Antiplatelet Drugs*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

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This article about currently available antiplatelet drugs is part of the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). It describes the mechanism of action, pharmacokinetics, and pharmacodynamics of aspirin, reversible cyclooxygenase inhibitors, thienopyridines, and integrin αIIbβ3 receptor antagonists. The relationships among dose, efficacy, and safety are thoroughly discussed, with a mechanistic overview of randomized clinical trials. The article does not provide specific management recommendations; however, it does highlight important practical aspects related to antiplatelet therapy, including the optimal dose of aspirin, the variable balance of benefits and hazards in different clinical settings, and the issue of interindividual variability in response to antiplatelet drugs.

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Abbreviations: ACE = angiotensin-converting enzyme; ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATT = Antithrombotic Trialists; CAPRIE = Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events; CHD = coronary heart disease; CI = confidence interval; COMMIT = Clopidogrel and Metoprolol Myocardial Infarction Trial; COX = cyclooxygenase; CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Events; EPIC = Evaluation of 7E3 for the Prevention of Ischemic Complications; ESPS = European Stroke Prevention Study; ESPRIT = European Stroke Prevention Reversible Ischemia Trial; FDA = Food and Drug Administration; GP = glycoprotein; INR = international normalized ratio; MI = myocardial infarction; NSAID = nonsteroidal antiinflammatory drug; OR = odds ratio; PCI = percutaneous coronary intervention; PE = pulmonary embolism; PG = prostaglandin; PTCA = percutaneous transluminal coronary angioplasty; RR = rate ratio; TIA = transient ischemic attack; TX = thromboxane; TTP = thrombotic thrombocytopenic purpura

Platelets are vital components of normal hemostasis and key participants in atherothrombosis by virtue of their capacity to adhere to injured blood vessels and to accumulate at sites of injury.[1] Although platelet adhesion and activation can be viewed as a physiologic repair response to the sudden fissuring or rupture of an atherosclerotic plaque, uncontrolled progression of such a process through a series of self-sustaining amplification loops can lead to intraluminal thrombus formation, vascular occlusion, and transient ischemia or infarction. Currently available antiplatelet drugs interfere with some steps in the activation process, including adhesion, release, and/or aggregation,[1] and have a measurable impact on the risk of arterial thrombosis that cannot be dissociated from an increased risk of bleeding.[2]

In discussing antiplatelet drugs, it is important to appreciate that approximately 10^{11} platelets are produced each day under physiologic circumstances, a level of production that can increase up to 10-fold at

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times of increased need.[3] Platelets are anucleate blood cells that form by fragmentation of megakaryocyte cytoplasm and have a maximum circulating life span of about 10 days in humans.[3] Platelets provide a circulating source of chemokines, cytokines, and growth factors, which are preformed and packaged in storage granules. Moreover, activated platelets can synthesize prostanoids (primarily, thromboxane [TX] A_2) from arachidonic acid released from membrane phospholipids through rapid coordinated activation of phospholipase(s), cyclooxygenase (COX)-1 and TX synthase (Fig 1). Newly formed platelets also express the inducible isoforms of COX (COX-2) and prostaglandin (PG) E synthase, and this phenomenon is markedly amplified in association with accelerated platelet regeneration.[4] Although activated platelets are not thought to synthesize proteins *de novo*, they can translate constitutive messenger RNAs into proteins, including interleukin-1β, over several hours.[5] Thus, platelets may play previously unrecognized roles in inflammation and vascular injury, and antiplatelet strategies may be expected to affect platelet-derived protein signals for inflammatory and/or proliferative responses.[1]

Negative modulation of platelet adhesion and aggregation is exerted by a variety of physiologic mechanisms, including endothelium-derived prostacyclin (PGI_2), nitric oxide, CD39/ecto-ADPase, and platelet endothelial cell adhesion molecule-1. Some drugs may interfere with these regulatory pathways, as exemplified by the dose-dependent inhibition of PGI_2 production by aspirin and other COX inhibitors.[2]

