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Contemporary Reflections on the Safety of Long-Term Aspirin Treatment for the Secondary Prevention of Cardiovascular Disease

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Abstract

Aspirin has been the cornerstone of therapy for the secondary prevention treatment of patients with cardiovascular disease since landmark trials were completed in the late 1970s and early 1980s that demonstrated the efficacy of aspirin for reducing the risk of ischemic events. Notwithstanding the consistent benefits demonstrated with aspirin for both acute and chronic cardiovascular disease, there are a number of toxicities associated with aspirin that have been showcased by recent long-term clinical trials that have included an aspirin monotherapy arm. As an inhibitor of cyclooxygenase, aspirin impairs gastric mucosal protective mechanisms. Prior trials have shown that up to 15–20% of patients developed gastrointestinal symptoms with aspirin monotherapy and roughly 1% of patients per year had a clinically significant bleeding event, including 1 in 1000 patients who suffered an intracranial or fatal bleed. These risks have been shown to be compounded for patients with acute coronary syndromes (ACS) and those undergoing percutaneous coronary intervention (PCI), who are also treated with other anti-thrombotic agents during the acute care/procedural period, as well as for an extended time period afterwards. Given observations of substantial increases in bleeding rates from many prior long-term clinical trials that have evaluated aspirin together with other oral platelet inhibitors or oral anti-coagulants, the focus of contemporary research has pivoted towards tailored anti-thrombotic regimens that attempt to either shorten the duration of exposure to aspirin or replace aspirin with an alternative anti-thrombotic agent. While these shifts are occurring, the safety profile of aspirin when used for the secondary prevention treatment of patients with established cardiovascular disease deserves further consideration.

1. Introduction

Cardiovascular disease afflicts nearly 27 million people in the United States, with more than 30 million predicted to be affected by the year 2030.[1, 2] For more than 30 years, aspirin

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has been the cornerstone of secondary prevention strategies designed to reduce the risk of ischemic events among patients with cardiovascular disease, including patients with coronary artery disease (CAD).[3] Meta-analyses of secondary prevention trials demonstrated a 19% reduction in serious vascular events for patients taking aspirin compared to placebo, and a 25% reduction in recurrent cardiovascular events in the subgroup of patients with prior myocardial infarction (MI).[4, 5] Consequently, practice guidelines in the United States and Europe strongly recommend the use of aspirin for the secondary prevention treatment of patients with stable, established CAD.[6, 7]

However, alongside its beneficial effects, aspirin does have side effects, most frequently gastrointestinal (GI) toxicity and bleeding, including GI, mucosal, and intracranial bleeding. Critical appraisals of aspirin's toxicity by the United States Preventive Services Task Force (USPSTF) and the European Society of Cardiology led to cautious recommendations for the use of aspirin in primary prevention, with the 2015 USPSTF guideline noting that aspirin should be used for patients without established cardiovascular disease only in cases where the patient has a 10-year risk of cardiovascular events $\geq 10\%$ and is at a low risk of bleeding. [8–10] Though the benefits of aspirin for the reduction of recurrent ischemic events in patients with established cardiovascular disease have been determined to outweigh the risks, aspirin is a relatively modest anti-platelet agent that has been shown to be associated with both a number of serious toxicities and a degree of residual risk of long-term ischemic events.

For the past 25 years, a variety of new anti-thrombotic agents have been developed (oral glycoprotein IIb/IIIa inhibitors, first- and second-generation P2Y₁₂ inhibitors, novel oral anti-coagulants, and protease-activated receptor antagonists) and pivotal clinical trials have sought to combine these new agents with background aspirin therapy to reduce recurrent cardiovascular events. Though many of these studies have demonstrated a reduction in ischemic events with the addition of a second (or third) antithrombotic agent to aspirin, all combinations have demonstrated an increased risk of bleeding. In patients with acute coronary syndromes (ACS) and those undergoing percutaneous intervention (PCI), the increased risk of bleeding with dual antiplatelet therapy (DAPT) is offset by considerable reductions in ischemic events, and DAPT for 12 months is the guideline-endorsed standard of care for these patients.[11–13] In recent clinical trials enrolling patients with stable CAD and PCI more than 12 months prior, the relatively modest benefit of extended-duration DAPT for the reduction of ischemic events has been offset by concerns about increases in bleeding complications with more aggressive antithrombotic therapy.[14, 15]

For this reason, several ongoing clinical trials are investigating alternative antithrombotic strategies: replacing aspirin monotherapy with an oral anticoagulant in patients with stable CAD,[16] stopping aspirin after 30 days but continuing a P2Y₁₂ inhibitor in stable patients undergoing PCI,[17], replacing replacing aspirin with an oral anticoagulant as part of dual therapy in patients with recent ACS,[18] and dropping aspirin in favor of a P2Y₁₂ inhibitor plus an oral anticoagulant in patients undergoing PCI who have an indication (like atrial fibrillation) for anticoagulation.[19–21] As these trials enroll patients, it is important to review aspirin's toxicity and side effects to establish a baseline by which alternative regimens should be judged. Thus, this review focuses upon the safety profile of aspirin when

used in the long-term setting to prevent recurrent cardiovascular events in patients with established cardiovascular disease and specifically does not address the safety profile of aspirin when initiated acutely for the treatment of myocardial infarction. We first discuss aspirin's mechanism of action and its implications for aspirin's toxicities and side effects, and then review data regarding side effects from pivotal and representative clinical trials.

