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Aspirin

A Historical and Contemporary Therapeutic Overview

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Among the many useful discoveries which this age has made, there are very few which better deserve the attention of the public that what I am going to lay before your Lordship.

——Reverend Edward Stone
—Chipping-Norton, Oxfordshire
—April 25, 1763

These prophetic words, written by Reverend Edward Stone in a 1763 letter to George Parker, the second Earl of Macclesfield, describe the results of the first clinical trial recorded in medical history.[1] Stone's report on the rediscovery of the medicinal value of willow bark among subjects suffering from malarial symptoms is considered a significant milestone in the development of aspirin. Although society now takes many of its beneficial effects for granted, aspirin did not suddenly appear for medicinal use after Reverend Stone's discovery. Instead, its tumultuous journey was fueled by individual scientific curiosity, accidental discoveries, and intense business rivalry.[1] No other drug is used by a greater number of people worldwide than aspirin, the benefits of which span centuries, beginning with the very first uses of willow bark by Egyptian physicians (Figure 1). Aspirin single-handedly transformed a coal-dye company into a pharmaceutical giant and has emerged as a cornerstone in the present-day therapies available for treating cardiovascular disease (CVD), pain, and inflammation. This article discusses the sentinel historical aspects of the discovery and clinical cardiovascular developments of aspirin, as well as its contemporary use in today's medical arena.

Pharmacological History of Aspirin

Historical Developments of Salicylates

On January 20, 1862, Edwin Smith made one of the most historically important purchases of his life. Well-regarded among his peers for his keen scholarship and intricate knowledge of Egyptology, Smith purchased, for £12, 2 worn papyrus scrolls in a local Luxor street market[1] that later turned out to be a formative medical textbook unlocking ancient Egyptian's practice of medicine. Although authorless, the Ebers Papyrus is 110 pages and considered the most comprehensive medical papyrus ever recovered; it dates back to 1534 BC[2] (Figure 2). It covers a wide range of medical conditions and ≈700 medicinal and herbal remedies, but the most important plant species mentioned is *tjeret* or *salix*, known today as willow. The Ebers Papyrus describes the use of this ubiquitous tree, which grew in most parts of the prehistoric world, as either a general-purpose tonic or an antiinflammatory/pain reliever for nonspecific aches and pains. By 216 AD, through trade, military contacts, and neighboring coastal city communications, willow had become a commonly used remedy across the civilized world.[1]

Hundreds of years later, in 1758, Reverend Edward Stone consumed the bark of an English willow tree.[1] In an attempt to find an effective and less costly remedy for "the agues" (now known to be malarial symptoms: fever, myalgias, and headache), Stone administered ground-up dried willow to ague sufferers and showed that the substance was, in fact, effective in treating these symptoms.[3]

The dawn of the 19th century was marked with significant change in terms of technological innovation, scientific inquiry, and economic prosperity. The first significant discovery in the race to identify and synthesize the active ingredient of willow came from Joseph Buchner, a professor of pharmacy at Munich University who, in 1828, refined willow into yellow crystals and labeled it salicin (after *salix*, Latin for willow). The French pharmacist Henri Leroux further refined the salicin extraction process in 1829,[4] only to be outdone by Raffaele Piria who, in 1838, produced a stronger compound from the crystal that he aptly named salicylic acid.[5]

Through the middle decades of the 19th century, the use of salicylate medications, which included salicin, salicylic acid, and sodium salicylate, grew significantly, and physicians increasingly knew what to expect clinically from these medicines: reduction of pain, fever, and inflammation. Unfortunately, the unpleasant side effects, specifically gastric irritation, limited their usefulness, and attempts to circumvent these untoward effects were unsuccessful until Ferdinand Runge discovered the compounds aniline and phenol in the residue left behind when burning coal (coal-tar). Runge's discovery, along with William Henry Perkins' quest for coal-tar–derived dyes, gave rise to the organic chemical industry and would later play a significant role in the development of aspirin.

By 1852, Charles Gerhart, a professor of chemistry at Montpellier University, determined that the molecular struc-

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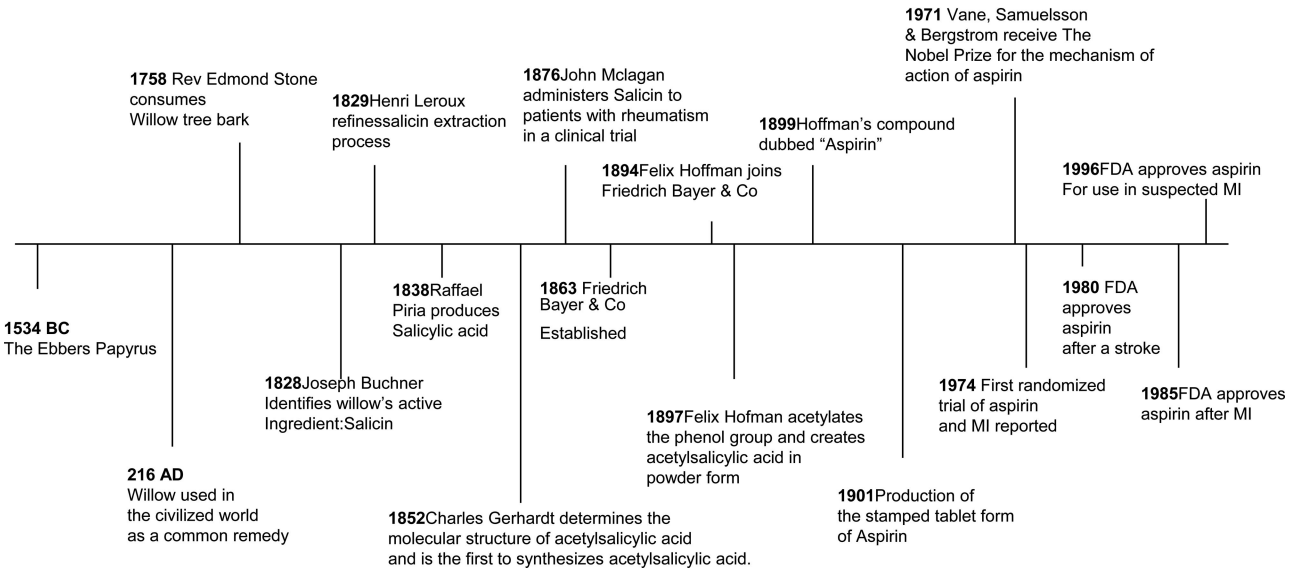

