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Aspirin: Its risks, benefits, and optimal use in preventing cardiovascular events

ABSTRACT

Aspirin has a well-established role in preventing adverse events in patients with known cardiovascular disease. However, its benefit in patients without a history of cardiovascular disease is not as clear, particularly in people with diabetes, in women, and in the elderly. Recent studies have provided insight into the risks of aspirin use, particularly bleeding, compared with its benefits in these subgroups.

KEY POINTS

Aspirin is as beneficial in low doses (eg, 81 mg daily) as it is in standard doses (325 mg) and poses less risk of gastrointestinal bleeding, although the bleeding risk is still twice as high as without aspirin.

Since the absolute reduction in heart attacks and strokes is less in primary prevention than in secondary prevention, the risk of bleeding may for some groups outweigh the benefit, and the decision to use aspirin must be more individualized.

Whether to prescribe aspirin for primary prevention depends on the combination of the individual patient's sex, age, and 10-year risk of myocardial infarction (in men) or of stroke (in women).

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A 57-YEAR-OLD WOMAN with no history of cardiovascular disease comes to the clinic for her annual evaluation. She does not have diabetes mellitus, but she does have hypertension and chronic osteoarthritis, currently treated with acetaminophen. Additionally, she admits to active tobacco use. Her systolic blood pressure is 130 mm Hg on therapy with hydrochlorothiazide. Her electrocardiogram demonstrates left ventricular hypertrophy. Her low-density lipoprotein (LDL) cholesterol level is 140 mg/dL, and her high-density lipoprotein (HDL) cholesterol level is 50 mg/dL. Should this patient be started on aspirin therapy?

Acetylsalicylic acid (aspirin) is an analgesic, antipyretic, and anti-inflammatory agent, but its more prominent use today is as an antithrombotic agent to treat or prevent cardiovascular events. Its antithrombotic properties are due to its effects on the enzyme cyclooxygenase. However, cyclooxygenase is also involved in regulation of the gastric mucosa, and so aspirin increases the risk of gastrointestinal bleeding.

Approximately 50 million people take aspirin on a daily basis to treat or prevent cardiovascular disease.¹ Of these, at least half are taking more than 100 mg per day,² reflecting the general belief that, for aspirin dosage, “more is better”—which is not true.

Additionally, recommendations about the use of aspirin were based on studies that included relatively few members of several important subgroups, such as people with diabetes without known cardiovascular disease, women, and the elderly, and thus may not re-

flect appropriate indications and dosages for these groups.

Here, we examine the literature, outline an individualized approach to aspirin therapy, and highlight areas for future study.

HISTORY OF ASPIRIN USE IN CARDIOVASCULAR DISEASE

- 1700s—Willow bark is used as an analgesic.
- 1897—Synthetic aspirin is developed as an antipyretic and anti-inflammatory agent.
- 1974—First landmark trial of aspirin for secondary prevention of myocardial infarction.³
- 1982—Nobel Prize awarded for discovery of aspirin mechanism.
- 1985—US Food and Drug Administration approves aspirin for the treatment and secondary prevention of acute myocardial infarction.
- 1998—The Second International Study of Infarct Survival (ISIS-2) finds that giving aspirin to patients with myocardial infarction within 24 hours of presentation leads to a significant reduction in vascular deaths.⁴

Ongoing uncertainties

Aspirin now carries a class I indication for all patients with suspected myocardial infarction. Since there are an estimated 600,000 new coronary events and 325,000 recurrent ischemic events per year in the United States,⁵ the need for aspirin will continue to remain great. It is also approved to prevent and treat stroke and in patients with unstable angina.

However, questions continue to emerge about aspirin's dosing and appropriate use in specific populations. The initial prevention trials used a wide range of doses and, as mentioned, included few women, few people with diabetes, and few elderly people. The uncertainties are especially pertinent for patients without known vascular disease, in whom the absolute risk reduction is much less, making the assessment of bleeding risk particularly important. Furthermore, the absolute risk-to-benefit assessment may be different in certain populations.