2. Pharmacology of Aspirin and Mechanisms of Toxicity

Aspirin's mechanism of action remained unknown until 1971, when John Vane described the inhibition of prostaglandin synthesis by aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) and identified this as their mechanism of action.[22] Later work identified aspirin's target as cyclooxygenase (COX), an enzyme that converts arachidonic acid to prostaglandin G₂. Prostaglandin G₂ is upstream of several other important molecules, including thromboxane A₂, which is a vasoconstrictor that also acts to increase platelet aggregation, and prostaglandins D₂, E₂, and I₂, all of which act to increase renal blood flow and inhibit gastric acid production.[3] Prostaglandin I₂, in contrast to thromboxane A₂, is also a vasodilator that reduces platelet aggregation. The effects of NSAIDs, including aspirin, on platelet inhibition, gastric acid production, and renal blood flow are largely determined by their ability to inhibit the production of prostaglandins and thromboxane via COX inhibition (Figure 1).

The effect of COX inhibition on various cell types is determined by how the cells process the prostaglandin G₂ that COX produces. Moreover, there are 2 separate subtypes of COX that are important to human health, COX-1 and COX-2, which are expressed in different cell types. COX-1 is expressed constitutively by platelets and gastric mucosal cells; COX-2 is expressed in renal cells, vascular endothelial cells, and neutrophils.[23–25] Downstream of COX-1, platelets convert prostaglandin G₂ primarily into thromboxane A₂ via platelet-specific thromboxane synthase and gastric mucosal cells process it into prostaglandins I₂ and D₂. [26] Downstream of COX-2, vascular endothelial cells, renal cells, and inflammatory cells process prostaglandin G₂ into prostaglandins I₂ and E₂. [23–25]

Because aspirin acts to irreversibly inhibit COX and platelets are unable to re-synthesize COX, aspirin's platelet inhibitory effect lasts for the lifetime of the platelet.[27, 28] In nucleated cells, inhibition of COX at the cellular level is temporary, since cells are able to re-synthesize COX. Moreover, though aspirin inhibits both COX-1 and COX-2, its is nearly 100-fold less efficient as an inhibitor of COX-2.[29, 30]

Thus, at low doses (100mg/day), aspirin completely inhibits platelet COX-1 activity and partially inhibits GI mucosal COX-1 activity.[24, 25, 31] Inhibition of platelet thromboxane A₂ mediates aspirin's primary antithrombotic activity and bleeding side effects, and inhibition of GI mucosal prostaglandins could lead to GI toxicity. Mechanistically, it is difficult to untangle aspirin's antithrombotic effect from its effects on gastric toxicity and impossible to separate its antithrombotic effect from its bleeding effects. By contrast, aspirin only has the potential to inhibit vascular, inflammatory, and renal COX-2 activity at higher daily doses.[26] Thus, it would not be expected that successful aspirin treatment for secondary prevention would be obligatorily be associated with cardiovascular or renal

toxicity in the same way that it should be with gastric and bleeding toxicities. A detailed discussion of the clinical risks versus benefits of aspirin dose, however, is beyond the scope of this review.

A. Renal and cardiovascular toxicity

Given its ability to inhibit both COX isoforms, aspirin could theoretically have nephrotoxic and cardiotoxic effects similar to the other NSAIDs, since inhibition of COX-2-mediated production of prostaglandin I₂ by vascular endothelial cells could cause vasoconstrictive and prothrombotic effects, and inhibition of COX-2-mediated production of prostaglandins I₂ and E₂ could reduce renal blood flow.[32, 33] Indeed, in healthy volunteers, exposure to aspirin doses as low as 325 mg/day have been shown to a paradoxical increase in platelet aggregation despite total thromboxane A₂ suppression.[34] Moreover, the COX-2 selective inhibitors, celecoxib, rofecoxib, and meloxicam, prevent vascular cell production of prostaglandin I₂ without preventing platelet production of thromboxane A₂, and have been shown to be associated with an increased risk of ischemic cardiovascular events.[35, 36] Thus, while inhibition of the COX-2 pathway may contribute to improved anti-inflammatory effects, the adverse cardiovascular consequences of selective COX-2 inhibitors highlight the careful balance between the anti-inflammatory and anti-platelet effects that are unique to aspirin.

B. Gastric toxicity

Aspirin's gastric toxicity arises from both direct gastric mucosal injury and reduced prostaglandin synthesis. Aspirin is acidic, which may cause direct topical injury to gastric mucosa.[37] As it is a weak acid, aspirin remains non-ionized and lipophilic within the strongly acidic gastric lumen, allowing it to penetrate the gastric mucous layer to the surface endothelial cells, where the environment is less acidic and allows for dissociation of aspirin and trapping of hydrogen ions. However, aspirin's systemic effects on GI toxicity are more important than its local, topical effects, which may explain the failure of enteric-coated aspirin to reduce GI complications.[38] Inhibition of prostaglandin synthesis by aspirin causes reductions in bicarbonate secretion, epithelial mucous production, epithelial cell proliferation, and mucosal blood flow.[37] The overall effect is to make the gastric lining more susceptible to injury and less able to heal itself following injury, whether caused by endogenous acid, pepsin or bile salts, or by exogenous factors like aspirin itself, other NSAIDs, alcohol, or *Helicobacter pylori* infection. Though mucosal injury is most often superficial and self-limited, aspirin's antiplatelet effects may paradoxically predispose these patients to gastrointestinal (GI) hemorrhage, especially when they are concurrently treated with anticoagulants or other potent antiplatelet agents such as P2Y₁₂ inhibitors.[39]

