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EDUCATIONAL ARTICLE

New Antiplatelet Strategies in Atherothrombosis and Their Indications

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Antiplatelet agents (APA) are used to reduce the risk of major cardiovascular events in various settings. When used for secondary prevention, antiplatelet monotherapy is associated with a relative risk reduction of such ischemic events of 25% compared to a placebo. New strategies are based on dual APA therapy. Aspirin-clopidogrel combination therapy is effective in situations of acute vessel injury such as myocardial infarction, coronary stenting and, possibly, peripheral stenting. GPIIb/IIIa inhibitors and loading doses of clopidogrel also have a place in these acute settings. In contrast, the aspirin-clopidogrel combination has proven disappointing in stable patients with cardiovascular disease, with no beneficial effect and, often, more bleeding events. Combination therapy with aspirin and extended-release dipyridamole may be more beneficial than very low doses of aspirin in ischemic stroke, but its use is limited by adverse effects. Overall, aspirin remains the first-line monotherapy of choice for patients with atherothrombosis, while clopidogrel is a valuable alternative. New antiplatelet strategies are in the pipeline, and clinically relevant laboratory tests of APA response may soon help to tailor treatment.

Keywords: Aspirin; Clopidogrel; Antiplatelet agents; Atherothrombosis.

Introduction

Platelets contribute to the initiation and aggravation of atherosclerosis in humans and in animal models. Major steps in arterial thrombosis include platelet activation and aggregation, both following contact with subendothelial structures and via thrombin generation.[1] Antiplatelet agents (APA) are therefore key tools in the treatment of atherothrombosis. In addition to their well-established role in thrombus formation, there is growing evidence that platelets are also involved in the progression of atherosclerotic lesions. When activated, platelets release granules containing cytokines and growth factors that, together with thrombin, contribute to the migration and proliferation of smooth-muscle cells and monocytes.[2] Thus, in addition to their preventive role in acute thrombosis, APA can also inhibit the platelet contribution to lesion progression.[3,4]

There are currently four major classes of antiplatelet drugs. Aspirin, thienopyridines (ticlopidine and clopidogrel) and phosphodiesterase (PDE) inhibitors (dipyridamole and cilostazol) are platelet function inhibitors, while the glycoprotein (GP) IIb/IIIa antagonists specifically prevents aggregation by inhibiting the fibrinogen receptor $\alpha_{IIb}\beta_3$.

For several years a one-drug-fits-all policy governed the secondary prevention of ischemic events in cardiovascular patients. Aspirin was most often prescribed. Recently, several trials have tested the efficacy and safety of new APA strategies, mostly APA combinations, in secondary prevention – the subject of this review.

Role of Platelets in Atherothrombosis

Platelet activation involves several mechanisms. After atherosclerotic plaque rupture, platelet adherence to subendothelial components like collagen triggers

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numerous amplification pathways required for the formation of a stable thrombus. Soluble agonists like thromboxane A2 (T×A2) and adenosine diphosphate (ADP) are the main amplifiers of platelet activation (Fig. 1). Following platelet activation the GPIIb/IIIa receptor undergoes a conformational change that allows activated platelets to stick together via bridges formed by the GPIIb/IIIa complex and proteins such as fibrinogen, fibrin, and von Willebrand factor. Activated platelets also stimulate the coagulation cascade and accelerate thrombin formation, further contributing to thrombus growth.

Aspirin

The antiplatelet effect of aspirin is mainly due to irreversible inhibition of cyclooxygenase (COX)-1 activity, which normally catalyzes the conversion of arachidonic acid to prostaglandin (PG) H2. PGH2 is a precursor of several bioactive prostanoids, including T×A2.[5] Although aspirin has a short half-life (15 to 20 min) in the human circulation, it induces a rapid and permanent defect in T×A2-dependent platelet function. As only 10% of the platelet pool is replenished each day, a single daily dose of aspirin is sufficient to maintain virtually complete inhibition of platelet $T\times A_2$ production.[6]

The ISIS-2 study represented an important milestone, by showing that aspirin reduced mortality after a myocardial infarction (MI) as effectively as streptokinase.[7] Several other trials followed, and a meta-analysis showed a 25% relative reduction in the risk of vascular death, myocardial infarction and stroke with antiplatelet therapy (mostly aspirin) compared to a placebo in various categories of high-risk cardiovascular patients.[8] In patients with acute myocardial infarction, the absolute reduction in risk was 3.8% at 1 month and the ''number needed to treat'' (NNT) for one month to avoid one major vascular event was 26. Current evidence suggests that a daily aspirin dose of 75–160 mg is optimal for long-term prevention in high-risk patients, together with a loading dose of 325 mg when an immediate antithrombotic effect is required (Table 1).[9,10]

The benefit of aspirin on coronary heart disease and stroke has been extensively studied, whereas fewer data are available on peripheral arterial disease (PAD). PAD is often associated with atherosclerosis in other vascular territories, and patients with this disorder are at markedly elevated risk of vascular events and death.[11] However, among 9214 patients with PAD included in the Antithrombotic Trialists' Collaboration Study, the 22% reduction in ischemic events referred to other APA than aspirin in 60% of cases. Nevertheless, the benefit of aspirin on cardiovascular events has been firmly demonstrated in a number of other high-risk settings,[12] and PAD patients are clearly a high-risk population.[13]

Aspirin is the antiplatelet drug recommended for PAD in the American College of Cardiology/American Heart Association guidelines[14] (level of evidence: A). The Inter-Society Consensus for the Management of

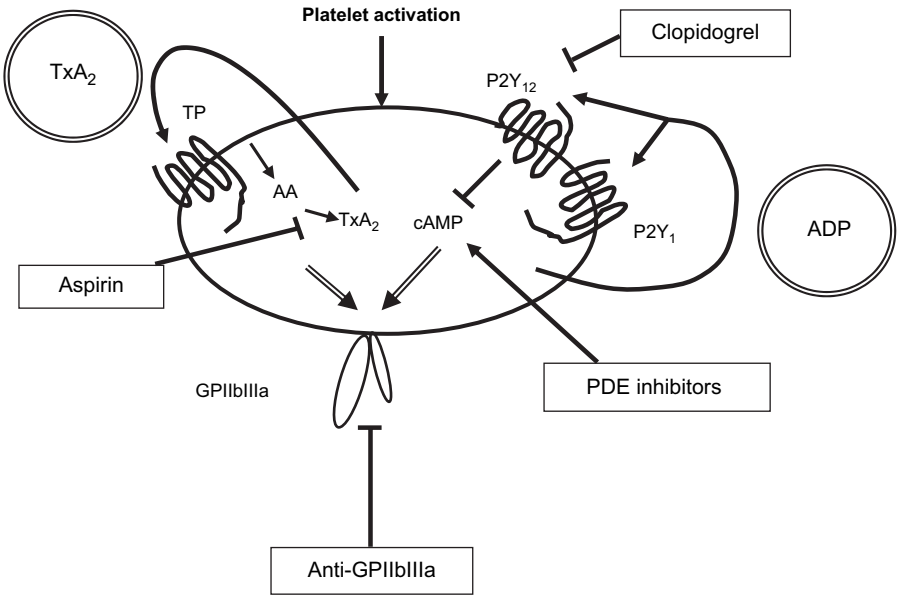

Fig. 1. Main amplification pathways of platelet activation and action of antiplatelet agents (APA). The two main amplification pathways are the thromboxane A2 (T×A2) and adenosine diphosphate (ADP) pathways, which are targeted by the most widely used APAs. AA: arachidonic acid, cAMP: cyclic adenosine monophosphate, PDE: phosphodiesterases.