Aspirin, Platelets, and Thrombosis: Theory and Practice
By Gerald J. Roth and David C. Calverley

"DOES ASPIRIN PREVENT heart attacks?" The question is asked by both patients and physicians who wonder how a pill for headaches could influence a lethal vascular event. Today, a wealth of evidence shows that aspirin does, indeed, prevent heart attacks and related thrombotic disorders such as strokes.1 Performed over more than two decades, the pertinent studies range from clinical epidemiology to molecular biology and include the observation that aspirin exerts its antithrombotic effect through a single specific reaction with an enzyme of blood platelets.2,3 This review traces the connection between aspirin, the platelet enzyme (cyclo-oxygenase), and the clinical data on thrombosis, noting issues such as the indications, doses, and risks of this unique medication.

THE MECHANISM OF THE ANTITHROMBOTIC EFFECT OF ASPIRIN
Earlier Insights Into Aspirin-Like Drugs and Prostaglandins

History, Structure, and Usage

From antiquity to the 1800s, salicylates from plant sources (white willow, Salix alba) provided a folk remedy for pain and fever.4 In the mid 1800s, salicylic acid was synthesized in Europe, followed shortly thereafter by the synthesis of acetyl-salicylic acid.5 The Bayer company developed acetyl-salicylic acid (ASA) as a commercial pharmaceutical product and trade-marked the compound as aspirin.6 Aspirin is now widely accepted as a treatment for headache and musculo-skeletal pain as implied in a doctor's well-worn suggestion: "Take two aspirin and call me in the morning." For example, average yearly consumption of aspirin in developed countries in 1985 approximated 100 tablets per person.7 A variety of aspirin-like agents are available, referred to as nonsteroidal anti-inflammatory drugs (NSAIDs).8 Several forms of NSAIDs, including aspirin, are shown in Fig 1.

Antithromostatic Effects

As an acetylated salicylate, aspirin was initially considered to be a prodrug or precursor of salicylic acid itself, implying that all salicylates (acetylated and nonacetylated) might have identical effects.9 However, investigators in the 1940s reported that aspirin is a more potent antithromostatic than salicylic acid.9 A decade later, observing that aspirin can induce clinically significant bleeding, Craven suggested that the drug might be useful as an antithrombotic agent,10 and several investigators in the 1960s affirmed this suggestion by describing the ability of aspirin to suppress platelet function.11,12 Other aspirin-like drugs vary in their effects on the hemostatic system. Usual doses of acetaminophen do not alter hemostasis, whereas agents such as ibuprofen exert a short-lived effect on platelets that resembles that of aspirin,8 but blocks the active site of prostaglandin cyclooxygenase in a reversible rather than a permanent manner.13

Prostaglandins (PGs)

PGs were discovered as unique biologic activities in human semen, leading to the subsequent definition of PG structures and substrates.14,15 Biosynthesis of PGs depends on exogenous stimuli that release the substrate, arachidonate, from membrane phospholipid stores.16 Through the 1960s, however, the general roles of PGs in physiology, the specific role of PGs in hemostasis, and the mode of action of the aspirin-like drugs all remained to be clarified.

A Watershed: The "PG Hypothesis"

In 1971, Vane published his observation that aspirin inhibits PG synthesis.19 The work brought together two separate areas of inquiry (PGs and NSAIDs) and stimulated intense study of the agonist (PG)-inhibitor (NSAID) relationship.20 Over the ensuing two decades, the basic tenets of the "PG hypothesis" were confirmed. (1) PGs mediate responses, such as inflammation, that are blocked by NSAIDs. (2) NSAIDs act by blocking PG synthesis.19 When used in high doses, such as greater than 4 g/d for rheumatoid arthritis, aspirin may affect pathways of inflammation that do not involve PGs;11,21 but in most clinical settings, the drug works through its effect on PGs.5,19

PG Structure and Function

PG synthesis involves four steps (Fig 2): (1) release of substrate (arachidonate, 20:4) from lipid stores by phospholipase; (2) formation of the "common" PG intermediate, PGH2, by PGH synthase; (3) rearrangement of PGH2 by cell-specific, branch pathways to give active endproducts (PGD2/E2/F2a, thromboxane, prostacyclin); and (4) breakdown of the active compounds to inactive metabolites.22-24

All prostanoid-forming cells synthesize the "common" intermediate, PGH2,22 but they differ dramatically in their production of "cell-specific" PG products, which are categorized as either "stable" or "unstable." "Stable" products such as PGD2/E2/F2a, resist hydrolysis in blood plasma and mediate a number of physiologic processes (inflammatory, reproductive, renal, neurologic) in a variety of tissues and organs.23 However, the prostanoids of greatest interest in thrombosis are "unstable" compounds (platelet throm-
A. Salicylates

Salicylic Acid

Acetyl-Salicylic Acid (Aspirin-ASA)

B. Para-aminophenols

Acetaminophen

C. Non-salicylate Aspirin-like Agents

Ibuprofen


boxane-TxA2, endothelial prostacyclin-PGI2) that undergo rapid hydrolysis in water (seconds, minutes) and exert local, opposing hemostatic/antihemostatic effects.25 Thromboxane promotes the formation of hemostatic plugs by aggregating platelets and constricting blood vessels, whereas prostacyclin counteracts thromboxane by suppressing platelet aggregation and dilating vessels.26 The implications of the thromboxane/prostacyclin "balance"27 for the use of aspirin as an antithrombotic agent are discussed in a later section.