C. Bleeding

Since aspirin's major mechanism of action in the prevention of cardiovascular events is the inhibition of platelet activity, bleeding is an expected side effect. In a recent observational cohort study conducted in Italy, 186,425 patients taking aspirin (< 300 mg daily) were matched with 186,425 controls.[40] The risks of GI bleeding requiring hospitalization and intracranial hemorrhage were approximately 50% higher in those patients taking aspirin. Importantly, despite the increased relative risk of major bleeding with aspirin, the absolute

risk only increased from 3.60 bleeds per 1000 patient years in the control arm to 5.58 bleeds per 1000 patient years in the cohort treated with aspirin. A meta-analysis of observational studies including patients taking high- and low-dose aspirin demonstrated a 2-fold increase in the relative risk of GI hemorrhage in patients taking aspirin; this relative risk increase corresponded to an additional 1 to 2 GI bleeds per 1000 patient-years.[41] A meta-analysis of clinical trials that compared aspirin to placebo for multiple indications demonstrated a 22% increase in the incidence of hemorrhagic strokes, corresponding to 1 to 2 hemorrhagic strokes per 10,000 patient-years.[5, 31]

D. Anaphylaxis and upper respiratory symptoms

In addition to prostaglandin G₂, arachidonic acid is converted into the leukotrienes – potent inducers of airway swelling, bronchoconstriction, and mucous secretion. Prostaglandin E₂, production of which is inhibited by aspirin, is also a bronchodilator. The combination of these effects can produce the syndrome of aspirin-exacerbated respiratory disease, characterized by chronic rhinosinusitis with nasal polyps, asthma, and acute upper and lower respiratory tract reactions in response to asthma ingestion. This syndrome is present in 7% of patients with asthma, but is far less common in the broader population of patients with CAD.[42, 43] COX inhibition also appears to be responsible for urticarial reactions to aspirin, which develops in patients with and without chronic urticaria. The prevalence of aspirin hypersensitivity – either aspirin-exacerbated respiratory disease or aspirin-induced urticaria – ranges from 0.6 to 2.5% in studies of the general population.[44] However, multiple protocols exist to safely and rapidly desensitize patients to aspirin. In a cohort of 1306 patients admitted to a Spanish coronary care unit with ACS, 24 (1.8%) had a history of aspirin hypersensitivity. All were safely treated with an aspirin desensitization strategy involving pre-treatment with antihistamines and corticosteroids followed by 8 escalating doses of aspirin given every 15 minutes; one patient developed hives during the desensitization protocol but was nevertheless safely desensitized to aspirin.[45]

3. Safety Profile of Aspirin When Compared with Placebo for Patients with a Prior MI

For the secondary prevention treatment of patients with cardiovascular disease, aspirin was initially compared with placebo in multiple trials that included a long-term exposure to blinded study drug. Six trials enrolling a total of 10,859 patients treated for a mean duration of 27 months were completed in the late 1970s and early 1980s, and compared aspirin with placebo in patients with a prior MI, randomizing them to high-dose aspirin (300 mg – 1 gram daily) vs. placebo.[4, 5] These trials reported on aspirin's side effects compared to placebo in considerable detail, and provide much of the data for aspirin's tolerability in the population of patients with CAD.

The earliest trial examining the performance of aspirin for secondary prevention in patients with prior MI, Cardiff-1, enrolled only men, who were screened immediately after hospital discharge following MI and randomized to 300 mg aspirin daily vs. placebo.[46] Specific side effects were not reported, but 3.6% of the enrolled patients withdrew from the trial due to side effects, which the authors describe as “occasionally gastrointestinal.” Cardiff-2 was a

larger trial, and enrolled both men and women who were screened immediately following hospital discharge for MI, and who were randomized to 300 mg of aspirin three times daily vs. placebo.[47] Of 832 patients in the aspirin arm, 98 withdrew from the trial due to side effects that were not specified, but only 8 patients were reported to have a GI bleed. Notably, however, 89 patients in the placebo arm also withdrew from the trial due to side effects, suggesting that aspirin was nearly as well tolerated as placebo at the high doses tested.

Further observations on the safety and tolerability of aspirin were developed from a group of blinded, placebo-controlled trials that also evaluated aspirin as a secondary prevention treatment for prior MI patients. The Coronary Drug Project Aspirin (CDP-A) trial, Aspirin Myocardial Infarction Study (AMIS), and Persantine-Aspirin Reinfarction Study (PARIS) enrolled patients with a recent or remote prior MI, randomized patients to aspirin vs. placebo, and reported details of the side effects observed with aspirin, whereas the the German-Austrian Aspirin Trial (GAMIS) did not report details on the side effects (other than those that led to the discontinuation of blinded study drug) observed with aspirin vs. placebo.[48–51] (Table 1) All 4 trials randomized patients to high dose aspirin vs. placebo: The aspirin dose in CDP-A was 324 mg daily, 500 mg twice daily in AMIS, 324 mg three times daily in PARIS, and 500 mg three times daily in GAMIS. The most commonly reported symptoms were related to the GI tract, with up to 18% of patients developing a composite of symptoms suggestive of peptic ulcer, gastritis, or gastric mucosal erosion that occurred significantly more frequently in the aspirin group. For both stomach pain and heartburn, there did appear to be a dose-response relationship, with both reported more frequently in AMIS and PARIS than CDP-A. The trials also noted higher rates of nausea, vomiting, and melena in aspirin-treated patients. In many cases, these GI symptoms were severe: In PARIS, up to 25% of patients randomized to aspirin temporarily or permanently discontinued study drug due to GI complaints compared with 10.3% of patients randomized to placebo.