Figure 1. Timeline of historical events in the development of aspirin.

ture of salicylic acid consisted of a central 6-carbon benzene ring with 2 attached hydroxyl group and carboxyl group components. By replacing the hydroxyl group with an acetyl group, Gerhardt became the first person to chemically synthesize acetylsalicylic acid.[6] Unfortunately, Gerhardt's compound turned out to be impure and unstable and attracted no further interest.

The first rigorous clinical trial involving salicylates is credited to John Maclagan. Maclagan, a Dundee Royal Infirmary physician, administered salicin to patients with rheumatism. Published in *The Lancet*, Maclagan's study found that those patients who received salicin experienced a remission of fever and joint inflammation.[7]

Figure 2. The Ebers Papyrus.[2]

The process of developing aspirin was more effectively taken up by a German scientist, Hermann Kolbe of Marburg University, in 1859. Until this time, most aspirin discoveries occurred in isolated laboratories because the pharmaceutical industry was in its infancy and the close relationship that would develop between science, medicine, and drug production was still to come[1]; that is, when Friedrich Bayer and Johann Friedrich Weskott established a joint business venture known as Friedrich Bayer & Company. Friedrich Bayer & Company was one of many German coal-dye companies that shot up over Germany in hopes of exploiting Perkin's and Runge's discovery of synthesizing organic dye. After taking the helm of Bayer's overall management in 1890, Carl Duisberg created a pharmaceutical group headed by the chemist Arthur Eichengrün, as well as a group for drug testing lead by Heinrich Dreser. In 1894, under the tutelage of Eichengrün, a young chemist named Felix Hoffman (Figure 3)[8] joined the pharmaceutical group and began to modify the structure of salicylic acid in a way that effectively reduced the side effects of aspirin. On August 10, 1897, Hoffman managed to acetylate the phenol group and obtain acetylsalicylic acid in its purest form. It soon appeared through clinical testing that acetylsalicylic acid never failed in its effect on pain, inflammation, or fever and produced no unpleasant side effects, and Hoffman's pure and stable compound quickly received praise among practicing clinicians. On February 1, 1899, this compound was registered under "aspirin," and in 1904, the original powdered form of aspirin (Figure 4)[8] became a stamped tablet. Currently, ≈40 000 tons of aspirin are produced every year worldwide, and in the United States alone, >50 million people take 10 to 20 billion aspirin tablets regularly for the prevention of CVD.[9]

Mechanisms of Action

Although universally accepted as an effective pain reliever and fever-reducing agent, before 1971 the workings of this small white tablet remained elusive to scientific investigation.

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Figure 3. Felix Hoffman. By acetylating the phenol group of salicylic acid, he obtained acetylsalicylic acid in its purest form.[8] Reprinted with permission from Bayer HealthCare.

In 1966, the *New York Times* called aspirin "the wonder drug that nobody understands."[1]

Discovered in 1935 by Ulf von Euler and Glodblatt and later characterized as a product of arachidonic acid by Bergstrom, prostaglandins were believed to be essential to myriad physiological functions and closely linked to the regulation of fever, inflammation, and pain (Figure 5). It was within this background of knowledge that John Vane and Priscilla Piper discovered the release of prostaglandins and a "rabbit aorta contracting substance" during anaphylaxis in guinea-pig isolated lung.[10] In a sentinel study published in June 1971, Vane would go on to describe the dose-dependent inhibition of prostaglandin synthesis to nonsteroidal anti-inflammatory drugs (aspirin, indomethacin and sodium salicylate)[11] (Figure 6)[12] and share the Nobel Prize for Medicine with both Begnt Samuelsson and Sune Bergstrom.

Figure 4. Aspirin in its original crystal powder form.[8] Reprinted with permission from Bayer HealthCare.

The target for aspirin is now known to be cyclooxygenase (COX) or prostaglandin endoperoxidase synthase (Figure 5), which was successfully isolated in 1976 by Hemler et al.[13] COX is a membrane-bound hemoprotein and glycoprotein that exists as 3 isoforms (COX-1, -2, and -3). Aspirin selectively acetylates the hydroxyl group of 1 serine residue (Ser 530) located 70 amino acids from the C terminus of the enzyme,[14] thereby causing a bulky group on the Ser 530 oxygen that effectively inhibits arachidonic acid access to the active binding site, leading to irreversible COX-1 inhibition[15] (Figure 7).[16]

In addition to the rush to identify the mechanism of the antiinflammatory properties of aspirin, scientists in the 1970s began focusing on other biological effects of aspirin. Specifically, Samuelsson identified the product Piper and Vane previously called "rabbit aorta contracting substance" as thromboxane A_2, a potent vasoconstrictor and stimulator of platelet aggregation.[16a] By inhibiting thromboxane A_2–dependent platelet aggregation and aggregation-dependent release of adenosine diphosphate, aspirin was viewed not only as an antiinflammatory but also as an effective antithrombotic agent, a revelation that would later prove to have enormous health benefit.

