

ASHP Therapeutic Position Statement on the Daily Use of Aspirin for Preventing Cardiovascular Events

Statement of Position

The effectiveness of aspirin as an antiplatelet agent in preventing cardiovascular events and the progression of coronary heart disease (CHD) has been demonstrated in clinical trials in various patient groups. However, despite adequate evidence of benefit, many eligible patients are not treated with aspirin.¹⁻³ Using aspirin for the prevention of cardiovascular events is considered a quality marker by the Centers for Medicare and Medicaid Services, the National Quality Forum, and the Joint Commission on Accreditation of Healthcare Organizations. ASHP supports the daily use of aspirin as an adjunct to other effective drug therapies and modifying controllable risk factors for CHD for the following indications: (1) primary prevention of cardiovascular events in adults with increased CHD risk (10-year risk of at least 6% based on Framingham risk scoring)⁴⁻⁶ and (2) secondary prevention of cardiovascular events in patients with a history of chronic stable angina⁷ or acute coronary syndromes (unstable angina, non-ST-segment elevation myocardial infarction [MI], and ST-segment elevation MI).⁸⁻¹⁰ The Framingham risk scoring system is a simple means of individualizing risk assessments and provides an estimate of total CHD risk over the course of 10 years.¹¹ These positions are consistent with recommendations by the American College of Cardiology and American Heart Association (ACC-AHA),⁶⁻¹⁰ the U.S. Preventive Services Task Force,⁴ the Sixth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy,¹² and the American Diabetes Association (Table 1).¹³

Aspirin should not be administered to patients with contraindications such as a known hypersensitivity to the agent or individuals at high risk for serious bleeding events (e.g., patients with history of gastrointestinal [GI] or cerebral hemorrhage). ASHP believes that modification of controllable cardiovascular risk factors (obesity, smoking, dyslipidemia, and hypertension), coupled with aspirin therapy, is the primary method of reducing the likelihood of cardiovascular events. ASHP supports the role of clinicians in educating appropriate patients on how to reduce cardiovascular risk factors.^{6,10} The use of aspirin to prevent occlusion after invasive revascularization procedures and for the acute management of acute coronary syndromes is beyond the intended scope of this document.

Definitions

This therapeutic position statement is an update of the 1997 ASHP Therapeutic Position Statement on the Use of Aspirin for Prophylaxis of Myocardial Infarction¹⁴ and reflects newer data. For the purposes of this document, primary prevention refers to the long-term use of daily aspirin to prevent a first cardiovascular event (e.g., MI) for most patients. Secondary prevention refers to long-term use of daily aspirin to prevent cardiovascular events in patients with a history of chronic stable angina or acute coronary syndrome. Unstable angina, non-ST-segment elevation MI, and ST-segment elevation MI are considered acute coronary syndromes throughout this document.

Background

Mechanism of Action. Aspirin's efficacy in preventing MI is related to preventing thrombus formation by decreasing platelet aggregation.¹⁵ Aspirin is a nonsteroidal antiinflammatory drug (NSAID) that permanently inactivates the cyclooxygenase (COX)-mediated activity of prostaglandins through irreversible binding.¹⁶ There are two forms of COX: COX-1 and COX-2. COX-1 is responsible for the synthesis of thromboxane A₂ in platelets and the production of prostacyclin in vascular walls.¹⁷ Thromboxane A₂ is a vasoconstrictor and platelet-aggregating agent, while prostacyclin acts as a vasodilator and platelet inhibitor. COX-1 regulates prostaglandins in the gastric mucosa and kidneys. Irreversible inhibition of platelet function is evident within 15 minutes after taking a 325-mg dose of aspirin.¹⁸ COX-2 regulates prostaglandins that mediate inflammation, pain, and fever, and supports kidney function (by vasodilation of the afferent renal artery). Aspirin is a more potent inhibitor of COX-1 than COX-2 and suppresses thromboxane A₂ production with dosages as low as 30 mg daily,¹⁶ resulting in irreversible inhibition of platelet aggregation that lasts 10–14 days (the typical life span of platelets).