CDP-A did demonstrate a slightly higher incidence of urticaria and pruritis in the aspirin arm, but neither occurred in more than 1.1% of patients, and AMIS demonstrated opposite findings. Due to concern that aspirin-mediated prostaglandin I₂ suppression could contribute to renal insufficiency, both AMIS and PARIS monitored patients' serum creatinine concentration and there was no difference between the aspirin and placebo groups. None of these trials rigorously reported bleeding complications, but there is a suggestion of excess bleeding in the aspirin arm in AMIS. In GAMIS, 9 patients (2.8%) treated with aspirin stopped their study drug due to hemorrhage; no patients randomized placebo had a hemorrhage resulting in cessation of study drug.

Data from these trials have been included in several meta-analyses comparing aspirin with placebo for the prevention of cardiovascular events.[4, 5] In the meta-analyses, there was a 20% reduction in major coronary events (death or non-fatal MI) with the use of aspirin compared with placebo (RR = 0.80, 95% CI 0.73–0.88), corresponding to an absolute risk reduction of 1% per year. When used in patients with known vascular disease, aspirin reduced the risk of major coronary events to a similar degree in both men (RR = 0.81, 95% CI 0.72–0.92) and women (RR = 0.73, 95% CI 0.51–1.03), though with only 272 total coronary events in women, the reduction in coronary events for women was not significant.

Though there is insufficient data in the post-MI trials to draw conclusions regarding bleeding rate in aspirin and placebo-treated patients, data pooled from all secondary prevention trials comparing aspirin to placebo (including those enrolling patients with prior stroke) demonstrated increased risks of hemorrhagic stroke (RR 1.67, 95% CI 0.97–2.90) and major extracranial bleed (RR 2.69, 95% CI 1.25–5.76) with aspirin treatment compared to placebo. In another meta-analysis, which included only trials of low-dose aspirin, aspirin again increased the risk of all major bleeding (RR 1.71, 95% CI 1.41–2.03)(Figure 2).[52]

In patients with documented CAD but not necessarily with a prior MI, data from the Swedish Angina Pectoris trial (SAPAT), which randomized 2035 patients with stable angina and treated them with aspirin, 75 mg daily, or placebo for 50 months, demonstrated a 34% reduction in MI and sudden death, the trial's primary outcome.[53] However, a total of 20 patients (2.0%) randomized to aspirin suffered a major bleeding episode, which was defined as any bleed requiring transfusion, causing death, or having serious implications for the patient, compared to 13 (1.2%) in the placebo arm. Of the 20 major bleeding episodes, 11 were GI bleeds, of which 2 were fatal, and 6 were intracranial bleeds, of which 4 were fatal.

On the strength of evidence from SAPAT and the meta-analyses of aspirin's effect on preventing recurrent cardiovascular events in patients with prior MI, aspirin became established as the standard of care for secondary prevention in patients with CAD, and subsequent trials included aspirin as the active comparator in the control arm (Table 2). Aspirin therefore transitioned to becoming a benchmark therapy for the chronic secondary prevention treatment of cardiovascular disease.

4. Safety Profile of Aspirin as an Active Comparator Compared with Other Anti-Thrombotic Regimens

The Coumadin Aspirin Reinfarction Study (CARS), Combination Hemotherapy and Mortality Prevention (CHAMP) study, Warfarin Aspirin Reinfarction Study (WARIS II), and Aspirin and Coumadin After Acute Coronary Syndromes (ASPECT-2) study were the first studies to evaluate alternative antithrombotic regimens in patients with CAD. Each study enrolled only patients stabilized after MI, and randomized them to aspirin alone (160 mg daily, except in ASPECT-2, where the dose was 80 mg daily) or the combination of warfarin plus aspirin.[54–57] In each case, follow-up was at least 12 months, and no trial demonstrated a reduction in ischemic events with the addition of warfarin. CARS and CHAMP both defined major bleeding as intracranial bleeding, bleeding requiring surgical intervention or transfusion, bleeding contributing to death, or a drop of hemoglobin by 2 g/dl or more; in both trials, the rate of major bleeding was roughly 0.7% per year.[54, 55] WARIS II and ASPECT-2 had a more restrictive definition of major bleeding, including only bleeds that were fatal or required transfusion or surgery; nevertheless, major bleeding rates were similar. In all trials, less than 0.1% of patients randomized to aspirin suffered a fatal bleeding event. None of the trials reported specific side effects, but 12.6% of patients randomized to aspirin alone in CHAMP stopped treatment with the study drug.[55] In each case, treatment with warfarin plus aspirin or warfarin alone was associated with a higher rate of bleeding than aspirin monotherapy.

