

Lipid-lowering and anti-thrombotic therapy in patients with peripheral arterial disease

European Atherosclerosis Society/European Society of Vascular Medicine Joint Statement

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ABSTRACT

Patients with peripheral arterial disease (PAD) are at very high risk of cardiovascular events, but risk factor management is usually suboptimal. This Joint Task Force from the European Atherosclerosis Society and the European Society of Vascular Medicine has updated evidence on the management on dyslipidaemia and thrombotic factors in patients with PAD. Guidelines recommend a low-density lipoprotein cholesterol (LDL-C) goal of more than 50% reduction from baseline and <1.4 mmol/L (<55 mg/dL) in PAD patients. As demonstrated by randomized controlled trials, lowering LDL-C not only reduces cardiovascular events but also major adverse limb events (MALE), including amputations, of the order of 25%. Addition of ezetimibe or a PCSK9 inhibitor further decreases the risk of cardiovascular events, and PCSK9 inhibition has also been associated with reduction in the risk of MALE by up to 40%. Furthermore, statin-based treatment improved walking performance, including maximum walking distance, and pain-free walking distance and duration. This Task Force recommends strategies for managing statin-associated muscle symptoms to ensure that PAD patients benefit from lipid-lowering therapy. Antiplatelet therapy, either daily clopidogrel 75 mg or the combination of aspirin 100 mg and rivaroxaban (2 × 2.5 mg) is also indicated to prevent cardiovascular events. Dual antiplatelet therapy (aspirin and rivaroxaban) may be considered following revascularization, taking into account bleeding risk. This

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Joint Task Force believes that adherence with these recommendations for lipid-lowering and antithrombotic therapy will improve the morbidity and mortality in patients with PAD.

1. Introduction

Peripheral arterial disease (PAD), characterised by atherosclerosis in the arteries of the lower limb, poses an increasing health and societal burden world-wide. Already affecting more than 20% of individuals aged over 60 years [1,2], the prevalence will escalate as the population ages. This is highly relevant given that cardiovascular risk is higher among PAD patients than those with coronary artery disease (CAD) alone and increases with disease severity (Fig. 1) [3–5]. Five-year mortality with PAD is almost double that of CAD (25% versus 13%) and higher than for many cancers, equating almost exactly to Duke's stage B carcinoma of colon [3,6,7]. Despite recognition of this high attrition rate, however, mortality associated with PAD has essentially remained unchanged over the past 25 years (Fig. 2) [3,8], unlike the decline evident for CAD [3,9,10]. This poor prognosis can be largely attributed to sub-optimal management of cardiovascular risk factors [9], as recommended by evidence-based guidelines [11–13].

Although PAD and CAD are both caused by atherosclerosis and share common lesion features, the clinical course, therapeutic response and certain demographic features suggest that there are factors that make PAD subjects more susceptible to the clinical manifestations of atherosclerosis [14]. PAD is characterised by higher levels of systemic inflammation markers, and a higher prevalence of diabetes than CAD [15]. As for all phenotypes of atherosclerosis, dyslipidaemia is one of the most important modifiable cardiovascular risk factors in PAD [16].

The European Society of Vascular Medicine (ESVM) and the European Atherosclerosis Society (EAS) recognise the need for a renewed focus on the management of PAD. This Joint Statement provides clear and updated evidence-based consensus on the management on dyslipidaemia and thrombotic factors, with the aim of decreasing the appalling cardiovascular morbidity and mortality associated with PAD.

2. Lipid-lowering therapies in PAD

2.1. What is the evidence that elevated lipids and lipoproteins increase risk for PAD?

Despite controversy over the years, elevated lipids are now known to be associated with increased cardiovascular risk in PAD [16]. Indeed, in a previous report, a discordant lipid profile was reported in patients with PAD compared to unaffected controls [17]. As with all phenotypes of atherosclerosis, apolipoprotein (apo)B-containing lipoproteins, which

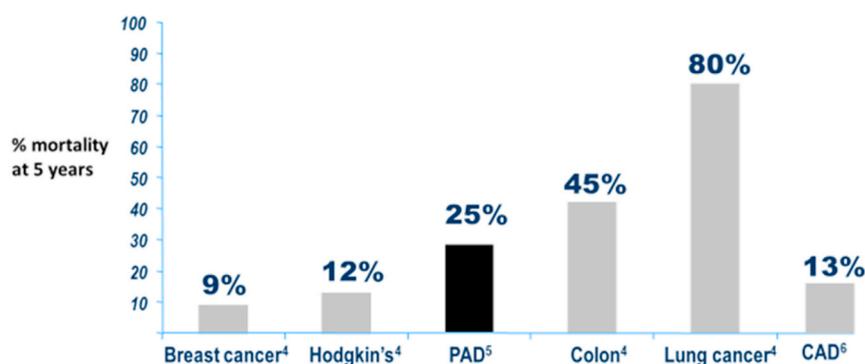
include all lipoproteins except high-density lipoproteins (HDL), are key players driving the initiation and progression of disease [18]. The archetypal apoB-containing lipoprotein is low-density lipoprotein (LDL), which is established as causal for atherosclerotic cardiovascular disease (ASCVD) [19,20]. There is also accumulating evidence to suggest a causal role for triglyceride-rich lipoproteins and their remnant particles in atherosclerosis [21].