The Mechanism of the Aspirin Effect on PG Synthesis: Acetylation of an Active-Site Serine Within Cyclo-Oxygenase

The central enzyme of PG synthesis, PGH synthase, contains heme and possesses both cyclo-oxygenase (oxygenates/arachidonate to PGG2) and peroxidase (reduces PGG2 to PGH2) activities.28-30 Aspirin affects PG synthesis in a highly specific way by blocking only the cyclo-oxygenase function of PGH synthase31 while leaving other PG elements unaffected (Fig 3). A novel and distinct PGH synthase was discovered recently in certain cells responding to exogenous stimuli, but this second form of the enzyme (PGH synthase-2) is not found in platelets and does not appear to relate to the antihemostatic and antithrombotic effects of aspirin.32

At a molecular level, aspirin blocks cyclo-oxygenase by acetylating the protein, and the reaction depends on both the intrinsic chemical properties of the drug and the affinity of the drug for the enzyme's active site.33 The acetyl moiety of aspirin (COCH3, Figs 1 and 3) is labile and susceptible to being transferred to biologic substrates (acylation). For example, aspirin "nonspecifically" acetylates a variety of proteins, lipids, and nucleic acids at millimolar concentrations.34 In contrast, aspirin acetylates cyclo-oxygenase in a highly "specific" fashion with the reaction going to completion within minutes at micromolar concentrations under mild conditions.35 The thousand-fold difference in aspirin concentrations needed for "nonspecific" versus "specific" acetylations reflects the affinity of the drug for a single serine residue under intracellular conditions.36 The "permanence" of acetylation results in the irreversible inactivation of platelet cyclo-oxygenase by aspirin.7,3 As a result, aspirin-modified platelets are affected for the rest of their circulating lifespans. This accounts for the "cumulative" effect of aspirin that one observes when the drug is first administered in low doses (5 to 75 mg/d) to patients, namely, a progressive daily increase in the aspirin-induced functional defect caused by the
ASPIRIN, PLATELETS, AND THROMBOSIS

Fig 3. The mechanism of aspirin's effect on platelets. The 599 amino acid polypeptide chain of PGH synthase (center wavy line: NH$_2$-terminal methionine-1, COOH-terminal leucine-599) exerts cyclo-oxygenase activity as shown above (oxygenation/cyclization of arachidonate to PGG2) and interacts with aspirin as shown below. The serine residue located at position 529 of the polypeptide chain of cyclo-oxygenase is acetylated through transfer of aspirin's acetyl group, as indicated in boldface. Covalently modified, acetylated PGH synthase carries a single acetyl group in its active site and lacks all cyclo-oxygenase activity.

steady accumulation of permanently modified platelets in the circulation.

Platelet and endothelial cyclo-oxygenase are equally sensitive to aspirin, as shown by direct experiments in intact cells. An earlier study compared the enzyme from blood vessel microsomes with that of platelets, and the result suggested that the platelet enzyme was more sensitive to aspirin. However, most observers consider the endothelial and platelet enzymes to be equivalent in their response to aspirin, particularly because they appear to be identical proteins that are encoded by the same gene.

Relative Aspirin-Sensitivity of PG Synthesis in Different Cells

Under in vivo conditions, platelet PG synthesis is approximately 10-fold more sensitive to orally administered aspirin than that of other cells (Table 1). Consequently, effective analgesic/antipyretic doses of aspirin are much higher than those needed to inhibit platelets. When used orally to treat headache or fever, aspirin is delivered to protein-synthesizing target tissues by postportal blood and 600 mg doses are required for effective therapy. Similar conditions apply to aspirin-inhibition of prostacyclin synthesis in vascular endothelial cells, because the vasculature consists of protein-synthesizing cells and lies, in large part, outside the portal circulation. Direct studies of patients show that inhibition of PG12 synthesis requires higher doses of aspirin than does blockade of TxA2 formation, although considerable overlap exists between the two effects, and no dose of aspirin will block TxA2 formation completely without affecting PG12 production. The exact basis of the "differential" sensitivity of PG12/TxA2 to oral aspirin remains somewhat unclear, but it does not lie in different aspirin susceptibilities of endothelial as opposed to platelet cyclo-oxygenase. Instead, the important distinctions between PG12 and TxA2 in regard to aspirin-dependent inhibition involve three distinct parameters: (1) the relative ability of a target cell to replace an inactive enzyme by protein synthesis; (2) the exposure of target cells to aspirin in portal versus postportal blood; and (3) the physiologic role of the prostanoid pathway in the cell of interest.