The development of oral glycoprotein IIb/IIIa inhibitors provided another opportunity to evaluate novel antithrombotic strategies in comparison to aspirin. The Sibrafiban Versus Aspirin to Yield Maximum Protection from Ischemic Heart Events Post Acute Coronary Syndromes (SYMPHONY), Evaluation of Oral Xemilofiban in Controlling Thrombotic Events (EXCITE), and the Oral Glycoprotein IIb/IIIa Inhibition with Orofiban in Patients with Unstable Coronary Syndromes (OPUS) trials randomized patients with CAD, most or all of whom with ACS, to either aspirin alone (80–162 mg) or aspirin plus an oral glycoprotein IIb/IIIa inhibitor.[58–61] Unlike the warfarin secondary prevention trials, these trials enrolled patients either very shortly after presentation with ACS or very shortly after PCI with stent placement, and as a result, patients in the aspirin-only arms of these trials were exposed to a variety of other antithrombotic agents along with aspirin.

EXCITE enrolled patients undergoing PCI; 71% of the patients enrolled underwent stent placement and received open-label ticlopidine for 14–28 days, such that the aspirin-only arm of the trial truly reflects dual antiplatelet therapy for this duration, followed by aspirin alone up to 182 days.[58] In this group, 41% of patients had any bleeding, including 1.8% of patients with moderate or severe bleeding. One (of 2442) patients had an intracranial bleed and 4 had a moderate or severe GI bleed; the study drug was stopped in 36 patients (1.5%) due to bleeding.

SYMPHONY and OPUS enrolled patients with ACS within 3–5 days of presentation; 10% of patients in SYMPHONY and 28% of patients in OPUS underwent PCI with stenting. In SYMPHONY and OPUS, patients undergoing coronary stent placement assigned to the only-aspirin group received open-label ticlopidine in addition to aspirin for 14–28 days before returning to aspirin alone for the remainder of follow-up. In both trials, nearly all patients were exposed to heparin or low molecular weight heparin around the time of trial enrollment. In OPUS, 11.4% of patients in the aspirin-only arm had a TIMI major or minor bleeding event at 10 months follow-up and 0.12% ($n = 4$) had a fatal bleeding event.[61] Most of these bleeding events (7.2%) came within the first 30 days after presentation, when patients were treated with multiple anticoagulants in the acute ACS setting. In SYMPHONY's aspirin-only arm, 401 patients (out of 3075) had major or minor bleeding (13.0%), with 3.9% of patients suffering a major bleeding event.[59] The overall early rate of aspirin discontinuation was 19.2%, though many patients later reported open label use; 44 patients (1.4%) stopped treatment with aspirin due to bleeding.

Neither SYMPHONY, EXCITE, nor OPUS demonstrated a reduction in ischemic endpoints with the combination of a glycoprotein IIb/IIIa inhibitor and aspirin compared to aspirin alone, and the addition of a glycoprotein IIb/IIIa inhibitor to aspirin increased bleeding rates. For this reason, glycoprotein IIb/IIIa inhibition was abandoned as a therapeutic target for long-term prevention of ischemic events in patients with CAD.

The subsequent development of the P2Y₁₂ inhibitors ticlopidine, and later, clopidogrel, offered investigators another target for the prevention of ischemic events. The Randomized, Blinded Trial of Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) investigated the efficacy of replacing aspirin with clopidogrel in a population of patients with atherosclerotic disease in any vascular bed. In CAPRIE, 19,185 patients with

MI within 35 days of randomization, ischemic stroke within 6 months of randomization, or ongoing intermittent claudication were randomized to aspirin, 325 mg daily, or clopidogrel, 75 mg daily, and treated for a mean follow-up period of 1.91 years.[62] Treatment with clopidogrel reduced the relative risk of vascular death, MI, or stroke by 8.7% (95% CI 0.3–16.5) without significant differences in safety. In the aspirin arm, 890 patients (9.3%) reported any bleeding complication, including 149 (1.55%) judged by the investigators to be severe. These severe bleeding events included 68 GI bleeding events (0.71%) and 41 intracranial hemorrhages (0.43%). The rate of bleeding complications in the aspirin arm was numerically higher than the rate in the clopidogrel arm, in which 47 (0.49%) suffered a severe GI bleed and 30 (0.31%) suffered a severe intracranial hemorrhage. In addition, 1686 patients in the aspirin arm (17.59%) reported upper GI discomfort, which was judged to be severe in 118 (1.23%). Overall, 11% of patients randomized to aspirin alone in CAPRIE stopped the drug due to bleeding, indigestion, or abnormal liver function tests; considerably larger proportions of patients reported minor adverse events that did not lead to treatment discontinuation.[62]

After CAPRIE demonstrated the long-term safety and efficacy of clopidogrel in patients with stable atherosclerosis, the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial tested the performance of clopidogrel in addition to aspirin, compared to aspirin alone, in patients with non-ST segment elevation ACS (NSTEMI-ACS). CURE demonstrated a significant reduction in recurrent ischemic events with the addition of clopidogrel to aspirin in patients with NSTEMI-ACS, though this came at a cost of increased bleeding. In CURE's aspirin-only arm, 8.5% of patients had a bleeding complication during 12-month follow-up, with 3.7% suffering a major bleed, defined by study investigators as any life-threatening bleed or one requiring transfusion of 2 or more units of blood.[60] Notably, more than one third of major bleeds were clearly procedurally related, with bleeding either at a retroperitoneal, surgical or arterial puncture site; however, the authors did not specify whether bleeding was procedural or nonprocedural.

