Antiplatelets and Stroke Outcomes: State of the Science

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KEYWORDS

• Antiplatelets • Stroke • Medications

Antiplatelet medications are currently used in the secondary prevention of ischemic stroke. These medications serve to prevent the formation of emboli and thrombus to avert further vascular occlusion and ischemia. The antiplatelet medications aspirin, clopidogrel (Plavix®), and extended release aspirin/dipyridamole (Aggrenox®) represent the mainstay of secondary prevention of ischemic stroke and transient ischemic attack (TIA). Although antiplatelet medications prevent platelet aggregation by different mechanisms, the end result is a significant decrease in the risk of secondary stroke, myocardial infarction (MI), and death.[1–3] Increasingly, the literature reflects hypotheses about the potential utility of aspirin (acetylsalicylic acid [ASA]) and clopidogrel antiplatelet therapy, as a preventative measure in patients at risk of stroke and as an approach to treat embolic ischemic stroke in the acute phase once it has occurred.[4] This article reviews the use of antiplatelets in secondary stroke prevention and in acute stroke treatment.

CURRENT ANTIPLATELET USE IN STROKE

Current evidence does not support the usefulness of antiplatelet medications as a primary prevention measure for stroke. To this end, the current approved use of antiplatelet medications in stroke is as a secondary prevention measure.[5] Current guidelines for prevention of recurrent stroke state that the use of aspirin (50–325 mg/d) monotherapy, aspirin and extended-release dipyridamole in combination (Aggrenox), or clopidogrel (Plavix) monotherapy are all acceptable options for initial therapy.[5]

Aspirin (50–1300 mg/day) has been shown to be effective as a secondary prevention measure in multiple randomized clinical trials.[2,6] The combination of extended release dipyridamole and aspirin (Aggrenox) has been shown to reduce the risk of stroke and death by 33% and the risk of stroke alone by 38%, as compared with placebo. A subsequent trial of extended release dipyridamole and aspirin (Aggrenox) versus aspirin alone showed a risk reduction of 18% with aspirin alone and 37% with

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Aggrenox.[2] When compared with aspirin, clopidogrel has been shown to be safe and decrease the risk of a composite outcome of ischemic stroke, MI, or vascular death by 8.7% ($P = .043$).[1] Although aspirin has been shown to be inferior when compared with Aggrenox and Plavix, its use is still recommended given its relative effectiveness and superior cost profile when compared with other medications.[7] Based on 2 large randomized controlled trials, the long-term use of aspirin and clopidogrel in combination is not recommended as a means of secondary stroke prevention, because the combination showed no superiority in preventing ischemic events and showed a twofold increase in bleeding events.[8,9] Of most concern was a significant increase (absolute risk increase 1.3%) in symptomatic intracranial hemorrhage (sICH), defined as the presence of bleeding within the brain tissue accompanied by a clinical neurologic worsening. Although long-term use of aspirin plus clopidogrel has been shown to significantly increase bleeding risk, acute, short-term use of aspirin and clopidogrel as a treatment measure, particularly in loading doses, has not been fully examined in the acute stroke population.

Thus, the efficacy of antiplatelet medications for secondary prevention of stroke has been well described in the literature. Yet few studies have assessed their use as an acute therapy for ischemic stroke.[4,10] The effectiveness of these agents is based on their pharmacologic activity in hemostasis and thrombus formation; thus, the mechanism of action of the medications, ASA and clopidogrel, is first considered.

Aspirin

Synthetic ASA, marketed as aspirin, has antipyretic, analgesic, anti-inflammatory, and antiplatelet properties. The antiplatelet effects of aspirin were first described by Gibson[11] and Craven,[12] who reported protective benefits with respect to stroke and MI. Because of its usefulness as an antiplatelet medication and its cost of approximately $0.01 per 81 to 325 mg dose, aspirin has become a cornerstone of secondary prevention in ischemic stroke and TIA.[13,14]

Antiplatelet mechanism of action of aspirin

The overall mechanism of the antiplatelet action of aspirin involves its blocking of arachidonic acid production, thereby halting thromboxane A_2 and prostaglandin biosynthesis in clot formation (**Fig. 1**).[15] Thromboxane A_2 and prostaglandin production are mediated by 2 key enzymes, cyclooxygenase-1 and -2 (COX-1 and COX 2). COX-1 is an enzyme that is present in most mammalian cells and is responsible for the production of prostanoids, such as prostaglandin, thromboxane, and prostacyclin. COX-2 is induced in response to inflammation and also produces the prostanoid molecules (PI_2-PF_2).

Both COX enzymes convert arachidonic acid to prostaglandin H_2 (PGH_2), the precursor of the prostanoids. As seen in **Fig. 1**, the metabolism of arachidonic acid by the PGH pathways results in the expression of multiple prostaglandins (PGI_2, PGE_2, PGD_2, and $PGF_{2\alpha}$) and thromboxane A_2.[16] Aspirin inhibits COX-1 and COX-2 and therefore inhibits the products of their activation, thromboxane A and prostaglandin. The thromboxane pathway induced by arachidonic acid is primary to platelet activation (see **Fig. 1**).

Aspirin's inhibitory effect on prostaglandin synthesis, and therefore platelet activation, results primarily from its inhibition of the COX enzymes (**Fig. 2**). These enzymes are physiologically active for responses other than arachidonic acid degradation, which may be adversely affected with the administration of aspirin. COX-1 is constitutional and involved in the regulation of renal blood flow and protection of gastric mucosa, platelet activation, and platelet aggregation through platelet surface receptor