A Unique Relationship: Aspirin and Platelets

Aspirin impairs platelet activation, implying that a prostanoid (PG) is involved in the activation process. However, the effect of aspirin on platelet PGs is an exceptional example of the general aspirin-PG relationship. One small dose of oral aspirin "permanently" impairs the function of all available platelets, with the effect lasting several days. The gradual recovery of platelet function after a dose of aspirin is the converse of aspirin's initial "cumulative" effect and reflects the appearance in the circulation of new, unaffected platelets that were formed in the marrow.

Table 1. Three Levels of Aspirin Therapy: 10-Fold Dose Increments

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose (mg)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithrombotic</td>
<td>60 mg</td>
<td>&quot;Platelet&quot; - Anucleate target, exquisite sensitivity, permanent/limitation effect</td>
</tr>
<tr>
<td>Analgesic/antipyretic</td>
<td>600 mg</td>
<td>&quot;Headache&quot; - &quot;Take two aspirin and call me in the morning&quot;</td>
</tr>
<tr>
<td>Antirheumatic</td>
<td>6,000 mg</td>
<td>&quot;Salicylate&quot; - Does not work through prostaglandins alone</td>
</tr>
</tbody>
</table>

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Anucleate Target

As fragments of the cytoplasm of bone marrow megakaryocytes, blood platelets lack a nucleus and are unable to synthesize new mRNA. Although retaining/ translating some megakaryocyte mRNA, blood platelets are generally incapable of protein synthesis, and those exposed to aspirin do not appear to replace their complement of inactive cyclo-oxygenase. The “anucleate” nature of platelets and the covalent nature of aspirin-dependent acetylation combine to produce the “permanence” of the aspirin effect on platelet PG synthesis. In contrast, nucleated cells such as endothelium can replenish their supply of cyclo-oxygenase after aspirin treatment by synthesizing new enzyme, and this ability to recover from aspirin treatment contributes to the reduced aspirin sensitivity of these cells as compared with platelets.

Exquisite Sensitivity

Small, infrequent doses. Platelet PG synthesis is almost completely inhibited by small, infrequent doses of oral aspirin. As gauged by several parameters (enzyme acetylation, urinary PG metabolites, ex vivo PG synthesis), oral aspirin inhibits platelet PG synthesis nearly completely when administered either as one “large/single” dose (>100 mg) or as daily “small/cumulative” doses (5 to 95 mg).

Infrequent doses. Daily oral administration of adequate doses of aspirin (>100 mg) is sufficiently frequent to block platelet PGs to a maximal extent. This fact implies that, in addition to platelets in the blood, a single dose (>100 mg) of aspirin will be exposed to a sufficient aspirin concentration to inhibit PG synthesis nearly completely. After transit through the portal circulation, aspirin is partially deacetylated/inactivated in the liver. Therefore, aspirin’s inhibitory effect on platelet function is partial because it is limited to only one of several intracellular signalling pathways. The aspirin effect is permanent because it involves covalent acetylation of cyclo-oxygenase.

Permanent, limited effect

As fragments of the cytoplasm of bone marrow megakaryocytes, blood platelets lack a nucleus and are unable to synthesize new protein and are unable to replace an inactive enzyme such as aspirin-modified cyclo-oxygenase. After oral ingestion, aspirin is absorbed from the upper GI tract with about the same time course as that of platelet entry into the portal circulation from preportal blood. During the time of aspirin absorption, the entire mass of platelets in a patient ingesting 100 mg or more of the drug will be exposed to a sufficient aspirin concentration to inhibit PG synthesis nearly completely. After transit through the portal circulation, aspirin is partially deacetylated/inactivated in the liver. Therefore, aspirin’s inhibitory effect on platelet function is partial because it is limited to only one of several intracellular signalling pathways. The aspirin effect is permanent because it involves covalent acetylation of cyclo-oxygenase.
mg) of oral aspirin also affects nascent, preformed platelets in marrow megakaryocytes before they enter the circulating blood over the next day. If this were not the case, platelet PG synthesis would increase by 10% during the day after exposure to aspirin, reflecting the rate of normal production of platelets with their circulating life span of 10 days.51 Although the extent of transport of orally absorbed aspirin to the marrow and the turnover/replenishment of cyclooxygenase in the platelet compartments of megakaryocyte cytoplasm are not defined, the available observations document the effect of aspirin on the enzyme in megakaryocytes.59 Consistent with the fact that megakaryocytes are inhibited by oral aspirin, higher doses of aspirin appear to affect an even earlier cohort of platelets that are developing in the marrow, accounting for the effective every-other-day treatment schedules noted in a later section.