2.0 Aspirin and Other COX Inhibitors

Aspirin has been thoroughly evaluated as an antiplatelet drug[6] and was found to prevent vascular death by approximately 15% and nonfatal vascular events by about 30% in a metaanalysis of > 100 randomized trials in high-risk patients.[7]

2.1 Mechanism of Action of Aspirin

The best characterized mechanism of action of the drug is related to its capacity to inactivate permanently the COX activity of prostaglandin H-synthase-1 and -2 (also referred to as COX-1 and COX-2).[8–12] These isozymes catalyze the first committed step in prostanoid biosynthesis (*ie*, the conversion of arachidonic acid to PGH_2) [Fig 1]. PGH_2 is the immediate precursor of PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and TXA_2. COX-1 and COX-2 are homodimers of a ~ 72 kd monomeric unit. Each dimer has three independent folding units: an epidermal growth factor-like domain; a membrane-binding domain; and an enzy-

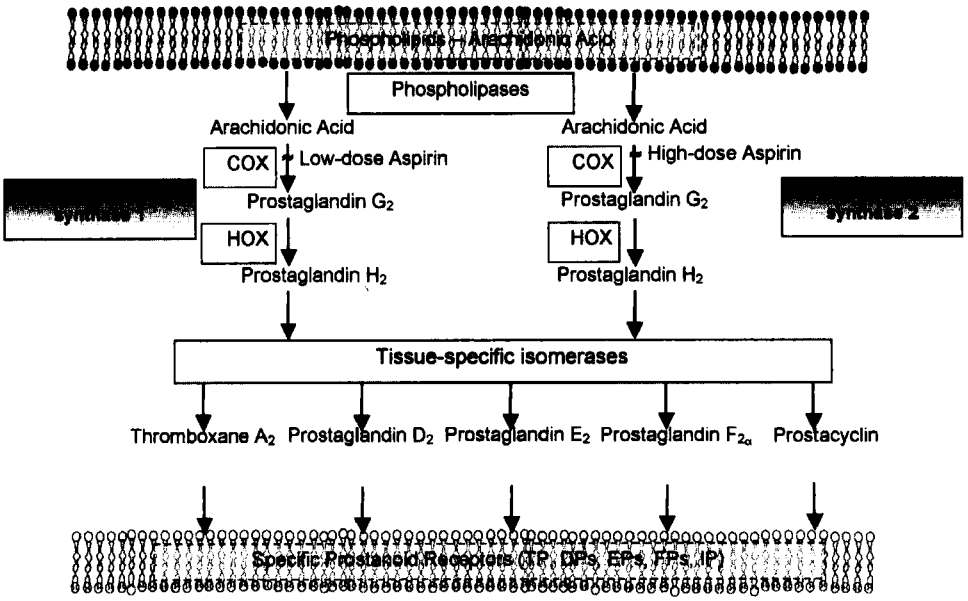

FIGURE 1. Arachidonic acid metabolism and mechanism of action of aspirin. Arachidonic acid, a 20-carbon fatty acid containing four double bonds, is liberated from the sn2 position in membrane phospholipids by several forms of phospholipase, which are activated by diverse stimuli. Arachidonic acid is converted by cytosolic PGH synthases, which have both COX and hydroperoxidase activity, to the unstable intermediate PGH_2. The synthases are colloquially termed *COXs* and exist in two forms, COX-1 and COX-2. Low-dose aspirin selectively inhibits COX-1, and high-dose aspirin inhibits both COX-1 and COX-2. PGH_2 is converted by tissue-specific isomerases to multiple prostanoids. These bioactive lipids activate specific cell membrane receptors of the superfamily of G-protein-coupled receptors. DP = PGD_2 receptor; EP = PGE_2 receptor; FP = $PGF_{2\alpha}$ receptor; IP = prostacyclin receptor; TP = TX receptor.