Dosage. The goal of aspirin dosing for prevention of cardiovascular events is to produce a low thromboxane:prostacyclin ratio that reduces platelet aggregation while maintaining coronary artery vasodilation. Attempts to determine an aspirin dosage that blocks thromboxane A₂ production without inhibiting prostacyclin synthesis have produced conflicting results.^{16,19} Aspirin dosages of 1000 mg daily inhibit both thromboxane A₂ and prostacyclin, while lower doses (i.e., 75–325 mg daily) primarily inhibit thromboxane A₂. In clinical trials, beneficial antithrombotic effects have been seen at aspirin dosages known to inhibit both thromboxane A₂ and prostacyclin synthesis.²⁰

Aspirin is an effective antithrombotic agent at dosages of 75–1500 mg daily; however, dosages of \leq 300 mg daily produce fewer GI effects than higher doses.¹⁶ A meta-analysis of randomized trials conducted by the Antithrombotic Trialists' Collaboration of antiplatelet therapy concluded that low-dose aspirin (75–150 mg daily) is an effective regimen for long-term use and that an initial dosage of at least 150 mg daily may be required in acute settings.²⁰ Patients with acute coronary syndromes should receive non-enteric-coated aspirin 160–325 mg, preferably chewed, as soon as possible after clinical presentation.^{7-10,12,21} Alternative or additional antithrombotic agents (i.e., clopidogrel) may be needed for patients with aspirin allergy, aspirin intolerance, or recurrent cardiovascular events despite aspirin therapy.¹⁶

Primary Prevention

Five randomized clinical trials of primary prevention have been conducted with adults who have cardiovascular risk factors. These trials have involved more than 50,000 patients.

Table 1.
Recommendations for the Use of Aspirin for the Prevention of Cardiovascular Events

Organization	Aspirin Recommendation(s) ^a
American College of Cardiology–American Heart Association ^{6–10}	Primary prevention: 75–160 mg daily for pts at high risk for CHD (those with 10-year risk ≥ 10%). Secondary prevention: 75 to 325 mg daily for pts with chronic stable angina; 162–325 mg (non-enteric-coated and chewed) initially, then 75–162 mg daily long-term for pts with ACS.
American College of Chest Physicians ¹²	Primary prevention: 75–162.5 mg daily in pts > 50 years of age with at least one major cardiovascular risk factor (smoking, hypertension, diabetes, hyperlipidemia, history of parental infarction). Secondary prevention: 75–162.5 mg daily for pts with chronic stable angina; 162.5 mg (non-enteric-coated and chewed) initially, then 75–162.5 mg daily long-term for pts with ACS.
American Diabetes Association ¹³	Primary prevention: 75–162 mg daily for pts with diabetes and increased CHD risk, including those over 40 years of age or who have additional risk factors (family history of cardiovascular disease, hypertension, smoking, dyslipidemia, albuminuria). Secondary prevention: 75–162 mg daily for pts with diabetes and history of myocardial infarction, vascular bypass procedure, stroke or transient ischemic attack, peripheral arterial disease, claudication, or angina.
United States Preventive Services Task Force ⁴	Primary prevention: pts at high risk for CHD (those with a 5-year risk ≥ 3%). Specific dosage recommendation not provided.

^aIn the absence of contraindications. CHD = coronary heart disease, ACS = acute coronary syndrome.

British Doctors' Trial. The British Doctors' Trial (BDT) was the first large-scale prospective study evaluating aspirin therapy for the primary prevention of cardiovascular events.²² It was an open-label, randomized, single-blind study of 5139 healthy male physicians that evaluated the effects of aspirin 500 mg daily on the endpoints of cardiovascular mortality, nonfatal MI, and nonfatal stroke over a mean of 5.8 years. Age was the common major cardiovascular risk factor among patients in this study. No significant difference was demonstrated between aspirin and placebo in nonfatal MI, nonfatal stroke, or cardiovascular mortality. The validity of the trial has been questioned because of the study design (open-label, single-blind), dosage of aspirin, lack of imaging studies to distinguish type of stroke (hemorrhagic versus ischemic), and exclusion of women.

