

# Aspirin Use in Primary Care

## EVIDENCE REVIEW

### Healthy Hearts for Oklahoma (H2O)

The Oklahoma Cooperative for AHRQ's

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# Aspirin for Primary and Secondary Prevention

## Introduction

For more than a century, aspirin has been one of the most widely-used and widely-studied drugs in the physician's armamentarium. It is an inexpensive, easily-available agent with analgesic, anti-inflammatory, and antipyretic effects. Aspirin also has anti-platelet properties, which is the basis for its use in patients at risk for, or who have already experienced, cardiovascular diseases, which are the leading causes of death in the U.S.<sup>1</sup>

Prescribing this classic drug, or guiding patients in their over-the-counter use of this drug, is not as straightforward as it might seem. Patients vary widely in the benefits they may receive from aspirin therapy, in their vulnerabilities to the risks posed by aspirin, in their use of other medications that may directly or indirectly alter aspirin's risk/benefit profile, and in their comorbidities and past medical histories, all of which complicate the decision-making process.

Primary care clinicians are uniquely positioned to improve the health and longevity of their patients by prescribing aspirin appropriately. A study by the United States Preventive Services Task Force (USPSTF) evaluating 24 clinical preventive services found that advising at-risk adults to consider taking daily aspirin was the most cost-effective preventive measure available for physicians.<sup>2</sup> The study estimated that if 90% of those who should be taking aspirin were doing so, an additional 45,000 lives would be saved each year.<sup>2</sup>

Despite this potential benefit, less than half of those who should be taking aspirin regularly are actually taking it.<sup>3</sup> Conversely, some people are taking daily aspirin who should *not* be taking it because they have contraindications that have not been recognized or revealed. Primary care providers can make a difference by identifying such patients and educating them about appropriate use of aspirin.<sup>4</sup> Determining patients' CVD risk and discussing appropriate aspirin use with them should be a priority for all family physicians.

## Aspirin mechanisms of action

Attempts in the late 19th century to make salicylic acid less bitter-tasting led to the creation of acetylsalicylic acid—the addition of an acetyl group to the molecule. This change gave the compound a new property: the acetyl group could be transferred to the active site of the enzyme cyclooxygenase (COX), irreversibly inhibiting its function and thereby blocking prostaglandin production.<sup>5</sup> This is what gives aspirin its analgesic, anti-inflammatory, and antipyretic properties. In platelets, however, the COX-1 isoform produces thromboxane A<sub>2</sub>, which aids in platelet aggregation.<sup>5</sup> By blocking COX-1 in platelets, aspirin inhibits platelet aggregation and can reduce thrombosis.

Aspirin permanently blocks the COX-1 receptor, so its effects in platelets, which lack a nucleus and cannot make new COX-1, lasts several days after a single dose. Aspirin's antiplatelet effects account for its ability to reduce the risk of arterial vascular thrombotic events such as myocardial

infarction (MI), stroke, and, to a lesser extent, venous thrombotic events. But aspirin's antiplatelet effects are also responsible for the risks that aspirin can pose, primarily gastrointestinal bleeding and hemorrhagic stroke.

The clinical challenge of prescribing aspirin lies in determining when the potential benefits of aspirin's antiplatelet effects outweigh the potential risks.

## Assessing patients for aspirin-associated risks

The primary adverse effect of aspirin is GI bleeding, the risk of which is dose dependent. The increased risk of GI bleeding exists even with low doses of aspirin. Doses < 100 mg daily increase the risk of GI bleeding 2-fold relative to patients not on aspirin, while higher doses ( $\geq$  300mg) increase the risk 4-fold.<sup>6</sup> In contrast, the benefit of aspirin is not dose-dependent and in many cases low-dose aspirin (81 mg) is best.

The risk of GI bleeding increases with age, and men have a higher risk of bleeding compared to women. Patients concomitantly taking NSAIDs or other antiplatelets and patients with peptic ulcer disease have a higher risk of GI bleeding when taking aspirin.