The rate of non-procedural bleeding in contemporary post-PCI patients taking aspirin was better elucidated in the Clopidogrel for the Reduction of Events During Observation (CREDO) study.[63] CREDO randomized 2116 patients undergoing PCI (67% for an ACS indication) to 1 of 2 regimens: 1) clopidogrel 300 mg prior to PCI, followed by 75 mg daily, plus aspirin, 325 mg daily, for 12 months; or 2) clopidogrel, 75mg daily, for 28 days following PCI, plus aspirin, 81–325 mg, daily for 12 months. The long-term results of CREDO can thus be conceptualized as a trial of aspirin plus clopidogrel versus aspirin alone. Overall, the rates of bleeding in CREDO's aspirin-only arm were comparable to those in CURE, OPUS, and EXCITE, with 12.2% of patients having TIMI major or minor bleeding over 12 months. However, the rate of TIMI major or minor nonprocedural bleeding was 1.5%, with 1% of patients suffering a bleeding complication after the first month.

Though CREDO attempted to control for procedural bleeding, its results remain complicated by the fact that most of its patients presented with ACS and thus were exposed to numerous antiplatelet and anticoagulant medications. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization study (CHARISMA) investigated the efficacy of adding clopidogrel to aspirin in a population of patients with stable atherosclerotic disease or risk

factors for atherosclerosis. CHARISMA randomized patients to aspirin alone (75–162 mg daily) or aspirin plus clopidogrel.[64] In a pre-specified subgroup analysis of 9,478 patients with documented atherosclerotic disease, the cohort of patients treated with aspirin alone had an incidence of GUSTO moderate or severe bleeding of 2.8% over 28 months, and 0.4% of patients developed intracranial bleeding. The addition of clopidogrel to aspirin increased the rate of major bleeding in these patients. Though patients with established atherosclerotic disease had a reduction in ischemic events with DAPT, the effect size was small (absolute risk reduction 1%) and the overall trial did not demonstrate a reduction in ischemic events.

Based on the results of CAPRIE, CURE, CREDO, and CHARISMA, 12 months of dual antiplatelet therapy with aspirin and clopidogrel became the standard of care for patients with ACS but not for patients with stable atherosclerotic disease, for whom aspirin alone was standard of care. However, neither CREDO nor CURE enrolled patients undergoing PCI with drug-eluting stents, and the duration of therapy with DAPT following drug-eluting stent placement was not well-established. In the Basel Stent Kosten Effektivitats Trial – Late Thrombotic Events (BASKET-LATE) a series of patients treated with drug-eluting or bare metal stents were treated for 6 months with DAPT, and then clopidogrel was stopped and patients were followed for an additional year. Over that year, 2.6% of patients that had undergone drug-eluting stent placement had a stent thrombosis event resulting in death or MI.[65] Though guidelines recommended 6 to 12 months of DAPT following PCI with drug-eluting stent,[66, 67] the optimal duration was unknown.

The Dual Antiplatelet (DAPT) study was designed to answer this question. DAPT enrolled 25,682 patients who had undergone placement of a drug-eluting stent 1 year prior and had tolerated (without a moderate or severe bleeding event) 1 year of treatment with aspirin plus a P2Y₁₂ inhibitor.[15] Patients were randomized to continuation of their P2Y₁₂ inhibitor or to continuation of aspirin only, at a dose of 75–162 mg, and were followed for 18 months. Continued treatment with a P2Y₁₂ inhibitor significantly reduced the rate of major adverse cerebrovascular and cardiovascular events by 29% (HR 0.71, 95% CI 0.59–0.89). In the aspirin-only arm ($n = 4476$), 84 patients suffered a GUSTO severe or moderate bleed (1.88%), and 85 patients suffered a BARC 3 or 5 bleed (1.90%). Prolonged DAPT reduced the risk of recurrent ischemic events (4.3% with DAPT vs. 5.9% with aspirin alone, $p < 0.001$), but came at a cost of increased moderate and severe bleeding (2.5% vs. 1.6%, $p < 0.001$). The effect of DAPT on clinical practice and guideline recommendations remains to be seen.

The Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS) study also evaluated the performance of aspirin versus aspirin plus a P2Y₁₂ inhibitor in stable patients who underwent stent placement at least 1 year prior to randomization. In PEGASUS, 21,162 patients with prior MI (83% with PCI) within 1 to 3 years, and who were currently tolerating aspirin, were randomized to a strategy of usual care or ticagrelor plus usual care and followed for a median of 33 months.[14] In the trial, 99.9% of patients received aspirin, and 97.3% received a dose between 75 and 100mg daily. Therefore, PEGASUS represents a contemporary trial of low-dose aspirin versus dual antiplatelet therapy in stable post-MI patients. Treatment with ticagrelor reduced the primary endpoint (a composite of death, MI,

or stroke) by 16% (HR 0.84, 95% CI 0.76–0.94). In the aspirin only arm, 1% of patients suffered a TIMI major or minor bleeding complication, 0.47% of patients suffered an intracranial bleed, and 1.5% of patients had bleeding that led to study drug discontinuation. The risk of bleeding was higher in the aspirin plus ticagrelor arm.

Importantly, both DAPT and PEGASUS explicitly required patients to be tolerating aspirin at the time of trial enrollment; DAPT required that patients tolerate a year of treatment with aspirin plus a P2Y₁₂ inhibitor prior to enrollment. Both trials also excluded patients with indications for anticoagulation. Despite the fact that these features would tend to prevent patients at risk of bleeding from enrolling, the incidence of bleeding events in the aspirin-only arms of these trials was comparable to prior trials. Thus, even in a contemporary population of patients known to tolerate aspirin, residual risk of bleeding exists.