ApoB-containing lipoproteins retained in the arterial wall initiate the atherosclerotic process [18]. Higher levels of apoB-containing lipoproteins in plasma promote the development and progression of atherosclerotic plaques. Hence, the concentration and total duration exposure of apoB-containing lipoproteins, together with the concentration of circulating LDL cholesterol (LDL-C), represent the overall atherosclerotic plaque burden of an individual person [22,23].

An increased ratio of apoB/apoAI (the apolipoprotein in HDL) was predictive of PAD risk in middle aged healthy men [24]. Genetic and epidemiologic studies provide insights into the role of specific apoB-containing lipoproteins that determine this risk. A genome-wide association study including over 30,000 PAD patients and 210,000 controls of the Million Veteran Program (MVP) identified variants in the genes encoding the LDL receptor (*LDLR*), lipoprotein lipase (*LPL*), and lipoprotein(a) [Lp(a)] (*LPA*) as drivers of PAD [25]. Interestingly, in replication analyses in more than 5000 PAD patients from the UK Biobank, the *LPA* variant was the top locus associated with PAD. This finding is supported by an epidemiologic study showing a dose-dependent association of Lp(a) molar concentration and PAD [26].

The MVP study also identified several variants that were associated with either hypercholesterolaemia or hypertriglyceridaemia and PAD [25]. These findings are important as epidemiologic support for an association between elevated LDL-C concentration and PAD is less consistent than for CAD. For example, in the Health Professionals Follow-up Study, hypercholesterolaemia contributed 17% of the PAD risk [27]. Furthermore, associations of total cholesterol levels, total cholesterol/HDL ratio, and triglyceride concentration with PAD were often attenuated or abrogated after multivariate adjustment [28]. More recently, a prospective study of more than 27,000 women without incident PAD found that elevated LDL-particle number (based on nuclear magnetic resonance measurement) and triglyceride-rich lipoproteins but not LDL-C concentration were associated with PAD risk [29].

While some uncertainties persist regarding the contribution of individual apoB-containing lipoproteins to the different clinical manifestations of atherosclerosis, particularly in symptomatic PAD, over



⁴American Cancer Society, Cancer Facts and Figures – <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf>; ⁵Sartipy et al. Eur J Vasc Endovasc Surg. 2018 Apr;55(4):529-536. doi:10.1016/j.ejvs.2018.01.019. ⁶Droz-Perroteau C. Six-year survival study after myocardial infarction: The EDLE prospective cohort study. Long-term survival after MI. <https://doi.org/10.1016/j.therap.2019.02.001>

Fig. 1. Comparison of 5-year mortality rates: PAD versus common cancers.

