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Lipid-lowering treatment in peripheral artery disease

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Peripheral artery disease (PAD) is characterized by increased cardiovascular (CV) risk, limb morbidity and all-cause mortality. According to the current guidelines (2016) of the American Heart Association/American College of Cardiology on the management of PAD patients, statin therapy is recommended for PAD patients in order to treat dyslipidemia and reduce CV risk.The present narrative review discusses the use of statins and other lipid-lowering drugs such as ezetimibe, fibrates, niacin, anacetrapib and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in PAD patients in terms of both CV and limb outcomes. The clinical implications of hypolipidemic drug therapy in special patient populations including those with metabolic syndrome, non-alcoholic fatty liver disease, chronic kidney disease and type 2 diabetes mellitus, which may frequently co-exist with PAD, are also considered.

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Introduction

Peripheral artery disease (PAD) represents a coronary heart disease (CHD) equivalent as recognized by the 2001 National Cholesterol Education Program Adult Treatment Panel III [1]. In this context, PAD is characterized by increased cardiovascular (CV) morbidity and mortality as well as total mortality [2,3•]. The most common risk factors for PAD are advanced age, type 2 diabetes mellitus (T2DM) and smoking, followed by dyslipidemia and hypertension [4]. Of note, dyslipidemia is frequently underdiagnosed and undertreated in PAD patients [5,6]. Apart from CHD, PAD has been associated with non-cardiac vascular diseases such as stroke, abdominal aortic aneurysms (AAA), carotid disease and atherosclerotic renal artery stenosis [7–10]. Links between PAD and metabolic diseases, including the metabolic syndrome (MetS) and non-alcoholic fatty liver disease (NAFLD), as well as chronic kidney disease (CKD) have also been reported [11–14]. These disorders may further increase CV risk [15–18].

According to the current guidelines (2016) of the American Heart Association (AHA)/the American College of Cardiology (ACC) on the management of PAD patients [19•], several drugs may be used to improve CV risk factors and reduce CV risk in these patients including antiplatelet, antihypertensive and hypolipidemic agents.

The present narrative review discusses the use of lipid-lowering drugs in PAD patients in terms of both CV and lower extremity outcomes. The use of these drugs in special patient populations such as those with MetS, NAFLD, CKD, and T2DM is also considered.

Statins

Statins remain the first-line lipid-lowering therapy to treat PAD patients as recommended by the current AHA/ACC guidelines [19•]. Statins may beneficially affect not only the quantity but also the quality of LDL-C, as they have been reported to reduce the number of small dense LDL (sdLDL) particles [20,21]. Furthermore, statins can improve HDL functionality [22]. The clinical significance of these lipid abnormalities has been discussed elsewhere [23•,24]. Apart from improvements in the lipid profile, statins exert pleiotropic properties including plaque stabilization, regression of atheroma and anti-inflammatory effects, thus minimizing CV risk in PAD patients [25•,26].

Statins in PAD patients

Statins were shown to decrease CV and limb morbidity as well as all-cause death in a cohort study of 1107 patients with intermittent claudication [27]. In patients with critical limb ischemia (CLI), statins reduced total mortality and CV events and increased amputation-free survival [28,29]. Similar benefits were observed in the First-Line Treatments in Patients With Critical Limb Ischemia (CRITISCH) registry following statin treatment; increased amputation-free survival was seen in several

populations of statin-treated patients including those with T2DM, CKD and older than 75 years as well as those undergoing endovascular therapy or bypass revascularization [30•]. Statin therapy also decreased total mortality in PAD patients with atrial fibrillation [31]. Furthermore, statin users had reduced CV mortality and fewer lower-extremity amputations in a nationwide database of PAD patients with T2DM [32]. Similarly, in the REACH registry, statin therapy was associated with lower rate of limb outcomes such as worsening symptoms, amputations and revascularization [33]. Improved limb salvage at one year was also observed in PAD patients undergoing endovascular or surgical interventions who were treated with a statin preoperatively [34]. Similar benefits were observed in those administered a statin postoperatively [35]. Furthermore, in patients with both above-knee and below-knee amputations, statins decreased one-year mortality [36]. However, there are studies not reporting reductions in amputation rate following statin treatment in PAD patients [37].

Achievement of LDL-C < 70 mg/dl at a short-term follow-up period (mean duration 4.8 months) after endovascular intervention for PAD was associated with reduced all-cause mortality and CV morbidity [38•]. Apart from lowering CV risk, attaining LDL-C targets in PAD patients can also improve limb symptoms [39]. Of note, high-intensity statin use (i.e. atorvastatin 40–80 mg or rosuvastatin 20–40 mg) was related to fewer CV events and improved survival compared with low-moderate statin therapy in patients with symptomatic PAD, despite similar LDL-C levels [40•].

Statins are recommended in PAD patients undergoing endovascular interventions as they can reduce revascularization rates and postoperative CV events [37]. Lower restenosis rates have been reported in statin-treated patients undergoing stent implantation in the femoropopliteal arteries [41]. Overall, statins may improve perioperative and long-term morbidity and mortality rates as well as infrainguinal bypass graft patency rates, graft restenosis and amputation incidence in PAD patients [42•,43]. Statins may also prolong pain-free walking time or distance and improve quality of life in PAD patients [37,44,45].

PAD patients are suboptimally treated with statins, although statin therapy is indicated in these high-risk individuals [46–48]. In this context, PAD patients (as well as those with ischemic stroke and DM) were less likely to receive statin therapy compared with CHD patients [49]. Admission to a vascular surgery department can increase prescription of statins at discharge [50,51]. Furthermore, PAD patients involved in a guideline-recommended risk-reduction educational program that promoted the use of drugs reducing CV risk such as statins, were reported to have fewer CV and limb events at the end of the seven-year follow-up period [52]. These findings strongly support the need to intensify the implementation of current guidelines, and especially statin use, in PAD patients.

Statins in PAD patients with comorbidities

CKD is frequently present in PAD patients, leading to increased limb and CV morbidity and mortality as well as worse outcomes following endovascular or surgical interventions [53,54]. Statins may improve renal function in different patient populations including those with CHD, MetS, T2DM, CKD, and PAD [55•,56–59]; these conditions often coexist. Statins have also been shown to decrease the risk of vascular events in patients with advanced CKD [60] and the risk of contrast-induced acute kidney injury (CI-AKI), an important side effect of contrast media administration [61•,62]. CI-AKI has been linked to increased CV and renal morbidity, total mortality and prolonged hospitalization [63].

Statins are beneficial in several patient populations including those with MetS, NAFLD, and T2DM. In these patients, statins can not only improve lipids but also decrease CV risk [64,65•,66]. In T2DM patients, statins may also reduce the risk for diabetic complications [67], whereas in NAFLD patients they can improve hepatic biochemical and histological features [15,17,65•]. Therefore, in PAD patients with these cardiometabolic comorbidities, statins may exert several beneficial effects and should be administered.

PAD patients are more likely to develop AAA [68,69]. Therefore, current AHA/ACC guidelines recommend performing a screening duplex ultrasound for AAA in patients with symptomatic PAD [19•]. Statins have been shown to lower CV mortality and slow AAA growth in patients with AAA but further evidence is needed to establish these associations as there are conflict reports [70,71].

Despite several beneficial effects, statins may increase the risk for new-onset diabetes (NOD) [72], especially in individuals at risk of developing T2DM such as women, obese, older (>70 years), of Asian ethnicity and those with prediabetes or MetS [73,74]. The statin-related risk for NOD depends on statin type and dose as well as duration of therapy [75]. Several molecular mechanisms have been proposed to explain the diabetogenic effect of statins [76]. There is a need to establish whether PAD patients are more prone to NOD development because in these patients several risk factors for NOD may coexist including older age, prediabetes, and MetS.

Ezetimibe

Ezetimibe has been reported to improve the lipid profile and exert anti-atherogenic, antioxidant, and anti-inflammatory properties, thus further reducing CV risk [77•].