Permanent, Limited Effect

In using aspirin as an antiplatelet agent, one seeks a "balance" between effectiveness and toxicity, treating thrombosis while avoiding bleeding. Aspirin has a limited effect on normal platelet function, causing a minimal prolongation of the bleeding time, a modest inhibition of in vitro aggregation, and only a slight decline in normal hemostatic function at a clinical level.11,12 The highly selective effect of aspirin on platelet PGs underpins its "limited" effect on overall platelet function. Platelet TxA2 synthesis is safely expandable in most patients because it is only one of several intraplatelet pathways that mediate activation (Fig 4C). For example, pathways involving protein kinase C activation and inositol release are not affected by aspirin,12,53 and the retention of these pathways preserves platelet function to a significant degree. Therefore, platelet PG synthesis is an attractive therapeutic target because of its distinct but limited contribution to activation in this particular target (platelets). Selective elimination of the TxA2 pathway by aspirin causes a clear-cut but modest decrease in platelet function and provides a limited but definite antithrombotic effect.

Correlating Platelet Cyclo-Oxygenase Inhibition With Prevention of Thrombosis: Molecular and Clinical Effects of Aspirin

Aspirin's antithrombotic effect could arise from the drug's actions on systems that do not involve PGs, because aspirin can influence other aspects of hemostasis such as fibrinolysis and plasma coagulation.54,55 However, these "nonprostanoid" effects of aspirin proceed only at concentrations that are irrelevant to the antiplatelet and antithrombotic activity of the drug. A close correlation exists between the aspirin concentrations (micromolar) that acetylate platelet cyclo-oxygenase, block enzyme activity/PG synthesis, and inhibit platelet function, with all three events occurring under the same conditions and with the same time course.3,2,1,1,2,3,7,12,54 The ability of low-dose aspirin (30 to 160 mg/d)13-64 to prevent clinical thrombosis provides the in vivo "clinical" correlate to the in vitro/ex vivo "molecular" data, because the only known effect of 30 to 160 mg of daily oral aspirin is the selective inhibition of platelet cyclo-oxygenase. The ability of low amounts (30 to 160 mg) of the drug to prevent thrombosis to the same extent as higher amounts (300 to 1,500 mg)13,65,66 provides essentially irrefutable evidence that aspirin exerts its antithrombotic effect by acetylation of platelet cyclo-oxygenase. If additional mechanisms are involved, their contributions appear to be minimal.

The Clinical Implication: Use Aspirin in Patients to Prevent Thrombosis

The data reviewed above give a straight-forward rationale for the clinical use of aspirin to prevent thrombosis, namely, aspirin inhibition of platelet function can exert a therapeutic effect in patients with thrombotic vascular disease by suppressing the contribution of platelets to thrombus formation. Trials of aspirin in patients also provide an opportunity to observe the role of platelet PGs in clinical thrombosis.

Current Evidence: Prevention of Clinical Thrombosis by Aspirin

The studies reviewed below show the effectiveness of aspirin in preventing certain thrombotic complications of vascular disease. In general, aspirin affects arterial rather than venous thrombosis, and most aspirin-responsive thrombi arise in the setting of atherosclerotic changes in an arterial vessel wall. The Federal Drug Administration has approved aspirin for unstable angina and after transient ischemic attacks and myocardial infarction.67,68

Studies in Cardiovascular Disease

Direct examination of coronary arteries after myocardial infarction shows a pathophysiologic sequence that begins with the disruption of an atherosclerotic plaque and leads to platelet accumulation and thrombus formation.69 Such pathologic information suggests that aspirin has the potential to prevent myocardial infarction.

Secondary Prevention of Myocardial Infarction (MI)

Eleven randomized, double-blind studies of aspirin in the prevention of recurrent MI in nearly 40,000 patients are available, six using aspirin alone (Table 2), three with aspirin.

Table 2. Aspirin in Patients After MI

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Months of Follow-Up</th>
<th>All Deaths (%)</th>
<th>Cardiac Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin</td>
<td>Placebo</td>
<td>Aspirin</td>
<td>Placebo</td>
</tr>
<tr>
<td>Elewood</td>
<td>1,239</td>
<td>12</td>
<td>10.8</td>
<td>8.0</td>
</tr>
<tr>
<td>CDPA</td>
<td>1,529</td>
<td>22</td>
<td>8.3</td>
<td>5.8</td>
</tr>
<tr>
<td>Elwood</td>
<td>1,882</td>
<td>12</td>
<td>14.8</td>
<td>12.3</td>
</tr>
<tr>
<td>Breddin</td>
<td>946</td>
<td>24</td>
<td>12.3</td>
<td>10.1</td>
</tr>
<tr>
<td>AMIS, adj</td>
<td>4,524</td>
<td>38</td>
<td>10.0</td>
<td>10.5</td>
</tr>
<tr>
<td>PAIRS II</td>
<td>1,216</td>
<td>41</td>
<td>12.8</td>
<td>10.5</td>
</tr>
<tr>
<td>Total</td>
<td>11,136</td>
<td>24</td>
<td>11.5</td>
<td>9.5</td>
</tr>
</tbody>
</table>

The data on cardiac events are graphed in Fig SC. Only aspirin trials are included.

The AMIS trial results are adjusted to balance entry parameters.

The portion of the PARIS trial using aspirin alone is summarized.

