

Anti-platelet therapy: Is it all over in peripheral artery disease?

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Peripheral artery disease (PAD) is probably much more common and important than we perceive, ranging in prevalence from 6% among patients over the age of 55 years to 18% based on Caucasian European populations (1). The prevalence of PAD rises with age, to 20% in those over 70 and even up to 60% in those over 85 years old (2). Patients with PAD have a three-fold risk of myocardial infarction, stroke, or death from cardiovascular causes (3). PAD is also well associated with a high amputation risk and poor quality of life, especially affecting those with diabetes, therefore creating a substantial economic burden (4).

The most recognised clinical manifestation of PAD is intermittent claudication of the lower limbs. This “pain” however intermittent is caused by ischaemia secondary to atherosclerotic arterial narrowing and is clearly a manifestation of systemic atherosclerosis (3). Indeed, a low ankle brachial pressure index (ABI) has been shown to be predictive of coronary heart disease and all-cause mortality (4) (relative risk 1.60; 95% confidence interval [CI] 1.32–1.95) (5). Over a five-year period, those with an ABI ≤ 0.9 have a two-fold risk of a cardiovascular event compared to those with an ABI > 0.9 (6). The Framingham Offspring Study in 1999 reported a PAD prevalence of 90% in those who undergo coronary angiography (7). Yet, PAD remains the most undermanaged, underdiagnosed, and understudied of all manifestations of atherosclerotic disease.

Known risk factors of other atherosclerotic disease are similar for PAD, and include age, smoking, high blood pressure and hyperlipidaemia. Disease risk factor modification studies have suggested that risk factor control itself is inadequate, and other therapeutic requirements are necessary in PAD. Other pathophysiological processes, such as low-grade inflammation may be involved, as the latter is independent risk factor for PAD (8, 9). Most recently, homocysteine, C-reactive protein, fibrinogen, lipoprotein, hypercoagulability and increased platelet activity have all been implicated as risk factors for atherosclerosis (10, 11).

In PAD, the main pathological process of obstruction of the arteries is caused by atherothrombosis, embolism, arteritis, and aneurysms (12). Platelets play an important role in the process of thrombosis at the site of plaque formation (13). Platelet activation markers, such as soluble CD40 ligand and P-selectin (14) levels, have been increased in studies of patients with PAD (15, 16). Urinary 11-dehydrothromboxane B2 has also been found to be increased in PAD, implicating a further platelet component (13).

The modern management of PAD is largely directed to symptom control but emphasis is directed mainly to prevention of systemic complications with ‘best medical therapy’, with percutaneous or surgical revascularisation being considered where optimised medical therapy fails. Indeed, the similarities between atherosclerotic risk factors and the role of platelets in both cardiovascular and cerebrovascular diseases have led to extensive extrapolation of evidence derived from coronary artery disease to PAD, for example, with regard to the use of anti-platelet agents (17, 18).

In this issue of *Thrombosis and Haemostasis*, Basili et al. (19) report results of a meta-analysis of 29 clinical randomised trials on anti-platelet therapy in PAD, assessing their prevention of cardiovascular

adverse events (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death). Their primary outcome measures showed a statistically significant effect of antiplatelet treatment on claudication (16%). For secondary outcomes, theophylline was associated with a statistically significant reduction of clinical outcomes (22%) when compared with control. Both aspirin (-15%) and picotamide (-21%) showed a reduction in cardiovascular outcomes but this was not shown to be statistically significant, and therefore their use was felt to be inconclusive. As recognised by Basili et al., sample sizes throughout the meta-analysis were small, and this lowers the power of the study to detect a meaningful statistical difference in measuring primary and especially secondary outcomes.

Given that PAD is generally understudied, this point surely affects any conclusions drawn from this meta-analysis or for that matter, what any other similar analysis can derive without further randomised control trials. Although claudication is the classical presentation of PAD, it is now known that most PAD patients are actually asymptomatic. Therefore, most of the trials reviewed by Basili et al. are outdated or even limited by their own inclusion criteria. The reader would want to know more about the individual data or characteristic risk factors used for various comparisons.

Importantly, PAD is commonly found in diabetic patients, yet only a few of the trials included in this study represent this important subset of patients. In the Framingham Heart Study, for example, 20% of the symptomatic PAD patients had diabetes mellitus (20). How does one interpret the effect of antiplatelet treatment on PAD without knowing how diabetes may or may not play a role in the overall significance of the results? For example, Falconer et al. (12) used cilostazol (an inhibitor of phosphodiesterase 3) and demonstrated no significant increase in walking distance between

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the diabetic and non-diabetic patients in a stable claudicants, but those with severe PAD with diabetes had a greater percentage increase (34%) in walking distance. Clearly, this is an example of an effect of diabetes on PAD management.

