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ASPIRIN IN CAD: Is it Still the King of the Ring in 2024?

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Abstract **Review Article**

With its 3,500-year history, aspirin is one of the most widely used medicines in the world. For a very long time, its place in secondary and sometimes even primary cardiovascular prevention was indisputable. However, a growing body of clinical data is calling this dogma into question. It is therefore necessary to reassess its efficacy and, above all, its safety in certain indications, such as primary cardiovascular prevention in at-risk populations, anti-platelet monotherapy following DES implantation, and post-acute coronary syndrome.

Keywords: cardiovascular prevention, Aspirin, HOST- EXAM study, STOPDAPT-3 study, ESC Recommendations, Prasugrel, DAPT.

1. HISTORICAL OVERVIEW

Aspirin is one of the most widely used medicines in the world. Known since the time of the Egyptians and Sumerians for its antipyretic and analgesic properties [1], it wasn't until 1897 that aspirin in its contemporary form was synthesized by Bayer Chemist Felix Hoffmann [1, 2], who gave it the name A-sprin, formed from acetylation (A-) and sprine (Spiraea ulmaria) [3]. Its effectiveness in the treatment of cardiovascular disease was later elucidated. By the way, Winston Churchill benefited from it after his first stroke [1]. In 1974, the first randomized trial in myocardial infarction was conducted by Peter Elwood [1]. It was approved by the FDA as a treatment for ischemic heart disease in 1985 [1], announcing the golden age of anti-platelet therapy in atheromatous coronary artery disease. For decades, aspirin was clearly the reference treatment for all clinical forms of ischemic coronary artery disease, but what is its place nowadays?

2. Efficacy and Safety of Aspirin in Primary Prevention

The role of aspirin in primary prevention continues to be clarified over time and through clinical trials. Several questions are at the heart of the debate: what is the place of anti-platelet agents in terms of primary prevention, and what is the best anti-platelet

Fig. 1: Aspirin by Bayer

Agent to offer where appropriate? Ahmed N Mahmoud and his team [4], have attempted to answer these questions through a meta-analysis of randomized clinical trials comparing aspirin with placebo. A total of 11 studies involving more than 150,000 patients were

included. The incidence of all-cause mortality was comparable with placebo (4.6% vs. 4.7, P = 0.30), as were the rates of cardiovascular mortality and stroke, which were similar in the two groups [4]. However, the risk of silent myocardial infarction was lower in the aspirin group [4]. The risk of major bleeding, on the other hand, was higher in the aspirin arm (in particular intratrabecular bleeding) (1.8% vs. 1.3 P < 0.0001) [4]. In the end, this meta-analysis demonstrated that aspirin was not associated with a reduction in cardiovascular risk in primary prevention, at the cost of an increased risk of major bleeding, particularly intracerebral bleeding. The only advantage related to aspirin prescription was a slight reduction in the risk of myocardial infarction [4]. The routine use of aspirin in primary cardiovascular prevention does not appear to be worthwhile, but what about for specific populations such as diabetics?

A. Primary Cardiovascular Prevention in Diabetics

It is now well established that diabetes increases cardiovascular risk, undoubtedly contributing to the development of atherosclerosis. Does this make it worth proposing low-dose aspirin for primary prevention in these patients? Louise Bowman con- ducted a randomized trial involving over 15,000 patients [5].

Cardiovascular events were significantly lower in the aspirin arm (8.5% vs. 9.6%; P=0.01) at the cost of a higher rate of bleeding, mainly gastrointestinal (4.1% vs. 3.2%; p=0.003) [5]. The benefit of aspirin in these patients was therefore outweighed by the increased risk of hemorrhage. This therapeutic approach does not appear to provide a clear benefit in this population, at least according to the results of this clinical trial.

B. ESC Recommendations on the Prevention of Cardiovascular Disease

According to the European Society of Cardiology, it is recommended that low-dose aspirin be offered as primary prevention therapy in patients with diabetes mellitus classified as high or very high cardiovascular risk in the absence of a clear contraindication [6]. On the other hand, this approach is not recommended for patients at low or intermediate risk, to avoid exposing patients to an increased risk of hemorrhage without any clear benefit in terms of cardiovascular risk [6]. The recommendations of the US Preventive Services Task Force are slightly less nuanced, contraindicating the use of aspirin in primary prevention what- ever the level of risk after the age of 60 [7]. This attitude may be considered in patients aged between 40 and 59 with a high cardiovascular risk whose risk of hemorrhage is not high [7].