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The efficacy of aspirin has not been subjected to a randomized trial in patients with evolving major strokes. Hence, the data are unclear in terms of aspirin benefit in this setting. Whereas aspirin is recommended after a TIA or minor ischemic stroke, the same cannot be said after a completed major stroke because the data do not show a definite benefit being conferred in this circumstance.  

### Studies in Cerebrovascular Disease

Aspirin after TIAs and minor strokes

A series of trials shows that aspirin is effective in preventing new or recurrent stroke and death after TIAs and minor strokes. To date, there have been 12 randomized trials reported in the English literature using aspirin as a secondary preventative measure in patients with previous cerebrovascular disease.  

The Antipla telet Trialists' Collaboration performed an analysis of 17 completed randomized trials in patients with cerebrovascular disorders involving aspirin, dipyridamole, sulfinpyrazone, and ticlopidine. Individually, several of the larger TIA trials showed a statistically significant risk reduction in death, nonfatal stroke, or nonfatal MI, illustrating the important role of sufficient numbers of study patients in providing definitive results in this disorder.

### Aspirin Use for Evolving or Completed Major Strokes

The efficacy of aspirin has not been subjected to a randomized trial in patients with evolving major strokes. Hence, the data are unclear in terms of aspirin benefit in this setting. Whereas aspirin is recommended after a TIA or minor ischemic stroke, the same cannot be said after a completed major stroke because the data do not show a definite benefit being conferred in this circumstance.

### Studies in Peripheral Vascular Disease

Five studies show a clear-cut benefit from aspirin, with and without dipyridamole, in preventing prosthetic shunt occlusion caused by thrombus formation.
The possibility remains that PG12 inhibition limits the beneficial effect of aspirin, as the data does not show an unequivocal role for "PG12 sparing" approaches in aspirin-based prevention of thrombosis.

Aspirin is not used in most forms of deep venous thrombosis. After hip fracture or elective hip replacement, aspirin has been used to prevent venous thrombosis with variable success, and its routine use in these settings cannot be recommended, although a possible beneficial effect has not been ruled out.

**The Relationship Between the Dose of Aspirin and Its Antithrombotic Effect**

The ability of ever-decreasing doses of aspirin (30 to 160 mg/d) to prevent thrombosis strains the limits of credibility. The available information points out that aspirin doses below 300 mg/d provide effective antithrombotic therapy.

**A Rationale for Using Lower Doses of Aspirin: Minimize the Problem of Inhibition of Prostacyclin (PGI2) Synthesis**

Because aspirin can block endothelial prostacyclin synthesis, the drug is potentially harmful if a decrease in PGI2 synthesis predisposes patients to thrombosis. In the field of antiplatelet therapy, this issue has engendered a continuing debate about both the importance of aspirin-mediated inhibition of endothelial prostacyclin synthesis and the dose of aspirin that spares PGI2. The controversy began with the description of PGI2 and both conflicting and confounding data have since been added, as chronicled in Table 4. Initially, different results were obtained concerning the relative susceptibility of platelet and endothelial cyclo-oxygenase to aspirin. Subsequently, selected forms/doses of aspirin were found to spare the production of systemic prostacyclin as determined by the measurement of urinary metabolites, but not to spare the same parameter when assessed as PGI2 production in vascular tissue or as PGI2 levels in blood from bleeding time wounds. The extent of prostacyclin biosynthesis in normal subjects appears to be miniscule, suggesting that normal PGI2 levels might be below those that could influence hemostasis. The clinical importance of "PGI2 sparing" can only be resolved by direct patient studies with aspirin doses or formulations that are more efficacious because they block platelet TXA2 and spare endothelial PGI2. An example of such a study is the Dutch TIA trial comparing 30 and 283 mg aspirin in 3,131 patients. The lower dose, which would be expected to "spare PGI2," was slightly more effective with fewer side effects than the dose of 283 mg, but the differences were not statistically significant. Therefore, the limited amount of clinical data does not show an unequivocal role for "PGI2 sparing" approaches in aspirin-based prevention of thrombosis. The possibility remains that PGI2 inhibition limits the beneficial effect of aspirin and that methods of aspirin administration that preserve PGI2 are useful. Unfortunately, years after the discovery of PGI2, the importance of aspirin's anti-PGI2 effect in antithrombotic therapy remains unclear. The advantage that may be gained by preserving PGI2 during aspirin therapy appears to be modest and difficult to measure, but still worthy of further pursuit.