Physicians' Health Study. The Physicians' Health Study (PHS) was a double-blind, placebo-controlled, randomized trial of 22,071 healthy male physicians that was designed to determine the effects of aspirin 325 mg every other day on cardiovascular mortality.²³ The group assigned to receive aspirin had a 44% relative risk reduction (RRR) for MI ($p < 0.00001$) and no significant reduction in overall cardiovascular mortality. Although not statistically significant, aspirin increased the relative risk of stroke (primarily hemorrhagic stroke) by 22%. Similar to the BDT, imaging studies were not conducted to confirm hemorrhagic strokes. This study was terminated prematurely after 4.5 years because of a significant reduction in the risk of MI in the aspirin-treated group and because more than 85% of patients who had a nonfatal MI during the study continued aspirin therapy, thereby confounding any subsequent mortality

analysis. Subgroup analysis indicated that aspirin reduced the risk of cardiovascular mortality only in patients age 50 years or older (RRR, 48%; $p = 0.02$), with no significant effect observed in patients age 40–49 years.

Thrombosis Prevention Trial.

The Thrombosis Prevention Trial (TPT) was a double-blind, placebo-controlled, randomized trial that evaluated aspirin 75 mg (controlled release) daily for the primary prevention of all ischemic heart disease (IHD), defined as the sum of coronary deaths and fatal and nonfatal MIs.²⁴ Only men ($n = 5499$) between 45 and 69 years of age at high risk of developing IHD were included. High IHD risk was determined using family history and Northwick Heart Study estimates. Although the Northwick Heart Study risk criteria are not widely accepted in clinical practice, they do include smoking status, blood pressure, and serum cholesterol. Therefore, these criteria are similar to the Framingham Risk Score in that they unequivocally

identify patients with major cardiovascular risk factors.¹¹ Low-intensity oral anticoagulation with warfarin (for a targeted International Normalized Ratio of 1.5) was incorporated into this study using a two-by-two factorial design. The RRR for IHD was 20% with aspirin ($p = 0.04$). The most pronounced effect was a 32% RRR in nonfatal IHD ($p = 0.004$). There was an increased risk of hemorrhagic and fatal strokes with aspirin therapy, but this was mostly observed in those patients who also received warfarin.

Hypertension Optimal Treatment Trial. The hypertension Optimal Treatment (HOT) trial was a double-blind, placebo-controlled, randomized trial that assessed the effect of aspirin 75 mg daily on the risk of major cardiovascular events (nonfatal MI, nonfatal stroke cardiovascular death) in 18,790 men and women with hypertension.²⁵ Cardiovascular-event reduction with different diastolic blood pressure targets was simultaneously evaluated in this trial. Patient age ranged from 50 to 80 years (mean, 61.5 years), and treatment lasted for a mean of 3.8 years. RRRs with aspirin were 15% for major cardiovascular events ($p = 0.03$) and 36% for all MIs ($p = 0.002$), with no difference in the risk of stroke. The number of fatal bleeding episodes (e.g., GI, cerebral) was similar between groups (7 in the aspirin-treated group and 8 in the placebo group). However, there were more nonfatal major bleeding episodes in patients receiving aspirin ($n = 129$) versus placebo ($n = 70$) ($p < 0.001$). Of these nonfatal bleeding episodes, the number of patients with cerebral bleeding was identical (12 in each group), and GI bleeding was more than twice as frequent in patients receiving aspirin ($n = 72$) versus placebo ($n = 34$). This was the first prospective clinical trial to include a large population of women

(~47%), and all had hypertension. These two populations had not been previously studied. The HOT trial provided evidence that aspirin is effective in reducing cardiovascular events when used for primary prevention in male and female patients with hypertension.