Overall, randomized clinical trials have validated several of aspirin's theoretical toxicities but disproved others. Despite a putative prothrombotic effect mediated by inhibition of vascular endothelial cell production of prostaglandin I₂ and a putative nephrotoxic effect mediated by inhibition of renal cell production of prostaglandins E₂ and D₂, aspirin has no documented nephrotoxic or cardiotoxic effects at doses ranging from 75mg to 1 gram daily. Aspirin-exacerbated respiratory disease was not described at all in these trials, and hives were no more common in aspirin-treated patients than in placebo-treated patients. By contrast, aspirin roughly doubled the risk of acute gout flares, with an absolute increase in incidence of these events by approximately 0.5% per year. Compared to placebo, aspirin treatment was also associated with a 2- or 3-fold increase in the risk of GI intolerance, depending on the dose of aspirin used and the GI side effect of interest. Aspirin increased the absolute risk of developing stomach pain by 6–7%, nausea by 2–6%, vomiting by 1–2%, and melena by 1%. Though the tolerability of these side effects were not well reported in the pivotal aspirin-versus-placebo trials, other studies showed many of these GI intolerances to be transient and able to be overcome without cessation of treatment.

The pivotal trials comparing aspirin to placebo did not report bleeding complications in a standard manner, but numerous other trials comparing aspirin to alternative anti-thrombotic trials did. In stable secondary prevention patients, the risk of clinically significant bleeding (GUSTO moderate/severe, TIMI minor/major, or any bleeding complication defined as fatal, life-threatening, or requiring surgery or transfusion) generally ranged from 0.5 to 1% per year of treatment, depending on the bleeding definitions used and the dose of aspirin. Even in the DAPT and PEGASUS cohorts of patients who were known to tolerate antiplatelet treatment, this risk persisted. Intracranial and fatal bleeds were rare, generally occurring in around 0.1% of patients per year of treatment, in line with estimates of the frequency of this complication in observational studies.[68] In patients with recent ACS exposed to multiple anticoagulant and antiplatelet agents in addition to aspirin, bleeding complications were more frequent; with a rate of bleeding often exceeding 10% annually, though much of this bleeding was procedurally-related, and still more was concentrated in the first month after ACS diagnosis, when patients were more likely to be exposed to multiple antithrombotic agents and may be critically ill.

6. Conclusion

Despite over 30 years of clinical trial and observational evidence demonstrating its efficacy for the prevention of recurrent cardiovascular events in patients with established CAD and its availability in the United States and United Kingdom without a prescription, aspirin does have side effects and toxicities. In the doses tested for secondary prevention of cardiovascular events, aspirin does not share the cardiovascular and renal toxicities of the other NSAIDs, largely due to its COX-1 selectivity. However, up to 20% of patients with established CAD will have GI symptoms when taking aspirin, and serious bleeding will affect between 1 in 200 and 1 in 100 patients treated with aspirin, depending on the dose use and the definition of serious bleeding. Based on aspirin's mechanism of action as an inhibitor of COX-1, with downstream inhibition of the production of platelet thromboxane A₂ and GI mucosal prostaglandins, uncoupling aspirin's GI and bleeding side effects from its therapeutic benefit is unlikely to be possible, especially in light of the failure of specific thromboxane A₂ receptor antagonists to prevent cardiovascular events.[69, 70] Moreover, aspirin's direct and indirect effects on GI mucosa are likely to potentiate the bleeding toxicities of both aspirin and other antiplatelet and anticoagulant medications, a particular concern for patients in need of DAPT that have a concurrent indication for anticoagulation, in whom the annual incidence of bleeding may exceed 15% with a incidence of intracranial bleeding approaching 2%.[39, 71]

It was for this reason that the What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting (WOEST) study evaluated treating patients with an indication for triple therapy with either aspirin, clopidogrel, and warfarin or clopidogrel plus warfarin.[72] The trial demonstrated that eliminating aspirin from the triple therapy regimen substantially reduced the risk of bleeding, and though the trial was not powered to detect a difference in ischemic outcomes, it did not show an excess in death, MI, stroke, or stent thrombosis in the group randomized to take clopidogrel and warfarin alone. As a result of WOEST, PEGASUS, DAPT, and multiple other studies, the optimal duration and composition of antiplatelet therapy for secondary prevention are under debate. A number of other trials are evaluating other aspirin-excluding regimens in patients with an indication for triple therapy,[19–21] the currently-enrolling COMPASS and GEMINI ACS trials will evaluate the efficacy of replacing aspirin with rivaroxaban in patients with stable CAD and ACS, respectively,[18, 16] and the GLOBAL LEADERS trial will replace a traditional 12-month DAPT regimen with 1 month of DAPT followed by 23 months of ticagrelor monotherapy.[17] The results of these studies and others will help determine aspirin's role in secondary prevention, balancing efficacy and side effects.