**Higher Aspirin Doses (900 to 1,500 mg/d) Lack Increased Effectiveness**

Clinicians seek to use the lowest amount of a drug that will give a maximal therapeutic effect. In the case of aspirin's antithrombotic effect, the point was addressed in the Anti-Platelet Trialists' Collaboration by the meta-analysis of 19 antiplatelet trials of aspirin in several thrombotic disorders. An indirect comparison of trials using 900 to 1,500 mg/d of aspirin versus placebo with trials using 300 to 325 mg/d versus placebo was reported, and higher doses were not more effective than lower doses when compared in this way. Patients treated with 900 to 1,500 mg experienced a 23% reduction in new vascular events, whereas those taking 320 mg showed a decrease of 24%. Therefore, a "plateau" appears to exist in the dose-response relationship of aspirin's antithrombotic effect. Once an effective "threshold" dose of aspirin is reached, maximal benefit results. Clinical and laboratory observations compliment each other in this regard, because aspirin inhibition of in vitro platelet PG synthesis shows a similar dose-response "plateau" with max-

### Table 4. Chronology of Concern That Aspirin Decreases Endothelial PGI2

<table>
<thead>
<tr>
<th>Year</th>
<th>Observation</th>
<th>Conclusion, Aspirin Considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td>Thromboxane (TXA2) defined as prothrombotic</td>
<td>Beneficial! blocks damaging platelet PG</td>
</tr>
<tr>
<td>1976</td>
<td>Prostacyclin (PGI2) described as antithrombotic</td>
<td>Harmful? may block protective PG</td>
</tr>
<tr>
<td>1978</td>
<td>Platelet enzyme more susceptible to ASA</td>
<td>Beneficial! if dose employed blocks platelet but not endothelial enzyme</td>
</tr>
<tr>
<td>1979</td>
<td>ASA effect equal on different enzymes</td>
<td>Harmful? since no dose would block either cell's PG enzyme selectively</td>
</tr>
<tr>
<td>1981</td>
<td>Prostacyclin synthesis in humans is miniscule</td>
<td>Beneficial! prostacyclin amounts appear too low to be relevant in thrombosis</td>
</tr>
<tr>
<td>1982-83</td>
<td>Incremental ASA doses block TXA2 &gt; PGI2</td>
<td>Beneficial! careful choice of ASA dose may preserve PGI2 synthesis</td>
</tr>
<tr>
<td>1980-87</td>
<td>All ASA doses block PGI2 in veins/shed blood</td>
<td>Harmful? no evidence that any ASA dose works selectively in vivo</td>
</tr>
<tr>
<td>1991</td>
<td>Low, slow-release doses of ASA &quot;spare&quot; PGI2</td>
<td>Beneficial! the ASA formulation can selectively block TXA2 in controls</td>
</tr>
<tr>
<td>1991</td>
<td>Dutch TIA trial finds 30 mg ASA effect &gt; 300 mg</td>
<td>Beneficial! but the &quot;optimal&quot; ASA dose is elusive and differences are small</td>
</tr>
</tbody>
</table>
nal blockade at micromolar concentrations. The clinical data reinforce the point that aspirin inhibits thrombosis by blocking platelet PG synthesis. Currently, no solid evidence is available that demonstrates an increased antithrombotic benefit of aspirin doses greater than 320 mg/d, and a significant amount of data points to the opposite, ie, that maximal benefit accrues from aspirin doses less than 320 mg/d.

Most aspirin trials in cerebrovascular disease have used higher doses of aspirin, in the range of 900 to 1,500 mg/d; and concern persists, based on an analysis of available data, that higher doses may be needed in subsets of patients with cerebrovascular thrombosis. However, a British study of TIA and minor stroke directly compared 300 mg with 1,200 mg doses of aspirin and found no statistically significant difference in efficacy. The evidence that higher doses of aspirin are needed in TIA and minor stroke is not compelling and stands in contrast to prevailing information about aspirin in related forms of vascular disease.

Lower Aspirin Doses (30 to 160 mg/d) May Be More Effective Than Standard Doses of 320 mg

The success of the trials using relatively low doses of aspirin suggest that only a portion of one adult 320 mg tablet per day is sufficient to prevent thrombosis. The only direct comparison was the Dutch TIA trial comparing 30 and 283 mg doses. A slight but statistically insignificant increase in therapeutic effect and decrease in toxicity was seen with the lower dose. By comparing the benefits achieved in different trials using different doses of aspirin, the observed effects appear to be roughly equivalent in patients with angina, bypass grafts, and after MI. The data do not resolve the question of the importance of “prostacyclin sparing” by low-dose aspirin. However, the results of the Second Anti-platelet Trialist overview support (nonsignificant trend, \( P = .06 \)) the use of lower doses of aspirin because trials using less than 160 mg/d showed a 28% odds reduction in vascular events, compared with 26% and 20% odds reductions in trials using 160 to 325 mg and 500 to 1,500 mg/d, respectively.

An Elusive Fact: The “Optimal” Dose of Daily Oral Aspirin to Prevent Thrombosis

The “optimal” antithrombotic dose lies somewhere between 30 and 320 mg of oral aspirin per day. Some lower limit of aspirin is required to accomplish the basic mission of the drug. Doses of less than 30 mg/d are unlikely to inhibit platelet PG synthesis completely and have not been subjected to clinical trials. All observers do not agree on any single effective lower dose, nor do all observers agree that the same dose of aspirin will work for every indication. However, the parameters of aspirin’s antithrombotic effect are remarkably consistent: (1) The intrinsic structural and functional properties of blood platelets do not vary in the thrombotic conditions of interest although platelet activation may be present. (2) The drug blocks platelet PG synthesis in every thrombotic disorder in which it is effective. (3) Platelets in different thrombotic disorders do not differ from normal platelets in their susceptibility to aspirin. In view of this information, the least amount of aspirin that blocks platelet PG synthesis to a maximal extent is likely to be the most effective and least toxic dose. Doses of 80 to 160 mg/d satisfy that requirement, administered daily for reasons of simplicity, maximal effect, and compensation for missed doses. A higher loading dose (320 mg) is valuable for achieving an immediate effect when therapy is initiated in the face of active thrombosis.