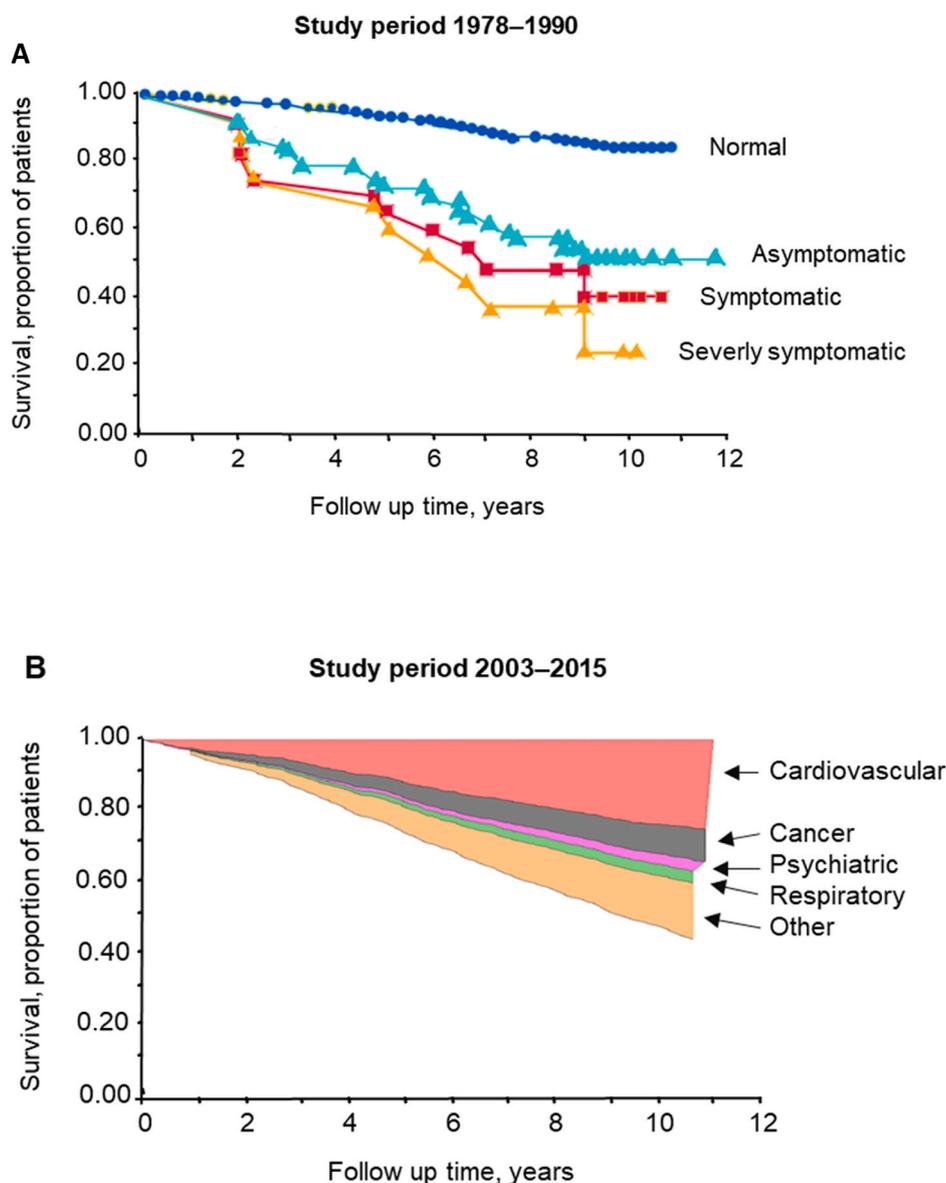


Fig. 2. Little change in PAD patient survival over the last 25 years. Comparison of 10-year survival (A) between 1978 and 1990 (modified from Criqui et al. [10]) and (B) between 2003 and 2015 (according to cause of death) (modified from Sartipy et al. [3]).

whelming evidence supports the collective role of these lipoproteins in driving PAD. Moreover, as LDL-C is unequivocally established as causal for ASCVD [19], it is therefore the primary target when treating dyslipidaemia in patients with PAD [30].

2.2. What are the lipid goals in PAD?

The 2019 European Society of Cardiology/EAS dyslipidaemia guidelines recommend LDL-C goals according to the 10-year risk for fatal cardiovascular events. Patients with PAD belong in the very high-risk category, with $\geq 10\%$ risk of a fatal cardiovascular event. In these patients, both LDL-C reduction by $\geq 50\%$ from baseline and an LDL-C goal of < 1.4 mmol/L (< 55 mg/dL) are recommended [30].

To attain this LDL-C goal treatment with a high-intensity statin at the maximal tolerated dose is recommended. If patients are unable to attain goal or report statin intolerance, a combination of statin (at a lower dose if statin intolerant) with ezetimibe is recommended, with addition of a PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor if

further LDL-C lowering is indicated [31]. Lipid levels should be monitored $8 (\pm 4)$ weeks after starting or adjusting treatment until LDL-C goal is achieved, and thereafter at least annually or as indicated.

Despite guideline recommendations, however, PAD patients are often underdiagnosed and inadequately managed compared with CAD patients, both for lifestyle intervention and pharmacotherapy [32]. As with other very high-risk groups, registries show disappointing results in terms of adherence with lifestyle and LDL-C goal achievement. In a study of symptomatic PAD patients, less than three-quarters did not attain an LDL-C level below 1.8 mmol/L (70 mg/dL) and nearly half had LDL-C levels above 2.5 mmol/L (100 mg/dL) [33]. Similar findings were reported among PAD patients included in studies of high cardiovascular risk populations [34,35].

2.3. What is the evidence that lipid-lowering therapy improves outcome in PAD?

While lipid-lowering therapy indisputably reduces cardiovascular

events in patients with CAD, evidence from prospective well-powered studies in PAD patients is more limited. In a systematic review of 18 trials of different lipid-lowering agents in 10,000 patients with lower limb PAD, lowering LDL-C concentration was associated with 20% reduction in total cardiovascular events and improvements in total walking distance and pain-free walking distance, but not ankle brachial index (ABI) [36]. Evidence for individual lipid-lowering therapies is summarized below.

2.4. Statins

Statins are guideline-recommended first line lipid-lowering therapy in patients with PAD, supported by definitive evidence of cardiovascular morbidity and mortality benefits [12,37,38]. Furthermore, there is also support for positive effects of lipid-lowering on major adverse limb events (MALE), as well as walking performance in patients with PAD.

2.4.1. Major adverse cardiovascular events (MACE) and MALE

There is clear evidence that statin treatment substantially improves cardiovascular outcomes and MALE in PAD patients. One meta-analysis evaluated 51 studies (2 randomized controlled trials, 20 prospective studies, and 29 retrospective studies) in 138,060 PAD patients with either stable claudication, critical limb ischaemia (CLI) or undergoing lower extremity revascularization, of whom 35% received a statin [39]. MACE included all-cause death, composite cardiovascular endpoints, cardiovascular death and stroke, and MALE included amputation and graft occlusion/revascularization. Statin treatment not only reduced all-cause mortality by 39%, cardiovascular death by 41%, cardiovascular outcomes by 34% and ischaemic stroke by 28%, but also reduced MALE by 30% and amputations by 35% (Table 1). Another meta-analysis of 19 studies in 26,985 patients with CLI, about half on a statin, showed 25% reduction in amputation and 38% reduction in fatal events. Statin therapy was also associated with improved overall patency rates and lower incidence of MACE [40].

