Aspirin: Promise and Resistance in the New Millennium

Carlo Patrono, Bianca Rocca

Abstract — Although conceived at the end of the 19th century, aspirin remains the gold standard of antiplatelet therapy. Approximately 100 randomized clinical trials have established its efficacy and safety in the prevention of myocardial infarction, ischemic stroke, and vascular death among high-risk patients treated for a few weeks, at one end of the spectrum, and in low-risk subjects treated up to 10 years at the other. Despite this wealth of data, several issues continue to be debated concerning the use of aspirin as an antiplatelet agent, and novel opportunities appear on the horizon for this 110-year-old drug. These issues include: (1) the optimal dose for cardiovascular prophylaxis; (2) the uncertain threshold of cardiovascular risk for its use in primary prevention; (3) the apparent gender-related difference in its cardioprotective effects; (4) the increasingly popular theme of aspirin “resistance”; (5) the opportunities of chemoprevention in colorectal cancer; and (6) the renewed interest in aspirin as an analgesic agent in osteoarthritic patients at high cardiovascular risk. The aim of this review is to address these issues by integrating our current understanding of the molecular mechanism of action of the drug with the results of clinical trials and epidemiological studies of aspirin as an antiplatelet drug. (Arterioscler Thromb Vasc Biol. 2008;28:s25-s32)

Key Words: antiplatelet therapy □ aspirin resistance □ primary prevention □ colorectal cancer □ osteoarthritis

The Optimal Dose of Aspirin

Placebo-controlled randomized trials have shown that aspirin is an effective antithrombotic agent when used long term in doses ranging between 50 and 100 mg/d, and there is a suggestion that it is effective in doses as low as 30 mg/d. Aspirin in a dose of 75 mg/d was shown to be effective in reducing the risk of acute myocardial infarction (MI) or death in patients with unstable angina and chronic stable angina as well as in reducing stroke or death in patients with transient cerebral ischemia and the risk of postoperative stroke after carotid endarterectomy. In the European Stroke Prevention Study (ESPS)-2, aspirin 25 mg twice daily was effective in reducing the risk of acute myocardial infarction (MI) or death in patients with prior stroke or transient ischemic attack (TIA). Moreover, in the European Collaborative trial on Low-dose Aspirin in Polycythemia vera (ECLAP) trial, aspirin 100 mg/d was effective in preventing thrombotic complications in patients with polycythemia vera, despite a higher-than-normal platelet count. The lowest effective dose of aspirin for these various indications is shown in the Table.
The clinical effects of different doses of aspirin have been compared directly in a relatively small number of randomized trials. In the United Kingdom-TIA (UK-TIA) study, no difference in efficacy was found between 300 and 1200 mg/d of aspirin. In a study of 3131 patients after a TIA or minor ischemic stroke, aspirin in a dose of 30 mg/d was compared with a dose of 283 mg/d, and the hazard ratio for the group receiving the lower dose was 0.91 (95% confidence interval [CI], 0.76 to 1.09). The ASA and Carotid Endarterectomy (ACE) trial reported that the risk of stroke, MI, or death within 3 months of carotid endarterectomy is significantly lower for patients taking aspirin 81 mg or 325 mg daily than for those taking 650 mg or 1300 mg (6.2% versus 8.4%; P=0.03). Thus, there is no convincing evidence from randomized studies that higher doses are more effective in reducing the risk of serious vascular events. In fact, both this limited set of randomized comparisons and the indirect comparisons reported in the overview of the Antithrombotic Trialists’ Collaboration are compatible with the reverse, ie, blunting of the antithrombotic effect at higher doses of aspirin, consistent with dose-dependent inhibition of prostacyclin (PGI₂). Such inhibition of PGI₂ may be a potential mechanism by which cyclooxygenase (COX)-2 inhibitors produce an excess risk of MI.

The antithrombotic effects of a range of aspirin doses have also been compared with an untreated control group in a number of thrombotic vascular disorders. The doses have varied between 50 and 1500 mg/d. Aspirin has been shown to be effective in the following conditions: unstable angina, chronic stable angina, aortocoronary bypass surgery, thromboprophylaxis of patients with prosthetic heart valves, thromboprophylaxis of patients with arterial venous shunts undergoing long-term hemodialysis, acute MI, transient cerebral ischemia, acute ischemic stroke, and polycythemia vera.