Guidelines on the use of aspirin to prevent cardiovascular disease (TABLE 1)^{6–10} have

TABLE 1

Summary of aspirin guidelines for preventing cardiovascular disease and stroke

Patients with documented coronary artery disease

(American Heart Association/American College of Cardiology^{6,7})

Aspirin 75–162 mg daily is recommended in all patients with coronary artery disease

Aspirin doses of 162 mg or higher offer no additional benefit in preventing cardiovascular disease

General population without known history of coronary artery disease or stroke

(United States Preventive Services Task Force⁸)

Encourage aspirin 75 mg daily when the potential cardiovascular disease benefit outweighs the risk of gastrointestinal bleeding

Current evidence is insufficient to assess risk vs benefit of aspirin use for cardiovascular disease prevention in patients age 80 and older

People with diabetes without history of myocardial infarction or stroke

(American Diabetes Association/ American Heart Association/American College of Cardiology⁹)

Aspirin 75–162 mg daily may be considered in people with diabetes with a 10-year cardiovascular disease risk of at least 10% and perhaps as low as 5%

Aspirin should not be recommended for cardiovascular disease prevention for men under age 50 and women under age 60 with 10-year cardiovascular disease risk < 5%

Women without history of coronary artery disease or stroke

(American Heart Association¹⁰)

Aspirin 81 mg daily or 100 mg every other day is recommended in women at high risk or women age 65 and older if blood pressure is controlled and benefit for stroke or myocardial infarction is greater than risk of bleeding

Aspirin therapy in diabetic women is reasonable unless contraindicated

evolved to take into account these possible disparities, and studies are taking place to further investigate aspirin use in these groups.

ASPIRIN AND GASTROINTESTINAL BLEEDING

Aspirin's association with bleeding, particularly gastrointestinal bleeding, was recognized early as a use-limiting side effect. With or without aspirin, gastrointestinal bleeding

TABLE 2

Risk factors associated with gastrointestinal bleeding

| |
|--|
| Age |
| History of ulcer disease |
| Concurrent use of nonsteroidal anti-inflammatory drugs |
| <i>Helicobacter pylori</i> infection |
| Alcohol use |
| Concomitant use of other anticoagulants |

is a common cause of morbidity and death, with an incidence of approximately 100 per 100,000 bleeding episodes in adults per year for upper gastrointestinal bleeding and 20 to 30 per 100,000 per year for lower gastrointestinal bleeding.^{11,12}

The standard dosage (ie, 325 mg/day) is associated with a significantly higher risk of gastrointestinal bleeding (including fatal bleeds) than is 75 mg.¹³ However, even with lower doses, the risk of gastrointestinal bleeding is estimated to be twice as high as with no aspirin.¹⁴

And here is the irony: studies have shown that higher doses of aspirin offer no advantage in preventing thrombotic events compared with lower doses.¹⁵ For example, the Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events/Organization to Assess Strategies for Ischemic Stroke Syndromes study reported a higher rate of gastrointestinal bleeding with standard-dose aspirin therapy than with low-dose aspirin, with no additional cardiovascular benefit with the higher dose.¹⁶

Furthermore, several other risk factors increase the risk of gastrointestinal bleeding with aspirin use (TABLE 2). These risk factors are common in the general population but were not necessarily represented in participants in clinical trials. Thus, estimates of risk based on trial data most likely underestimate actual risk in the general population, and therefore, the individual patient's risk of gastrointestinal bleeding, based on these and other factors, needs to be taken into consideration.

ASPIRIN IN PATIENTS WITH CORONARY ARTERY DISEASE

Randomized clinical trials have validated the benefits of aspirin in secondary prevention of cardiovascular events in patients who have had a myocardial infarction. Patients with coronary disease who withdraw from aspirin therapy or otherwise do not adhere to it have a risk of cardiovascular events three times higher than those who stay with it.¹⁷

Despite the strong data, however, several issues and questions remain about the use of aspirin for secondary prevention.