To some extent findings from these meta-analyses are confounded by inclusion of retrospective studies, as well as the fact that generally less than half of these patients were on a statin. To address these issues, this Joint Task Force conducted a meta-analysis of randomized controlled trials of statin-based treatment identified by MEDLINE searches which reported major cardiovascular events, cardiovascular mortality, or all-cause mortality in PAD patients [41–45]. Estimates for between group differences (statin versus control) were derived using both fixed-effects (Mantel & Haenszel method) [46] and random-effects models (DerSimonian & Laird method) [47], with the latter reported if there was significant heterogeneity. Overall, this analysis showed that statin treatment reduced MACE by 24% (odds ratio 0.76, 95% confidence interval [CI] 0.69–0.83), cardiovascular death by 17% (odds ratio 0.83, 95% CI 0.26–2.60) and all-cause mortality by 18% (odds ratio 0.82, 95% CI 0.69–0.97) (Fig. 3).

2.4.2. Outcome after limb intervention

There are limited data for the effect of statin treatment on outcomes after surgical and endovascular procedures. Pooled analysis of seven

studies in patients with CLI, did, however, indicate that statin treatment was associated with lower rates of loss of patency (hazard ratio 0.80, 95% CI, 0.66–0.96) [40].

2.4.3. Claudication development

There is some evidence that statin treatment can decrease the development and progression of PAD. For example, analyses from the Scandinavian Simvastatin Survival Study (4S), showed that cholesterol lowering with simvastatin reduced the incidence of carotid bruits and cerebrovascular events, as well as new-onset or worsening of angina pectoris and intermittent claudication [48]. The authors concluded that simvastatin may have a general anti-atherosclerotic effect not limited to the coronary bed. More recently, investigation of atheroma burden using serial whole body magnetic resonance angiography over 3 years showed that individuals with atheroma progression at follow-up were less likely to be on statin therapy (79% vs. 100%, $p = 0.04$), and had a significantly higher baseline atheroma score (17.6 ± 11.2 vs. 10.7 ± 5.1 , $p = 0.043$) [49].

2.4.4. Walking performance

Statin treatment was also shown to favourably impact walking performance in PAD patients with claudication. In one meta-analysis, maximal walking distance for patients on lipid-lowering therapy, notably statins, improved more than that reported with vasodilators, phosphodiesterase and platelet inhibitors (increase by 150 vs. 50 m) [50]. This benefit increased over time with maximal effect after several months of treatment but was not accompanied by improvement in ABI measurement. Another study showed no difference between patients with claudication doing exercise training treated with atorvastatin versus control, suggesting no added benefit from statin treatment [51].

The effects of statin-based treatment on walking performance were further investigated in the meta-analysis conducted by this Joint Task Force [41,42,45,51,52]. Two outcomes were evaluated: maximal walking distance and free-pain walking (both duration and distance) on a treadmill. Based on the random-effects model, statin treatment improved walking distance by 45 m (95% CI -64.7 to 154.7 m). There was also improvement in pain-free walking distance and duration (by 15.3 m [95% CI -56.8–87.5] and 54.9 s [95% CI 40.4–69.3], respectively).

2.5. Combination treatment with statin and ezetimibe

Guidelines recommend the addition of ezetimibe if very high-risk patients fail to attain LDL-C goal with maximally tolerated statin therapy. The cardiovascular benefits of this combination therapy is supported by results from IMPROVE-IT (IMproved Reduction of Outcomes: Vytorin Efficacy International Trial), in which ezetimibe on top of simvastatin therapy significantly reduced cardiovascular events (a composite of cardiovascular death, myocardial infarction, unstable angina requiring rehospitalization, coronary revascularization or non-fatal stroke) in patients with ACS (hazard ratio 0.936; 95% CI 0.89–0.99; $p = 0.016$) [53]. Subgroup analyses investigated the effects of this combination treatment in patients with polyvascular disease; 1005 (6%) had PAD and 1071 (6%) had stroke or transient ischaemic

Table 1

Effect of statin treatment on cardiovascular and major adverse limb events in patients with peripheral arterial disease.

Outcome	Relative risk reduction (%)	Hazard ratio (95% CI)
Composite cardiovascular events	34	0.662 (0.59–0.741)
Cardiovascular death	41	0.594 (0.455–0.777)
All-cause death	39	0.608 (0.543–0.680)
Major adverse limb events	30	0.702 (0.605–0.815)
Amputation	35	0.654 (0.522–0.819)

Results from a meta-analysis of 51 studies in 138,060 patients, 35% treated with a statin. Derived from Pastori et al. [39].