In 1991, Dan Simmons and coworkers discovered a second, inducible COX gene (Figure 5).[17] Unlike the constitutive COX-1 gene, the COX-2 gene was largely found in inflammatory cells and could be induced with mitogens, growth factors, tumor promoters, and lipopolysaccharides and in turn produced prostaglandin E_2 during pathophysiological processes such as hyperalgesia and inflammatory reactions. COX-1, on the other hand, produces prostaglandins involved mainly in physiological processes such as protection of the gastric mucosa and physiologically needed platelet aggregation.[18] Inhibition of COX-1–dependent platelet function can be achieved with low doses of aspirin given once daily. This is in contrast to COX-2, which requires higher doses of aspirin for inhibition, a consequence thought to be secondary to the fact that COX acetylation is determined by the oxidative state of the enzyme, which is inhibited in cells with high peroxide tone.[19] As a result, individual nonsteroidal antiinflammatory drugs (NSAIDs) show different potencies against COX-1 and COX-2 (Table 1),[20] which, as discussed in the last section, in part explains the variations in the side effects of NSAIDs at their antiinflammatory doses.

It is now realized that platelets play an important role in several diverse processes that go beyond just hemostasis and thrombosis such as promoting inflammatory and immune responses, maintaining vascular integrity, and contributing to

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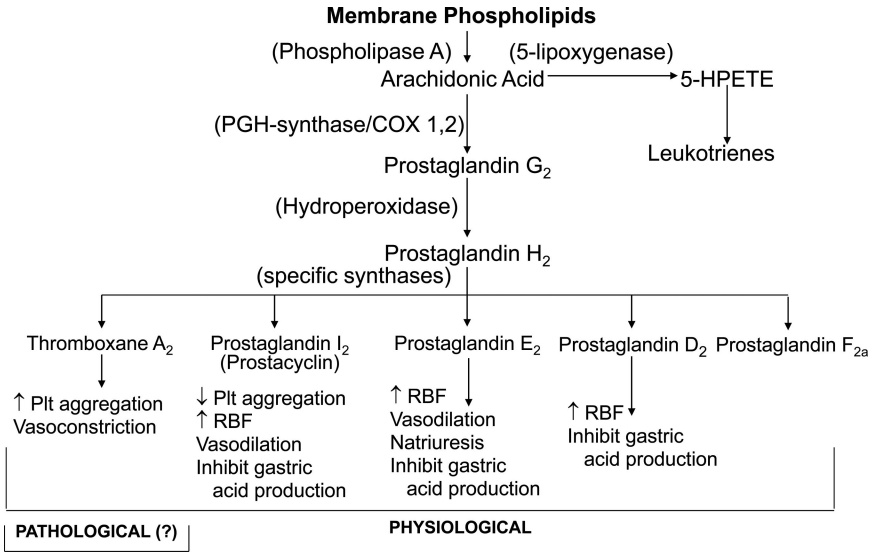

Figure 5. The production of prostaglandins from arachidonic acid and their physiological effects.

would healing.[21] By unraveling the effects on prostaglandin synthesis, the findings by Vane, Samuelsson, and Bergstrom collectively became very significant in that they provided a cohesive explanation of the manner in which aspirin exerted its numerous therapeutic effects.

Historical Cardiovascular Developments of Aspirin

Aspirin and Secondary Prevention in Stroke

Based on observations surrounding the inhibitory effect of aspirin on platelets,[22] the first large-scale randomized clinical trial assessing its cardiovascular benefit were in secondary prevention. The Canadian Cooperative Study Group (CCSG) trial randomized 585 stroke patients to receive aspirin or sulfinpyrazone, alone or in combination, for 26 months. The authors found that aspirin reduced the risk of stroke or death by 31% ($P<0.05$), but benefits were sex dependent, and the conclusion of this early secondary prevention study was that aspirin was indeed an efficacious drug for men with threatened stroke.[23] It is worth noting, however, that the gender specificity in this secondary prevention trial with aspirin was later discounted by appropriately powered studies.[24]

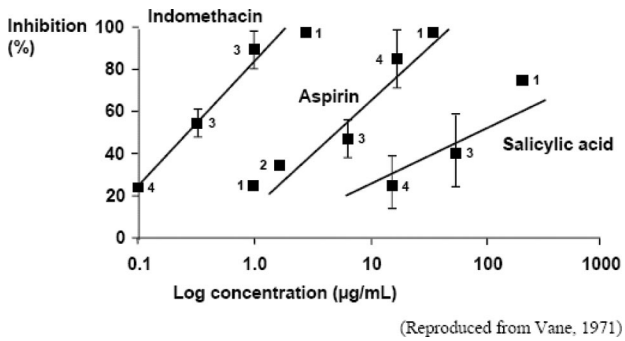

Figure 6. Dose-dependent inhibition of prostaglandin formation in guinea pig lung homogenate by 3 drugs (indomethacin, aspirin, and salicylic acid) thought to be involved by blocking the enzyme later identified as COX.[12] Reprinted with permission from Macmillan Publishers Ltd.

