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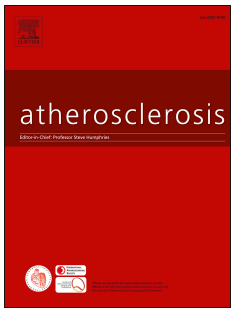

The challenge of peripheral arterial disease: How do we improve outcome?

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The challenge of peripheral arterial disease: how do we improve outcome?

Peripheral arterial disease (PAD) is a largely unrecognized complication of atherosclerotic cardiovascular disease (ASCVD). Yet PAD is very much an issue for clinicians in the 21st century, given that it typically presents in later life, usually in association with atherosclerotic complications in other vascular beds. Estimated to affect 10-20% of individuals aged 60 years or more,[1,2] the prevalence of PAD will undoubtedly escalate in response to changing population demographics and lifestyle. Already in 2010, more than 202 million individuals were affected by PAD, reflecting almost a 25% increase since 2000, with two-thirds living in low- and middle-income countries.[2] Whereas PAD increased by 13% in high-income regions over this decade, the rise in low to middle income regions was more than 2-fold (by 29%). Given that low to middle income regions have also seen larger increases in smoking and diabetes prevalence, both of which are powerful predictors of PAD,[3] there is clearly an urgent need for action to avoid this burgeoning global pandemic.

As either an initial or subsequent manifestation of ASCVD, PAD (diagnosed as an ankle-brachial index ≤0.90) is associated with more than doubling of the 10-year rates for coronary events, and cardiovascular and all-cause mortality.[4] Event rates are higher in individuals with ASCVD in multiple vascular beds (i.e. polyvascular disease).[5] There is also evidence to suggest greater coronary plaque vulnerability in both culprit and nonculprit lesions in patients with PAD with or without other cardiovascular complications.[6] Thus, the burden of PAD is substantial, both in terms of the impact on patient quality of life, as well as economic outcomes, the latter largely driven by the need for hospitalization and revascularization procedures.[7-9]

The main goals of treatment of patients with PAD are to reduce cardiovascular risk and improve functional capacity. Given the lack of awareness of PAD, however, undertreatment is an issue. The latest European guidelines recommend statin treatment in all patients with PAD, with low-density lipoprotein cholesterol (LDL-C) goals consistent with very high risk, i.e. < 1.8 mmol/L (<70 mg/dL) or a decrease by ≥50% if the initial LDL-C level is between 1.8 and 3.5mmol/L (70 and 135 mg/dL). Antiplatelet agents, angiotensin converting enzyme inhibitors/ angiotensin receptor blockers and antithrombotic agents are recommended for secondary prevention.[3] In practice, however, management is less than optimal. For example, in the US National Health and Nutrition Examination Survey (1999-2004) based on an estimated 7.1 million people with PAD, only 30% received a statin, 25% an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and only 36% aspirin.[10] Even with evidence that attainment of guideline-recommended LDL-C goal is associated with improved outcome,[11] adherence with statin therapy is often problematic.[12]

Thus, PAD represent a 'perfect storm' scenario when taking account of changing population demographics, and issues with diagnosis and treatment. Despite this, cardiovascular outcome studies have concentrated mainly on MI and stroke. Thus, new insights from the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects With Elevated Risk), which included a subgroup of patients with PAD, merit closer examination.

FOURIER: Evidence in PAD patients

The FOURIER trial showed that lowering LDL-C levels beyond guideline-recommended goals with the addition of the PCSK9 inhibitor evolocumab to intensive statin therapy reduces cardiovascular events in patients with clinical ASCVD.[13] In a separate analysis, there was no evidence to suggest a lower threshold for clinical benefit.[14] While the majority of patients in FOURIER had CHD, the trial also included a proportion of patients with PAD. Consequently, a key focus was to investigate whether the benefit observed in the overall study population would also translate to improved benefit in this PAD subgroup.

This analysis included 3,642 patients with symptomatic lower extremity PAD (defined as the presence of lower extremity intermittent claudication and an ankle brachial index <0.85, or prior peripheral revascularization or amputation for ischaemia), of whom 1,505 had no prior stroke or myocardial infarction (MI). The profile of these **patients** was consistent with that previously reported for PAD,[2] with a higher prevalence of major risk factors compared with patients without PAD (for example, hypertension: 85% versus 79% in those without PAD; smoking: 36% versus 27%; diabetes mellitus: 43% versus 35%).[15] The very high cardiovascular risk associated with PAD is reflected by absolute major cardiovascular event rates (MI, stroke or cardiovascular death; MACE] that were significantly higher than in individuals without PAD (16.8% versus 12.1% in the placebo groups, Kaplan-Meier rate at 2.5-years).

Treatment with evolocumab on top of statin resulted in comparable LDL-C reduction versus placebo to that observed in the total study population (decrease in LDL-C by 59% or 57 mg/dl [1.47 mmol/L] at 48 weeks versus statin alone), and led to a 27% (p=0.004) relative reduction in MACE event rates. The reduction in MACE events was even higher in PAD patients without prior MI or stroke (relative reduction 43%, p=0.0095, Table 1). As shown in the FOURIER study as a whole, the lower the level of achieved LDL-C the greater the benefit, with no lower threshold for benefit.

Evolocumab treatment was also associated with a 37% relative reduction in risk for major adverse limb events (MALE), defined as acute limb ischaemia, major amputation, or urgent peripheral revascularization for ischaemia; this reduction was even higher in PAD patients without a

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