Primary Prevention Project. The Primary Prevention Project (PPP) was an open-label, randomized, controlled trial evaluating aspirin 100 mg and vitamin E 300 mg daily in 4495 men and women (mean age, 64.4 years).²⁶ The primary endpoint was a mixed endpoint of cardiovascular death, nonfatal MI, and nonfatal stroke. All patients had one or more of the following major cardiovascular risk factors: hypertension, dyslipidemia, diabetes mellitus, obesity, family history of premature MI, and age over 65 years. This trial was terminated prematurely after a mean follow-up of 3.6 years. A 29% RRR in the primary endpoint was demonstrated with aspirin therapy (2.0% versus 2.8% for aspirin and placebo, respectively) ($p = 0.035$). Moreover, the RRR with aspirin was 44% for cardiovascular death (0.8% and 1.4% for aspirin and placebo, respectively) ($p < 0.05$) and 23% for total cardiovascular events (6.3% versus 8.2% for aspirin and placebo, respectively) ($p < 0.05$). Bleeding events (e.g., GI, intracranial, ocular, epistaxis) were more frequent with aspirin (1.1% versus 0.3% for aspirin and placebo, respectively) ($p < 0.0008$). However, of the four patients who had fatal bleeding, one was receiving aspirin and three were taking placebo.

Primary Prevention in Patients with Diabetes. Diabetes is a major risk factor for cardiovascular events and considered a CHD risk equivalent.²⁷ The American Diabetes Association recommends enteric-coated aspirin (75–162 mg daily) as a primary prevention strategy for high-risk diabetics with one of the following risk factors: family history of CHD, smoking, hypertension, obesity, microalbuminuria, macroalbuminuria, dyslipidemia, and age over 40 years.¹³ However, no prospective, randomized clinical trials have specifically evaluated aspirin for the primary prevention of cardiovascular events in patients with diabetes.

The best evidence supporting the use of aspirin for primary prevention in diabetes comes from post hoc analyses of the PHS, HOT trial, and PPP. There were 497 diabetic patients enrolled in the PHS. The RRR of MI with aspirin in patients with diabetes was 61% (4.0% and 10.1% for those receiving aspirin and placebo, respectively).^{13,23} The HOT trial included 1501 patients with diabetes, and the benefits of aspirin on major cardiovascular events and MI were the same for patients with diabetes and the population studied.²⁵ However, a post hoc analysis of the 1031 patients with diabetes in the PPP revealed a nonsignificant 10% RRR in the primary endpoint of combined cardiovascular death, stroke, and MI (3.9% and 4.3% for patients receiving aspirin and placebo, respectively) (relative risk, 0.90; 95% confidence interval [CI], 0.50–1.62).²⁸ Similarly, there were no differences in total cardiovascular events (10.2% and 11.5% for the aspirin and placebo groups, respectively) (relative risk, 0.89; 95% CI, 0.62–1.26) in patients with diabetes. Results from post hoc analyses are used primarily to generate hypotheses and have limited value. They cannot provide a definitive answer as to whether aspirin reduces cardiovascular events in patients with diabetes.

Summary of Primary Prevention. The BDT and PHS had mixed results, but a subanalysis of the PHS suggested a significant reduction in the risk of nonfatal MI that was limited to men 50 years of age or older. The TPT provided evidence supporting cardiovascular risk reduction in high-risk men with low-dose aspirin therapy; however, it also demonstrated an increased risk of hemorrhagic stroke that was confounded by the concurrent use of warfarin. More conclusive findings were seen in the HOT trial and the PPP, both of which demonstrated cardiovascular risk reduction with low-dose aspirin therapy (75–100 mg daily) in men and women age 50 years or older with at least one major cardiovascular risk factor.