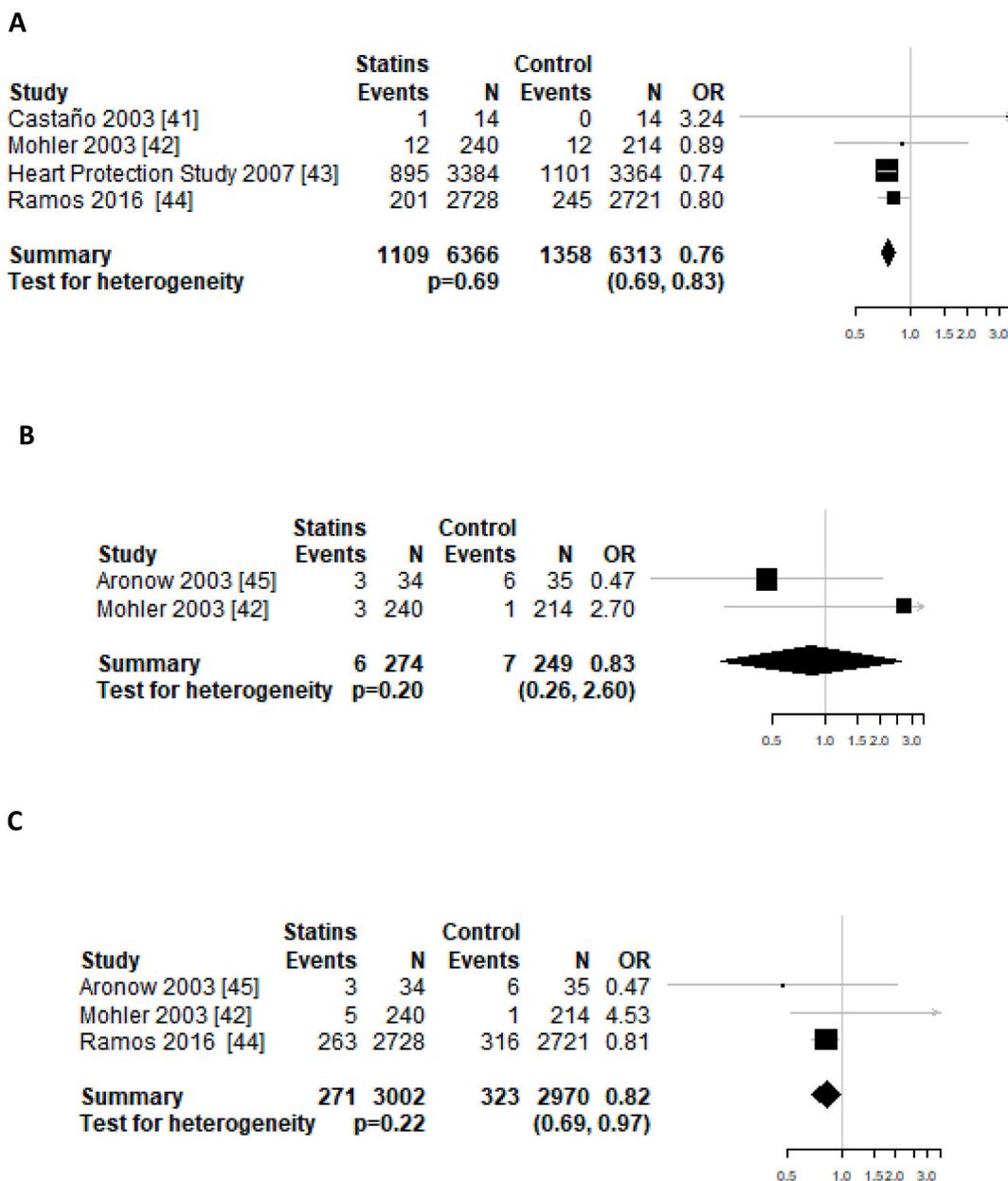


Fig. 3. Effect of statin-based treatment on the risk of cardiovascular outcomes and all-cause mortality in patients with PAD. Meta-analysis of randomized controlled trials of statin therapy, showing the effects of statin-based treatment on risk for MACE (Panel A), cardiovascular death (Panel B) and all-cause mortality (Panel C). Analyses based on data in Castano et al. [41], Mohler et al. [42], Heart Protection Study Collaborative Group et al. [43], Ramos et al. [44] and Aronow et al. [45]. *Panel A:* Effect of statin-based treatment on risk for MACE. *Panel B:* Effect of statin-based treatment on risk of cardiovascular death. *Panel C:* Effect of statin-based treatment on risk of all-cause mortality.

attack at baseline, with concomitant type 2 diabetes in over one-third [54]. Patients with polyvascular disease were at higher risk, with 7-year Kaplan-Meier cardiovascular event rates 39.8% and 60.0% with concomitant type 2 diabetes vs. 29.6% in those with ACS alone.

