

Antithrombotic therapy in peripheral artery disease – antiplatelet therapy, anticoagulants, both or none

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Introduction

Peripheral arterial disease (PAD) is characterised by a progressive narrowing or occlusion of the major arteries in the lower limbs as a result of atherosclerosis. PAD has a high incidence and prevalence, but often goes unnoticed as approximately two thirds of patients with PAD are asymptomatic (1, 2). The prevalence of symptomatic PAD ranges between 3% and 11% (1–4), while an overall prevalence including symptomatic and asymptomatic PAD was reported up to 30% at the age of 70 years or older (4). Apart from age, risk factors and biomarkers associated with PAD are male sex (5, 6), black race (7), smoking (8), diabetes (9), hypertension (10), renal insufficiency (11, 12), dyslipidaemia (13), C-reactive protein (13), and fibrinogen (13). Symptoms vary from mild intermittent claudication, to critical limb ischaemia resulting in rest pain and eventually ulceration, tissue loss and gangrene, forcing to amputation (14).

Besides lower limb complications, patients with PAD are at high risk of cardiovascular and cerebrovascular ischaemic events, for PAD is just one manifestation of atherosclerosis, a systemic disease affecting the whole arterial system (15, 16). Also, patients with PAD may have activated platelets as indicated by biomarkers such as soluble CD40 ligand and P-selectin (17, 18), as well as procoagulant activity as

measured by higher circulating tissue factor levels compared with healthy controls (19). In comparison with patients with coronary artery disease (CAD) or cerebrovascular disease (CVD), patients with PAD have the highest risk of all-cause or vascular death, and the second highest risk of myocardial infarction (MI) and stroke (16). Despite the growing awareness that asymptomatic PAD is an important marker of generalised atherosclerosis, the systemic consequences, even of symptomatic PAD, are still underestimated in comparison with the presence of CAD and CVD (20).

Treatment of PAD

Progression of atherosclerotic disease is prevented by management of cardiovascular risk factors and co-morbidities through lifestyle modification and pharmacotherapy, including antithrombotics, antihypertensives and statins. Although PAD progresses pathologically, its symptoms remain fairly stable over time (21, 22). Only about 25% of PAD patients require local treatment (21, 22). Local treatment of disabling intermittent claudication or critical limb ischaemia consists of revascularisation by means of percutaneous transluminal angioplasty (PTA), with or without stenting, endarterectomy or bypass surgery, pending on clinical symptoms, co-morbidities and anatomy of vessels and lesions (23).

respectively, no statistically significant reduction in odds of cardiovascular death, MI or stroke was demonstrated, although the trends were favouring antiplatelet therapy compared with no antiplatelet therapy. A pooled odds ratio (OR) for these three specific PAD categories was not reported. In the updated meta-analysis published in 2002, antiplatelet drugs have been shown to reduce the odds of non-fatal MI, non-fatal stroke, and cardiovascular death statistically significant with 23% in the pooled cohorts with PAD, the effect being consistent across patients with and without vascular interventions (25). It is important though to realise that the trials included were small, nearly two-third of the trials studied platelet inhibitors other than aspirin, and they were individually inconclusive. Hence, there is no formal evidence that aspirin is effective for the prevention of vascular events in patients with PAD, but because the effects of aspirin in PAD patients are consistent with the overall high risk population and with the overall effect of platelet inhibitors, it became the first choice therapy. Aspirin dose comparisons revealed no differences in effect, therefore lifelong use of aspirin is advised in current PAD guidelines at a once daily low dose of 75 mg to 100 mg (23, 26). So far, only the CHARISMA trial provided data on dual antiplatelet therapy with aspirin and clopidogrel compared with aspirin. A post-hoc analysis of the cohort included with PAD demonstrated a non-significant 15% relative risk (RR) reduction for cardiovascular death, MI, or stroke, at the cost of a significant two-fold risk increase of minor bleeding (27). Patients who do not tolerate aspirin are recommended clopidogrel 75 mg once daily as an alternative (23, 26), based on the subgroup analysis in the CAPRIE trial that showed a 24% RR reduction of cardiovascular events in PAD patients treated with clopidogrel vs. aspirin, with similar bleeding risks in both treatment

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Antiplatelet therapy

The mainstay of antiplatelet therapy is aspirin, initially provoked by the meta-analysis of randomised trials of antiplatelet therapy published by the Antiplatelet Trialists' Collaboration in 1994 (24). Interestingly, in the pooled cohorts with claudication, peripheral grafts, or peripheral angioplasty,

groups (27). The main reason for this restricted recommendation is the higher costs of clopidogrel.