Bleeding risk must be considered, since gastrointestinal bleeding is associated with a higher risk of death and myocardial infarction in patients with cardiovascular disease.¹⁸ Many patients with coronary disease are on more than one antiplatelet or anticoagulant therapy for concomitant conditions such as atrial fibrillation or because they underwent a percutaneous intervention, which further increases the risk of bleeding.

This bleeding risk is reflected in changes in the most recent recommendations for aspirin dosing after percutaneous coronary intervention. Earlier guidelines advocated use of either 162 or 325 mg after the procedure. However, the most recent update (in 2011) now supports 81 mg for maintenance dosing after intervention.⁷

Patients with coronary disease but without prior myocardial infarction or intervention. Current guidelines recommend 75 to 162 mg of aspirin in all patients with coronary artery disease.⁶ However, this group is diverse and includes patients who have undergone percutaneous coronary intervention, patients with chronic stable angina, and patients with asymptomatic coronary artery disease found on imaging studies. The magnitude of benefit is not clear for those who have no symptoms or who have stable angina.

Most of the evidence supporting aspirin use in chronic angina came from a single trial in Sweden, in which 2,000 patients with chronic stable angina were given either 75 mg daily or placebo. Those who received aspirin had a 34% lower rate of myocardial infarction and sudden death.¹⁹

A substudy of the Physicians' Health

For secondary prevention, the benefits of aspirin clearly outweigh the risks

TABLE 3

Primary prevention trials of aspirin therapy

| Trial | Year | Population | Age (years) | Dosing | Follow-up (years) | Findings |
|----------------|-------------|--|--------------------|------------------------|--------------------------|---|
| BDT | 1988 | Male physicians | Most < 70 | 300 or 500 mg daily | 6 | No difference in myocardial infarction, 50% reduction in transient ischemic attack, nonsignificant reduction in vascular and nonvascular deaths |
| PHS | 1989 | Male physicians | 53 | 325 mg every other day | 5 | 44% reduction in risk of myocardial infarction |
| HOT | 1998 | Hypertensive patients | 62 | 75 mg daily | 3.8 | Major cardiovascular events reduced by 15% and myocardial infarction reduced by 36% |
| TPT | 1998 | Men without prior cardiovascular disease | 58 | 75 mg daily | 6.7 | Reduced composite end point of coronary death and fatal and nonfatal myocardial infarction by 23% |
| PPP | 2001 | Patients with at least one cardiovascular risk factor | 64 | 100 mg daily | 3.6 | Significant reduction in cardiovascular deaths and events |
| WHS | 2005 | Healthy women | 55 | 100 mg every other day | 10.1 | Significant reduction in major cardiovascular events, ischemic stroke, and myocardial infarction in women over age 65 |
| JPAD | 2008 | People with diabetes without atherosclerotic disease | 65 | 81 mg or 100 mg daily | 4.37 | No significant reduction in cardiovascular events |
| POPADAD | 2008 | People with diabetes with asymptomatic peripheral arterial disease | 60 | 100 mg daily | 6.7 | No significant reduction in cardiovascular events |
| AAA | 2010 | Men and women with abnormal ankle-brachial index | 62 | 100 mg daily | 8.2 | No significant reduction in vascular events |

AAA = Aspirin for Asymptomatic Atherosclerosis³¹; BDT = British Doctors' Trial²³; HOT = Hypertension Optimal Treatment²⁷;

JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes³⁰; PHS = Physicians' Health Study²⁴;

POPADAD = Prevention and Progression of Arterial Disease and Diabetes Trial²⁹; PPP = Primary Prevention Project²⁶; TPT = Thrombosis Prevention Trial²⁵;

WHS = Women's Health Study.²⁸

Study, with fewer patients, also noted a significant reduction in the rate of first myocardial infarction. The dose of aspirin in this study was 325 mg every other day.²⁰

In the Women's Health Initiative Observational Study, 70% of women with stable cardiovascular disease taking aspirin were tak-

ing 325 mg daily.²¹ This study demonstrated a significant reduction in the cardiovascular mortality rate, which supports current guidelines, and found no difference in outcomes with doses of 81 mg compared with 325 mg.²¹ This again corroborates that low-dose aspirin is preferential to standard-dose aspirin in

women with cardiovascular disease.