Given the risks of chronic aspirin therapy, primary prevention of cardiovascular events should be reserved for patients with moderate risk for CHD who do not have contraindications to aspirin therapy. A meta-analysis of the BDT, PHS, TPT, and HOT trial concluded that aspirin for primary prevention is “safe and worthwhile” for patients with a 10-year CHD risk of $\geq 15\%$ and is “safe but of limited value” for patients with a 10-year CHD risk of 10–15%.²⁹ A more recent analysis that included the PPP data concluded that the benefits of aspirin for primary prevention outweigh the risks at a 10-year CHD risk of $\geq 10\%$.³⁰ For primary prevention, the U.S. Preventive Services Task Force recommends a 5-year CHD risk of $\geq 3\%$ (10-year CHD risk of 6%) at which “benefit outweighs risk,” while the AHA uses 10% as the recommended 10-year CHD risk cutoff.^{4,6} Therefore, there is consensus that the benefits of primary prevention outweigh the risks for patients with a 10-year CHD risk of $\geq 10\%$. For patients with a 10-year CHD risk of 6–10%, slightly more CHD events are avoided than hemorrhagic strokes or major GI bleeding events are caused.⁴ Therefore, these patients should be viewed as potential candidates for aspirin therapy.

Although post hoc analyses of patients with diabetes provide conflicting results, diabetes incurs significant risk for CHD. Aspirin for primary prevention of cardiovascular events should be considered in patients with diabetes based on the collective benefits seen in the HOT trial and PPP. This is consistent with the American Diabetes Association recommendations for aspirin therapy in patients with diabetes who are over 40 years old.¹³ There are little data on primary prevention in patients 80 years of age or older, especially in those who have multiple comorbidities, are frail, have a high risk for falling, and are nursing-home residents. As these patients are at higher risk for serious aspirin-associated adverse effects, aspirin therapy for the primary prevention of cardiovascular events in the very elderly is controversial.

Secondary Prevention

Chronic Stable Angina. Before the PHS, no clinical trial had examined antiplatelet therapy for the primary prevention of MI among patients with chronic stable angina. A subgroup analysis of 333 men with chronic stable angina from the PHS indicated that aspirin reduced the relative risk of acute MI by 87% ($p < 0.001$).³¹ The Swedish Angina Pectoris Aspirin Trial found a 34% RRR in the occurrence of a first MI over a four-year follow-up period in patients receiving 75 mg of aspirin daily, compared with patients receiving placebo.³² This randomized, double-blind trial involved 2035 patients (48% were women). The 2002 ACC–AHA guidelines for chronic stable angina include a class IIa recommendation (the weight of evidence where opinion is in favor of usefulness

and efficacy) for prophylactic aspirin therapy to prevent MI and death.⁶

Acute Coronary Syndromes. The benefit of aspirin therapy for preventing cardiovascular events in patients with acute coronary syndromes (unstable angina, non-ST-segment elevation MI, ST-segment elevation MI) has been definitively demonstrated in several trials involving a total of 4018 participants.^{33–36} Meta-analysis of randomized trials treating unstable angina or non-ST-segment elevation MI suggests that aspirin therapy reduces the relative risk of either death or MI over a period of five days to two years by 49% (6.4% and 12.5% of patients receiving aspirin and placebo, respectively) ($p < 0.0005$).⁹ There are no direct comparisons of efficacy at different aspirin dosages for cardiovascular-event prevention in patients with unstable angina or non-ST-segment elevation MI.

One meta-analysis by the Antithrombotic Trialists' Collaboration reviewed 18,788 patients with a history of MI from the 12 most important randomized clinical trials of antiplatelet agents.²⁰ Therapy consisted primarily of aspirin alone, and treatment was initiated for at least two years (mean, 27 months). These data showed that antiplatelet therapy reduced the relative risk of nonfatal MI by 28% ($p < 0.0001$), vascular death by 15% ($p < 0.0006$), and overall mortality by 11% ($p = 0.02$).²⁰ No antiplatelet therapy has been shown to be superior to aspirin in patients with a history of MI, and daily dosages of 80–325 mg appear to be effective in reducing the risk of cardiovascular events.⁸

Summary of Secondary Prevention. The 2002 ACC–AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation MI recommend initiating daily aspirin therapy with at least 162 mg as soon as possible after clinical presentation, with 75–325 mg daily indefinitely thereafter.⁹ The 2004 ACC–AHA guidelines for the management of patients with ST-segment elevation MI are similar but recommend 75–162 mg daily as maintenance therapy after ST-segment elevation MI.⁸ Aspirin therapy is considered a class I recommendation (evidence supports that treatment is useful and Effective) for all acute coronary syndromes. The initial dose of aspirin should be chewed and then swallowed during acute coronary syndromes to attain a rapid onset of action.