Although the relative risk reduction associated with ezetimibe plus simvastatin was consistent in patients with or without concomitant polyvascular disease, the absolute benefit was substantially higher in patients with polyvascular disease, especially those with concomitant type 2 diabetes (absolute risk reductions 4.2% and 9.1% vs. 1.7% in those with ACS alone). These translated to a number needed to treat to prevent one event of 24 in patients with polyvascular disease and 11 with concomitant type 2 diabetes versus 59 in those with ACS alone [54]. These findings reinforce the greater cardiovascular benefit from further LDL-C lowering with the combination of ezetimibe and simvastatin.

2.6. Combination treatment with statin and a PCSK9 inhibitor

Monoclonal antibodies against PCSK9, i.e., evolocumab and alirocumab, are highly efficacious treatments that reduce LDL-C by 60% on top of statin therapy and are associated with significant reduction in cardiovascular events in outcomes studies in very high-risk populations [55,56]. Prespecified analyses of these trials have also demonstrated cardiovascular and limb benefit in PAD patients.

2.6.1. What is the evidence that PCSK9 inhibitors, on top of statins, improve outcome in PAD patients?

The FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial investigated treatment with evolocumab against a background of intense statin therapy (with or without ezetimibe) in 27,564 patients with coronary,

cerebrovascular, or peripheral arterial atherosclerosis [55]. A pre-specified analysis included 3642 patients with confirmed lower limb PAD, identified by intermittent claudication and an ABI <0.85, or with a prior peripheral vascular procedure [57]. At the time of randomization, 57% of patients had a history of peripheral revascularization, 3% had undergone amputation, and 69% had an ABI <0.85 and claudication. Almost all were on a statin and 89% were also on antiplatelet therapy. These patients were at higher absolute risk of both MACE and MALE when compared with those with atherosclerosis affecting other vascular beds. Treatment with evolocumab significantly reduced the primary end point (a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) by 21%, as well as the risk of MALE by 42% [57]. Thus, FOURIER was the first randomized trial to demonstrate that intensive LDL-C lowering decreases the risk of MALE with no safety concerns.

Subsequent analyses of the ODYSSEY OUTCOMES study in 18,924 patients with recent acute coronary syndrome provides further insights [56]. Patients were randomized to alirocumab on top of maximally tolerated statin or statin alone. In those patients who also had PAD (3.2% of the total study population), treatment with alirocumab was associated with 7% reduction in relative risk for the primary endpoint (a composite of coronary heart disease death, nonfatal myocardial infarction, fatal or nonfatal ischaemic stroke, or unstable angina requiring hospitalization) [58]. In patients with atherosclerosis in three vascular territories, the relative risk reduction was substantially higher (by 36% versus 15% for the overall study population) [58]. In a subsequent analysis including all patients with a history of PAD, treatment with alirocumab significantly reduced the risk for PAD events (a composite of critical limb ischaemia, limb revascularization, and amputation for ischaemia) by 41%, corresponding to an 8.6% absolute reduction in risk at 3 years. Notably, the ODYSSEY OUTCOMES Study Investigators identified baseline Lp(a) but not LDL-C concentration as a predictor of the reduction in risk for PAD events with alirocumab [59].

Finally, combined analysis of both trials conducted by this Joint Task Force showed that treatment with a PCSK9 inhibitor, on top of maximally tolerated statin therapy, was associated with a significant 24% reduction in cardiovascular events (odds ratio 0.76, 95% CI 0.64–0.91), although the difference in all-cause mortality did not achieve statistical significance (odds ratio 0.85, 95% CI 0.67–1.09) [57,58].

2.7. How to manage muscle adverse effects with statins

Beyond efficacy, the adverse effects of statin therapy, notably perceived or reported muscle pain and cramping, merit consideration in the setting of PAD, given their potential detrimental impact on treatment compliance. Statin associated muscle symptoms (often referred to as SAMS) cover a broad range of clinical presentations, including pain or itching, stiffness, tenderness or cramping, and may affect about 15–20% of patients, more frequently women than men [60,61]. Clinical presentation of muscle symptoms is highly heterogeneous, although muscle pain and weakness are usually symmetrical and proximal and affect large muscle groups including the thigh, buttock, calves, and back muscles, typically occurring 4–6 weeks after starting treatment [62]. The risk of muscle pain with statins is increased in patients aged over 80 years, as well as those with a smaller body frame, excessive alcohol intake, or hypothyroidism. The onset of new symptoms may occur with an increase in statin dose or after initiation of an interacting drug [63]. People who have exercised regularly before taking statins are less likely to experience muscle pain.

The underlying mechanisms of muscle pain in statin users are not completely elucidated. Preclinical studies showed that statins decrease mitochondrial function, attenuate energy production and alter muscle protein degradation. Additionally, statins cause spontaneous and irregular leaks of calcium from storage within muscle cells and provoke muscle contraction; unregulated calcium leak may also cause damage to muscle cells leading to muscle pain and weakness [64].