Prevention of GI bleeding is important in high-risk individuals who would benefit from the cardiovascular benefits of aspirin. Buffered or enteric-coated aspirin does not reduce the risk of GI bleeding compared to plain tablets.<sup>7</sup> In patients with healed peptic ulcer disease, restarting aspirin along with a proton pump inhibitor (PPI) decreases the risk of recurrent bleeding. Patients treated with aspirin and a PPI have lower bleeding rates than patients treated with clopidogrel alone.<sup>8</sup> A PPI should also be prescribed for patients with a history of GI bleeding, those taking dual antiplatelet therapy, and those concomitantly taking anticoagulant medications. Eradication of *Helicobacter pylori* infection in affected patients also reduces the risk of aspirin-induced bleeding.<sup>9</sup>

Aspirin use may also increase the risk for hemorrhagic stroke. In the 2002 Antithrombotic Trialists Collaborative (ATC) meta-analysis, antiplatelet use among high-risk patients was associated with an increase in fatal or non-fatal hemorrhagic stroke, but a decrease in fatal or non-fatal ischemic stroke.<sup>10</sup> Taken as a whole, the absolute risks were smaller than the benefits in all categories of patients studied, and the overall risk of stroke was reduced significantly in patients on antiplatelet therapy.<sup>10</sup>

# Secondary prevention

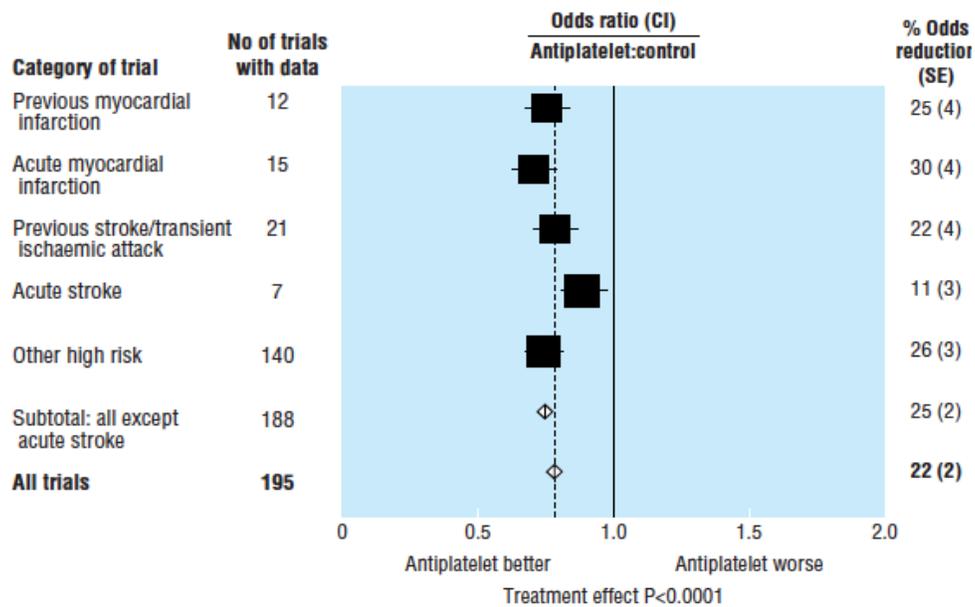
## Review of the evidence

The large benefits of aspirin for secondary prevention were made clear by the ATC meta-analysis.<sup>11</sup> This seminal publication combined data from 287 studies including 135,000 patients with acute or prior vascular disease (Figure 1). It found that serious vascular events (non-fatal MI, non-fatal stroke, cardiovascular death) were significantly reduced among patients receiving aspirin compared to placebo (10.7% versus 13.2%,  $p < .0001$ ).

