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Who needs acetylsalicylic acid? Some order after many studies

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The role of acetylsalicylic acid (ASA) in cardiovascular prevention is essentially consequence of its ability to inhibit platelet aggregation, thus reducing the impact of atherosclerotic disease. The preventive power of this drug is clear when used in patients with previous cardiovascular event (myocardial infarction, stroke, etc.), but the data are less dependable when considering patients who did not experienced a cardiovascular event or in the diabetic population, in whom recent studies reported neutral results in term of efficacy, in face of an increase in the risk of bleeding. Furthermore, the interpretation of the efficacy results of ASA should be reconsidered in light of the increasing clinical complexity, not addressed in the clinical studies on which current evidences are based. Accordingly the rationale for ASA use in cardiovascular prevention is ever more of current interest, and requires a particular attention, considering the crucial role of antithrombotic therapy in the foreseeable future. What could be learned on the use of ASA in cardiovascular prevention after a century since its chemical synthesis? In secondary prevention, supporting evidences have now a couple of decades of history, and the use of the drug appears to be firmly established: in this setting, the benefits clearly surpass the risks. On the other hand, in primary prevention, where age and diabetes are among the main risk factors, the risk/benefit ratio for prophylactic therapy with ASA does not support its widespread use. Deciding when this treatment should be implemented should require a *case-by-case* evaluation, considering, first, the correction of each risk factor, whose control has led to a reduction of global cardiovascular mortality. The other fundamental aspect is the compliance to the treatment, particularly in patients subjected to multiple drugs regimens, in whom the physician should take into account the specific needs of the patient, as not to provide a mere prescription service.

Acetylsalicylic acid (ASA) is one of the oldest drugs used, with a history dating back over a century. Although initially used and still for its analgesic/antipyretic/anti-inflammatory effect, scientific progress has brought the drug to the fore, above all, because of its anti-platelet aggregation action.[1] The anti-aggregating action is the consequence of the irreversible inhibition of the COX-1 enzyme at platelet level thanks to the acetylation of a serine residue that inhibits the production of thromboxane A2, therefore, platelet aggregation, for the entire life of the platelet itself. This effect occurs already at low doses of drug (30 mg/day) although, assuming a certain individual variability, the doses currently used in clinical practice are usually greater.[2] The dose administered is the element that differentiates the different clinical applications of aspirin which is effective on platelets at doses $<$100 mg/day while it can control pain, inflammation, and fever for much higher doses that can also inhibit COX-3 and range from 1 to 3 g/day.

The wide diffusion of the drug, due to the meticulous knowledge of the pharmacokinetic and pharmacodynamic principles, together with the accumulated clinical experiences, have made it a cornerstone of antithrombotic

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therapy and one of the main weapons to use in the fight against cardiovascular diseases, suggested by the main guidelines in use around the world.

In this regard, the efficacy and safety of ASA have been evaluated in different populations, from apparently healthy subjects (primary prevention) up to patients with acute myocardial infarction (AMI), ischaemic stroke, and peripheral arterial disease (secondary prevention). Most of the information derived from randomized trials on the topic of secondary prevention is summarized by the work of the Antithrombotic Trialists' Collaboration published in Lancet in 2009. According to the authors' analysis, conducted on over 17 000 subjects with high cardiovascular risk, the ASA reduces the risk of major cardiovascular events (6.7% vs. 8.2% per year, $P < 0.0001$), with reduced risk of stroke (2.08% vs. 2.54% per year, $P = 0.002$) and of acute coronary events (4.3% vs. 5.3% per year, $P < 0.0001$).[3]

Despite the convincing evidence, today's transposition of the results of the studies is today more difficult due to some limitations that prevent its systematic use in a context of more general clinical complexity such as that of modern medicine. In particular, most studies were conducted some decades ago and do not reflect current clinical conditions especially in terms of multi-pathology and poly-pharmacotherapy. Furthermore, the dosages of the drug used are far from those approved for today's clinical practice.[1] However, given the impossibility to ignore the accumulated evidence and to replicate clinical studies based on the rigorous comparison methodology without breaking professional ethics (randomized trials vs. placebo), both American and European cardiology guidelines recommend the daily use of ASA for secondary prevention of patients with coronary heart disease at the dosage of 81–325 and 75–100 mg, respectively.[4]