The lack of formal evidence for aspirin in patients with PAD prompted first Berger et al. recently to conduct a meta-analysis that included only randomised trials (n=18) comparing aspirin, with or without dipyridamole, with placebo or control (28). This resulted in a pooled RR for non-fatal MI, non-fatal stroke, or cardiovascular death of 0.88 (95% confidence interval [CI], 0.76–1.04) for all trials including a total of 5,269 patients, and for aspirin monotherapy vs. placebo or control (N=3019) the RR was 0.75 (95% CI, 0.48–1.18). Importantly, 41% of the weight in the pooled analysis came from the POPADAD trial (29), which showed no effect of aspirin relative to placebo at all in patients with diabetes mellitus and asymptomatic PAD. Excluding this trial with 1,276 patients from the meta-analysis resulted in an outcome event rate of 6.7% in the cohorts treated with aspirin (with or without dipyridamole) vs. 8.9% in the control group, a RR of 0.83 (95% CI, 0.67–1.02), corresponding with 17% RR reduction, only just failing statistical significance. This lack of statistical significance is in our view firstly due to heterogeneity of trials and insufficient effect size, as different populations were included and many trials were not specifically designed for cardiovascular outcome assessment. Secondly it is due to low statistical power, caused by the small number of patients included in the separate trials (239 on average excluding the POPADAD trial), and even the pooled number of patients (5,269) is 20-times lower than the 103,149 patients with CAD and CVD included in the Antiplatelet Trialists' Collaboration meta-analysis (25).

Secondly, Basili et al. had a different approach by meta-analysing 29 antiplatelet trials that only included patients (N=10,735) with claudication or an ankle-brachial index ≤ 0.99 , the manifestation in the majority of PAD patients, thus excluding trials that had enrolled surgically treated patients or patients with critical ischaemia (30). The OR for cardiovascular death, MI, or stroke with any antiplatelet therapy vs. control was 0.84 (95% CI, 0.73–0.97). This was mainly driven by the

10 trials (N=5,095) with thienopyridines (OR 0.78; 95% CI, 0.64–0.95). Importantly, nine of these trials allocated patients to ticlopidine, although effective, a thienopyridine hardly used anymore for haematologic safety reasons. The tenth trial, that attributed 51% of the weight, was the PAD subgroup of the earlier mentioned CHARISMA trial (27), that compared aspirin plus clopidogrel vs. aspirin alone, i.e. comparing two antiplatelet regimens. The odds ratio of the four trials that allocated to aspirin or control (N=1,900) was 0.85 (95% CI, 0.65–1.10), thus a small and non-significant effect size, also here caused by the POPADAD trial (26), that contributed 1,600 of the 1,900 patients, and attributed 72% weight to the pooled result.

In conclusion, to date there is no evidence for antiplatelet therapy in patients with asymptomatic PAD and without CAD or CVD. Despite the paucity and shortcomings of individual trials and meta-analyses resulting in lack of formal evidence, the current recommendations are to treat all symptomatic PAD patients who are at risk for not only peripheral complications but also for ischaemic events in other arterial beds with low-dose aspirin. Therefore, and given the high burden and costs of an adequately designed and sufficiently large trial, it is unlikely that this formal evidence will ever become available. Because of the high risks of these events, also when treated with aspirin, we plead for the need of sufficiently sized trials to study the benefits and risks of newer, potentially more effective antiplatelet agents in PAD patients. One such trial (TRA 2P-TIMI 50, trial identifier NCT00526474) that studies the effect of adding a thrombin receptor antagonist (SCH 530348) to standard antiplatelet therapy, including aspirin and clopidogrel, in a broad range of patients with atherosclerosis, including PAD, is underway.