Adverse Effects

Bleeding events are the most serious adverse effects of chronic aspirin therapy. Cerebral bleeding (hemorrhagic stroke, intracranial hemorrhage) and GI bleeding are considered major adverse effects, with epistaxis and purpura considered minor adverse events. Statistically insignificant increases in the frequency of hemorrhagic stroke and intracranial hemorrhage were seen in the first three large studies of men treated with aspirin for primary prevention of MI,^{22–24} but such increases were not observed in the more recent HOT and PPP trials.^{25,26} One meta-analysis evaluating four of these primary prevention trials (BDT, PHS, TPT, and HOT trial) estimated the relative risk of hemorrhagic stroke to be 1.36 (95% CI, 0.88–2.1).³⁷ Another metaanalysis that included 14 secondary prevention and 2 primary prevention trials showed a significantly increased risk of hemorrhagic stroke (relative risk, 1.84; 95% CI, 1.24–2.74) and estimated

that an additional 12 hemorrhagic strokes may occur with aspirin use in 10,000 patients over three years.³⁸ However, this contrasts with the estimated 137 fewer MIs and 39 fewer ischemic strokes seen in 10,000 patients who received aspirin therapy over the same time. The increased risk of bleeding must be compared with the reduced risk of cardiovascular events (including ischemic stroke) when using aspirin for primary or secondary prevention and is especially important in patients receiving aspirin as primary prevention who have a 10-year CHD risk of 6–10%.

GI effects are the most common adverse effects of aspirin.³⁹ Most of the adverse effects (indigestion, nausea, heartburn, constipation) associated with long-term aspirin therapy are dose related. However, the risk of serious GI bleeding does not appear to be dose related. A meta-analysis of 24 randomized control trials showed the rate of GI hemorrhage to be 1.42% with placebo versus 2.47% with aspirin (odds ratio [OR], 1.68; 95% CI, 1.51–1.88).⁴⁰ Although patients in trials that used aspirin 50–162.5 mg daily had a lower risk of GI bleeding than did those receiving 300–1500 mg daily (ORs, 1.59 and 1.96, respectively), meta-regression analysis showed no relation between dose and risk. While minor GI adverse effects (e.g., dyspepsia) can be minimized by the use of enteric-coated or buffered formulations or with concomitant administration of histamine H₂-receptor antagonists, risk of serious GI hemorrhage is not reduced with these modalities.⁴¹ Misoprostol or proton-pump inhibitor therapy are the only concomitant agents shown to reduce the risk of serious NSAID-associated GI bleeding in high-risk individuals.^{41–43} Risk factors for NSAID-associated GI bleeding include history of GI ulcer or hemorrhage, age over 60 years, high-dosage NSAID therapy, concurrent use of corticosteroids, and concurrent use of anticoagulants.⁴¹ Concurrent use of other antiplatelet agents or the presence of thrombocytopenia increases risk of bleeding. Moreover, the very elderly (≥ 75 years) are at high risk for aspirin-associated adverse effects and have a higher risk of mortality with NSAID-associated GI ulcerations.