Current guidelines are largely driven by data from the AntiThrombotic Trialists' Collaboration (ATTC) meta-analysis, and recommend a dose of 75 mg to 325 mg aspirin for patients with PAD (21). In comparing the effects of different antiplatelet agents, the ATTC found no clear evidence of any differences in the effects between the various agents (22). Primary prevention studies demonstrate a 12% reduction in adverse outcomes but in secondary prevention studies, aspirin itself reduced the risk of vascular events by a fifth (21).

What do recent clinical trials tell us?

The POPADAD study (23) included patients who were diabetic with PAD, who were asymptomatic for cardiovascular disease, and reported no benefit for aspirin therapy with a hazard ratio (HR) of 0.98 (95%CI) (24). Indeed, mortality was no different between aspirin and placebo. The criticism of this trial is that although it adds to the evidence that aspirin is likely no to be of benefit in primary prevention it was probably severely underpowered.

In patients with cardiovascular disease, clopidogrel offers a small advantage over aspirin (25). In the CHARISMA trial (26) the symptomatic subgroup patients with documented cardiovascular disease showed a marginal benefit of dual therapy with clopidogrel with aspirin (6.9%) versus aspirin (7.9%) alone. When a comparison of subgroups with PAD was made to others studies, namely the CAPRIE trial (25), the cardiovascular event reduction rate escalated to 46% in the whole population and 16% in the PAD group (25, 26). The trial was felt to be underpowered and its subgroup analysis showed a reduction which questions the current trend against guidelines.

The JPAD trial (27) included 2,539 patients with PAD and type 2 diabetes. The

trial set out to demonstrate the efficacy of anti-platelet agents in preventing cardiovascular events in this group of patients. Patients were followed up for 4.4 years and aspirin was associated with a non-significant reduction HR .80 (95% CI) in fatal/non-fatal atherosclerotic events, with no difference in all cause mortality (HR .90). However, this study was again statistically underpowered to detect differences between therapies and adverse effects. When analysing the events per patient ratio to demonstrate a significant difference, surely a longer follow-up was required in order to draw conclusion from the primary endpoint and question current guidelines. Interestingly, in the subgroup analysis of patients over 65 years of age there was a significant reduction with aspirin when compared to control (HR .68, CI 95%) in prevention of atherosclerotic events. Is this unassuming benefit to go unnoticed?

In September 2009, the Aspirin for Asymptomatic Atherosclerosis (AAA) trial (28) results were reported at the European Society of Cardiology meeting. This trial randomised 3,350 patients at high risk for cardiovascular and cerebrovascular accidents with the use of ABI ≤ 0.95 (28). The study concluded that aspirin had no effect on reported events when compared to placebo, but increased the risk of major haemorrhage. The trial again was probably underpowered, and many patients were non-compliant (40%).

Thus, these contemporary trials have been disappointing for the benefits of aspirin. Perhaps the incremental effect of aspirin over and above the effects of other well established 'best medical therapy' drugs such as statins and angiotensin-converting enzyme (ACE) inhibitors, as well as the recognition of good blood pressure control and smoking cessation, etc – has resulted in the non-significant effects of aspirin observed in recent trials.

Furthermore, the use of anti-platelet agents in graft patency merits a brief comment. For example, Dixon et al reports 4.5 years of follow-up of 640 patients that the use of dipyridamole plus aspirin had a significant effect in reducing stenosis and improving the patency of new grafts (29).

What are the implications for guidelines?

How can these data be interpreted in support of guideline changes? If one were to only look at the CLIPS trial (30), one would see a trial which included both asymptomatic PAD patients as well as a high number of diabetic subjects but unfortunately was let down with poor follow-up with a mean of only two years and only 366 of the planned 2,000 patients randomised. In the aspirin alone group, there was a 65% risk reduction in cardiovascular events.

However, evidence based guidelines cannot be drawn from an under-diagnosed condition and trials with underpowered statistical analysis. PAD management needs better conducted clinical trials independent of those on cardiovascular disease extrapolation. Understandably, patient recruitment, compliance and awareness need to be improved but ignoring the increasing prevalence of the disease cannot continue. In the United States, in those over the age of 40 years, 8–12 million people are affected by PAD (3), and this number is increased to >27 million when Europe is added (31).

Can we really ignore that the prevalence will increase further with our ageing population, increasing diabetic and renal disease patterns? In perspective, following the diagnosis of claudication in five years, a quarter of these patients would have died. The cause mostly attributed to cardiovascular or cerebrovascular event. Of the existing patients, 25% would have experienced a non-fatal event during that period (32). At this point, the pragmatist would argue that any risk reduction would be relevant.

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