Aspirin and Vein Graft Occlusion

The benefit of aspirin in preventing recurrent vascular events extended beyond just native CVD. Leading up to the 1980s, coronary vein graft disease was a significant contributor to morbidity after coronary artery bypass surgery and was seen to be largely responsible for recurrent angina, myocardial infarction (MI), and reduced left ventricular function.[25] Targeting the underlying mechanism of postoperative thrombotic and intimal proliferation occlusion of aortocoronary bypass grafts, and knowing that aspirin improved shortened platelet survival, Chesebro et al[26] found reduced distal anastomosis occlusion rates at <1 month, >1 month, and 1 year among those patients randomized to receive perioperative dipyridamole and postoperative aspirin compared with placebo. The benefit of aspirin (100 to 325 mg daily) on graft patency when given within 6 hours after coronary artery bypass graft surgery has subsequently been confirmed by a large meta-analysis of 17 randomized controlled trials,[27] and is thought to be secondary to the interruption of platelet deposition on subendothelial structures of the vein graft.

Aspirin and Secondary Prevention in Acute Coronary Syndromes

On the basis of prior work that elucidated the antiplatelet and antithrombotic effects of aspirin and the underlying processes that promote atherosclerotic plaque rupture, it is not surprising that this drug has become a cornerstone in the immediate therapies used in managing patients with acute coronary syndromes, as well as a measure for secondary prevention. The landmark Second International Study of Infarct Survival (ISIS-2) study conclusively showed the efficacy of administering aspirin within 24 hours to patients presenting with an acute MI.[28] Aspirin 162 mg, either alone or in combination with a fibrinolytic agent, provided a 15-month absolute risk reduction of nonfatal reinfarction of 2.4% (relative risk reduction, 23%) and 5.2% (relative risk reduction, 42%), respectively, and form the evidence largely supporting the current American College of Cardiology/American Heart Association Class I recommendation for all patients

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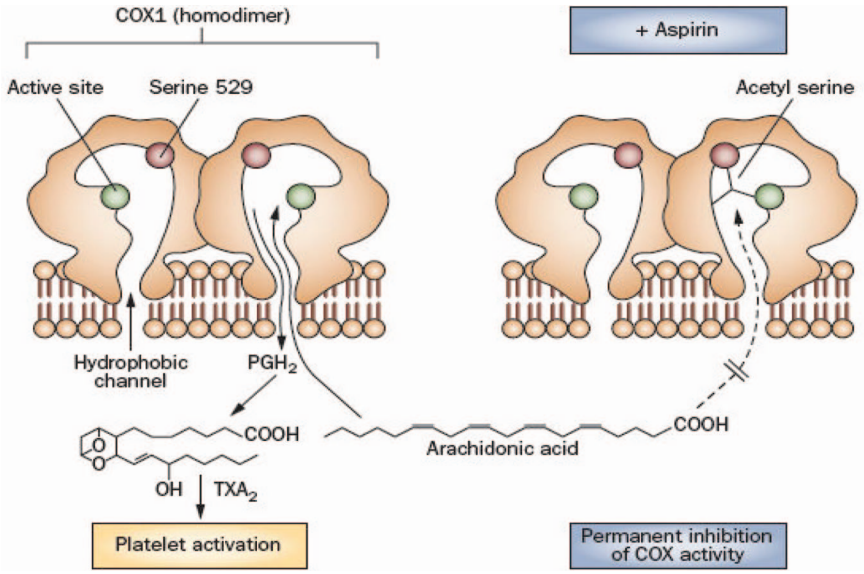

Figure 7. Inhibition of the COX active binding site of arachidonic acid (AA) by aspirin.[16] Reprinted with permission from the Nature Publishing Group.

with suspected MI (ST-elevation MI) to receive aspirin 162 to 325 mg.

As in those patients presenting with an ST-elevation MI, aspirin has been shown to provide significant benefit as secondary prevention among patients with unstable coronary syndromes (unstable angina/non–ST-elevation MI). To date, 4 clinical trials have demonstrated the effectiveness of aspirin in reducing the risk of death or recurrent MI by >50% for those patients presenting with unstable angina/non–ST-elevation MI.[29–32] These observed benefits subsequently led to the 1985 Food and Drug Administration approval for the use of aspirin in both the treatment and secondary prevention of acute MI. The recently published 2009 Antithrombotic Trialists' Trial (ATT) collaboration further supports these findings by conclusively establishing the role of aspirin in the secondary prevention of occlusive vascular disease (Figure 8).[33]