Anticoagulant therapy

Oral anticoagulants (OAC) have been widely used for more than 30 years, especially in Europe, without clear evidence of efficacy and safety. Only four small randomised trials including in total 793 patients compared long-term OAC with con-

trol in patients with prior lower limb revascularisation or intermittent claudication (reference [32] describes two subsequent trials in chronic PAD patients by De Smit and Van Urk) (31–33). Pooling of data demonstrated that OAC treatment was associated with trend toward reduced all-cause mortality (OR, 0.73; 95% CI, 0.5–1.07), graft occlusion was significantly lower (OR, 0.63; 95% CI, 0.44–0.89), at the cost of an increased major bleeding risk (OR, 3.46; 95% CI, 2.03–6.56).³⁴

Antiplatelet or anticoagulant therapy?

Hope for a more effective treatment than aspirin triggered a few investigators to conduct head to head comparative trials.

The Dutch BOA Study included from 1995 until 1998 a total of 2,650 patients after infra-inguinal bypass surgery from 77 medical centres throughout the Netherlands (35). To study the effects of OAC and aspirin in preventing bypass occlusion, lower limb amputation, and ischaemic events, these patients were randomly allocated to OAC with a target international normalised ratio (INR) range of 3.0–4.5 or aspirin (100 mg carbasalate calcium daily). After a mean follow-up period of 21 months no overall difference in graft occlusions was found; however, pre-specified analysis by graft material demonstrated that OAC had a favourable effect in preventing vein graft occlusions (hazard ratio [HR], 0.69; 95% CI, 0.54–0.88), whereas aspirin showed better results in patients with non-venous grafts (HR, 1.26; 95% CI, 1.03–1.55). Although underpowered for assessing the risk of the composite outcome of vascular death, MI, stroke or amputation, a tendency favouring anticoagulation compared aspirin was found (HR, 0.89; 95% CI, 0.75–1.06), at the cost of a two-fold increase in major bleeding risk (HR, 1.96; 95% CI, 1.42–2.71).

With the greater risk of bleeding with anticoagulant therapy, guidelines recommend antiplatelet treatment after infra-inguinal bypass surgery to prevent graft occlusion regardless of bypass material, and stress only to apply OAC in patients at high risk of bypass occlusion or limb loss (26).

In our view, the only indication for OAC is to preserve venous graft patency, hereby bearing in mind that it is generally also more effective in lowering the rate of ischaemic events, including amputations, at an acceptable risk of bleeding. The second trial, the WAVE trial, included a mixed population with symptomatic PAD in the lower extremities (82%) and carotid or subclavian arteries (36). Between April 2000 and September 2003, 2,161 patients from seven countries were randomly allocated to OAC (target INR 2.0–3.0) plus antiplatelet therapy (aspirin, or thienopyridines in 8%), or antiplatelet therapy (aspirin, or thienopyridines in 6%), and followed for a mean of 35 months. The risk of MI, stroke, or death from cardiovascular causes did not differ significantly between the two antithrombotic regimens (RR, 0.92; 95% CI, 0.73 to 1.16). On the other hand a more than three-fold increase in life-threatening bleeding was found (RR, 3.41; 95% CI, 1.84 to 6.35), as well as similar increases in moderate and minor bleeding complications.

Bleeding complications and consequences

From research in populations with CAD and CVD evidence showing the adverse consequences from bleeding complications in terms of mortality and ischaemic vascular events is piling up (37–42). Until recently, the outcome after bleeding complications in patients with PAD has not been studied. We found that also in patients with PAD, as in patients with CAD or CVD, major bleeding was independently associated with major ischaemic complications. In the cohort included in the Dutch BOA Study, major bleeding was associated with a three-fold increased risk of subsequent ischaemic events (crude HR, 3.0; 95% CI, 1.9–4.6; adjusted HR, 3.0; 95% CI, 1.9–4.7) (43). A subsequent study in a larger and more heterogeneous PAD cohort, created by merging the BOA and WAVE databases, will shed further light on this important matter and will hopefully provide improved risk models to predict bleeding and ischaemic complications. As a consequence

of the association between bleeding and subsequent increased risk for ischaemic complications, future antithrombotic therapies with new antiplatelet and anticoagulant drugs have to be, besides effective, safe in terms of not increasing and ideally decreasing the bleeding risk, relative to current regimens.

