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Controversy in cardiology: clopidogrel or acetylsalicylic acid in the treatment of chronic coronary syndromes?

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Secondary prevention of patients with chronic coronary syndrome is based on the long-term use of a single anti-aggregating drug which is traditionally represented by acetylsalicylic acid (ASA) in light of the results of studies and meta-analyses which have demonstrated a clear anti-ischaemic efficacy against of an acceptable increase in the risk of bleeding, especially intracranial and gastrointestinal bleeding. The availability of drugs such as clopidogrel, which inhibits platelet activity through the P2Y12 receptor pathway, has called into question this paradigm, also in consideration of the fact that the scientific evidence that supports the use of ASA in secondary prevention is based on dated studies with some limitations. Over the last few years, randomized trials have demonstrated how clopidogrel has an efficacy profile comparable to that of ASA and a safety profile that is sometimes even better. In light of the new evidence, it is therefore legitimate to ask whether in this clinical scenario, ASA should still be considered the drug of choice or whether clopidogrel could represent the preferable alternative.

Introduction

In patients with atherosclerotic coronary disease (CAD) undergoing percutaneous coronary intervention (PCI), current guidelines recommend the use of dual antiplatelet therapy (DAPT) for the prevention of new cardiovascular events for a variable duration of time depending on the clinical presentation, bleeding risk, and ischaemic risk. Upon suspension of DAPT and in the absence of indication for oral anticoagulant therapy, the guidelines recommend continuing a single antiplatelet agent and acetylsalicylic acid (ASA), at a dosage of 75–100 mg/day, which represents the first-choice treatment.[1]

Recently, the role of this drug as a cornerstone in secondary cardiovascular prevention in patients with chronic coronary syndrome has been the subject of debate. On the one hand, it has been demonstrated that chronic treatment with ASA is associated with a significant increase in intracranial and extracranial bleeding (especially gastrointestinal); on the other hand, it must be recognized that the studies supporting its use were conducted in the 1970s and 1980s and are, therefore, now dated and it cannot be taken for granted that they can be applied to today's clinical practice which has been enriched with new secondary prevention measures.

Furthermore, the availability of other antiplatelet drugs such as P2Y12 receptor inhibitors that inhibit platelet activity through pathways other than that of cyclooxygenase, inhibited by ASA, offers the possibility of alternative strategies in the long-term treatment of patients with coronary heart disease. Clopidogrel represents the progenitor of this class of antiplatelets and numerous pieces of evidence have emerged over the past few years which have demonstrated its effectiveness

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and safety in the chronic treatment of patients with CAD, proposing it as a valid alternative to ASA.[2]

The historical meta-analyses supporting the use of acetylsalicylic acid

The majority of the scientific community considers ASA to be the antiplatelet treatment of choice in the secondary prevention of patients with CAD. The evidence supporting this drug comes from studies conducted in the 1970s and 1980s, which were subsequently summarized by the different meta-analyses of the Anti-Thrombotic Trialist (ATT) Collaboration.[3-6]

The first ATT meta-analysis was published in 1988 and included 25 randomized trials for a total of over 29 000 patients with a history of myocardial infarction, unstable angina, ischaemic stroke, or transient cerebral ischaemia. The most interesting data were that antiplatelet treatment (in most of the studies ASA at a dosage varying from 300 to 1500 mg/day) was associated with a 15% reduction in the risk of vascular death and a 30% reduction in the risk of non-fatal myocardial infarction and stroke.[3]

The second ATT meta-analysis was published in 1994 and represented an effort to define the role of anti-aggregation in different clinical scenarios and in patients with different risk profiles. The meta-analysis included 145 studies and among the 20 000 patients with a history of previous myocardial infarction undergoing antiplatelet therapy, a 4% reduction in the absolute risk of new cardiovascular events at 2 years was documented ($P < 0.001$). In this case, the most used drug was ASA at doses varying between 75 and 325 mg/day.[4]