Aspirin in Primary Prevention of CVD

Prior experiences with aspirin predating the discoveries surrounding its antithrombotic properties in the 1950s[33a] and 1960s suggested that aspirin-like substances may have a benefit in preventing an initial "coronary occlusion."[34] The value of aspirin for the primary prevention of thrombotic cardiovascular events has been investigated extensively in 6 large, randomized, controlled, primary prevention trials (Table 2),[35–40] as well as in meta-analyses.[41,42] The Physician's Health Study was the first reported large study investigating the utility of aspirin for primary prevention of CVD. This large study randomized 22 071 healthy male physicians between 40 and 84 years of age to receive 325 mg of aspirin or a placebo daily. After 5 years of treatment, the investigators found a statistically significant reduction (44%; $P<0.00001$) in the risk of a first MI among those patients taking aspirin. Three other randomized clinical trials found similar overall risk reduction in cardiovascular events among patients taking aspirin. In 2002, the Antithrombotic Trialists' Collaboration (ATC) published a meta-analysis including 195 randomized trials of aspirin alone compared with control involving 135 640 patients at high risk of occlusive arterial disease. The analysis found that among those patients allocated to antiplatelet therapy (mainly aspirin), the combined outcome of any serious vascular event was reduced by about one quarter; nonfatal MI was reduced by one third; nonfatal stroke was reduced by one quarter; and vascular mortality was reduced by one sixth. Moreover, in each of these high-risk categories, the authors state that the absolute benefits outweighed the absolute risks of major extracranial bleeding.[24] It is noteworthy that some of the primary prevention trials (excluding the Women's Health Study [WHS], Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes [JPAD], Prevention of Progression of Arterial Disease and Diabetes [POPADAD], and Aspirin for Asymptomatic Atherosclerosis [AAA]) evaluating the effects of aspirin on primary prevention were conducted before the use of other effective therapies, namely antihypertensive medications and statins.[43] Nonetheless, the benefits of aspirin for primary prevention in the 6 trials that were included were consistent regardless of concomitant use of primary prevention therapies. On the basis of data from 5 randomized controlled trials (excluding the WHS) that collectively showed a 28% reduction in MI with aspirin use, the United States Preventative Services Task Force (USPSTF) in 2002 strongly recommended that clinicians consider the use of aspirin with adults at risk for coronary heart disease.[44]

More recent data published in 2009 questioned the actual benefit of aspirin use in primary prevention. Arguing that

Table 1. Dose and Time Dependence of the Effects of Aspirin on Platelets and Inflammatory Cells[20]

Cellular Target	Enzyme	Single Dose, mg	Cumulative Effects on Repeated Dosing	Daily Dose, mg
Platelets	COX-1	100	Yes	50–81
Inflammatory cells	COX-2	±650	No	3000–5000

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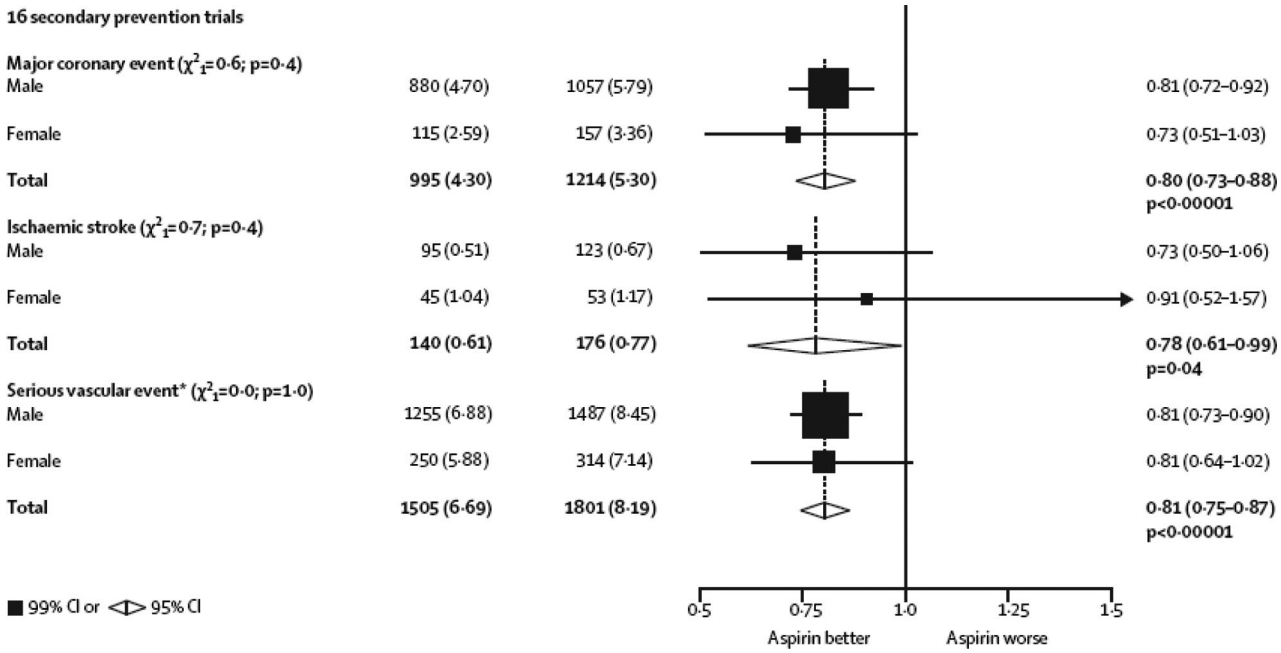

Figure 8. Selected outcomes in secondary prevention trials of aspirin by sex.[33] Reprinted with permission from Elsevier.

previous meta-analyses of primary prevention trials were not based on individual participant data, Baigent et al[33] believed the 2002 ATC meta-analysis could not adequately compare the actual benefits and bleeding risks of aspirin use in patients at increased risk of CVD. By analyzing individual participant data, the authors determined that aspirin allocation yielded a modest 12% relative reduction in serious vascular events (0.51%/y for acetylsalicylic acid versus 0.57%/y for control; $P=0.001$) with an increase in major extracranial and gastrointestinal bleeding (0.1%/y versus 0.07%/y; $P<0.001$). Moreover, there was no significant trend in the protective effects of aspirin in participants at very low, low, moderate, and high estimated risk. The authors concluded that the majority of participants in the earlier primary prevention trials were at low absolute risk of coronary heart disease (≈70% of participants were at very low and low risk) and that, in this population, aspirin is of uncertain net value because the reduction in occlusive events is small and offset by a small increase in serious intracranial and extracranial bleeding.[33] It now appears that the relative size of either the risk or the benefit is too imprecisely known in a low-risk population to accurately predict the overall health effect of widespread aspirin use in an otherwise healthy population.[45] The point should be made, however, that there appears to be a continuous gradient between primary (according to risk) and secondary prevention of CVD by aspirin and the precise point at which the balance between the risks and benefits become equal remains to be established.