These findings have not been validated in larger prospective trials. Thus, current guidelines for aspirin use may reflect extrapolation of aspirin benefit from higher-risk patients to lower-risk patients.

Nevertheless, although the debate continues, it has generally been accepted that in patients who are at high risk of vascular disease or who have had a myocardial infarction, the benefits of aspirin—a 20% relative reduction in vascular events²²—clearly outweigh the risks.

■ ASPIRIN FOR PRIMARY PREVENTION

Assessing risk vs benefit is more complex when considering populations without known cardiovascular disease.

Only a few studies have specifically evaluated the use of aspirin for primary prevention (TABLE 3).^{23–31} The initial trials were in male physicians in the United Kingdom and the United States in the late 1980s and had somewhat conflicting results. A British study did not find a significant reduction in myocardial infarction,²³ but the US Physician's Health Study study did: the relative risk was 0.56 (95% confidence interval 0.45–0.70, $P < .00001$).²⁴ The US study had more than four times the number of participants, used different dosing (325 mg every other day compared with 500 or 300 mg daily in the British study), and had a higher rate of compliance.

Several studies over the next decade demonstrated variable but significant reductions in cardiovascular events as well.^{25–27}

A meta-analysis of primary prevention trials of aspirin was published in 2009.²² Although the relative risk reduction was similar in primary and secondary prevention, the absolute risk reduction in primary prevention was not nearly as great as in secondary prevention.

These findings are somewhat difficult to interpret, as the component trials included a wide spectrum of patients, ranging from healthy people with no symptoms and no known risk factors to those with limited risk factors. The trials were also performed over several decades during which primary prevention strategies were evolving. Additionally, most of the participants were middle-aged, nondiabetic men, so the results may not nec-

essarily apply to people with diabetes, to women, or to the elderly. Thus, the pooled data in favor of aspirin for primary prevention may not be as broadly applicable to the general population as was once thought.

Aspirin for primary prevention in women

Guidelines for aspirin use in primary prevention were initially thought to be equally applicable to both sexes. However, concerns about the relatively low number of women participating in the studies and the possible mechanistic differences in aspirin efficacy in men vs women prompted further study.

A meta-analysis of randomized controlled trials found that aspirin was associated with a 12% relative reduction in the incidence of cardiovascular events in women and 14% in men. On the other hand, for stroke, the relative risk reduction was 17% in women, while men had no benefit.³²

Most of the women in this meta-analysis were participants in the Women's Health Study, and they were at low baseline risk.²⁸ Although only about 10% of patients in this study were over age 65, this older group accounted for most of the benefit: these older women had a 26% risk reduction in major adverse cardiovascular events and 30% reduction in stroke.

Thus, for women, aspirin seems to become effective for primary prevention at an older age than in men, and the guidelines have been changed accordingly (FIGURE 1).

More women should be taking aspirin than actually are. For example, Rivera et al³³ found that only 41% of eligible women were receiving aspirin for primary prevention and 48% of eligible women were receiving it for secondary prevention.

People with diabetes

People with diabetes without overt cardiovascular disease are at higher risk of cardiovascular events than age- and sex-matched controls.³⁴ On the other hand, people with diabetes may be more prone to aspirin resistance and may not derive as much cardiovascular benefit from aspirin.