The meta-analysis showed that, among these high risk patients, allocation to antiplatelet therapy reduced non-fatal myocardial infarction (MI) by one third, non-fatal stroke by one quarter, and cardiovascular mortality by one sixth, with no apparent adverse impact on death from other causes.<sup>11</sup> Non-fatal stroke includes both ischemic and hemorrhagic stroke. The beneficial effect of antiplatelets was seen among all sub-categories of high-risk patients. Compared to patients not treated with anti-platelets, the following effects were observed:

- Patients with prior myocardial infarction treated for just over 2 years had a 25% reduction in major vascular events, including a small but significant decrease in non-fatal stroke. The excess risk of major extracranial bleeding was 1 per 1000 treated patients per year
- Patients with prior stroke or TIA treated for almost 2.5 years had a 22% reduction in major vascular events that was largely driven by a decrease in non-fatal stroke. Treatment with antiplatelets resulted in 1-2 excess major extracranial bleeding events per 1,000 patients per year
- Other high risk patients also benefited from antiplatelet use. Patients with symptomatic PAD had a 23% reduction in major vascular events. Similar effects were observed among patients with coronary artery disease, including stable and unstable angina.

**Figure 1. Proportional effects of antiplatelet therapy on serious vascular events<sup>11</sup>**



Proportional effects of antiplatelet therapy on vascular events (myocardial infarction, stroke, or vascular death) in five main high risk categories. Stratified ratio of odds of an event in treatment groups to that in control groups is plotted for each group of trials (black square) along with its 99% confidence interval (horizontal line). Meta-analysis of results for all trials (and 95% confidence interval) is represented by an open diamond.

## Clopidogrel in secondary prevention

The CAPRIE trial evaluated clopidogrel as an alternative to aspirin for secondary prevention in high-risk patients.<sup>12</sup> More than 19,000 patients with recent MI, recent stroke, or peripheral arterial disease (PAD) were randomized to clopidogrel 75mg daily or aspirin 325mg daily. By the end of follow-up, clopidogrel had a small but significant advantage over aspirin in reducing the risk of serious vascular events (5.3% vs. 5.8%,  $p=0.04$ ). Rates of intracranial hemorrhage were low but similar between the two groups, however gastrointestinal bleeding was lower in the clopidogrel group. Subsequently the CHARISMA trial studied aspirin (75-162 mg daily) plus clopidogrel (75mg daily) compared to aspirin alone (75-162mg daily) in high-risk patients.<sup>13</sup> The combination antiplatelet therapy was not better than aspirin alone and resulted in higher rate of bleeding.

## Dipyridamole in secondary prevention

Dipyridamole has both vasodilator and antiplatelet properties. It has been studied in combination with aspirin in clinical trials designed to assess efficacy in stroke prevention. A Cochrane review of 29 randomized trials involving 23,019 patients confirmed the superiority of the combination of aspirin and dipyridamole over aspirin alone for prevention of vascular events in patients with a history of TIA or stroke but found no evidence of a benefit of the combination in studies involving patients with a history of coronary or peripheral arterial disease or in other high-risk patients.<sup>14</sup> Combination treatment of dipyridamole and aspirin compared with aspirin had an RR of 1.03 (95% CI, 0.87 to 1.22) for vascular death and an RR of 0.90 (95% CI, 0.80 to 1.00) for vascular events.<sup>14</sup>

## Aspirin dosing for secondary prevention

The optimal dose of aspirin will maximize preventive efficacy and minimize bleeding risk. Several trials comparing lower dose (<75 mg daily) with higher doses (≥75 mg daily) in high-risk patients have not found any difference in efficacy, although few studies have examined the effect of doses < 75 mg daily. In the ATC meta-analysis, the proportional reduction in serious vascular events was 32% with aspirin 75-150mg daily and 26% with aspirin 160-325mg daily.<sup>10</sup> Rates of major extracranial bleeding were similar across all doses < 325mg daily. For most patients, a daily aspirin dose between 81-162mg will optimize the benefit-risk tradeoff for secondary prevention.

**Table 1. Summary guidelines for antiplatelet therapy for secondary prevention**

Condition	Definition	Aspirin	Other antiplatelet regimens
<b>Stable CAD</b> <sup>15,16</sup>	Prior MI, prior coronary revascularization, coronary stenosis > 50%, or cardiac ischemia on non-invasive testing	Aspirin 75-162mg daily	Clopidogrel 75mg daily*
<b>Prior stroke or TIA</b> <sup>17</sup>	Non-cardioembolic ischemic stroke or TIA	Aspirin 50-325mg daily	Aspirin 25mg and dipyridamole 200mg BID**; Clopidogrel 75mg daily*; Aspirin and clopidogrel if given within 24 hours of stroke and continued up to 21 days
<b>Symptomatic PAD</b> <sup>18</sup>	Intermittent claudication, critical limb ischemia, lower extremity revascularization or amputation	Aspirin 75-325mg daily	Clopidogrel 75mg daily*

\* Consider clopidogrel if aspirin intolerant or allergic; \*\* Alternative first line therapy

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**BOTTOM LINE: Strong evidence shows that aspirin for secondary prevention is effective in patients at risk for recurrent occlusive vascular events such as MI, ischemic stroke, unstable or stable angina, previous MI, stroke or cerebral ischemia, or PAD. Most patients should be treated with aspirin alone. Clopidogrel alone should be used in cases of aspirin allergy or intolerance.**

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# Primary prevention

## Review of the evidence

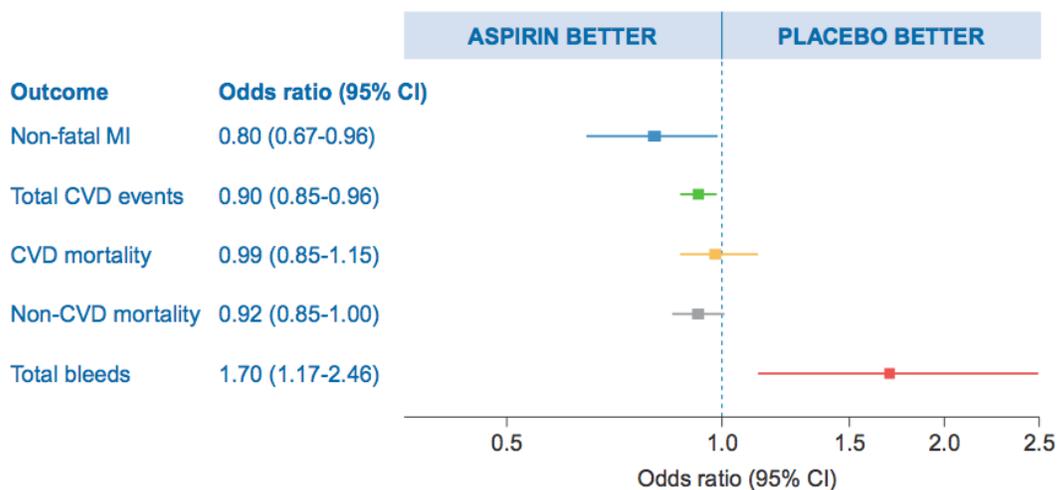
The benefits of aspirin across a wide range of secondary prevention trials led, in the 1980s, to trials of aspirin for the prevention of first MI or ischemic stroke among asymptomatic individuals (primary prevention). The British Doctors' Trial<sup>19</sup> and the Physician's Health Study,<sup>20</sup> among others, found reductions in major vascular events that were smaller than aspirin's effect as secondary prevention.

A 2012 meta-analysis of nine large clinical trials involving 102,621 patients evaluated the role of aspirin for the primary prevention of cardiovascular disease (i.e., in patients who have not yet had a cardiovascular event) (Figure 2).<sup>21</sup> This study, which was an expansion of an earlier meta-analysis,<sup>22</sup> found that aspirin in primary prevention reduced total CVD events by 10% (OR 0.90; 95% CI 0.85-0.96), driven primarily by reduction in nonfatal MI (OR 0.80; 95% CI 0.67-0.96). Aspirin did not, however, bring about significant reductions in CVD death or all-cause mortality, while it did cause an increased risk of bleeding.<sup>21</sup>

Other key points from the 2012 meta-analysis:

- Although absolute rates of major bleeding incidents were low, aspirin was associated with a 30% increase in such events.
- The number needed to treat (NNT) to avoid 1 nonfatal MI event over 6 years was 162 (NNT was 120 to avert 1 CVD event over the same period). In comparison, the NNT for nonvascular death was 292.
- At least 1 nontrivial bleeding event was caused for every 73 persons treated with aspirin for approximately 6 years.
- The 10-year absolute risk for cardiovascular events in these studies was < 5%.