THE RELATIONSHIP BETWEEN THE DOSE OF ASPIRIN AND ITS ADVERSE EFFECTS

Urticaria and related idiosyncratic reactions will exclude rare patients from the use of aspirin. Gastric irritation and decreased renal and hemostatic function are more common adverse effects.

Dose-Dependent Gastrointestinal and Renal Side Effects

Aspirin induces gastrointestinal (GI) irritation and bleeding by a mechanism that may involve both inhibition of PG synthesis and direct damage to gastric and intestinal mucosa through contact with ingested drug tablets. Clinical and endoscopic data show the dose-dependency of aspirin’s GI toxicity, and antithrombotic trials with aspirin corroborate this fact. For example, GI complaints and noncompliance increase with aspirin doses of 900 to 1,500 mg compared with 300 mg or placebo. However, the gastric mucosa appears to adapt to aspirin, and various preparations of aspirin (enteric coating, buffered preparations) and two therapeutic modalities (misoprostol, ranitidine) may moderate the GI toxicity of the drug.

Studies of the GI toxicity of aspirin doses less than 320 mg/d have given inconsistent results, with some trials indicating low levels of toxicity and others recording essentially no such adverse effects. Therefore, the available information on GI toxicity provides another reason to use lower aspirin doses to prevent thrombosis, namely, with 80 to 160 mg/d doses, one minimizes GI toxicity.

Suppression of renal PG synthesis with attendant vasostimulation is unlikely to occur with 80 to 160 mg doses of aspirin, reiterating the argument to use lower doses of the drug in thrombosis.

The Dose-Independent Decrease in Hemostatic Function Caused by Aspirin

The bleeding disorder induced by aspirin is usually subtle and goes unrecognized in hemostatically normal individuals as a mild increase in bruising or mucosal bleeding. The antihemostatic and antithrombotic effects of aspirin are inseparable because both result from inhibition of PG synthesis and direct damage to gastric and intestinal mucosa. The concept of “prostacyclin sparing” by aspirin is unlikely to occur with 80 to 160 mg doses of aspirin, reiterating the argument to use lower doses of the drug in thrombosis.
were observed in the aspirin group over 5 years, compared with 2 such events in the controls. The same toxicity has been observed in some primary prevention trials but not in others, and it is not seen in secondary trials in which an increase in intracerebral bleeding may be obscured by a concomitant decrease in thrombotic, occlusive strokes. In many secondary prevention trials, aspirin significantly reduces the risk of both fatal and nonfatal stroke. The incidence of serious bleeding caused by the dose-independent, antithrombotic effect of aspirin is not easily quantitated, but the potential threat of increased intracerebral bleeding should be a strong deterrent to the indiscriminant or uncritical use of aspirin for the primary prevention of thrombosis.

The Potential Role of Subclinical Bleeding Disorders in Aspirin-Induced Hemorrhage

Aspirin is well-known to exacerbate the bleeding tendency of hemophilia and patients with von Willebrand disease (vWD). However, not all individuals who are predisposed to bleeding are fully aware of their disability. Some may not have been evaluated or diagnosed accurately. The estimated incidence of mild forms of hemophilia, vWD, congenital platelet defects, and unclassified bleeding disorders varies widely and may range between 1% and 0.01% in various populations. Subclinical bleeding disorders are relevant to the bleeding problems seen with aspirin, particularly when the drug is administered to broad populations for primary prevention of thrombosis. In this instance, aspirin may exacerbate an underlying bleeding diathesis in rare individuals, and severe bleeding may result. Hemostatic evaluation of these individuals with aspirin-induced bleeding might show cryptic hemostatic disorders.

CURRENT STATUS: CLINICAL USE OF ASPIRIN TO PREVENT THROMBOSIS

Status of Aspirin in Relation to Other Antiplatelet Agents

Aspirin is insufficient antiplatelet therapy in some clinical settings. With impending or evolving thrombosis such as that found after coronary angioplasty or during thrombolysis for acute myocardial infarction, certain patients may benefit from more potent agents. For example, the murine monoclonal antibody 7E3 directed against platelet glycoprotein IIb-IIIa can completely suppress platelet aggregation, and hirudin can effectively block the activity of thrombin on platelets and plasma coagulation. These agents differ from aspirin in being intravenous therapy that can be applied in acute thrombotic settings and that can depress hemostatic function to a profound degree.