Early primary prevention studies included few people with diabetes. Subsequent meta-analyses of trials that used a wide range of aspi-

Elderly patients are at higher risk of gastrointestinal bleeding than younger patients

Algorithm for aspirin use for secondary and primary prevention

FOR SECONDARY PREVENTION, give aspirin if the patient has:

Prior myocardial infarction, stroke, or ischemic limb^{45–47}

Documented atherosclerosis in the coronary, cerebrovascular, or peripheral arteries

FOR PRIMARY PREVENTION, balance risks and benefits of aspirin

In men, considerations include⁸:

Aspirin is effective at preventing myocardial infarction
Aspirin increases risk of gastrointestinal bleeding and hemorrhagic stroke

Assess risk of myocardial infarction
(<http://hp2010.nhlbi.nih.net/atpiiii/calculator.asp>);
give aspirin if:
Age 45–49 and 10-year risk $\geq 4\%$
Age 60–69 and 10-year risk $\geq 9\%$
Age 70–79 and 10-year risk $\geq 12\%$

In women, considerations include⁸:

Aspirin is effective at preventing ischemic stroke
Aspirin has smaller effect on the risk of gastrointestinal bleeding than in men and no apparent effect on hemorrhagic stroke

Assess risk of stroke
(www.westernstroke.org/PersonalStrokeRisk1.xls);
give aspirin if:
Age 55–59 and 10-year risk $\geq 3\%$
Age 60–69 and 10-year risk $\geq 8\%$
Age 70–79 and 10-year risk $\geq 11\%$

FIGURE 1

rin doses found a relative risk reduction of 9%, which was not statistically significant.^{9,35,36}

But there is some evidence that people with diabetes, with³⁷ and without²² coronary disease, may be at higher inherent risk of bleeding than people without diabetes. Although aspirin may not necessarily increase the risk of bleeding in diabetic patients, recent data suggest no benefit in terms of a reduction in vascular events.³⁸

The balance of risk vs benefit for aspirin in this special population is not clear, although some argue that these patients should be treated somewhere on the spectrum of risk between primary and secondary prevention.

The US Preventive Services Task Force did not differentiate between people with or without diabetes in its 2009 guidelines for aspirin for primary prevention.⁸ However, the debate is reflected in a change in 2010 American College of Cardiology/American Diabetes Association guidelines regarding aspirin use in people with diabetes without known cardiovascular disease.³⁹ As opposed to earlier recommendations from these organizations in favor of aspirin for all people with diabetes regardless of 10-year risk, current recommen-

dations advise low-dose aspirin (81–162 mg) for diabetic patients without known vascular disease who have a greater than 10% risk of a cardiovascular event and are not at increased risk of bleeding.

These changes were based on the findings of two trials: the Prevention and Progression of Arterial Disease and Diabetes Trial (POPADAD) and the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) study. These did not show a statistically significant benefit in prevention of cardiovascular events with aspirin.^{29,30}

After the new guidelines came out, a meta-analysis further bolstered its recommendations.⁴⁰ In seven randomized clinical trials in 11,000 patients, the relative risk reduction was 9% with aspirin, which did not reach statistical significance.

Statins may dilute the benefit of aspirin

The use of statins has been increasing, and this trend may have played a role in the marginal benefit of aspirin therapy in these recent studies. In the Japanese trial, approximately 25% of the patients were known to be using a statin; the percentage of statin use was not

Statin therapy may dilute the benefit of aspirin and make it unnecessary for some patients

reported specifically in POPADAD, but both of these studies were published in 2008, when the proportion of diabetic patients taking a statin would be expected to be higher than in earlier primary prevention trials, which were performed primarily in the 1990s. Thus, the beneficial effects of statins may have somewhat diluted the risk reduction attributable to aspirin.

Trials under way in patients with diabetes

The evolving and somewhat conflicting guidelines highlight the need for further study in patients with diabetes. To address this area, two trials are in progress: the Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D) and A Study of Cardiovascular Events in Diabetes (ASCEND).^{41,42}

ACCEPT-D is testing low-dose aspirin (100 mg daily) in diabetic patients who are also on simvastatin. This study also includes prespecified subgroups stratified by sex, age, and baseline lipid levels.