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Abbreviations

CREDO	Clopidogrel for the Reduction of Events During Observation
SPAF	Stroke Prevention in Atrial Fibrillation

SALT	Swedish Aspirin Low Dose Trial
EAST	European Atrial Fibrillation Trial
TPT	Thrombosis Prevention Trial
PPP	Primary Prevention Project
HOT	Hypertension Optimal Treatment
SAPAT	Swedish Angina Pectoris Aspirin Trial
APRICOT	Aspirin Versus Coumadin in the Prevention of Reocclusion and Recurrent Ischemia After Successful Thrombolysis

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KEY POINTS

- Aspirin is the mainstay of secondary prevention for patients with coronary artery disease, but has a number of toxicities, including gastrointestinal discomfort, urticaria, and bleeding.
- In clinical trials enrolling patients treated with aspirin monotherapy for secondary prevention, up to 1 in 20 patients will develop gastrointestinal symptoms, 1 in 100 will have a clinically significant bleed, and 1 in 1000 will have an intracranial or fatal bleeding event.
- Ongoing clinical trials will help define the optimal duration and composition of antithrombotic therapy for secondary prevention

Figure 1. Aspirin exerts its physiologic effects via inhibition of prostaglandin synthesis

Footnote: Adapted from: Fuster V, Sweeny JM. Aspirin: A historical and contemporary therapeutic overview. *Circulation* 2011;123(7):768–778

Figure 2. Aspirin increases the risk of major bleeding compared to placebo

Footnotes:

From: McQuaid KR and Laine L. "Systematic Review and Meta-analysis of Adverse Events of Low-dose Aspirin and Clopidogrel in Randomized Controlled Trials." *Am J Med* 2006;119(8):624–638. The authors included studies of adults assigned to low-dose aspirin (75–325 mg/day) for secondary prevention. Summary statistics were calculated using a random effects model; heterogeneity was calculated using the chi-squared test, and significant heterogeneity was defined as $p < 0.1$. For this analysis, $p = 0.47$, indicating no significant heterogeneity.

Table 1

Side effects reported in aspirin versus placebo trials

Symptom	CDP-A		AMIS		PARIS-1		GAMIS*	
	Aspirin 324mg daily	Placebo	Aspirin 500mg BID	Placebo	Aspirin 324mg TID	Placebo	Aspirin 500mg TID	Placebo
Symptoms suggestive of peptic ulcer or gastritis	**	**	23.7%	14.9%	18.1%	13.2%	**	**
Stomach pain	12.5%	6.3%	14.5%	4.4%	17.2%	7.7%	5.0%	3.6%
Heartburn	5.6%	3.9%	11.9%	4.8%	9.4%	5.2%	**	**
Nausea	5.1%	3.2%	8.3%	1.9%	**	**	**	**
Vomiting	**	**	1.3%	0.2%	3.2%	1.0%	**	**
Gastritis	5.4%	3.9%	**	**	**	**	**	**
Peptic ulcer	2.8%	2.2%	**	**	1.3%	0.3%	1.3%	0.3%
Melena	2.8%	1.5%	2.7%	1.7%	**	**	**	**
Melena or hematochezia	**	**	**	**	6.4%	2.5%	**	**
Gout flare	2.6%	0.9%	2.4%	1.4%	**	**	**	**

* Only side effects severe enough to result in study drug discontinuation reported;

** : Data not reported

Abbreviations: CDP-A: Coronary Drug Project – Aspirin Arm; AMIS: Aspirin Myocardial Infarction Study; PARIS-1: Persantine-Aspirin Reinfarction Study; GAMIS: German-Austrian Aspirin Trial

Table 2

Bleeding frequency with aspirin when used as the active comparator treatment regimen for clinical trials with follow up of at least 12 months

Study	Aspirin dose	Comparator	Duration	Significant bleed (%/year)	Major GI bleed (%/year)	Intracranial bleed (%/year)	Fatal bleed (%/year)
WARIS II	160mg	Warfarin (target INR 2.8–4.2) OR warfarin (target INR 2–2.5) plus aspirin	48 months	0.17%	0.13%	0.04%	0%
ASPECT-2	80mg	Warfarin (target INR 3–4) OR warfarin (target INR 2–2.5) plus aspirin	12 months	0.89%	**	0%	0%
CHAMP	160mg	Warfarin (target INR 1.5–2.5) plus aspirin	32 months	0.72%	0.46%	0.22%	0.10%
CAPRIE	325mg	Clopidogrel 75mg daily	23 months	0.82%	0.26%	0.23%	0.15%
CURE	75–325mg	Clopidogrel 75mg daily plus aspirin	12 months	1.40%	0.75%	0%	0.20%
CREDO	81–325mg	Clopidogrel 75mg daily plus aspirin	12 months	0.75%	0.32%	0%	**
CHARISMA	75–162mg	Clopidogrel 75mg daily plus aspirin	28 months	1.19%	0.46%	0.18%	0.10%
DAPT	75–162mg	Clopidogrel 75mg daily plus aspirin	18 months	1.20%	**	**	0.07%
PEGASUS	75–100mg	Ticagrelor 60mg or 90mg BID plus aspirin	33 months	0.47%	**	0.16%	0.09%

** Data not reported; Significant bleed: TIMI major or minor bleeding, GUSTO moderate or severe bleeding, other trial-defined major bleeding (see text)

Abbreviations: WARIS II: Warfarin Aspirin Reinfarction Study; ASPECT-2: Aspirin and Coumadin After Acute Coronary Syndromes; CHAMP: Combination Hemotherapy and Mortality Prevention; CAPRIE: Randomized, Blinded Trial of Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events; CURE: Clopidogrel in Unstable Angina to Prevent Recurrent Events; CREDO: Clopidogrel for the Reduction of Events During Observation; CHARISMA: Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization study; DAPT: Dual Antiplatelet; PEGASUS: Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin