Aspirin – Issues in Daily Practice: An Update

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Aspirin compounds are among the oldest known medicinal substances. Hippocrates, in the 5th century BCE, described a bitter powder extracted from willow bark that could ease aches and pains and reduce fever. Native Americans used it for headaches, fever, pain, rheumatism, and chills. The active extract of the bark, called sallicin after the latin name for the White Willow (*Salix alba*), was isolated to its crystalline form in 1828. Aspirin was patented on 6 March 1899 by Bayer & Co. In 1950 Lawrence Craven, a general practitioner from California, was the first to report that aspirin may prevent myocardial infarction, and in 1956 reported that it may also prevent strokes. It was not until the 1970s that the mechanism of action of aspirin was elucidated by a British pharmacologist named John Vane, who in 1982 received the Nobel prize for this discovery.

Today aspirin plays a pivotal role in the treatment and prevention of cardiovascular disease, atheromatous plaques, and acute coronary syndromes. Aspirin works by inhibiting the prostaglandin-producing enzyme cyclooxygenase, which converts arachidonic acid into prostaglandins. Prostaglandins possess several important physiologic characteristics that affect inflammation, fever, gastric mucosal protection, regulation of renal function, and platelet aggregation. COX exists in two isoforms, COX-1 and COX-2. COX-1 is present in nearly all cells, while COX-2 exists mainly in vascular endothelial cells and is absent in mature platelets (although it is present in newly formed platelets). Prostaglandin is converted into at least five different bioactive prostanoids including thromboxane A2 and prostacyclin. TXA2 is released by platelets in response to different stimuli and induces platelet aggregation, thus amplifying the response to diverse agonists including collagen, thrombin and adenosine diphosphate. In contrast, prostacyclin inhibits platelet aggregation, induces vasodilation, inhibits the proliferation of vascular smooth muscle cells, protects the myocardium against oxidant stress and is anti-atherogenic. Aspirin, even in low doses, irreversibly acetylates platelet COX-1 in platelets, resulting in reduced prostaglandin synthesis and TXA2 production throughout the 8–10 day lifetime of a platelet. Because COX-1 inhibition in platelets is irreversible and since platelets are anucleate, they cannot resynthesize COX-1. Therefore, even low doses of aspirin lead to more than 95% suppression of TXA2 generation. After a single dose of aspirin, platelet COX-1 activity recovers by about 10% per day (in line with platelet turnover). In contrast to TXA2, which is largely derived from COX-1, vascular prostacyclin is derived mainly from COX-2 and is less susceptible to inhibition by low doses of aspirin. Therefore, low doses of aspirin do not reduce prostacyclin synthesis, which in turn does not affect blood pressure or renal function, or interfere with the antihypertensive effects of diuretics or angiotensin-converting enzyme inhibitors.

Aspirin is rapidly absorbed in the stomach. Plasma levels peak 30–40 minutes after the ingestion of uncoated aspirin. Enteric-coated formulations may take up to 3–4 hours to reach plasma peak levels. The oral bioavailability of enteric-coated aspirin is approximately 40–50%, with sustained release and microencapsulated preparations having considerably lower bioavailability [1]. After being absorbed, aspirin comes into contact with platelets in the portal circulation. The half-life of aspirin is only 15–20 minutes, but since its effect lasts for the lifetime of a platelet there is complete dissociation between the pharmacokinetic and pharmacodynamic properties of aspirin, allowing for once-daily dosing.

Aspirin for the treatment and prevention of CVD

Low risk individuals and primary prevention

Primary prevention of coronary heart disease involves the treatment of people at risk, without clinical manifestation of the disease, in an attempt to prevent cardiovascular events. As the risk of coronary artery disease has been shown to be related to platelet activity and inflammation, and because of aspirin's antiplatelet and anti-inflammatory properties, aspirin treatment has been proposed for primary prevention. Aspirin has been evaluated in six primary prevention trials [2-7] including more than 96,000 subjects with variable cardiovascular risk [Table 1]. A meta-analysis of the first five trials [8] indicates that aspirin

COX = cyclooxygenase
TXA2 = thromboxane A2
CVD = cardiovascular disease

Table 1. Primary prevention trials

Study, year [ref]	No. of patients	Age (yrs)	Regimen	MI	*P*	Stroke	*P*
Physicians Health Study, 1989 [2]	22,071 healthy males	40–84	325 mg aspirin every other day and placebo	-44%	< 0.001	+22%	NS
Primary Prevention Project, 2001 [3]	4,495 men & women with some CV risk factors	> 50	100 mg aspirin daily and no treatment	-31%	NS	-33%	NS
Hypertensive Optimal Treatment 1998 [4]	18,790 men and women with mild to moderate hypertension and no stroke or MI within 12 months	50–80	75 mg aspirin daily and placebo	Men -42% Women -19%	0.001 NS	-1% Combined for men and women	NS
British doctors' trial 1988 [5]	5139 healthy male physicians	50–78	500 mg aspirin daily and no treatment	-3%	NS	+17%	NS
Thrombosis Prevention Trial 1998 [6]	5499 males at high risk for IHD	45–69	75 mg aspirin daily and placebo	-20%	0.04	NA	NA
Women's Health Study 2005 [7]	39,876 healthy women	> 45	100 mg aspirin every other day and placebo	2%+	NS	-17%	0.04

reduces the risk of non-fatal MI by about one-third, but has little effect on stroke or cardiovascular death. In weighing the benefits of aspirin for primary prevention versus its adverse effects it was concluded that aspirin treatment for primary prevention is safe and beneficial at coronary event risk > 1.5%/year; safe but of limited value at coronary risk of 1%/year; and unsafe at coronary risk of 0.5%/year. In the Physician's Health Study, a subgroup analysis evaluating aspirin's anti-inflammatory effects [9] showed that the benefit of aspirin was largely confined to men who had elevated levels of C-reactive protein. In contrast to the first five primary prevention trials, the Women's Health Study, which included a population of 39,876 healthy women over 45 years old, showed no reduction in MI but suggested that aspirin treatment may protect this population against stroke [7]. It should be noted that most of these trials included few people above the age of 70, in whom the risk of CAD and stroke rises. Aspirin use probably reduces the risk of MI in men over the age of 50. Primary prevention of CAD should begin with lifestyle modifications and treatment of cardiovascular risk factors. Only then should aspirin be considered on an individual basis, based on an assessment of cardiovascular risk, calculated as the Framingham risk score [10]. Aspirin should probably be initiated in those whose global coronary risk is more than 1.5%/year, whereas those with a risk of 0.6%/year would probably not benefit from treatment. Among patients with a risk of 0.7–1.4%/year other factors should be considered.

High risk populations and secondary prevention

Secondary prevention denotes treating patients with established cardiovascular disease in an attempt to prevent coronary events. A large meta-analysis – The Antithrombotic Trialists' Collaboration [11], evaluating a large number of randomized trials of antiplatelet regimens versus control and including 135,000 patients with atherosclerosis, as well as individual studies [12] – has shown that a daily dose of 75–150 mg aspirin reduces the risk of a serious vascular event by approximately 25%. These doses were as effective as higher daily doses. The CAST Trial [13] (21,106 patients presenting with an acute stroke) showed a 10% reduction of recurrent stroke or death in patients treated with aspirin 160 mg as compared to placebo. There is no convincing evidence that the dose required to achieve the antithrombotic effect of aspirin varies in different clinical settings. Due to lack of data it remains uncertain whether doses < 75 mg are as effective as higher doses.

Aspirin in acute coronary syndromes

Acute coronary syndrome refers to the spectrum of cardiac disease, from unstable angina to ST segment elevation MI. In the ISIS-2 trial [14] a single dose of aspirin 160 mg, administered within 24 hours of the onset of symptoms of a suspected MI and continued on a daily basis for 35 days, produced an absolute risk reduction of 2.4% in mortality (relative risk reduction 23%). When aspirin was combined with streptokinase the absolute RR was 5.2% (RRR 42%). There was no increase in the risk of hemorrhagic stroke or gastrointestinal bleeding in the aspirin-treated patients, and only a small increase in minor bleeding. Several other trials conducted during the 1980s proved aspirin's efficacy in the setting of both unstable angina [15-17] and acute MI [18]. According to the Antithrombotic Trialists' Collaboration [11], one vascular event would be prevented for every 1000 patients with suspected AMI treated with aspirin for 5 weeks. In clinical situations where an immediate antithrombotic effect is required, a loading dose of 162–325 mg should be given in order to produce rapid and complete inhibition of TXA2, regardless of whether the patient is already receiving aspirin on a regular basis [18]. It should be noted that more rapid buccal absorption occurs with non-enteric-coated aspirin [18].

Aspirin treatment in patients with atrial fibrillation

Although aspirin treatment might provide adequate treatment for patients at low risk (essentially healthy patients under the age of 75), it offers only modest protection against stroke for patients with atrial fibrillation at moderate to high risk (previous stroke or transient ischemic attack, hypertension, CAD, heart failure, left ventricular ejection fraction < 35%, mitral stenosis or prosthetic valves, and diabetes), not treated with warfarin [19]. Three randomized trials that compared aspirin therapy in daily doses of 75, 100 and 325 mg with warfarin therapy and with placebo reported a reduction in RR of about 25% with doses of 325 mg aspirin as compared to placebo, but aspirin was less effective than

MI = myocardial infarction
CAD = coronary artery disease
RR = risk reduction
RRR = relative risk reduction
AMI = acute myocardial infarction

warfarin for stroke prevention (47% RR in favor of warfarin) [11]. Nevertheless, aspirin is less expensive, safer and more convenient, thus making it an acceptable substitute for patients unable to receive anticoagulation therapy, or patients with lone AF who are at low risk for stroke. Aspirin might be more efficacious in patients with AF who also suffer from hypertension or diabetes by preventing their atherosclerotic, non-embolic causes of stroke [19].

Adverse effects

Bleeding, especially gastrointestinal bleeding, is one of the most significant adverse effects of aspirin. Much effort has been directed to determine the lowest effective dose of aspirin to prevent cardiovascular morbidity and mortality. The efficacy and safety of aspirin and its risk-benefit ratio have been evaluated in several populations ranging from apparently healthy persons to patients with acute atherothrombotic events (MI and stroke), in both the short and long term.

Long-term therapy with low dose aspirin doubles the risk of fatal and major bleeding (mostly of GI origin), responsible for one to two events per 1000 patients per year in middle-aged populations [12]. The two COX-1-dependent mechanisms that contribute to the increased risk of upper GI bleeding are the inhibition of TXA2-induced platelet aggregation and impaired synthesis of prostaglandin E2, which mediates cytoprotection in the GI mucosa [1]. While the former effect is independent of the aspirin dose (> 30 mg), the latter effect is dose-dependent. Based on a meta-analysis evaluating 192,036 patients treated with different doses of aspirin [20], as well as other trials [21], it appears that aspirin-induced GI toxicity is dose-dependent. Several reports [22] have shown an increased risk with older age, reaching up to 7 cases per 1000 patients over 80 years. The major consideration with aspirin use is finding the balance between preventing vascular occlusion and causing major bleeding. In patients at moderate to high risk for cardiovascular complications (> 1.5% per year) the benefit of aspirin therapy is thought to outweigh its risks. It is worth noting that enteric-coated aspirin should not be assumed to be less risky and cause less GI bleeding than plain formulations.

Other adverse effects of aspirin are less common. Little information is available regarding the risk of intracranial hemorrhage associated with aspirin use. In one meta-analysis it was shown to be less than one event per 10,000 patients per year [12]. Some suggest that high doses (> 1 g/day) of aspirin might also inhibit the synthesis of prostacyclin in the endothelium, which could paradoxically lead to thrombosis and vasoconstriction, as is the case in selective COX-2 inhibitors; however, concrete information on this issue is both scarce and contradictory.

Combined aspirin and warfarin therapy

A frequently faced dilemma is whether to continue aspirin therapy when starting patients on warfarin treatment. Many hesitate to prescribe this dual therapy to elderly patients because of the associated risk of bleeding. A systematic review and meta-analysis [23] of nine trials evaluating combined therapy versus warfarin monotherapy (five trials involved patients with mechanical valves, three involved patients on warfarin as routine post-MI therapy, and only one focused on patients with AF) showed a clear overall benefit of combined therapy in patients with mechanical valves. Post-MI patients seemed to have a reduced risk of thromboembolic events but no decrease in overall mortality, while no conclusions were drawn from the AF trial since it was terminated early. A recently published meta-analysis addressing the issue of combined therapy versus aspirin therapy alone after AMI or acute coronary syndrome [24] concluded that a combined treatment strategy is beneficial for high risk cardiovascular patients, as long as patients at the highest risk of bleeding are excluded (there was a threefold increase in major bleeding in this group). This benefit was found to be greatest during the first 3 months of therapy, although the combined endpoints continued to diverge for at least 5 years. A population-based study looking into bleeding complications with combined aspirin and warfarin therapy following AMI in elderly patients [25] concluded that combined therapy does lead to a modest increase in bleeding risk in this group of patients, but the overall risk is small. Independent clinical predictors of future bleeding in elderly patients, irrespective of the medications prescribed, were age, known peptic ulcer disease, cardiovascular disease, chronic renal failure, diabetes, and bleeding during AMI hospitalization. Thus, the decision to prescribe dual therapy should be individualized: patients with mechanical valves may benefit from combined therapy [23-25], whereas in other clinical settings such as AF, where data are inconclusive, dual therapy should not be recommended [19]. To date, no adequate studies have addressed the issue of whether patients treated with warfarin who undergo percutaneous coronary intervention should also be treated with platelet inhibitor drugs. According to the combined American Heart Association/American College of Cardiology/and the European Society of Cardiology guidelines [19] patients undergoing PCI and stent implantation should receive combined therapy with warfarin and clopidogrel (for a 9–12 month period). Adding aspirin to this regimen is not recommended and might contribute more risk than benefit. After the period of dual therapy (i.e., 9–12 months), warfarin may be continued as monotherapy in the absence of a subsequent coronary event [19].

Aspirin resistance

Not all patients derive the same clinical benefit from aspirin therapy. In recent years a new entity entitled "aspirin resistance" has emerged. Some have found the term "resistance" problematic since it has been used to describe both failure of the agent to prevent the condition for which it was prescribed and failure to achieve its objective as measured in the laboratory. Because clinical outcomes are driven by multiple factors, platelets being only one facet of the overall picture, it has been proposed that patients who have recurrent clinical events while on therapy be classified as having "failure of therapy," and limiting the term "resistance" to those patients

AF = atrial fibrillation
GI = gastrointestinal

PCI = percutaneous coronary intervention

for whom the agent does not achieve its pharmacological objective [26].

Laboratory/biochemical resistance

Laboratory resistance to aspirin can be evaluated by using measures of platelet TXA2 production (serum and urinary thromboxane levels) or TXA2-dependent platelet function (e.g., by optical aggregometry or platelet function analyzer, known as PFA-100). Neither urinary nor serum thromboxane levels are specific for platelet thromboxane synthesis because thromboxane can be derived from non-platelet origins [27], such as monocytes, macrophages and endothelial cells within atherosclerotic plaques. Platelet function tests are not specific for TXA2 because platelet adhesion can be mediated by other pathways (e.g., ADP, thrombin, Von Willebrand factor, and endothelial shear stress).

Various studies have evaluated the prevalence of biochemical resistance [28,29], which has been reported to range from 5.5 to 56.8%. However, these studies have several limitations including small sample size, different dosing regimens of aspirin, non-adherence to therapy, and lack of agreement between various tests used. Gum et al. [28] found aspirin resistance to be more common among women and non-smokers, with a trend toward increased age in patients with aspirin resistance. There were no differences in aspirin sensitivity by race, diabetes, platelet count, and renal or liver disease.

Clinical resistance

Aspirin has been shown to reduce the risk of a serious vascular event by only 25%, thus recurrent atherothrombotic events are not uncommon. Aspirin treatment failure may be associated with various conditions: notably, non-adherence to taking aspirin as prescribed was found to account for recurrent events in up to 40% of patients [30]; drug interactions such as non-steroidal anti-inflammatories may antagonize the activity of aspirin by blocking its access to the COX-1 binding site; as well as other proposed mechanisms [Table 2].

Is there a relationship between clinical and biochemical resistance?

Several studies that investigated the association between biochemical aspirin resistance and treatment failure suggest that biochemical resistance increases the risk of vascular events [31-34]. Data from these studies suggesting a linear association between increasing aspirin resistance and vascular events should be examined cautiously as they have several limitations. None of these studies assessed patient compliance to treatment or examined the reproducibility of biochemical resistance. Some used very high doses of aspirin (up to 1500 mg/day) [31], and most did not adjust for potential confounders. Although a number of recent studies have reported an association between platelet function tests and clinical outcomes, there is no convincing evidence to suggest that increasing the aspirin dose to above 75–150 mg/day improves clinical outcomes [11], nor are there specific indications for switching patients from aspirin to an alternative treatment such as clopidogrel. Since the clinical implications of platelet function tests remain unclear and their assessment in large clinical trials has not yet been sufficiently researched, platelet function in standard routine clinical practice is not currently indicated. Further research is required to find reliable, specific and standardized measures of platelet function that will correlate with clinical episodes of ischemic events. Until such time, clinicians should probably not test their patients for aspirin resistance or alter their treatment on the basis of these tests.

Table 2. Various causes of aspirin treatment failure

Causes of aspirin treatment failure
• Poor compliance
• Inadequate dose
• Reduced absorption
• Drug interactions: i.e., non-steroidal anti-inflammatory drugs
• Biosynthesis of thromboxane in pathways not blocked by aspirin (monocytes, macrophages, and endothelial cells)
• Platelet activation by pathways not blocked by aspirin (red cell-induced activation, ADP, collagen)
• Increased platelet turnover
• Genetic polymorphism of: COX-1, COX-2, TXA2.
• Tachyphylaxis due to prolonged administration
• Non-atherothrombotic causes of vascular events: embolism, vasculitis

Aspirin allergy

Three types of aspirin hypersensitivity reactions are known: respiratory (asthma/rhinitis), cutaneous (urticaria/angioedema), and systemic (anaphylactic reaction). The prevalence of these hypersensitivity reactions is not known. Aspirin-induced respiratory disease, implicated in 10–15% of all cases of asthma [35], is usually seen in young adults and is more prevalent in females. The most susceptible patients are those with a history of asthma or rhinitis. The mechanism of aspirin-induced asthma is thought to be the inhibition of COX-1, which reduces the production of prostaglandins, thereby inducing an increase in leukotrienes. The cutaneous reaction consists of urticaria, which can occur with or without angioedema, and tends to occur more frequently during adulthood and in young females. The most susceptible patients to these reactions are those with a history of atopic reactions such as hay fever, asthma or urticaria. As with asthma, the proposed mechanism for the atopic reaction involves COX-1 inhibition. In contrast to the first two reactions, which occur minutes to hours after ingestion, aspirin-induced anaphylactic reaction occurs within minutes (sometimes almost immediately) following aspirin ingestion and is characterized by hypotension, pruritus, tachypnea, laryngeal edema and altered sensorium. Angioedema with hypotension is generally considered an anaphylactic rather than a cutaneous reaction to aspirin, with treatment as for any other anaphylactic reaction.

Currently, the only way to establish aspirin hypersensitivity in a patient is by provocation tests – either oral or bronchial. Several highly variable desensitization protocols [35,36], without a universally accepted methodology, are available for the treatment of aspirin allergy. In practice, when a patient develops a serious

ADP = adenosine diphosphate

allergic reaction or even a milder reaction that brings him or her to low compliance with the drug, it seems more reasonable to switch to an alternative drug such as clopidrogel rather than continuing treatment with aspirin.

Aspirin withdrawal

Aspirin treatment is sometimes discontinued either deliberately by the physician (before surgical procedures or due to bleeding) or because of poor patient compliance. Some suspect that discontinuing aspirin may lead to biological platelet aggregation called the "rebound phenomenon." After aspirin discontinuation, the recovery of COX activity may occur rapidly, with increased synthesis of TXA2 by fresh platelets [37]. A meta-analysis reviewing the risks/benefits of aspirin withdrawal versus its continuation in the perioperative setting [38] found that withdrawal precedes up to 10.2% of acute cardiovascular syndromes, and may expose patients to increased cardiovascular morbidity and mortality. The time interval between discontinuation and a recurrent clinical event was 8.5 ± 3.6 days for acute coronary syndrome, 14.3 ± 11.3 days for acute cerebral events, and 25.8 ± 18.1 for acute peripheral arterial syndromes.

Surgical intervention during concurrent aspirin therapy is associated with an increase in the rate of bleeding by a factor of 1.5, but is not associated with a rise in the severity of bleeding complications (with the exception of intracranial surgery and possibly transurethral prostatectomy) [38]. With regard to coronary artery bypass surgery the majority of trials show an increase in the transfusion rate in patients continuing aspirin therapy, although recent smaller trials [39] have shown that discontinuing aspirin before surgery is not only unnecessary but may be harmful. Current AHA and ACC joint guidelines [40] state that due to the value of aspirin in the treatment of ACS, continuation of its treatment will often outweigh the increased risk of perioperative bleeding. In certain patients in an appropriate clinical setting, including stable angina, low risk plaque morphology, and others, cessation of aspirin therapy 7–10 days before elective bypass surgery seems prudent to decrease the risk of postoperative bleeding. Surveys among physicians concerning aspirin withdrawal in this situation show wide variations in clinical practice. Controlled clinical trials are needed.

Other benefits of aspirin treatment

It has been suggested that aspirin has other benefits aside from cardiovascular risk reduction and those previously described. Among them are a decreased risk of Alzheimer's disease and a chemopreventive effect on adenomas in the large bowel, reducing the risk of colorectal cancer. However, the extent of these benefits is beyond the scope of this review.

Table 3. Recommended treatment for various population groups regarding aspirin

	Population	Recommendation for aspirin treatment	Comments	Ref.
Primary prevention	Men:			
	High risk > 1.5%/year	75–160 mg		2,4,8
	Intermediate 0.7–1.4%/year	Individual		
	Low < 0.7%/year	Not recommended		
	Women	50 mg	Non-significant reduction in MI, Significant reduction of stroke.	7
Secondary prevention	All	75–160 mg		11-13
Atrial fibrillation	All	325 mg	Inferior to treatment with warfarin. Should not be combined with warfarin.	11,19
Warfarin treatment	Warfarin indication:			
	Mechanical valves	Probable benefit		23
	ACS	Probable benefit		23-25
	Atrial fibrillation	Not recommended	Lack of trials	23

Summary

We have summarized current knowledge regarding primary and secondary prevention of cardiovasular disease, with an emphasis on aspirin resistance and adverse effects. The use of combined therapy of aspirin and warfarin was discussed and the role of aspirin in patients with AF was reviewed according to the latest guidelines [Table 3]. The issue of primary prevention remains only partially resolved, though it would seem that male patients at moderate to high risk for CVD may benefit. On the other hand, the role of aspirin for secondary prevention in high risk populations and in ACS is well established. A dose of 75–150 mg/day has been validated in numerous studies with higher doses showing no additional effects. Aspirin should not be regarded as an innocent drug, since prolonged use in low risk populations carries the risk of serious adverse events, primarily bleeding. Adverse events seem to increase linearly with increased doses. Patient compliance remains a major issue regarding treatment failure and achieving clinical benefit and should be stressed at every physician-patient encounter. Further research is required to develop testing methods that are reliable, standardized and accurate for aspirin resistance, and currently such testing is not recommended. Withdrawal of aspirin treatment should not be considered an innocent act as it may cause susceptibility to atherothrombotic events.

AHA = American Heart Association
ACC = American College of Cardiology

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