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Review

Low-dose aspirin for primary prevention of cardiovascular events in patients with diabetes: Benefit or risk?

M. Leggio [a,*], M.G. Bendini [b], E. Caldarone [c], M. Lombardi [c], P. Severi [a,c], S. D'Emidio [c], D.C. Stavri [c], M. Armeni [d], V. Bravi [e], A. Mazza [b]

[a] Department of Medicine and Rehabilitation, Cardiac Rehabilitation Operative Unit, San Filippo Neri Hospital–Salus Infirmorum Clinic, Rome, Italy
[b] Cardiology Division, Santa Maria della Stella Hospital, Orvieto, Italy
[c] Physical Medicine and Reurorehabilitation Operative Unit, Salus Infirmorum Clinic, Rome, Italy
[d] Department of Research, EDUCAM (C.R.O.M.O.N., S.Os.I., A.I.R.O.P.), Rome, Italy
[e] Still Osteopathic Institute, Rome, Italy

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ABSTRACT

Primary prevention aims to avert the onset of cardiovascular disease (CVD) by targeting its natural causes and risk factors; secondary prevention includes strategies and therapies that address preclinical or clinical evidence of CVD progression. The value of aspirin for primary CVD prevention is controversial because of increased bleeding, which may offset the overall modest benefits in patients with no overt CVD. In contrast, the benefits of aspirin for secondary prevention have been repeatedly and convincingly demonstrated to outweigh the risk of bleeding. Diabetes mellitus is a strong risk factor for cardiovascular events, and has been associated with an increased risk of both first and recurrent atherothrombotic events. Therefore, prevention of CVD, the major cause of mortality in patients with diabetes, is one of the most important therapeutic goals. Although the benefit of low-dose aspirin for secondary prevention of CVD is well established, its role for primary prevention remains inconclusive and controversial in diabetes patients. The benefit of aspirin for patients with CVD clearly exceeds the risk of bleeding, and even though a modest benefit has also been demonstrated in primary prevention, the trade-off for aspirin initiation against the increased risk of intracranial and gastrointestinal bleeding is more uncertain. Thus, aspirin for primary CVD prevention should be highly individualized, based on a benefit–risk ratio assessment for the given patient. In conclusion, the mere presence of diabetes is apparently not enough for aspirin to confer a benefit that clearly outweighs the risk of bleeding, and further evidence to the contrary is now needed.

Introduction

Primary prevention aims to avert the onset of cardiovascular disease (CVD) by targeting its natural causes and risk factors. At a different level, secondary prevention includes strategies and therapies that address preclinical or clinical evidence of CVD progression. Both primary and secondary prevention of atherothrombosis—a key mechanism behind non-fatal myocardial infarction (MI), ischaemic stroke and death—involves the use of pharmacological agents to counteract the process of clot formation. Acetylsalicylic acid, also known simply as aspirin, has been manufactured and marketed since 1899, but it took around 60 years to appreciate its antithrombotic potential as an antiplatelet agent. The value of aspirin for primary CVD prevention is controversial because of concerns that increased bleeding may offset the overall modest benefits of the drug in adults with no overt manifestation of atherothrombosis [1]. In contrast, secondary prevention is the setting in which the benefits of aspirin have been repeatedly and convincingly demonstrated to outweigh the risk of bleeds [2].

The individual likelihood of life-long cardiovascular events may be a significant modifier of the net benefit of aspirin in both primary- and secondary-prevention settings. Diabetes has been associated with an increased risk of both initial and recurrent atherothrombotic events. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million by 2030, which poses substantial and urgent questions as to how to deal with the

* Corresponding author at: Department of Medicine and Rehabilitation, Cardiac Rehabilitation Operative Unit, San Filippo Neri Hospital–Salus Infirmorum Clinic, Via della Lucchina 41, 00135 Rome, Italy.
E-mail address: mleggio@libero.it (M. Leggio).

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anticipated additional burdens of new-onset and recurrent CVD [3]. While the benefit of aspirin for secondary prevention in diabetes is currently undisputed [2], the larger arena of controversy is represented by the use of aspirin for primary CVD prevention.

Diabetes is a strong risk factor for cardiovascular events [4,5]. Platelet activation plays a causative role in the development of such events in the setting of type 2 diabetes (T2D), where platelet activation and aggregation are exaggerated [2,6,7]. Guidelines published in the early 2000s recommended the use of low-dose aspirin for primary prevention in patients with diabetes over a certain age or in the presence of concomitant cardiovascular risk factors [8–10]. This recommendation was based largely on the results of randomized clinical trials showing positive effects with low-dose aspirin in healthy volunteers [11–13], in patients with hypertension [14] and for secondary prevention in patients after MI [15].