Table 2. Randomized Controlled Trials on Aspirin in the Primary Prevention of Cardiovascular Events

Study	Year	n	Mean Follow-Up, y	Population	Acetylsalicylic Acid Dose Used	Outcomes
BDT[36]	1988	5139	5.6	Healthy male physicians	500 mg/d	No impact on death, MI, or stroke
US Physician Health Study[35]	1988	1086	5.0	Healthy male physicians	325 mg on alternate days	44% reduction in risk of MI in the acetylsalicylic acid group
Thrombosis Prevention Trial[37]	1998	5499	6.7	High-risk men	75 mg/d	32% reduction in nonfatal events
HOT[38]	1998	9399	3.8	Men and women with diastolic hypertension	75 mg/d	35% reduction in MI
PPP[39]	2001	4495	3.7	Men and women with ≥1 CHD risk factor	100 mg/d	Significant reduction in CV death rate and CV events
WHS[40]	2005	39 876	10.1	Female health professionals	100 mg on alternate days	No significant change in MI or CV death risk; women >65 y of age benefit most

BDT indicates British Doctors Study; HOT, Hypertension Optimal Treatment; PPP, Primary Prevention Project; and CHD, coronary heart disease.

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Aspirin for Primary Prevention in Specific Populations

Diabetics

The uncertain clinical benefits of aspirin use in primary prevention extend to specific subgroup populations as well. Although the evidence from 6 primary prevention trials suggests some benefit of aspirin in diabetic patients, evidence from other more recent randomized trials enrolling a modest number of diabetic patients is less promising (POPADAD, JPAD, AAA).[46–48] In a systematic review of randomized controlled trials comparing the benefit of aspirin as primary prevention among patients with diabetes mellitus, Calvin et al[49] found no significant benefit from aspirin compared with placebo in terms of mortality, MI, and ischemic stroke (risk reduction, 1.12, 1.19 and 0.70, respectively, in patients with and without diabetes mellitus). The effect of aspirin for the primary prevention of cardiovascular events in adults with diabetes mellitus is currently unclear, with trials to date reporting conflicting results. In an attempt to reconcile the available evidence, the American Diabetic Association/American Heart Association/American College of Cardiology Foundation recently published a scientific statement suggesting that aspirin should not be used for primary prevention of cardiovascular events in diabetics at low CVD risk (men <50 years of age and women <60 years of age with no major additional CVD risk factors; 10-year CVD risk <5%).[50]

Impact of Gender

Although available randomized evidence suggests no differences in response to aspirin for primary[33] and secondary[24] prevention between men and women, in a gender-specific meta-analysis of the primary prevention trials (which included the WHS), aspirin was associated with a decrease in major cardiovascular events in both men and women.[42] Among the 51 342 women studied, aspirin therapy was associated with a significant 12% reduction in cardiovascular events and a 17% reduction in stroke (mainly reduced ischemic stroke). Importantly, there was no significant effect of aspirin on MI or cardiovascular mortality in the women studied. Conversely, among the 44 114 men studied, there was a 14% reduction in cardiovascular events and a 32% reduction in MI but no significant effect on stroke or cardiovascular mortality. According to the absolute risk reduction calculated during the trials, the number needed to treat to prevent 1 stroke among women during the 6.4 years of follow-up was 411, and the number needed to treat to prevent an acute MI in men was 118.[51] The WHS demonstrated that even in a low-risk population, stroke was a more common event than MI (≈1.4 strokes for every MI), thereby making an argument for recommending aspirin as primary prevention in women. This gender-specific benefit is now reflected in the 2009 updated USPSTF recommendation statement, which encourages men 45 to 79 years of age to use aspirin when the benefit of reducing an MI outweighs the harm of bleeding and similarly encourages women 55 to 79 years of age to use aspirin when the benefit of a reduction in ischemic strokes outweighs the risk of bleeding. Possible explanations for the differences in primary cardioprotection between men and women may be related to altered aspirin metabolism, differing event rates among the sexes, and aspirin resistance,[42] but may also reflect how gender is a marker of overall CV risk for a given age.

Stroke Prevention

The effectiveness of aspirin in preventing ischemic stroke was reported in the collaborative meta-analysis by the ATC in 2002. Among the high-risk patients, those allocated to antiplatelet therapy reduced the combined outcome of any serious vascular event by ≈25% and nonfatal stroke by 25%. Aspirin was the most widely studied antiplatelet agent and accounted for an ≈25% relative risk reduction in nonfatal stroke compared with placebo. In view of the previously mentioned limitations of the initial 2002 meta-analyses, the 2009 ATT collaborative analysis of all large primary prevention trials with aspirin reexamined the benefit of aspirin prevention for stroke.[33] In this analysis, aspirin in the primary prevention trials had no net effect on strokes of known or unknown cause or on the aggregate of all strokes (0.20%/y versus 0.21%/y; $P=0.4$). In the secondary prevention trials, however, aspirin significantly reduced the aggregate of all strokes by about one fifth (2.08%/y versus 2.54%/y; $P=0.002$).[33] Furthermore, in both the primary and secondary prevention trials, the proportional reduction in stroke did not significantly depend on age or sex, as was suggested by prior analyses.[42]

Balance of Benefit and Risk

As the risk of experiencing a major vascular event increases, so does the absolute benefit of the antiplatelet prophylaxis with aspirin. This is supported by the 2009 ATC. As previously mentioned, the absolute reduction of serious vascular events resulting from aspirin use was modest and had no effect on vascular death or overall mortality compared with control subjects in primary prevention. At the same time, there was an absolute increase in the risk of hemorrhagic stroke and major extracranial hemorrhage (0.01%/y, $P=0.05$; and 0.03%/y, $P<0.0001$). Conversely, among secondary prevention patients treated with aspirin, the authors identified an incidence of hemorrhagic stroke of 0.17%/y with aspirin versus 0.09%/y with placebo. Importantly, the patients with higher risk of hemorrhagic stroke were those who had maximal absolute risk reduction of serious vascular events with aspirin.