Alternative Antithrombotic Approaches

Clopidogrel or ticlopidine can be safely used in patients with a true aspirin allergy, but clopidogrel is preferred over ticlopidine because of its lower risk of severe hematologic toxicity. Clopidogrel has also demonstrated a reduced risk of cardiovascular events in certain populations. In one large outcome-based, double-blind trial of clopidogrel versus aspirin, patients with atherosclerotic vascular disease were randomized to receive either clopidogrel 75 mg daily or aspirin 325 mg daily.⁴⁴ The rate of the primary endpoint (a composite of ischemic stroke, MI, and vascular death) was lower with clopidogrel than aspirin (5.32% versus 5.83%) ($p = 0.043$). The RRR was modest (8.7%), and the absolute risk reduction was very small (0.5%). Nonetheless, clopidogrel is a reasonable alternative for aspirin-allergic patients with atherosclerotic vascular disease for secondary prevention of cardiovascular events. Warfarin may also be used as an alternative for patients who cannot tolerate aspirin.⁴⁵ However, patients receiving clopidogrel may have a lower risk of bleeding than do patients receiving warfarin. Outcomes data regarding combinations of aspirin with warfarin or aspirin with ximelagatran have shown fewer cardiovascular events in patients with a history of MI, but the risk

of major bleeding is increased with these combinations.^{46,47} Therefore, the role of combination antithrombotic therapy for the prevention of cardiovascular events is not well defined.

Controversial Issues

Concurrent administration of aspirin with certain NSAIDs (e.g., ibuprofen) has been associated with a blunting of the cardioprotective effects of aspirin.^{48,49} However, data from in vitro platelet aggregation studies and observational studies suggest that the intermittent use of NSAIDs or the use of selective COX-2 inhibitors (e.g., diclofenac, rofecoxib) may not alter aspirin's effects.⁵⁰ As prospective studies have not addressed the issue, this interaction should be considered speculative.

Approximately 5% of the U.S. population is believed to be resistant to the antiplatelet effects of aspirin based on platelet aggregation testing.⁵¹ While this phenomenon has been referred to as "aspirin resistance," it may be more appropriately referred to as a "variable response" to aspirin therapy. No clear definition of aspirin resistance has been established. Patients with cardiovascular disease and aspirin resistance are estimated to have a higher risk of cardiovascular events than those who are aspirin responsive.⁵¹ Patients with diabetes, heart failure, previous stroke, or coronary artery disease are believed to be at risk for aspirin resistance.^{28,52–55} While variable responses to aspirin have been demonstrated in a portion of these populations, platelet-aggregation testing to assess responsiveness to aspirin is not routinely recommended. The definitive implication of aspirin resistance on clinical outcomes is considered incomplete until prospective studies have properly evaluated this issue.

Summary

ASHP believes that patients at risk for CHD and without contraindications to aspirin therapy should use aspirin to prevent cardiovascular events. It is an effective, low-cost, and relatively safe but underutilized option to prevent cardiovascular events. Given the possible complications of long-term therapy, careful patient selection and increased public awareness of benefits and risks of aspirin therapy are warranted. ASHP acknowledges that the cardiovascular risk-reduction benefits of aspirin must always be weighed against the potential risk of major bleeding episodes (e.g., GI hemorrhage). For primary prevention, the benefits of aspirin therapy outweigh its risks in most patients with a 10-year risk of $\geq 10\%$ based on Framingham risk scores. The margin of benefit versus risk is lower for patients with a 10-year CHD risk of 6–10%, but these individuals may still be candidates for therapy. Despite conflicting data from post hoc analyses of diabetic patients in primary prevention studies, aspirin therapy should be recommended to patients with diabetes for the primary prevention of cardiovascular events. For secondary prevention, the benefits of aspirin therapy strongly outweigh the risks for most patients.

ASHP believes that clinicians need to be actively involved in educating health care professionals about the benefits of using aspirin for preventing MI. Patients with increased risk for CHD (10-year risk of at least 6% based on Framingham risk scores) should be educated to modify controllable risk factors for CHD (obesity, smoking, dyslipidemia, and hypertension) and view aspirin as a possible adjunct to, not a replacement for, these efforts. Well-controlled clinical trials are needed to determine the benefits and risks of aspirin

therapy in the very elderly, as well as the consequences of combining aspirin with nonselective NSAIDs.

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