. Another RCT comparing nebivolol with hydrochlorothiazide presented similar results, suggesting that nebivolol does not have negative effects in high risk patients [30]. In the same lines are the results from most meta-analyses showing no negative effect of