Conclusions

In conclusion, the mainstay of antithrombotic therapy in symptomatic PAD patients remains low-dose aspirin. OAC may be used in patients treated with venous bypass grafts, specifically with high risk for occlusion as is the case with for example long, distal grafts. Clearly, the combination of anticoagulant and antiplatelet therapy cannot be recommended in a broad PAD population. Until today, no data are available to support OAC alone in PAD patients. For the relative paucity of data in PAD patients we plead for the conduct of trials with new antiplatelet therapies and with new anticoagulants such as direct thrombin inhibitors and factor Xa inhibitors, that may increase efficacy without increasing bleeding risks.

References

1. Fowkes FG, Housley E, Cawood EH, et al. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1991; 20: 384–392.
2. Stoffers HE, Rinkens PE, Kester AD, et al. The prevalence of asymptomatic and unrecognized peripheral arterial occlusive disease. *Int J Epidemiol* 1996; 25: 282–290.
3. Criqui MH, Fronek A, Barrett-Connor E, et al. The prevalence of peripheral arterial disease in a defined population. *Circulation* 1985; 71: 510–515.
4. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *J Am Med Assoc* 2001; 286: 1317–1324.
5. Balkau B, Vray M, Eschwege E. Epidemiology of peripheral arterial disease. *J Cardiovasc Pharmacol* 1994; 23 (Suppl 3): S8–16.
6. Kannel WB, Skinner JJ, Jr., Schwartz MJ, et al. Intermittent claudication. Incidence in the Framingham Study. *Circulation* 1970; 41: 875–883.
7. Kennedy M, Solomon C, Manolio TA, et al. Risk factors for declining ankle-brachial index in men and women 65 years or older: the Cardiovascular Health Study. *Arch Intern Med* 2005; 165: 1896–1902.
8. Price JF, Mowbray PI, Lee AJ, et al. Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease: Edinburgh Artery Study. *Eur Heart J* 1999; 20: 344–353.
9. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 2004; 141: 421–431.
10. Safar ME, Priollet P, Luzy F, et al. Peripheral arterial disease and isolated systolic hypertension: the ATTEST study. *J Hum Hypertens* 2009; 23: 182–187.
11. O'Hare AM, Vittinghoff E, Hsia J, et al. Renal insufficiency and the risk of lower extremity peripheral arterial disease: results from the Heart and Estrogen/Progestin Replacement Study (HERS). *J Am Soc Nephrol* 2004; 15: 1046–1051.
12. O'Hare AM, Rodriguez RA, Bacchetti P. Low ankle-brachial index associated with rise in creatinine level over time: results from the atherosclerosis risk in communities study. *Arch Intern Med* 2005; 165: 1481–1485.
13. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *J Am Med Assoc* 2001; 285: 2481–2485.
14. Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg* 1997; 26: 517–538.
15. Dawson I, Sie RB, van der Wall EE, et al. Vascular morbidity and mortality during long-term follow-up in claudicants selected for peripheral bypass surgery. *Eur J Vasc Endovasc Surg* 1998; 16: 292–300.
16. Steg PG, Bhatt DL, Wilson PW, et al. One-year cardiovascular event rates in outpatients with atherosclerotic disease. *J Am Med Assoc* 2007; 297: 1197–1206.
17. Bennett PC, Silverman SH, Gill PS, et al. Peripheral arterial disease and Virchow's triad. *Thromb Haemost* 2009; 101: 1032–1040.
18. Blann AD, Tan KT, Tayebjee MH, et al. Soluble CD40L in peripheral artery disease. Relationship with disease severity, platelet markers and the effects of angioplasty. *Thromb Haemost* 2005; 93: 578–583.
19. Rao AK, Vaidyula VR, Bagga S, et al. Effect of antiplatelet agents clopidogrel, aspirin, and cilostazol on circulating tissue factor procoagulant activity in patients with peripheral arterial disease. *Thromb Haemost* 2006; 96: 738–743.
20. McDermott MM, Mehta S, Ahn H, et al. Atherosclerotic risk factors are less intensively treated in patients with peripheral arterial disease than in patients with coronary artery disease. *J Gen Intern Med* 1997; 12: 209–215.
21. Dormandy J, Mahir M, Ascady G, et al. Fate of the patient with chronic leg ischaemia. A review article. *J Cardiovasc Surg (Torino)* 1989; 30: 50–57.
22. Hertzner NR. The natural history of peripheral vascular disease. Implications for its management. *Circulation* 1991; 83: 112–119.
23. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *Eur J Vasc Endovasc Surg* 2007; 33 (Suppl 1): S1–S5.
24. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myo-

- cardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. *Br Med J* 1994; 308: 81–106.
25. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *Br Med J* 2002; 324: 71–86.
 26. Sobel M, Verhaeghe R. Antithrombotic therapy for peripheral artery occlusive disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133: 815S–843S.
 27. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996; 348: 1329–1339.
 28. Berger JS, Krantz MJ, Kittelson JM, et al. Aspirin for the prevention of cardiovascular events in patients with peripheral artery disease: a meta-analysis of randomized trials. *J Am Med Assoc* 2009; 301: 1909–1919.
 29. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *Br Med J* 2008; 337: a1840.
 30. Basili S, Raparelli V, Vestri A, et al. Comparison of efficacy of antiplatelet treatments for patients with claudication. A meta-analysis. *Thromb Haemost* 2010; 103: 766–773.
 31. Arfvidsson B, Lundgren F, Drott C, et al. Influence of coumarin treatment on patency and limb salvage after peripheral arterial reconstructive surgery. *Am J Surg* 1990; 159: 556–560.
 32. de Smit P, van Urk H. Dutch oral anticoagulation trial. *Act Chir Austr* 1992; 24: 5.
 33. Kretschmer G, Herbst F, Prager M, et al. A decade of oral anticoagulant treatment to maintain autologous vein grafts for femoropopliteal atherosclerosis. *Arch Surg* 1992; 127: 1112–1115.
 34. The effects of oral anticoagulants in patients with peripheral arterial disease: rationale, design, and baseline characteristics of the Warfarin and Antiplatelet Vascular Evaluation (WAVE) trial, including a meta-analysis of trials. *Am Heart J* 2006; 151: 1–9.
 35. The Dutch BOA Study Group. Efficacy of oral anticoagulants compared with aspirin after infrainguinal bypass surgery (The Dutch Bypass Oral Anticoagulants or Aspirin Study): a randomised trial. *Lancet* 2000; 355: 346–351.
 36. Anand S, Yusuf S, Xie C, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med* 2007; 357: 217–227.
 37. Budaj A, Eikelboom JW, Mehta SR, et al. Improving clinical outcomes by reducing bleeding in patients with non-ST-elevation acute coronary syndromes. *Eur Heart J* 2009; 30: 655–661.
 38. Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation* 2006; 114: 774–782.
 39. O'Donnell MJ, Kapral MK, Fang J, et al. Gastrointestinal bleeding after acute ischemic stroke. *Neurology* 2008; 71: 650–655.
 40. Rao SV, O'Grady K, Pieper KS, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. *Am J Cardiol* 2005; 96: 1200–1206.
 41. Segev A, Strauss BH, Tan M, et al. Predictors and 1-year outcome of major bleeding in patients with non-ST-elevation acute coronary syndromes: insights from the Canadian Acute Coronary Syndrome Registries. *Am Heart J* 2005; 150: 690–694.
 42. Spencer FA, Moscucci M, Granger CB, et al. Does comorbidity account for the excess mortality in patients with major bleeding in acute myocardial infarction? *Circulation* 2007; 116: 2793–2801.
 43. van Hattum ES, Algra A, Lawson JA, et al. Bleeding increases the risk of ischemic events in patients with peripheral arterial disease. *Circulation* 2009; 120: 1569–1576.