SAMS significantly contribute to very high discontinuation rates of

statin therapy (up to 75%) [65]. Anecdotally, this proportionally affects many patients with PAD who already have muscle problems in the legs. Treatment non-adherence may have a marked impact on the cardiovascular benefits of statin treatment. In one meta-analysis, patients who were adherent to statin treatment had a 15% lower risk of cardiovascular events compared with those with low adherence [66]. To overcome SAMS, the use of an alternative statin which is metabolised via different hepatic cytochromes is generally recommended, for example the use of rosuvastatin instead of atorvastatin or simvastatin or vice versa.

SAMS are manageable; studies indicate that 90% of patients reporting muscle symptoms are able to tolerate an alternative statin [67]. Another recommended approach is the combination of the maximally tolerated statin dose and a non-statin lipid-lowering therapy such as ezetimibe to attain LDL-C goal.

2.8. Conclusions

Taken together, the available literature shows that patients with PAD are at very high cardiovascular risk and should be targeted to achieve guideline-recommended LDL-C goal. Statin-based treatment has been shown to substantially reduce the risk of MACE and MALE by about 25%. The addition of a PCSK9 inhibitor further decreases this risk. Statin-based treatment has also been associated with improved walking performance, including maximum walking distance, and pain-free walking distance and duration.

Perceived or reported muscle symptoms should be assessed and every effort made to ensure that the patients remain on lipid-lowering therapy. Recommended strategies include the use of a lower statin dose combined with a non-statin lipid-lowering therapy such as ezetimibe to attain LDL-C goal.

3. Antithrombotic therapies in PAD

3.1. What can we learn from genetic studies?

Patients with PAD are at high risk of MACE and MALE due to underlying atherothrombotic disease. Genetic studies provide novel insights into thrombotic factors associated with this risk. A genome-wide association study of PAD patients and controls of the MVP (discussed previously) identified a new PAD risk variant in Factor V (Factor V Leiden) that was uniquely associated with PAD, but not other vascular beds. The association of this variant with PAD risk increased with disease severity and was highest with PAD related amputation (odds ratio 1.62) [25]. Given that Factor V Leiden is the most common cause for inherited thrombophilia, this finding underlines the prominent role of thrombosis in the pathogenesis of PAD. Another study showed that CLI in PAD patients was associated with thrombotic luminal occlusion in the absence of advanced atherosclerosis [68]. Furthermore, the close functional relationship between Factor V and Factor Xa in the coagulation cascade supports preventive approaches targeting Factor Xa, as illustrated by the COMPASS trial with the combination of low-dose rivaroxaban and aspirin versus aspirin alone [69].

3.2. What is the evidence that antithrombotic therapy reduces MACE and MALE in PAD?

Current management of symptomatic PAD includes antiplatelet monotherapy (either aspirin 75–100 mg daily or clopidogrel 75 mg daily), with improved benefit from more intense antiplatelet therapy [12, 70,71]. The Antithrombotic Trialist Collaboration study in 6200 patients with intermittent claudication demonstrated significant reduction in MACE with antiplatelet therapy (most commonly aspirin) versus control (6.4% vs 7.9%) [72]. A subsequent post hoc analysis of the CAPRIE trial (n = 6452) showed that clopidogrel was superior to aspirin in patients with clinical PAD, with significant reductions in cardiovascular mortality (hazard ratio 0.76, 95% CI 0.64–0.91) and MACE (hazard ratio 0.78, 95%

CI 0.65–0.93) [73]. Although a post hoc analysis of 3906 asymptomatic and symptomatic PAD patients included in the CHARISMA trial indicated reduction in myocardial infarction with both aspirin and clopidogrel vs. aspirin monotherapy (hazard ratio 0.63, 95% CI 0.42–0.95), this was also associated with a significantly increased risk of bleeding (hazard ratio 1.99, 95% CI 1.69–2.34) [74].

Following below-the-knee bypass grafting, dual antiplatelet therapy (DAPT) was shown to reduce the primary efficacy endpoints (composite of index-graft occlusion or revascularization, above-ankle amputation of the affected limb, or death) in patients receiving a prosthetic but not venous graft [75]. In patients with stent implantation, prolonged DAPT should be considered with a recent acute coronary syndrome and/or percutaneous coronary intervention (<1 year), stenting of the last patent coronary artery, and multiple coronary vessel disease in diabetes patients with incomplete revascularization. In support, the PRODIGY trial demonstrated benefit with prolonged DAPT (24 months vs 6 months) after acute coronary syndrome only in patients with concomitant PAD (hazard ratio 0.54, 95% CI 0.31–0.95) [76]. Additionally, the PEGASUS-TIMI 54 trial demonstrated that DAPT (ticagrelor plus aspirin) in stable patients with prior myocardial infarction (1–3 years) significantly reduced the risk of MALE (acute limb ischaemia and peripheral revascularization) in a subgroup of patients with PAD (hazard ratio 0.65, 95% CI 0.44–0.95) [77].