The third ATT meta-analysis was published in 2002 and focused on reduced ASA doses (75–150 mg/day) concluding once again that the drug was associated with a significant reduction in vascular events and this benefit was far superior to the increased risk of bleeding.[5]

The fourth meta-analysis was published in the *Lancet* in 2009 and includes the main studies in which ASA was used in primary and secondary prevention. Regarding the second scenario, 16 trials were included for a total of over 17 000 patients classified as high risk. Treatment with ASA demonstrated a significant reduction in the risk of a vascular event considered serious (6.7 vs. 8.2% per year, $P < 0.0001$), overall strokes (2.08 vs. 2.54% per year, $P = 0.002$), and coronary events (4.3 vs. 5.3% per year, $P < 0.0001$). The other side of the coin was an expected increase in the risk of major bleeding, of approximately two and a half times, but without a significant increase in intracranial haemorrhages.[6]

The incontrovertible fact that emerges from these meta-analyses that have made the history of cardiology is that, in patients with CAD, the use of ASA reduces ischaemic events, despite an acceptable increase in haemorrhagic risk. However, it should be underlined that the studies included in these meta-analyses present some major limitations that could limit their application in contemporary cardiology: they are predominantly young patients (average age generally <70 years), male, who have been treated with different dosages of ASA and generally higher than that normally used. Probably, the biggest limitation is represented by the fact that the secondary prevention strategies of 50 years ago are in no way comparable to the current ones, which make use of different pharmacological categories, simply think of the enormous progress made in the field of treatment of dyslipidaemias with the achievement of increasingly ambitious LDL targets. At this point, it is therefore legitimate to ask whether the documented benefit is linked to the drug itself or more generally to the use of an antiplatelet drug in monotherapy.

Studies supporting clopidogrel

CAPRIE (randomized, blinded, trial of Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events) was one of the first randomized studies comparing clopidogrel and ASA. The trial enrolled over 19 000 patients with established atherosclerosis, defined as the presence of a recent ischaemic stroke, a recent myocardial infarction, or symptomatic peripheral arterial disease (PAD), randomized to clopidogrel 75 mg/day or ASA 325 mg/day. The primary efficacy endpoint was the composite of vascular death, myocardial infarction, and ischaemic stroke. At a mean follow-up of just under 2 years, treatment with clopidogrel reduced the relative risk of the primary endpoint by 8.7% compared with ASA [95% confidence interval (CI) 0.3–16.5; $P = 0.043$]. This benefit was achieved in the presence of a similar risk of intracranial bleeding between the two groups (0.33 vs. 0.47%) and a risk of gastrointestinal bleeding in favour of clopidogrel (0.52 vs. 0.72%). The large number and heterogeneity of the study population allowed a subgroup analysis, which, however, documented a favourable effect of ASA in patients with a history of previous myocardial infarction, with a reduction in the relative risk of events of 3.7%; on the contrary, clopidogrel proved successful in patients with ischaemic stroke and especially in those with PAD, with a relative reduction in the risk of events of 7.3 and 23.8%, respectively.[7] It is precisely in light of these results that European and Canadian guidelines subsequently suggested clopidogrel and not ASA as the drug of choice in patients with PAD.[8,9]

More recently, the HOST-EXAM (Harmonizing Optimal Strategy for Treatment of Coronary Artery Stenosis-Extended Antiplatelet Monotherapy) study randomized 5438 patients with a history of previous PCI to monotherapy with clopidogrel or ASA. At a 24-month follow-up, the primary endpoint of death, myocardial infarction, stroke, re-hospitalization for acute coronary syndrome, and major bleeding BARC (Bleeding Academic Research Consortium) ≥ 3 was significantly reduced in the clopidogrel group compared with the ASA group, with a relative risk reduction of 27% [hazard ratio (HR) 0.73; 95% CI 0.59–0.90; $P = 0.0035$]. The primary endpoint occurred in 152 patients (5.7%) in the clopidogrel group, and in 207 patients (7.7%) in the ASA group with an absolute reduction in the risk of events of 2% (95% CI 0.6–3.3) and a 'number needed to treat' (NNT) equal to 51. As regards the secondary endpoints, the incidence of death from all causes (1.9 vs. 1.3%, $P = 0.101$), cardiac death (0.7 vs. 0.5% $P = 0.374$), and non-fatal myocardial infarction (0.7 vs. 1.0%, $P = 0.150$) was comparable between the two study arms. On the contrary, the incidence of stroke (0.7 vs. 1.6%, $P = 0.002$), re-hospitalizations for acute coronary syndrome (2.5 vs. 4.1%, $P = 0.001$), and major bleeding (1.2 vs. 2.0%,

$P = 0.035$) was significantly lower in patients treated with clopidogrel. The secondary ischaemic composite endpoint of cardiac death, non-fatal myocardial infarction, stroke, acute coronary syndrome rehospitalizations, and definite and/or probable stent thrombosis occurred in 99 subjects (3.7%) treated with clopidogrel and in 146 subjects (5.5%) treated with ASA (HR 0.68, 95% CI 0.52–0.87; $P = 0.0028$), with an absolute risk reduction of 1.7% (95% CI 0.6–2.8) and an NNT of 59. Bleeding occurred in 61 (2.3%) patients treated with clopidogrel and in 87 (3.3%) patients treated with ASA (HR 0.70, 95% CI 0.51–0.98; $P = 0.036$), with an absolute risk reduction of 0.9% (0.0–1.8) and an NNT of 111. Minor gastrointestinal complications (epigastralgia, dyspepsia, abdominal pain, nausea, vomiting, diarrhoea, and constipation) were also documented predominantly in the ASA group (11.9 vs. 10.2%, $P = 0.048$). The beneficial effect of clopidogrel on the reduction of ischaemic and haemorrhagic events was maintained in all subgroups analysed: age > or <65 years, previous acute coronary syndrome, diabetes mellitus, renal insufficiency, multivessel coronary disease, and concomitant use of proton pump inhibitors.[10]

In light of the results of the HOST-EXAM, are we really ready to give up the good old ASA even in secondary prevention? Certainly, the great merit of this study lies in the fact that it was the first randomized study to compare the two monotherapies, demonstrating the efficacy and safety of clopidogrel in a population of post-PCI patients that we can define as 'modern' because they were treated with latest generation drug-eluting stents and highly effective statins. The results of the primary endpoint are strengthened in light of the results of the secondary endpoint and if we consider that the Kaplan–Meier curves begin, but above all continue to diverge, starting from the ninth month, thus suggesting an efficacy sustained with prolonged clopidogrel monotherapy. This trial presents, however, some major limitations: the study design, open and not blinded; the fact that it was only conducted in a South Korean population and therefore the results cannot be generalized to other ethnic groups and also the duration of follow-up which was initially only 2 years.

It is precisely to overcome this last aspect that the observation period of the patients was extended and the results of the HOST-EXAM Extended study were recently published. At a follow-up of 5.8 years, it is confirmed that the primary endpoint is consistently reduced with clopidogrel compared with ASA (12.8 vs. 16.9%; HR 0.74, 95% CI 0.63–0.86; $P < 0.001$), with a reduction also in the secondary thrombotic endpoint (7.9 vs. 11.9%; HR 0.66, 95% CI 0.55–0.79; $P < 0.001$) and in the secondary bleeding endpoint (4.5 vs. 6.1%; HR 0.74, 95% CI 0.57–0.94; $P = 0.016$), with no differences regarding all-cause mortality (6.2 vs. 6.0%; HR 1.04, 95% CI 0.82–1.31; $P = 0.742$). Furthermore, in the study with prolonged follow-up, a higher percentage of patients discontinued ASA therapy, therefore, suggesting greater therapeutic compliance with clopidogrel.[11]