Thus, aspirin is an effective antithrombotic agent in doses between 50 and 1500 mg/d. Results of the Dutch TIA study suggest that 30 mg/d also is effective. There is no evidence that low doses (50 to 100 mg/d) are less effective than high doses (650 to 1500 mg/d) and, in fact, the opposite may be true. These clinical findings are consistent with saturability of platelet COX-1 inactivation at doses as low as 30 mg/d.

There is evidence, however, that doses of approximately 300 mg/d produce fewer gastrointestinal (GI) side effects than doses of approximately 1200 mg/d. There is also some evidence that a dose of 30 mg/d produces fewer side effects than 300 mg/d. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Investigators have retrospectively investigated the relationship between the aspirin dose (the CURE protocol recommended 75 to 325 mg daily) and risk of major bleeding. This study was a randomized comparison of clopidogrel and placebo on a “background” of aspirin therapy. Patients with acute coronary syndromes receiving aspirin ≤100 mg/d had the lowest rate of major or life-threatening bleeding complications both in the placebo (1.9%) and clopidogrel (3%) arms of the trial. Bleeding risks increased with increasing aspirin dose, with or without clopidogrel.

Efficacy and Safety of Low-Dose Aspirin in the Prevention and Treatment of Atherothrombosis in High-Risk Patients

The efficacy and safety of aspirin has been evaluated across the entire spectrum of atherothrombosis, from apparently healthy low-risk individuals to patients presenting with an acute MI or an acute ischemic stroke. Among patients with occlusive vascular disease, both individual studies (reviewed in ref 1) and a meta-analysis of antiplatelet therapy trials have shown that low-dose aspirin reduces the risk of a serious vascular event by approximately one quarter. This represents a composite of one-third reduction in nonfatal MI, one-quarter reduction in nonfatal stroke, and one-sixth reduction in death from a vascular or unknown cause. Because each of these proportional reductions applies similarly to all categories of patients with vascular disease, the absolute benefits of aspirin in the individual patient can be estimated by applying a one-third reduction to her or his absolute risk of nonfatal MI, a one-quarter reduction to the risk of nonfatal stroke, and a one-sixth reduction to the risk of vascular death. Thus, among a wide range of patients with vascular disease, in whom the annual risk of a serious vascular event ranges from 4% to 8%, aspirin typically prevents at least 10 to 20 fatal and nonfatal vascular events for every 1000 patients treated for 1 year (number needed to treat: 50 to 100).

Observational studies and a meta-analysis of trials among high-risk patients have demonstrated that long-term therapy with low-dose aspirin is associated with a 2-fold increased risk of major extracranial (mostly, upper GI) bleeding. This proportional excess hazard appears similar regardless of the variable underlying cardiovascular risk of

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<th>Table. Vascular Disorders for Which Aspirin Has Been Shown to Be Effective and Lowest Effective Dose</th>
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<tr>
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<td>Men at high cardiovascular risk</td>
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<td>Acute ischemic stroke*</td>
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*Higher doses have been tested in other trials and not found to confer any greater risk reduction.
Efficacy and Safety of Low-Dose Aspirin in Patients at Intermediate Risk of Vascular Complications

As can be seen in Figure 1, depicting the absolute benefit and hazard produced by aspirin in 7 primary prevention trials, 39-44 the number of major vascular events avoided does not clearly outweigh the number of major bleeds caused in most of these trials, and the 2 lines only begin to separate from each other above an annual baseline risk of 1.5%. Because at least 3 of these trials (Hypertension Optimal Treatment [HOT], Thrombosis Prevention Trial [TPT], and Primary Prevention Project [PPP]) were carried out in people selected for being at “high” cardiovascular risk, it is perhaps surprising that the actual rate of vascular events in these “high-risk” subjects was not markedly higher than that of unselected apparently healthy subjects (eg, compare the rate of events in TPT and in the British Doctors Study). Risk prediction algorithms use multiple risk factors that are individually weak screening tools, so that their combination in a risk prediction algorithm is also weak and lacks adequate sensitivity and specificity.

Because disease rates rise exponentially above 60 years of age, and because demographic changes will result in large increases in the elderly population in the coming years, the potential for prevention in this group is substantial. However, the balance of risk and benefit is uncertain in older individuals (in whom the bleeding risks also increase) 45 because the amount of randomized evidence in those aged 70 or over is limited (around 10% of the primary prevention trial population). Further randomized trials among elderly individuals would therefore help to strengthen the evidence in this important group.