CVD is a major cause of mortality in patients with diabetes [16,17] and, therefore, its prevention is one of the most important therapeutic goals of diabetes care. Although the benefit of low-dose aspirin for secondary prevention of CVD is well established, its benefit for primary prevention remains controversial, especially in diabetes [18–22]. The American Diabetes Association (ADA), American Heart Association (AHA) and American College of Cardiology Foundation (ACCF) jointly stated that, for primary prevention of CVD, low-dose aspirin use is reasonable for diabetes patients at high risk [23–25]. This accords with the recommendations for men aged $>$ 50 and women aged $>$ 60 who have one or more of the following additional cardiovascular risk factors: smoking; hypertension; dyslipidaemia; family history of premature CVD; and albuminuria. In contrast, the European Society of Cardiology (ESC) and other associated societies have stated that aspirin is no longer recommended for primary prevention in all patients with diabetes [26]. Nevertheless, clinical trial data for the use of aspirin in primary prevention are limited: even when several large trials of aspirin in primary prevention examined its effects in subgroups with diabetes, subgroup analyses failed to demonstrate any significant effect of aspirin in reducing vascular events because the studies were underpowered.

As a consequence, the role of low-dose aspirin therapy for primary prevention of CVD remains inconclusive and controversial even for high-risk diabetes patients.

Aspirin pharmacology and implications of aspirin use in diabetes

Pharmacokinetics

After ingestion, immediate-release aspirin is completely and rapidly absorbed by passive diffusion across membranes in the stomach and upper small intestine. The absorption rate depends on the drug formulation, presence or absence of food and gastric pH. Unlike the uncoated form, enteric-coated aspirin is erratically absorbed by gastrointestinal mucosa, resulting in lower bioavailability [27]. Plasma levels peak within 30–40 min (uncoated formulation) or 3–4 h (enteric-coated formulation) after oral intake. The half-life of aspirin is only 15–20 min, but the antiplatelet effect lasts longer because of the irreversible mechanism of action that blocks exposed platelets over its entire lifespan (7–10 days) and, therefore, is only reversed through generation of new platelets. These estimates indicate that aspirin has a rapid onset of effect, but a narrow window of opportunity to inhibit circulating platelets.

Mechanism of action

Aspirin acts by irreversibly blocking cyclooxygenase (COX) activity of prostaglandin H synthases 1 and 2, resulting in inhibition of thromboxane A2 and prostacyclin generation. With chronic administration, typical low-dose regimens (ranging from 75 mg to 100 mg) clearly exceed the minimum dose required for platelet inhibition while also addressing interindividual variability. Along the thromboxane A2 pathway, aspirin inhibits platelet activation and aggregation, two essential steps in the pathophysiology of thrombosis and MI. Inhibition of platelet activation at vascular injury sites has other indirect, non-thromboxane A2-mediated consequences, such as the reduced release of inflammatory cytokines, oxygen radicals and growth factors [27]. In contrast to thromboxane A2, prostacyclin is implicated in several anti-atherogenic effects and vascular thromboresistance [28]. As low-dose aspirin has no measurable effects on COX-2- and prostacyclin-mediated vascular functions, it neither increases blood pressure, impairs renal function nor interferes with the antihypertensive effects of diuretics and angiotensin-converting enzyme (ACE) inhibitors. However, permanent COX-1 inactivation can increase the risk of upper gastrointestinal bleeding through two distinct mechanisms: inhibition of thromboxane A2-mediated platelet aggregation; and dose-dependent impairment of prostacyclin-mediated cytoprotection in gastrointestinal mucosa. The latter increases the risk of bleeding and perforation by promoting new mucosal lesions and worsening preexistent ones by four- to 10-fold when aspirin is used at analgesic doses [27]. Antisecretory therapy (such as the use of proton-pump inhibitors) reduces the risk of upper gastrointestinal bleeding [29,30].

Drug interactions

Concomitant use of reversible COX-1 inhibitors [non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and naproxen] exert a competitive effect on the irreversible acetylation of platelets by aspirin [31,32], although this pharmacodynamic interaction is not observed with NSAIDs that have some degree of COX-2 selectivity (the '-coxibs') [31]. In a large registry of patients with previous MI, the use of NSAIDs in combination with aspirin was associated with an increased risk of both bleeding and thrombotic events, even after short-term treatment [33]. Therefore, although fewer data are available on the clinical consequences of this drug interaction for primary prevention, the association should be tentatively avoided, particularly with ibuprofen and naproxen, and a strategy for preventing gastrointestinal complications should be put in place instead.

Aspirin responsiveness

Recently, considerable debate has taken place over the prevalence of so-called 'aspirin resistance', particularly in high-risk patients, such as those with diabetes. However, aspirin resistance (defined as the failure of aspirin to fully inactivate platelet COX-1) is a rare, or perhaps even non-existent, phenomenon [34,35]. The reason that the prevalence of aspirin resistance varies considerably in the literature is that it is often identified by assays that do not specifically assess COX-1 activity [36,37]. In fact, while several assays can detect aspirin-induced effects, the results obtained are not always specific for the degree of COX-1 inhibition and may be affected by other platelet-signalling pathways. Furthermore, the prevalence of inadequate aspirin effects could be affected by the characteristics of the tested population: patients with diabetes, who are characterized by a hyperreactive platelet phenotype, may persist with high platelet reactivity despite aspirin therapy [2]. These patients may have complete COX-1 blockade, yet be erroneously interpreted as having aspirin resistance because of the type of platelet-function test used (non-COX-1-specific). When tests that specifically assess COX-1 are used, aspirin resistance is infrequently observed and more commonly attributed

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