3. P2Y12 INHIBITORS OR ASPIRIN MONOTHERAPY AF- TER Des Implantation?

It is at the moment recommended that aspirin monotherapy should be continued after the period of dual anti-platelet therapy after DES implantation [8], with clopidogrel monotherapy reserved for patients allergic to aspirin [8]. However, few studies have compared aspirin with clopidogrel monotherapy in the long term. One of these is the **HOST-EXAM** study [9], a multi- centric randomized clinical trial (37 sites) conducted in South Korea, which compared aspirin 100 mg versus clopidogrel 75 mg as monotherapy after a minimum dual therapy period of 6 months, for a total study duration of 24 months. Continuation of clopidogrel significantly reduced the occurrence of the primary composite endpoint (all-cause mortality, ischemic stroke, nonfatal myocardial infarction, rehospitalization for acute coronary syndrome, or major bleeding). This absolute risk reduction was evaluated at 2% (5.7% vs. 7.7%, p=0.0035). The reduction in the secondary composite endpoint (cardiovascular mortality, nonfatal myocardial infarction, ischemic stroke, rehospitalization for acute coronary syndrome, or BARC $\preceq$ 2) was also in favor of clopidogrel (3.7 vs. 5.7 p=0.0028). Based on the results of this clinical trial, it would appear that clopidogrel monotherapy in the long term is a strategy that reduces the occurrence of cardiovascular events, while exposing patients to a lower risk of bleeding.

4. Aspirin in Acute Coronary Syndromes

Is it possible to replace aspirin in patients with immediate acute coronary syndromes and offer monotherapy with an anti-p2y12 agent? This is the question that the **STOPDAPT-3** study [10], sought to answer. Six thousand and two patients treated for acute coronary syndrome or at high risk of bleeding were ran- domized into two groups: Prasugrel 3.75mg/d - DAPT aspirin (81 mg/dl to 100 mg/d) + Prasugrel (3.75mg/d). A loading dose of 20 mg was administered to all patients. Two primary objectives were assessed: the occurrence of major bleeding (superiority study) and the occurrence of cardiovascular events (non-inferiority study). At the end of the one-month study. The non-aspirin group was non-inferior to the DAPT group for the primary cardiovascular endpoint (4.12% and 3.69%, p=0.01) [10], although there was a statistical signal in favor of an excess of acute coronary events such as unplanned revascularization and stent thrombosis. There was no significant difference between the two groups for the primary endpoint of servers bleeding (4.47 vs. 4.71, p=0.66) [10]. Moreover, Parsugrel alone was not inferior to dual anti-platelet therapy in terms of cardiovascular events, its use did not reduce the rate of major bleeding events [10]. There was also a relatively higher albeit statistically insignificant, rate of unplanned revascularization and stent thrombosis [10]. Dual antiplatelet therapy at least in the month following an acute coronary syndrome should therefore be the strategy to adopt, according to the results of this clinical trial.

The latest recommendations from the European Society of Cardiology, published in 2023, confirm the long-term indication for aspirin in patients with post-acute coronary syndrome [11]. With prior aspirin/P2Y12

inhibitor biotherapy for 12 months in the absence of high bleeding risk [11].

5. CONCLUSION

The increased risk of hemorrhage secondary to the administration of low-dose aspirin significantly reduces its indications in primary prevention. It should therefore be reserved for diabetic or young patients (40 to 59 years old) at high or very high cardiovascular risk associated with a low risk of hemorrhage. In DES post-implantation, replacing low-dose aspirin with Clopidogrel as a long-term post-DAPT treatment is a reasonable approach, and the use of Clopidogrel in this indication should not be reserved solely for patients allergic to aspirin. However, aspirin still has its place in the post-acute coronary syndrome, and should initially be used as part of a dual anti-platelet therapy, followed by long-term monotherapy. Even if aspirin has left its place in certain indications, it remains one of the essential treatments to be administered as part of cardiovascular prevention.

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