Another important category of individuals for whom aspirin might be considered is those with diabetes mellitus. Despite current guidelines on the routine use of aspirin in these patients, evidence that the benefit of antiplatelet prophylaxis outweighs the risk of major bleeding complications in this setting is largely inadequate. Only 1 trial of aspirin versus placebo has been conducted among diabetic patients. In the Early Treatment Diabetic Retinopathy (ETDRS) trial, 46 diabetic patients were eligible if they had mild or moderate retinopathy and were randomized to aspirin 650 mg/d versus placebo. Among 3711 randomized patients, only 6% had a history of MI, and the mean annual risk of a major coronary event was 2.5%. However, although there was a marginally significant 17% reduction (HR=0.84) in major coronary events, there was no significant effect on stroke or vascular death. Consequently, there remains considerable uncertainty about the benefits and risks of aspirin among diabetic patients with no known vascular disease, and this is another area where further trials would be useful. One such trial, A Study of Cardiovascular Events in Diabetes (ASCEND), is currently ongoing in the United Kingdom.

Another interesting paradigm of “intermediate-risk” patients is that provided by myeloproliferative disorders, a heterogeneous group of diseases involving clonal hematopoietic stem cells that includes polycythemia vera, essential thrombocythemia, idiopathic myelofibrosis, and chronic myelogenous leukemia. In both polycythemia vera and essential thrombocythemia, thrombotic complications are a major cause of illness and death in untreated patients. 46 In the former condition, a recently completed placebo-controlled randomized trial of aspirin 100 mg/d has demonstrated that this regimen of antiplatelet therapy can safely prevent both arterial and venous thrombotic complications.9 Interestingly, despite the lack of any evidence for the efficacy and safety of low-dose aspirin in essential thrombocythemia, all such patients recruited in a recently published randomized trial of hydroxyurea versus anagrelide were treated with aspirin 75 to 100 mg/d. 47
individuals with no clinically apparent vascular disease. The decision to prescribe low-dose aspirin in a person with no history of vascular disease must rely on an individual judgment that the likely benefits of aspirin will exceed any risks. On the basis of the available evidence from 7 primary prevention trials, low-dose aspirin therapy for 4 to 10 years prevents nonfatal MI by one quarter, but it has no clear protective effect against ischemic stroke or vascular death. Therefore, assessing the benefits and risks of low-dose aspirin requires balancing any absolute reduction in nonfatal MI (1 to 3 per 1000 treated for 1 year) against an increased risk of major GI bleeding (1 to 2 per 1000) and hemorrhagic stroke (0.1 to 0.2 per 1000).

It has been suggested that low-dose aspirin may be appropriate for individuals whose estimated annual risk of a coronary event, based on a risk prediction algorithm, exceeds a particular threshold. Various guidelines have adopted this approach using risk thresholds for coronary events ranging from 0.6% to 1.5% per year. In particular, the suggestion that aspirin therapy is safe and worthwhile at a coronary event risk ≥1.5% per year is potentially attractive. However, as shown in Figure 1, we lack clinical trial data in the area of cardiovascular risk that is intermediate between the observed risk in the placebo arm of the TPT\(^+\) (approximately 1.5%) and that of the Swedish trial in patients with chronic stable angina\(^3\) (approximately 3.5%).

Moreover, it should be emphasized that current estimates of the absolute excess of major bleeding complications associated with low-dose aspirin therapy are likely to underestimate the potential harm in individuals at increased risk of bleeding complications, who were typically excluded from aspirin trials. Although many gastroenterologists would recommend the use of proton pump inhibitors to reduce such risk, the best strategy to minimize the burden of GI toxicity associated with low-dose aspirin is currently uncertain, and more studies are needed to resolve this uncertainty.

Is There a Gender-Related Difference in the Cardioprotective Effects of Low-Dose Aspirin?