With regard to secondary prevention of ischaemic stroke, the most effective and safest dose of ASA to be used is still a topic of debate. In the original placebo trials, the doses used varied widely between 50 and 1300 mg/day.[5] Subsequent evidence was accumulated that treatment with increasing doses of ASA did not lead to significant differences in terms of reducing the risk of recurrent ischaemic stroke, but a significant increase in the risk of bleeding in a dose-dependent fashion.[6] For this reason, currently, the guidelines recommend lower dosages, between 75 and 325 mg/day.[5]

As regards primary cardiovascular prevention, the use of ASA is controversial, with some experiences that suggest a protective role and others that do not identify clear benefits (Table 1). The aforementioned analysis of the Antithrombotic Trialists' Collaboration, carried out on ~95 000 medium-low risk individuals, indicated a 12% reduction in major cardiovascular events in response to ASA therapy, mainly due to the reduction of non-fatal MI risk (0.18% vs. 0.23% per year; $P < 0.0001$); without a significant effect on stroke and cardiovascular mortality.[3]

A more recent meta-analysis for the US Preventive Services task force, including 11 studies for a total of ~120 000 patients, confirmed the reduction in the risk of non-fatal AMI (22% compared to placebo), confirming once again the absence of significant effects on ischaemic stroke, cardiovascular, or all causes mortality. Curiously, considering selectively the data concerning those patients taking doses lower than 100 mg/day, the positive results on the prevention of AMI were confirmed and a 14% reduction in the risk of non-fatal ischaemic stroke and a trend in improvement for all causes mortality.[7]

A particular fact that emerges from almost all studies is the observation that diabetic patients, despite being burdened with a cardiovascular risk of 2–3 times higher than non-diabetics, do not derive a greater benefit from ASA therapy as would be desirable on the basis of their increased intrinsic cardiovascular risk.[3] The reasons proposed for this dissociated trend between basic risk and preventive effect are manifold and range from the (unlikely) possibility of a glycation of ASA binding sites to COX-1 up to a modification of platelet kinetics that would be subject to a faster turn-over which would lead to a greater presence in the circulation of platelets able to aggregate. The recent ASCEND study, a double-blind randomized vs. placebo trial, focused on this particular population of patients, analysed data from ~15 000 diabetic patients treated with ASA in primary prevention for a median of 7.4 years. The incidence of serious cardiovascular events was significantly lower in patients taking 100 mg/day of ASA compared to placebo (8.5% vs. 9.6%; $P = 0.01$), although an increase was recorded in parallel of the risk of major bleeding (4.1% vs. 3.2%; $P = 0.003$) which counterbalances the clinical benefit. Taking a risk/benefit ratio, it would be necessary to treat 91 patients for 7.4 years to avoid a cardiovascular event, causing major bleeding for every 112 patients treated.[8]

The ARRIVE study analysed the prospect of using ASA in a more complex setting like that of general medicine. During a 5-year follow-up, the intention-to-treat analysis showed no benefit of the drug in terms of the primary cardiovascular goal. However, the interpretation of the results of the study is made difficult by the nature of his experimental design whereby many patients have modified the 'belonging' to the treatment group as a result of both drop-in and drop-out effects per control in the analysis per-protocol 100 mg/day of ASA reduced the risk of AMI by 47% ($P = 0.0014$); the 19% reduction for the composite cardiovascular endpoint almost reached statistical significance ($P = 0.0756$).[9]

Primary cardiovascular prevention has also been studied in the geriatric population and of particular interest are the results deriving from the ASPREE studies. In almost 20 000 subjects over 70 years of age, followed by a median of 4.7 years, with no history of cardiovascular disease, dementia, or disability, the use of 100 mg/day of ASA did not show any statistically significant benefit (reduction risk of 5% with non-significant P), showing instead an increased risk of major bleeding (38%; $P < 0.001$), but not of fatal bleeding.[10] Therefore, in light of the absence of a clear cardiovascular benefit and increased bleeding risks, the authors express unfavourably on the use of ASA in elderly patients.

What can we then conclude about the use of the ASA for cardiovascular prevention after more than a century after its chemical synthesis? Despite evidence that can count a few decades of history, the use of ASA in secondary

prevention is essential, as the benefits clearly outweigh the risks. As for primary prevention, where age and diabetes are certainly among the main risk factors, the risk-benefit ratio for a prophylactic therapy with ASA does not lean towards its widespread use. Decisions about its use should be evaluated on a case-by-case basis, probably considering in the first instance the treatment of individual risk factors, which in fact led to a reduction in global cardiovascular mortality. The other aspect of fundamental importance is the expected compliance with the therapy itself, especially in those patients with poly-pharmacy, in light of the patient's needs and preferences, so as not to make the medical act a mere prescription exercise.

Conflict of interest: none declared.

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