CORONARY AND PERIPHERAL ARTERY ATHEROSCLEROSIS: WHAT CHOICE FOR ANTIPLATELET THERAPY

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Abstract

Atherosclerosis is a systemic, multifocal chronic inflammatory disorder involving various vascular districts and leading to variable symptoms and vascular events. Peripheral Arterial Disease (PAD) represents one frequent initial manifestation of atherosclerosis. Moreover, the prevalence of PAD has been steadily raising over the last decades. Patients with PAD have a 2-3 fold increased risk of MI, stroke and vascular death, but, PAD greatly magnifies ischemic risk also in patients with a previous myocardial infarction and in patients with an acute coronary syndrome.

This brief overview discusses the evidence of the efficacy of available antiplatelet treatments in patients with PAD without or with concomitant coronary artery disease.

Peripheral arterial disease: epidemiology and pathophysiology

Atherosclerosis is a systemic, multifocal chronic inflammatory disorder involving various vascular districts and leading to variable symptoms and vascular events. The initial clinical presentation of athero-thrombotic cardiovascular disease labels the patient as coronary, cerebrovascular or peripheral and the choice of antiplatelet agents and evidence of their efficacy for secondary prevention are significantly influenced by this. From a recent large cohort study on almost 2 million people aged ≥30 years and free from cardiovascular problems it turns out that the majority of initial cardiovascular manifestations (66%) are not myocardial infarctions, and that almost 50% are not coronary [1]. Peripheral Arterial Disease (PAD) represents one frequent initial manifestation of atherosclerosis. Peripheral arterial disease has a prevalence of 6 to 18% in

the population above 55 years, with a steady increase with ageing reaching over 20% at 70 years and up to 60% over 85 years. This translates in over 8.5 million cases in the USA and over 200 million worldwide. Moreover, the overall prevalence of PAD has been raising over the last decades, with a 23% rise from 2000 to 2010, both in high- and low-income countries and in both males and females, making it a serious public health problem [2]. Patients with PAD have a 2-3 fold increased risk of MI, stroke and vascular death with an annual event rate of around 5%. Moreover, differently from what previously thought, local disease progression is rather frequent, with up to 27% of patients eventually undergoing amputation [3-6].

Not only PAD increases the cardiovascular risk when manifesting alone, but it also greatly magnifies ischemic risk in patients with a previous myocardial infarction. For example, a recent post-hoc analysis of the PEGASUS-TIMI 54 trial, that evaluated whether the addition of either of two doses of ticagrelor (90 and 60 mg b.i.d.) to aspirin reduces recurrent ischemic cardiovascular events in stable patients with prior myocardial infarction [7], showed that the presence of concomitant PAD is associated with a greatly increased ischemic risk [8]. Also in patients with an acute coronary syndrome, concomitant PAD increases the risk of subsequent cardiovascular events [9].

PAD is associated with enhanced in vivo platelet activation (Gresele TH, Davì Gresele, Circulation), in particular in patients with associated cardiovascular risk factors, such as diabetes mellitus, hypercholesterolemia and smoking [10,11]. The generation of platelet arterial thrombi is then triggered by the exposure, upon plaque rupture, of collagen fibres [12] and by the localized generation of small traces of thrombin initiated by tissue factor-rich athermanous plaques, and facilitated by hyper-reactive platelets [13,14]. Thromboxane A_2 (TxA_2), synthesized by cyclooxygenase-1 (COX-1) of platelets, and ADP, released by locally activated platelets, recruit additional platelets and contribute to arterial thrombus formation. The understanding of these mechanisms has brought to the development of the antiplatelet interventions currently used in patients with Coronary Artery Disease (CAD) and PAD, i.e. aspirin, that blocks COX-1 and thus TxA_2 formation, ADP-($P2Y_{12}$)-receptor blockers, that prevent feedback activation by platelet-released ADP, and more recently thrombin (PAR-1)-receptors blockers, that neutralize the platelet-activating activity of thrombin generated at the site of plaque rupture [15].

Aspirin in the prevention of cardiovascular events in PAD

Aspirin has been evaluated for the prevention of ischemic cardiovascular events in PAD in several clinical trials carried out over a 36 years period. However, most of the studies were flawed by design faults and all by an insufficient sample size. Even the largest single study, the aspirin for prevention of cardiovascular events (AAA) trial, which included over 3.000 PAD patients with a median follow-up of 8.2 years [16], was statistically underpowered: in fact the actual event rate observed in the study was lower that expected, and for this reason, the follow-up greatly prolonged respect to what originally planned, a phenomenon repeatedly reported in PAD trials, with anticipated/achieved primary endpoint rates in the control arms of even one quarter than those expected [17].

On the other hand, several meta-analyses concur in concluding that in patients with PAD aspirin treatment results in a non-significant decrease of cardiovascular events [18,19].

Other antiplatelet agents in PAD

Clopidogrel, a $P2Y_{12}$-ADP receptor blocker, has been compared to aspirin in a large, head-to-head comparative trial in patients with previous atherothrombotic events (CAPRIE trial). This was the first direct comparison between two different antiplatelet agents and included more than 19.000 patients with prior MI, stroke or with PAD followed for an average of around 2 years. While the overall result was marginally in favour of clopidogrel (absolute risk reduction – ARR – 0.51%, number needed to treat – NNT – to prevent one cardiovascular event =196), a post-hoc, not-pre-specified analysis of the patient subgroups divided by qualifying condition showed a much more striking benefit of clopidogrel in the subgroup of patients enrolled for a PAD (RRR 1.15, NNT 87) [20].