The PANTHER meta-analysis

Gragnano et al. recently published the results of the PANTHER meta-analysis (P2Y12 Inhibitor or Aspirin Monotherapy as Secondary Prevention in Patients with Coronary Artery Disease: An Individual Patient Data Meta-Analysis of Randomized Trials). This is an 'individual patient data' meta-analysis, i.e. obtained with the data of individual patients enrolled in the analysed trials that compared monotherapy with ASA vs. monotherapy with P2Y12 receptor inhibitors in the secondary prevention of patients with CAD. The primary endpoint was the composite of cardiovascular death, myocardial infarction, and stroke; the key secondary endpoints were major bleeding (Type 3 or 5 according to the BARC classification) and net clinical benefit (NACE). Other secondary endpoints included the individual components of the primary endpoint and then all-cause death, definite and/or probable stent thrombosis, ischaemic and haemorrhagic stroke, any type of bleeding, and gastrointestinal bleeding. Seven randomized clinical trials were considered eligible for inclusion in the meta-analysis, but for each study, several patients were excluded because they were deemed ineligible. Ultimately, the PANTHER population included a total of 24 325 patients, 12 147 assigned to the ASA group and 12 178 assigned to the P2Y12 receptor inhibitors group (clopidogrel 62% and ticagrelor 38%). The average duration of treatment was 557 days. The two groups were well balanced in the main clinical characteristics, the average age was 64 years, with 22% women and 25% diabetics. In approximately 60% of cases, the subjects reported a history of acute coronary syndrome, while in 40% of cases, they reported chronic coronary syndrome. Regarding the efficacy results, the authors of the meta-analysis concluded that monotherapy with P2Y12 receptor inhibitors compared with monotherapy with ASA is associated with a lower risk of events included in the primary endpoint (HR 0.88, 95% CI 0.79–0.97; $P = 0.012$) with an NNT of 121 at 2 years. The risk of major bleeding was comparable between the two groups (HR 0.87, 95% CI: 0.70–1.09; $P = 0.23$). NACE was also reduced by single therapy with P2Y12 inhibitors (HR 0.89, 95% CI 0.81–0.98; $P = 0.020$). Regarding the secondary endpoints, however, the risk of myocardial infarction was significantly lower with monotherapy with P2Y12 receptor inhibitors compared with monotherapy with ASA (HR 0.77, 95% CI 0.66–0.90; $P < 0.001$), with an NNT of 136; for stroke, a trend was identified that did not reach statistical significance (HR 0.84, 95% CI 0.70–1.02; $P = 0.076$), while no difference was found in cardiovascular mortality and mortality from all causes. Furthermore, the risk of gastrointestinal bleeding, definite and probable stent thrombosis, and haemorrhagic stroke was significantly lower in patients treated with P2Y12 inhibitors compared with those treated with ASA. The result of stent thrombosis, as the authors rightly point out in the discussion of the work, could in some way be linked to the fact that more than one-third of the patients in the P2Y12 receptor inhibitor group were treated with a more potent drug such as ticagrelor. In any case, the overall results were confirmed in all prespecified subgroups, including the type of P2Y12 inhibitor (clopidogrel or ticagrelor). The authors of the meta-analysis, therefore, concluded that based on the results achieved, long-term monotherapy with P2Y12 receptor inhibitors could be preferable to that with ASA in the secondary prevention of patients with CAD.[12]

What do the guidelines tell us?

During the last congress of the European Society of Cardiology, updated guidelines on the treatment of acute coronary syndromes were released which also addressed the controversial topic of chronic antiplatelet therapy. Although the results of the PANTHER meta-analysis had already been made known, the authors of the guidelines continue to indicate ASA as an antiplatelet drug to be used as a first choice in monotherapy for secondary prevention in patients with CAD and without indication for anticoagulant treatment (Class I, Level of Evidence A). Therapy with P2Y12 receptor inhibitors can be considered an alternative to ASA, especially in some subgroups of patients such as those with increased risk of gastrointestinal bleeding, but the class of recommendation remains IIB, Level of Evidence A.[1]

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Data availability

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