**Figure 2. Effect of primary prevention aspirin on cardiovascular outcomes and bleeding<sup>21</sup>**



## Gender and aspirin

The Women's Health Study (WHS), published in 2005, demonstrated a significant decrease in risk of first stroke but not non-fatal MI or cardiovascular death among its mostly younger participants.<sup>23</sup> A subgroup analysis of women older than 65 years showed that aspirin reduced the risk of non-fatal MI to a similar degree as in other studies. Meta-analyses of the aspirin trials have shown no difference in response to aspirin between men and women.<sup>10,21</sup>

## Diabetes and aspirin

Diabetes is associated with a 2 to 4-fold increase in the risk of major cardiovascular events compared to age- and sex-matched controls.<sup>24</sup> Because of this, many previous guidelines encouraged the use of aspirin by all patients with diabetes. Recent meta-analyses show that aspirin provides a similar level of benefit to patients with diabetes as it does for patients without this disease for secondary prevention.<sup>16,10,25,26</sup>

Two recent large studies have examined the role of aspirin in primary prevention among diabetics with otherwise low risk of having a cardiovascular event. The 2014 Japanese Primary Prevention Project compared 100 mg/d of coated aspirin to no aspirin among 14,464 people, ages 60 to 85 with high blood pressure, high cholesterol or diabetes, but without coronary or cerebral artery disease. After five years, the two groups had no significant differences in heart attacks or strokes.<sup>27</sup> The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial also found no evidence to support the use of aspirin in primary prevention for those with diabetes and asymptomatic peripheral arterial disease.<sup>28</sup>

The weight of current evidence thus suggests that diabetic patients at very low risk of vascular events should not take aspirin for prevention, even at a low dose.<sup>5</sup> The American Diabetic Association recommends that low-dose aspirin (75-162mg daily) only be used by adults with diabetes who are at increased CVD risk (10-year risk of CVD over 10%) and who are *not* at increased risk of bleeding.<sup>24</sup> This recommendation would include most men over 50 years and women over 60 years who have one or more risk factors, including smoking, hyperlipidemia, hypertension, family history of premature CVD, or albuminuria.

## Risk assessment

The balance between preventing thrombotic events and causing bleeding with aspirin critically depends on the absolute thrombotic versus hemorrhagic risk of the patient. Thus, in individuals at low risk for vascular occlusion, the very small reduction in cardiovascular events with low-dose aspirin is probably offset by bleeding complications. In contrast, in patients at high risk of cardiovascular or cerebrovascular complications, the substantial absolute benefit of aspirin prophylaxis clearly outweighs the harm.

In primary prevention, the evidence from randomized, controlled trials shows conclusive benefits on preventing MI and stroke, but the data on CVD death remain inconclusive. Based on the risk of bleeding events when aspirin is used for secondary prevention, the benefits of primary prevention with aspirin outweigh the risks only when the patient's risk of a cardiovascular event reaches 6 to 10 percent over 10 years.

The USPSTF recommends prescribing aspirin for primary prevention in patients in whom the benefit of preventing a vascular event is greater than the risk of bleeding. Consistent with these guidelines, we recommend assessing cardiovascular and bleeding risk for men over the age of 45 years and women over the age of 55 years and calculating the net benefit of using aspirin for primary prevention.

### Cardiovascular risk

We recommend using a validated tool for calculating 10-year risk of cardiovascular disease. The 2009 USPSTF guideline specifically recommends calculating the 10-year risk of MI in men and 10-year risk of stroke in women.<sup>1</sup> The draft version of a pending update of the USPSTF guidelines advocates calculating 10-year risk for men and women using the American College of Cardiology/ American Heart Association pooled risk equations, which estimates risk of 10-year “hard” CV endpoints, including CV death, MI, or stroke.<sup>29</sup> The pooled risk equations calculator may overestimate CV risk in some subgroups and has not yet been validated for use in assessing benefit of aspirin for primary prevention. See Table 2 for a summary of tools used to calculate CV risk.

**Table 2. USPSTF-recommended online risk calculators**

Online Risk Calculators	
<b>10 year risk of combined cardiovascular event</b>	ACC/AHA ASCVD calculator: <a href="http://tools.cardiosource.org/ASCVD-Risk-Estimator/">http://tools.cardiosource.org/ASCVD-Risk-Estimator/</a> Reynolds risk score: <a href="http://www.reynoldsriskscore.org">http://www.reynoldsriskscore.org</a>
<b>10 year risk of MI</b>	Framingham risk calculator: <a href="http://cvdrisk.nhlbi.nih.gov/calculator.asp">http://cvdrisk.nhlbi.nih.gov/calculator.asp</a>
<b>10 year risk of stroke</b>	UCLA risk calculator: <a href="http://stroke.ucla.edu/#calculaterisk">http://stroke.ucla.edu/#calculaterisk</a>

### Bleeding Risk

Aspirin use is associated with significantly increased bleeding risk in patients with the following risk factors: concomitant NSAID use, upper gastrointestinal tract pain, and gastrointestinal ulcers.<sup>1</sup> The decision to initiate aspirin for primary prevention in these patients should be carefully balanced with bleeding risk after a discussion between provider and patient. No validated online or electronic calculator is yet available to assess bleeding risk in the context of primary prevention with aspirin. Estimated population average risks for aspirin-associated GI bleeding by age and gender are presented in Table 3.

**Table 3: Major 10-year bleeding risk with aspirin treatment<sup>30</sup>**

Age	Risk of serious upper GI complications over 10 years	
	Men	Women
< 60	8/1,000	4/1,000
60–69	24/1,000	12/1,000
70–79	36/1,000	18/1,000

### Calculating net benefit

The level at which cardiovascular risk is high enough that aspirin treatment should reduce the number of CV events more than it would increase the number of serious bleeding events is summarized in Table 4. Table 4 reflects the 2009 USPSTF guidelines; as discussed above, sex differences in response to aspirin, especially in older adults, have likely been previously overestimated.

These calculations assume that patients are not taking concomitant NSAIDs, do not have upper GI pain, and do not have a history of GI ulcer. Shared decision making is strongly encouraged for patients whose risk is close these 10-year risk levels, especially if bleeding risk factors are present. The recommendation to take aspirin becomes stronger as the patient’s 10-year risk increases above these thresholds.

**Table 4: Risk level at which CVD events prevented (benefit) exceeds GI harms<sup>1</sup>**

Favorable Net Benefit from Aspirin Use			
Age	10-year MI risk (men)	Age	10-year stroke risk (women)
45–59	≥ 4 %	55–59	≥ 3 %
60–69	≥ 9 %	60–69	≥ 8 %
70–79	≥ 12 %	70–79	≥ 11 %

## Guideline summary

Table 5. 2009 USPSTF guidelines for aspirin use for primary prevention

Population	Recommendation
Men, Age 45-79	Use low-dose aspirin (75-100mg/day) when the potential benefit due to reduction in MI outweighs potential harm due to increase in major gastrointestinal bleeding.
Women, age 55-79	Use low-dose aspirin (75-100mg/day) when the potential benefit due to reduction in ischemic stroke outweighs potential harm due to increase in major gastrointestinal bleeding.
Men and women, 80 years and older	The current evidence is insufficient to assess the balance of benefits and harms of aspirin for primary cardiovascular disease prevention
Women younger than 55 and men younger than 45 years	Routine aspirin use is not recommended for primary cardiovascular disease prevention

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**BOTTOM LINE:** Use three steps in assessing patients for the appropriateness of aspirin for primary prevention: calculate CV risk; consider bleeding risk; estimate the net potential benefit for the patient. The principal cardiovascular effect for aspirin for primary prevention is on nonfatal MI and stroke, with no conclusive benefit with regards to fatal MI, fatal stroke, or overall cardiovascular death. The use of aspirin increases the risk of bleeding, hence the decision to use aspirin for primary prevention needs to be individualized by the physician after a thoughtful discussion with the patient. Aspirin should not be routinely recommended for primary prevention for all patients unless future trials show a clear benefit.

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