Clinical Problems With Aspirin and Future Directions

Aspirin Resistance

Unfortunately, not all patients clinically benefit from aspirin to the same extent. The phenomenon of aspirin resistance has received significant attention in recent years. Rather than exhibiting resistance per se, patients who experience recurrent cardiovascular events while taking aspirin are more appropriately labeled as having "treatment failure." Treatment failure is likely related to variable responsiveness to aspirin and involves both pharmacological and pharmacokinetic mechanisms. "Aspirin resistance" has also been used to describe platelet nonresponsiveness or a reduced antiplatelet effect as measured by a number of commercially available in

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vitro assays that lack sensitivity, specificity, and reproducibility. Lordkipanidze et al[52] measured platelet aggregation in 201 patients with stable coronary artery disease who were taking aspirin (>80 mg daily) and found a wide prevalence of variability and poor correlation among the 6 assays tested.

Multiple factors can contribute to a reduced effect of aspirin on platelet reactivity, and several mechanism have been proposed, including COX-1–related and COX-1–nonrelated pathways. Genetic influences,[53] the type of aspirin preparation, medication noncompliance, and premature discontinuation of aspirin have all been shown to contribute to the overall observation of aspirin treatment failure and variable responsiveness.

The clinical effects of aspirin variable responsiveness on cardiovascular outcomes have been extensively investigated. Snoep et al[54] addressed the question of whether patients identified as being nonresponsive to aspirin (by in vitro assays) also exhibited increased recurrent cardiovascular events. The findings from this meta-analysis showed that the prevalence of aspirin nonresponsiveness ranged from 5% to 65%, with a pooled odds ratio of all cardiovascular events of 3.8 (95% confidence interval, 2.3 to 6.1). The major criticisms of this analysis and many of the earlier studies assessing aspirin responsiveness are the heterogeneity of the methodologies used to assess platelet aggregation, the various doses of aspirin used, and the lack of consistent assessment of participant aspirin compliance.[16]

Treating aspirin nonresponsiveness has been a challenge, and currently there is no established therapeutic approach to manage and overcome aspirin nonresponsiveness in patients treated with low-dose aspirin. In some patients, increasing the dose of aspirin or adding omega-3 fatty acids may overcome aspirin-reduced in vitro responsiveness; however, there are limited data supporting this.[55]

Interestingly, there is a paradoxical observation that while most of the published trials have demonstrated an association between ex vivo platelet inhibition and clinical outcomes[54] and that, when compared with standard dosing regimens, higher doses of aspirin inhibit platelet function more effectively, there is no current evidence to support the benefit of higher doses of aspirin to reduce clinical outcomes.

Optimal Dose and Preparation of Aspirin

Given the chronicity of aspirin therapy used to treat CVD, optimal dosing to minimize adverse effects and to maximize beneficial effects is paramount. Randomized clinical trials have shown that aspirin is an effective antithrombotic agent at 50 to 100 mg/d[56] and even as low as 30 mg/d.[9,57] There is no evidence from clinical trials showing that higher doses of aspirin are more effective in reducing the risk of serious vascular events. In fact, the reverse may be true. In the Aspirin and Carotid Endarterectomy Trial, the composite outcome of MI, stroke, or death within 3 months of carotid endarterectomy was significantly lower among patients taking 81 to 325 mg aspirin daily than in those taking 650 to 1300 mg.[58] Moreover, observational data from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) and Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trials suggest that patients receiving <100 mg/d had the lowest rate of major life-threatening bleeding and doses >100 mg were associated with no clear benefit.[59,60] It has also been reported that doses of ≈300 mg/d produce fewer gastrointestinal side effects than doses of ≈1200 mg/d.[61] From the currently available clinical data, it seems appropriate to recommend 75 to 81 mg/d in the setting of CVD prevention because higher doses do not better prevent cardiovascular events but increase bleeding risk.

Aspirin is available in various forms: regular, buffered, or enteric coated. Coating an aspirin tablet with inactive ingredients or buffering agents resists disintegration in the stomach and lowers hydrogen ion concentration, respectively. However, neither of these preparations protects against clinically relevant gastrointestinal bleeding compared with regular aspirin.[62] A nitroderivative of aspirin has been synthesized (NCX-4016) and has been shown to reduce thrombin activation of platelets more effectively than aspirin while reducing gastrointestinal damage.

Bleeding Risks in Primary Prevention

Bleeding in the acute setting leads to an increased risk of death even if the bleeding is not considered severe,[63] and has been closely linked to the main risk factors for coronary disease.[33] As mentioned, the use of aspirin for either primary or secondary prevention of coronary artery disease is largely a risk-benefit calculation. The decision of which patients to treat must weigh the benefits of improved protection from cardiovascular events against the risk of bleeding. In the 2009 ATT analysis of individual data from the 6 primary prevention studies, aspirin use in primary prevention had a borderline absolute increase in the risk of hemorrhagic stroke (0.01%/y; $P=0.05$) and a significantly increased risk of major extracranial hemorrhage (0.03%/y; $P<0.0001$), but no net protective effect on stroke or vascular mortality.[33] Together, these observations support the interpretation that in primary prevention among patients without previous CVD, aspirin is of uncertain net value because the reduction in occlusive events must be weighed against any increase in bleeding.

Aspirin causes 2- to 3-fold increase in the risk of dose-related peptic ulcer bleeding, a risk that does not seem to be reduced by the use of enteric-coated aspirin.[62] Sung et al[64] showed that among individuals who had peptic ulcer bleeding, continuous low-dose aspirin use increased the risk of recurrent bleeding but resulted in lower overall cardiovascular and cerebrovascular mortality rates. As mentioned, in patients at very low risk of cardiovascular events, the small absolute benefit is partially offset by the exposure of healthy subjects to an unnecessary bleeding risk.

NSAIDS, Aspirin, and the "Polypill"

Other key issues involving the use of aspirin for cardiovascular protection include the concomitant use of NSAIDS. In studies involving healthy control subjects, the antiplatelet effect of aspirin is attenuated by 2 nonselective NSAIDS, ibuprofen[65] and naproxen.[66] The mechanism of this interaction is presumed to be from competition with aspirin for a binding site on the COX-1 enzyme. Data regarding the clinical relevance of this interaction are conflicting, but it is

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Table 3. Ongoing Clinical Trials Involving Aspirin

Trial	Design	Clinical Setting
ASCEND	Primary prevention	Aspirin±omega-3 fatty acids in asymptomatic diabetics
JPPP	Primary prevention	Aspirin in elderly, at-risk Japanese patients
ASPREE	Primary prevention	Aspirin in elderly men and women
ARRIVE	Primary prevention	Aspirin in moderate-CHD-risk patients (10%–20% 10-y risk)
POISE-2	Primary prevention	Aspirin and 30-d risk of major vascular events in patients with or at risk of CHD undergoing noncardiac surgery
SILENCE	Secondary prevention	Aspirin and prevention of recurrent cerebrovascular lesions, strokes, and TIAs
ASPIRE	Secondary prevention	Aspirin in preventing recurrent symptoms in patients with VTE
UMPIRE FOCUS Kanyini-GAP	Secondary prevention	Polypill vs individual pill adherence
IMPACT	Primary prevention	Polypill vs individual pill adherence

CHD indicates coronary heart disease; TIA, transient ischemic attack; VTE, venous thromboembolism; ASCEND, A Study of Cardiovascular EveNts in Diabetics; JPPP, Japanese Primary Prevention Project; ASPREE, ASPirin in Reducing Events in the Elderly; POISE-2, Peri-Operative ISchemic Evaluation-2; SILENCE, Silent Infarction Longitudinal Evaluation on New Cardiovascular Events; ASPIRE, ASPirIn to prevent REcurrent Venous Thromboembolism; UMPIRE, Use of a Multidrug Pill In REducing Cardiovascular Events; FOCUS, Fixed dOse Combination drUg for Secondary cardiovascular prevention; IMPACT, IMProving Adherence using Combination Therapy; and Kanyini-GAP, Kanyini Guidelines Adherence with the Polypill Study.

possible that ibuprofen and other nonselective NSAIDS may interfere with the beneficial effects of aspirin, and it is reasonable to avoid regular NSAID use in patients taking low-dose aspirin for cardiovascular protection.[67]

Some believe the polypill, a combination of aspirin and other medications in a single tablet, could reduce ischemic heart disease by 88% and strokes by 80% with a low rate of adverse events among all individuals >55 years of age. Proponents of this approach cite the imprecise nature of risk prediction with inaccurate algorithms and risk scales, as well as the cost and modest risk-level reductions observed with lifestyle modification in low-risk populations.[68] More than 50% of patients with chronic conditions show poor compliance to medication treatment, and <30% follow recommended lifestyle modifications relating to treatment complexity. Thus, a polypill could be an effective vehicle for secondary prevention in high-risk patients mainly by improving treatment adherence.[69] The feasibility of this approach is currently being evaluated in ongoing clinical trials (Table 3).

Conclusion

Aspirin is the most commonly used medication worldwide,[70] and its fascinating history dates back to Egyptian healers who used willow bark to treat join pain. Since then, ≈26 000 scientific and medical articles on aspirin have been published. Scientific discoveries describing the action of aspirin on prostaglandin synthesis and its beneficial effects on inflammation, pain, and fever sparked an enormous area of public health: the prevention and treatment of CVD. The discovery of aspirin and its underlying mechanism also exposed new areas of science (prostaglandin synthesis and platelet inhibition) and allowed further development of novel antiplatelet agents and antiinflammatory medications. Soon after the discovery of its antithrombotic qualities, secondary prevention studies suggested a significant benefit with aspirin. Today, few can deny the robust data supporting aspirin in preventing recurrent cardiovascular events. However, the exact role of aspirin in primary prevention in still uncertain. Several clinical trials involving aspirin are planned or are currently ongoing, with the goal of better identifying at-risk populations and modes of delivery (Table 3). The biggest challenge for the antithrombotic future of aspirin will be the determination of the precise population that will continue to derive the greatest benefits yet minimizes harmful side effects. In addition, emerging data on aspirin and the reduction of colorectal cancer incidence and mortality has opened a new, noncardiovascular role of aspirin that requires further study.[71]

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