Although gender-based differences in salicylate metabolism have been reported, these do not appear to influence the pharmacodynamics of the antiplatelet effect of aspirin, which is substantially identical in men and women, both in terms of dose and time dependence.\(^2\,\,5\)

A gender-related difference in the production of 15-epi-lipoxin A\(_4\) has been reported in healthy subjects treated with low-dose aspirin (81 mg/d for 8 weeks).\(^5\) 15-Epi-lipoxin A\(_4\) is synthesized via the transcellular metabolism of 15R-hydroxy-eicosatetraenoic acid (15R-HETE), which is produced by aspirin-acetylated COX-2. Aspirin-treated females showed a positive correlation between age and 15-epi-lipoxin A\(_4\) levels, whereas a negative correlation was observed in men. The clinical significance of this observation is presently unknown because of the lack of convincing evidence for a gender-based difference in the cardioprotective effect of aspirin in high-risk patients.\(^2\,\,3\)

At variance with the results of the first 5 primary prevention trials of low-dose aspirin, in which most or all randomized subjects were men, the Women’s Health Study found no evidence of a protective effect of aspirin 100 mg given on alternate days against MI, but a marginally significant 17% reduction in the risk of stroke (relative risk 0.83; 95% CI, 0.69 to 0.99; \(P=0.04\)). It should be noted that stroke represented a secondary end point of the study and that the overall effects of 10-year prophylaxis with aspirin on the primary end point (a combination of nonfatal MI, nonfatal stroke, and death from cardiovascular causes) failed to reach statistical significance (relative risk 0.91; 95% CI, 0.80 to 1.03; \(P=0.13\)). Despite the large sample size of approximately 40 000 initially healthy women and the long duration of follow-up, the Women’s Health Study was probably underpowered to detect a moderate treatment effect because of the lower than expected rate of vascular events (only 0.3% per year in the control group) and lower than expected relative risk reduction associated with aspirin (9% versus 25%). Thus, its results should be viewed within the context of all randomized evidence from aspirin trials.\(^2\,\,3\) Moreover, the results of a gender-specific random-effects meta-analysis of the data from 6 primary prevention trials performed by Ridker et al should be considered within the limitations of subgroup analysis.

Women have a somewhat lower risk of arterial thrombosis as well as upper GI bleeding than men, though both increase substantially in postmenopausal age. Thus, it is not expected that the balance of benefits and risks of low-dose aspirin is importantly influenced by gender.

Aspirin “Resistance”

Although the early characterization of the antiplatelet effects of aspirin was based on measurements of bleeding time and use of Born’s optical platelet aggregometry, it was not until the discovery of thromboxane (TX) \(\text{A}_2\) and the development of mechanism-based biochemical end points that the human pharmacology of platelet inhibition by aspirin could be properly described in the early 1980s. An intriguing finding of FitzGerald et al was that adenosine diphosphate-induced platelet aggregation was maximally inhibited by aspirin 40 to 80 mg/d but tended to return to baseline values on chronic dosing with higher doses up to 2600 mg/d, despite profound and persistent suppression of TX\(\text{A}_2\) biosynthesis in vivo. This is possibly the first description of so-called “aspirin resistance.” However, it was not until 10 years later that the term actually surfaced in the medical literature in a couple of articles by Helgason et al describing inadequate inhibition of platelet aggregation by aspirin in some patients with cerebrovascular disease. Since then, about 190 papers have been published on aspirin resistance with an exponential growth after 2002. The term “resistance” has been used to describe the inability of aspirin to produce a measurable response on ex vivo tests of platelet function, to inhibit TX\(\text{A}_2\) biosynthesis in vivo, or to protect individual patients from recurrent thrombotic complications.

Acetylation of platelet COX-1, inhibition of TX\(\text{A}_2\) production, and prevention of thrombotic complications (Figure 2) share 2 rather unusual features: They are measurable effects of a once-daily regimen of aspirin administration, despite a 20-minute half-life of the drug, and they show...
It is important to emphasize that the clinical development of low-dose aspirin as an antiplatelet agent was largely guided by mechanistic understanding of its unique mode of action and by characterization of the time and dose dependence of its effects on TXA2 biosynthesis. Platelet aggregation measurements were not particularly useful in this endeavor, and they completely failed in guiding the clinical development of the “super-aspirin” of the nineties, ie, oral GPIIb/IIIa blockers. Thus, the track record of clinical significance of these platelet functional measurements is not particularly brilliant, and it is somewhat surprising that so much emphasis was put on their reliability in the many studies of aspirin “resistance” published during the last 5 years.

