The peripheral arterial disease subgroup in the CHARISMA trial: does it tell us anything new?

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This editorial refers to ‘Patients with peripheral arterial disease in the CHARISMA trial1† by P.P. Cacoub et al. on page 192

Peripheral arterial disease (PAD) is recognized as a serious cardiovascular disorder, in both epidemiological and prognostic terms. PAD is estimated to affect >27 million patients in Europe and the USA alone, and its prevalence is expected to increase further because it is typically associated with type II diabetes mellitus and with advanced age, conditions that will both steadily increase in the next decades.1 PAD patients are at markedly increased risk of major cardiovascular events; in particular, PAD is associated with a cardiovascular risk similar to that of patients with a previous myocardial infarction (MI) and with a life expectancy comparable with that of patients with some of the most common tumours.1,2 Patients with a previous MI or stroke who also have asymptomatic PAD have a significantly worse cardiovascular prognosis,3 and the combined presence of a low ankle–brachial index (ABI; ≤0.9) and traditional cardiovascular risk factors approximately doubles the risk of total mortality, cardiovascular mortality, and major coronary events across all risk score categories.4

However, paradoxically, despite the epidemiological and prognostic importance of PAD, relatively few clinical trials with cardiovascular protective agents have been carried out specifically in PAD; in particular, antiplatelet therapy is used in PAD based essentially on meta-analyses,5 extrapolation of results from trials in other conditions,6 or subgroup analyses of large clinical trials enrolling patients with various clinical manifestations of atherosclerosis,7 and not on results of clinical trials specifically enrolling patients with various clinical manifestations of atherosclerosis. Moreover, it highlights that this population is still largely undertreated: a significantly lower percentage of them were treated with statins or angiotensin-converting enzyme (ACE) inhibitors as compared with patients with a previous MI or stroke. Indeed, despite the widening of the therapeutic armamentarium, PAD patients still face a high incidence of cardiovascular events. If one compares the annual event rate of the aspirin-treated patients in the CAPRIE trial (5.83%)7 with that of the aspirin group in the CHARISMA trial (3.12%),9 carried out 10 years later, and then makes the same comparison for the PAD subgroups of the two trials, the event rate decreases by 46% in the whole population at risk but only by 16% in the PAD subgroup. One likely explanation of this discrepancy is the low implementation of secondary prevention treatments in PAD.

In a previous post hoc analysis of patients with prior MI, ischaemic stroke, or symptomatic PAD in the CHARISMA trial, a significant incremental benefit of adding clopidogrel to aspirin was evident in patients with previous MI or stroke but not in patients with PAD.11 The present post hoc analysis differs from the previous one because it cumulates 258 asymptomatic PAD patients to the 2838 symptomatic patients previously analysed, and this allows significant superiority of aspirin plus clopidogrel to be shown on two cardiovascular
endpoints. This rather striking gain obtained by the addition of only a small group of patients is doubly strange if one considers that the group of asymptomatic PAD patients belongs to the larger asymptomatic subgroup of the whole CHARISMA trial population in which there was a 20% relative increase in the rate of major cardiovascular events with clopidogrel and a highly statistically significant increase of cardiovascular death. One additional perplexing finding comes from the comparison of the PAD subgroup in the CAPRIE and CHARISMA trials. The large benefit of clopidogrel vs. aspirin in the PAD subgroup of the CAPRIE trial has been interpreted as an expression of the lack of efficacy of aspirin in PAD. If this were true, one would expect that the combination of clopidogrel plus aspirin should provide approximately the same benefit over aspirin as that shown by clopidogrel alone vs. aspirin in the CAPRIE trial; this was not the case, suggesting once again that subgroup post hoc analyses, even from large clinical trials, may provide misleading results.

One unexplained finding of the present subanalysis is that the bleeding risk of PAD patients tended to be higher compared with the rest of the population at risk, independently of treatment; moreover, MI, the endpoint for which superiority of the drug combination was shown, was the least frequent outcome event, while epidemiologically it is the most frequent cardiovascular event in PAD. In addition, diabetes, the most important risk factor for PAD, was less prevalent in the PAD population than in the non-PAD population, although this may be due to the inclusion criteria of the trial. Although sometimes unexpected findings in clinical trials may hide important clinical information, it is quite plausible that some of the odd results of the present post-hoc analysis may be due to chance because of the fragmentation generated by subgroup analyses. Risks of subgroup analyses have been previously highlighted and are not limited solely to the increased likelihood of spurious significant results, but also to the fact that the effects found are composite, and it may be difficult to attribute them only to a differential clopidogrel benefit in the two treatments groups.

One eye-catching observation of this subgroup analysis is that PAD patients in the CHARISMA trial tended to be on a significantly lower aspirin dose than the rest of the patient population, a potentially interesting finding in view of recent results showing that higher urinary 11-dehydro thromboxane B2 levels were a determinant of cardiovascular risk in the CHARISMA population, and that aspirin doses <150 mg/day were associated with higher urinary 11-dehydro thromboxane B2. However, randomization to clopidogrel did not reduce the hazard of cardiovascular events in patients with high urinary 11-dehydro thromboxane B2 excretion, and this sounds as if it is contradictory to the present subgroup analysis in PAD.

The PAD subgroup of the CHARISMA trial does not tell us anything that may change the current therapeutic indications for PAD. Cacoub and co-workers correctly acknowledge that their results should be viewed as merely hypothesis generating and that they need confirmation with appropriately designed prospective studies, but it is hard to expect that, based on these findings, someone will embark on a prospective trial on the combination of aspirin plus clopidogrel in the overall PAD patient population. Cardiovascular risk reduction in PAD involves multiple approaches, including walking exercise, risk factor modifications, and the use of statins or ACE inhibitors. Improvement of the cardiovascular prognosis of PAD may come from the better implementation of cardioprotective medications and from improved efficacy of antiplatelet treatments. It seems more likely that novel approaches, such as the antagonism of thromboxane receptors or of the thrombin PAR-1 receptor, will improve efficacy over aspirin in PAD rather than the addition of clopidogrel to aspirin.

**Conflict of interest:** none declared.

**References**

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