Based on these results, most guidelines or expert opinions suggested clopidogrel as a possible alternative, and sometimes as a first choice, over aspirin in patients with PAD.

However, a post-hoc, subgroup analysis can only be taken as hypothesis-generating for new studies and not as evidence of efficacy, and unfortunately so far no confirmatory studies on the efficacy of clopidogrel in preventing ischemic events in patients with PAD have been performed.

On the other hand, a meta-analysis has suggested that, differently from aspirin, thienopyridines are effective in PAD [19].

Most recently, the results of a trial comparing clopidogrel (75 mg/day) with ticagrelor (90 mg b.i.d.) in over 13.000 PAD patients (EUCLID trial) were reported, showing no superiority of the stronger $P2Y_{12}$-antagonist ticagrelor over clopidogrel in preventing major adverse cardiovascular events [21]. Unfortunately, in this trial there was no aspirin as a comparator and the results are thus difficult to interpret. Indeed, the observed cardiovascular event rates in the two groups (over 5% per 100 patient years combining major adverse cardiovascular events and major adverse limb events – MACE and MALE) might be compatible with little effectiveness of both treatments.

Given the proven superiority of the combination of aspirin and clopidogrel over aspirin alone in patients with acute coronary syndromes, a large clinical trial of secondary prevention with this drug combination in patients with atherothrombosis, which included also a group of high risk subjects with no prior cardiovascular events (CHARISMA trial) was carried out. The overall results showed no superiority but an increased risk of major haemorrhage with the combination as compared with aspirin alone [22]. A subgroup analysis of this trial assessing out of the enrolled patients only the secondary prevention population showed a significant benefit of the drug combination over aspirin in patients with prior MI or prior ischemic stroke, but not in the population with PAD [23]. The combination of aspirin and clopidogrel has been assessed also in patients with severe PAD undergoing below-knee peripheral by-pass surgery (CASPAR trial), but here too no superiority was proven over aspirin alone [24].

Thus, no evidence is available from clinical trials of the clinical benefit of aspirin plus clopidogrel in PAD.

A recent subgroup analysis of the PEGASUS-TIMI 54 trial, that evaluated two doses of ticagrelor (90 mg and 60 mg b.i.d.) on top of aspirin in stable patients with previous MI, showed that the addition of ticagrelor in the subpopulation of patients that had PAD in addition to a previous MI reduced MACE and MALE, with an absolute risk reduction larger than that observed in the overall trial population [9]. In light of the above commented EUCLID trial results, these data suggest that a combination of aspirin and ticagrelor, rather than ticagrelor alone, might be a useful approach to high-risk PAD patient, however an ad hoc designed, prospective trial should confirm this hypothesis.

The most innovative development of antiplatelet therapy in the last few years have been direct PAR-1 antagonists. One of these, vorapaxar, has shown superiority over placebo in a large trial in patients with prior ischemic cardiovascular events treated with aspirin and most also with a thienopyridine, although at the price of a significant increase of moderate/severe bleeding (HR 1.66, p>0.001) [25]. This is the first study ever to show superiority of the addition of an extra antiplatelet agent to aspirin in chronic secondary prevention of ischemic major cardiovascular events.

The net clinical benefit (including both MACE and severe bleeding) of adding vorapaxar to standard therapy appeared to be strongly dependent on the cardiovascular risk level, with high risk patients having the greatest benefit (ARR 3.5%, NNT 29). Among predictors of high-risk one was PAD [26].

Interestingly, a subgroup analysis of patients with qualifying peripheral artery disease (n=3.787) showed that vorapaxar significantly reduced acute limb ischemia and peripheral revascularization, suggesting that vorapaxar might have a role in preventing progression of limb arterial disease [27].

Based on these studies vorapaxar (Zontivity®) has been approved by FDA and EMA for secondary prevention of MACE, in addition to standard antiplatelet therapy, in patients with prior MI or PAD.

Conclusions

PAD represents a serious public health problem and associates frequently with other clinical manifestations of athero-thrombotic cardiovascular disease, first of all with CAD. Despite of this, PAD is largely under-diagnosed and undertreated. A recent assessment of the drug prescription rate of recommended treatments in patients with PAD showed that antiplatelet therapy is largely underused in patients that present with a PAD either alone or together with CAD [28]. Antiplatelet therapy is the cornerstone of treatment for secondary prevention of cardiovascular events and, although uncertainty remains about the effectiveness of aspirin and more in general of antiplatelet therapies in patients with PAD without previous major ischemic events, a careful evaluation of the individual future cardiovascular risk must be made and antiplatelet treatment must be started when risk overcomes the required threshold for indication to primary prevention [29]. Vorapaxar, a PAR-1 antagonist, has been recently registered for clinical use in patients with PAD and may represent an interesting option

for those at especially high risk, including those with a previous MI. An optimal implementation of best available medical therapy and risk factor control is strongly required to limit the "epidemic" of PAD.

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