The daily dose of aspirin currently recommended by all international guidelines represents a 3- to 10-fold excess over the minimum amount of the drug necessary to fully inactivate platelet COX-1 on repeated daily dosing (20 to 30 mg). This excess can accommodate, at least in part, interindividual variations in drug absorption, body weight, platelet count, and turnover. Thus, it is not surprising that the interindividual variability in the degree of suppression of platelet TXA2 production is quite limited, even in the presence of a high platelet count. In view of the remarkable consistency in the platelet TXA2-suppressing effect of aspirin, the European Society of Cardiology Task Force on Antiplatelet Agents and the Platelet Physiology Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis recommend that no test of platelet function be performed to assess the antiplatelet effect of aspirin in the individual patient.

As with any drug (antithrombotic, lipid lowering, or antihypertensive) used to prevent atherothrombosis, treatment “failure” can occur with aspirin—perhaps not surprisingly, given the multifactorial nature of atherothrombosis. Thus, there is no scientific basis to change antithrombotic therapy in the face of a treatment “failure,” as we cannot be sure whether a second vascular event occurring in the same patient reflects the same pathophysiological sequence of events that led to the first. Moreover, we have no controlled evidence that changing therapy is a more effective strategy than maintaining an evidence-based therapy. Increased awareness of the factors that may interfere with the desired antiplatelet effect of aspirin, particularly avoidable interactions with some traditional nonsteroidal antiinflammatory drugs (NSAIDs), may result in better patient care than requesting platelet function tests of questionable clinical significance.

Finally, given the size of the relative risk reduction associated with long-term antiplatelet prophylaxis (typically, 25% to 30% in high-risk patients), novel studies aiming to detect an attenuation or loss of this protective effect, as a function of specific causes of interindividual variability in response to aspirin, should have adequate sample size to detect such a small “signal.” None of the studies published so far meet these requirements, and estimates of relative risk of recurrent atherothrombotic events associated with aspirin “resistance” are simply unrealistic.

Aspirin and Colorectal Cancer
Colon cancer is the second leading cause of cancer death. Randomized clinical trials have shown a decreased risk of colorectal adenoma recurrence in high-risk subjects who were given aspirin or selective COX-2 inhibitors (Figure 3). Moreover, observational studies have associated a decreased risk of colorectal cancer with aspirin or NSAID use. In the most recent cohort study, regular aspirin use conferred a significant one-third reduction in the risk of colorectal cancers that overexpressed COX-2, but not in COX-2-negative tumors. A reduction of the risk of COX-2–positive tumors
was also found with increasing aspirin dose and increasing duration of use.\textsuperscript{75}

Both the mechanism(s) and dose dependence of the chemopreventive effect of aspirin are uncertain. Although the observational study of Chan et al\textsuperscript{76} suggests the involvement of COX-2 inhibition, the 2 randomized trials of aspirin for the prevention of adenoma recurrence used a single daily administration of 81 to 325 mg with no apparent dose effect.\textsuperscript{70,71} Although the size of the apparent protection against the early stage of colorectal adenoma formation is somewhat smaller with aspirin than with selective COX-2 inhibitors (Figure 3), it should be emphasized that further development of the latter as chemopreventive agents was halted because of a doubling of MI risk.\textsuperscript{76}

In contrast to coxibs, aspirin remains a viable option for the chemoprevention of colorectal neoplasms, and further studies are warranted to define the optimal dose and dosing schedule to improve its benefit/risk profile in this setting.

**Aspirin in Osteoarthritic Patients at High Cardiovascular Risk**

Recently, the American Heart Association has proposed a “stepped-care” approach to the management of patients with concurrent osteoarthritis and heart disease.\textsuperscript{77} According to this approach, physicians should first consider agents with the lowest reported risk of cardiovascular events, including acetaminophen, aspirin, tramadol, and narcotic analgesics.\textsuperscript{78} Unfortunately, there is little randomized evidence on which to base a rational choice of drug with respect to either efficacy or cardiovascular safety.\textsuperscript{78} As noted above, indirect comparisons of aspirin trials in high-risk patients as well as a limited number of randomized comparisons suggest that increasing the dose of aspirin from 75–100 to 650–1300 mg/d might undermine its cardioprotective effects. However, the efficacy and GI safety of analgesic doses of aspirin are largely based on very old studies, and there is clearly a need for modern-era clinical trials evaluating aspirin vis-à-vis traditional NSAIDs in osteoarthritic patients with known cardiovascular disease.

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