Other oral antiplatelet agents, such as sulfipyrazone, sulcloxidil, dipyridamole, and ticlopidine, have not supplanted aspirin. For example, aspirin is less expensive, associated with fewer side effects, and more effective than sulfipyrazone. Repeated studies show that dipyridamole generally provides no added benefit when combined with aspirin, although it may have a limited role with aspirin in coronary bypass grafting and with warfarin in patients with mechanical mitral valves. Ticlopidine is an effective oral antiplatelet agent whose active form appears to be a metabolite of the parent compound. It has been directly compared with aspirin in a group of patients with cerebrovascular disease and shown to be more effective than aspirin in these individuals. However, ticlopidine has significant reversible toxicity against the bone marrow and GI tract, and the drug has not been studied in sufficient detail to warrant its widespread use. Currently, ticlopidine is recommended for patients who experience recurrent thrombosis during aspirin therapy or for those who are aspirin-intolerant.

Indications and Dosages for Aspirin Therapy

Clinical use of aspirin is changing (Fig. 5). In the future, the drug may be used more as an antithrombotic and less as an analgesic/antipyretic because of concern over Reye syndrome in children and because of the availability of other effective NSAIDs for pain and fever such as acetaminophen and ibuprofen. The major current controversy regarding aspirin as an antithrombotic is its use as primary prevention in individuals who have not yet experienced a thrombotic event. Because the primary prevention studies are in not in agreement and show rare but significant cerebrovascular bleeding complications, a current recommendation is to reserve aspirin as a primary preventative for patients with identified risk factors for atherosclerosis such as smoking, hypertension, hyperlipidemia, and diabetes. Additional trials of aspirin for primary prevention are underway, with one using warfarin in addition to aspirin in patients with risk factors for atherosclerotic vascular disease. Aspirin use in secondary prevention of thrombosis is noted above.

Final judgments on the optimal dose/form of aspirin must come from direct study of individual disease states. Based on current data, 80 to 160 mg per day by mouth provides the maximal antithrombotic effect of the drug. This dose corresponds to one or two "baby/child" tablets (80 mg each) of aspirin taken orally, once each day.

Management of Toxicity

To minimize the risk of bleeding, a bleeding history is essential to aid in detecting the rare patient with a subclinical bleeding diathesis. If an aspirin-treated patient must undergo surgery, the platelet defect induced by aspirin can be circumvented by waiting 3 to 7 days for the return of normal platelets from the marrow. However, aspirin’s antithrombotic and antihemostatic effects cannot be separated, and the bleeding risk from aspirin can be minimized but not eliminated. Similarly, GI irritation is an inescapable, although usually minor and manageable, complication of aspirin therapy that can be minimized by using lower doses of the drug.

Risk-Benefit and Cost-Effectiveness Considerations

Patient management during aspirin therapy is simple and inexpensive. The workup before starting aspirin includes a bleeding history and a platelet count. On rare occasions, additional hemostatic tests are required. The follow-up evaluation during treatment generally consists only of inquiries about bleeding and GI upset. For the majority of patients...
A Inexpensive, oral drug  

B Significant drop in function, known risk of bleeding

Fig 5. Aspects of the clinical use of aspirin as an antithrombotic agent. (A) The antithrombotic dose of daily oral aspirin is less than one adult 320 mg tablet. Doses of 80 or 160 mg give complete inhibition of platelet PG synthesis and a maximal therapeutic effect in published studies. (B) Aspirin exerts its antithrombotic effect by eliminating platelet PG synthesis, thereby blocking \( \text{TXA}_2 \) formation. The elimination of \( \text{TXA}_2 \) synthesis leads to a moderate decrease in platelet function and a concomitant mild hemostatic defect. (C) Multiple studies show the clinical benefit of aspirin. The 6 secondary prevention trials listed in Table 2 included 11,136 patients studied over an average of 24 months. Aspirin treatment led to a 31% risk reduction in cardiac events as compared with placebo, an example of aspirin as effective chronic antithrombotic therapy in defined patients with vascular disease.

taking low doses of aspirin, both risks and costs are minimal. The future development of additional antiplatelet agents is an attractive goal; but, currently, no available drug compares favorably to aspirin as a long-term, oral antiplatelet agent.

CONCLUDING REMARKS

Aspirin has “stood the test of time” as an antithrombotic agent. Studies over several decades provide a solid base of information about the drug, starting with platelet cyclo-oxygenase inhibition and ending with the prevention of thrombosis. The links between these observations are sound, and the actions, indications, doses, and risks of aspirin are well-defined. Questions remain concerning the optimal dose and formulation of aspirin and concerning its use in primary prevention and in cerebrovascular disease. However, as the field of clinical thrombosis increases in complexity, the simplicity of aspirin stands out. It is a critically important antiplatelet component of many therapeutic regimens directed against arterial thrombosis. Properly used in appropriate patients, aspirin reduces the incidence of vascular deaths by about 15% and that of nonfatal vascular events by about 30%, a dramatic clinical benefit that results from the unique effect of aspirin on platelets.

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