While plasma coagulation is also implicated as a contributor to peripheral events, trials of therapeutic anticoagulation using vitamin K antagonists in PAD patients showed little benefit and caused increased bleeding. Inhibition of thrombin generation with a low dose Factor Xa inhibitor added to antiplatelet therapy can reduce ischaemic risk, as demonstrated by the COMPASS trial in patients with stable CAD or PAD [69,78]. The combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily reduced the risk of MACE by 28% (hazard ratio 0.72,

95% CI 0.57–0.90), as well as limb events, including MALE by 46% (hazard ratio 0.54, 95% CI 0.35–0.84), acute limb ischaemia by 44% (hazard ratio 0.56, 95% CI 0.32–0.99), and MALE plus major amputation by 46% (hazard ratio 0.54, 95% CI 0.35–0.82). There was, however, an increase in major bleeding but not fatal or critical organ bleeding (hazard ratio 1.61, 95% CI 1.12–2.31). Thus, the COMPASS trial demonstrated for the first time that antithrombotic treatment in patients with PAD reduces both MACE and MALE, including amputation, although at the risk of increased bleeding [79].

Finally, VOYAGER PAD compared rivaroxaban 2.5 mg twice daily plus aspirin and aspirin alone in 6564 PAD patients who had undergone lower-extremity revascularization [80]. The primary efficacy outcome was a composite of acute limb ischaemia, major amputation for vascular causes, myocardial infarction, ischaemic stroke or cardiovascular death. Three-year Kaplan-Meier estimates showed a significant 15% reduction in the primary outcome in the rivaroxaban group (17.3% vs. 19.9% with placebo, hazard ratio 0.85, 95% CI, 0.76–0.96; $p = 0.009$). The absolute risk reduction was 1.5% at 6 months, 2.0% at one year and 2.6% at 3 years. While TIMI major bleeding did not differ significantly between the groups, the incidence of ISTH (International Society on Thrombosis and Haemostasis) major bleeding was significantly higher with rivaroxaban and aspirin than with aspirin alone. It was estimated that for every 10,000 patients treated for one year, rivaroxaban 2.5 mg twice daily added to aspirin would prevent 181 primary efficacy outcome events at the cost of 29 principal safety outcome events [80].

Taken together, the results from the VOYAGER PAD trial complement and extend findings from the COMPASS trial. Thus, for patients with extensive PAD, especially those who have undergone revascularization for PAD, addition of rivaroxaban to the treatment regimen may be considered weighing concomitantly the bleeding risk.

Recommendation 1. Statins, at the highest tolerated dose, are indicated in patients with PAD for the prevention of cardiovascular events.

Recommendation 2. Low-density lipoprotein cholesterol (LDL-C) should be lowered to <1.4 mmol/L (<55 mg/dL) and by >50% if pre-treatment values are 1.8–3.5 mmol/L (70–135 mg/dL).

Recommendation 3. Combination treatment with a statin and ezetimibe may be considered to improve LDL-C goal attainment. This approach could allow better tolerance of a lower dose of statin in patients with statin side effects.

Recommendation 4. A PCSK9 inhibitor should be added if LDL-C levels remain 50% higher than goal despite statin treatment, with or without ezetimibe.

Recommendation 5. Antiplatelet therapy is indicated to prevent further cardiovascular events. This should be either clopidogrel 75 mg/day, or the combination of aspirin 100 mg/day and rivaroxaban (2 x 2.5 mg/day).

Recommendation 6. Dual antiplatelet therapy (DAPT) should be given for at least one month after drug coated balloon angioplasty, and for 3 months after either drug eluting or covered stent implantation.

Recommendation 7. Based on results from the VOYAGER study, combination therapy with aspirin (100 mg/day) and rivaroxaban (2 x 2.5 mg/day) should be considered for DAPT post-intervention.

Fig. 4. Recommendations of the European Atherosclerosis Society/European Society of Vascular Medicine Task Force for the management of PAD patients.

4. Key recommendations

Based on the evidence discussed in this statement, this Joint EAS-ESVM Task Force provides recommendations for the management of PAD patients (Fig. 4). Optimal management of dyslipidaemia, together with guideline recommended antithrombotic therapy, are essential to improve the morbidity, disability and mortality of this increasingly prevalent – but underdiagnosed and undertreated - condition.

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Editorial note

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Declaration of competing interest

CB, IB, PPoredos none.

JJFB sits on the PAD Advisory Board of Bayer.

MB is a consultant for Biotronic, Cook Ltd and Boston scientific.

ALC participates in the speaker bureau for Akcea, Amgen, Sanofi, Esperion, Kowa, Novartis, Ionis Pharmaceuticals, Mylan, Menarini, Merck, Recordati, Regeneron, Daiichi Sankyo, Astrazeneca, Aegerion, Amryt, Sandoz. He is a consultant on advisory boards for Akcea, Amgen, Sanofi, Esperion, Kowa, Novartis, Ionis Pharmaceuticals, Mylan, Menarini, Merck, Recordati, Regeneron Daiichi Sankyo, Genzyme, Aegerion, Sandoz. The work of ALC at MultiMedica been supported by Ministry of Health - Ricerca Corrente - IRCCS MultiMedica.

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