The ASCEND trial will use the same aspirin dose as ACCEPT-D, with a target enrollment of 10,000 patients with diabetes without known vascular disease.

More frequent dosing for people with diabetes?

Although not supported by current guidelines, recent work has suggested that people with diabetes may need more-frequent dosing of aspirin.⁴³ This topic warrants further investigation.

Aspirin as primary prevention in elderly patients

The incidence of cardiovascular events increases with age³⁷—but so does the incidence of gastrointestinal bleeding.⁴⁴ Upper gastrointestinal bleeding is especially worrisome in the elderly, in whom the estimated case-fatality rate is high.¹² Assessment of risk and benefit is particularly important in patients over age 65 without known coronary disease.

Uncertainty about aspirin use in this population is reflected in the most recent US Preventive Services Task Force guidelines, which do not advocate either for or against regular aspirin use for primary prevention in those

over the age of 80.

Data on this topic from clinical trials are limited. The Antithrombotic Trialists' Collaboration (2009) found that although age is associated with a risk of major coronary events similar to that of other traditional risk factors such as diabetes, hypertension, and tobacco use, older age is also associated with the highest risk of major extracranial bleeding.²²

Because of the lack of data in this population, several studies are currently under way. The Aspirin in Reducing Events in the Elderly (ASPREE) trial is studying 100 mg daily in nondiabetic patients without known cardiovascular disease who are age 70 and older.⁴⁵ An additional trial will study patients age 60 to 85 with concurrent diagnoses of hypertension, hyperlipidemia, or diabetes and will test the same aspirin dose as in ASPREE.⁴⁶ These trials should provide further insight into the safety and efficacy of aspirin for primary prevention in the elderly.

FUTURE DIRECTIONS

Aspirin remains a cornerstone of therapy in patients with cardiovascular disease and in secondary prevention of adverse cardiovascular events, but its role in primary prevention remains under scrutiny. Recommendations have evolved to reflect emerging data in special populations, and an algorithm based on Framingham risk assessment in men for myocardial infarction and ischemic stroke assessment in women for assessing appropriateness of aspirin therapy based on currently available guidelines is presented in **FIGURE 1**.^{6,8,47–49} Targeted studies have advanced our understanding of aspirin use in women, and future studies in people with diabetes and in the elderly should provide further insight into the role of aspirin for primary prevention in these specific groups as well.

Additionally, the range of doses used in clinical studies has propagated the general misperception that higher doses of aspirin are more efficacious. Future studies should continue to use lower doses of aspirin to minimize bleeding risk with an added focus on re-examining its net benefit in the modern era of increasing statin use, which may reduce the absolute risk reduction attributable to aspirin.

One particular area of debate is whether enteric coating can result in functional aspirin resistance. Grosser et al⁵⁰ found that sustained aspirin resistance was rare, and “pseudoresistance” was related to the use of a single enteric-coated aspirin instead of immediate-release aspirin in people who had not been taking aspirin up to then. This complements an earlier study, which found that enteric-coated aspirin had an appropriate effect when given for 7 days.⁵¹ Therefore, for patients who have not been taking aspirin, the first dose should always be immediate-release, not enteric coated.

■ SHOULD OUR PATIENT RECEIVE ASPIRIN?

The patient we described at the beginning of this article has several risk factors—hypertension, dyslipidemia, left ventricular

hypertrophy, and smoking—but no known cardiovascular disease as yet. Her risk of an adverse cardiovascular event appears moderate. However, her 10-year risk of stroke by the Framingham risk calculation is 10%, which would qualify her for aspirin for primary prevention. Of particular note is that the significance of left ventricular hypertrophy as a risk factor for stroke in women is higher than in men and in our case accounts for half of this patient’s risk.

We should explain to the patient that the anticipated benefits of aspirin for stroke prevention outweigh bleeding risks, and thus aspirin therapy would be recommended. However, with her elevated LDL-cholesterol, she may benefit from a statin, which could lessen the relative risk reduction from additional aspirin use. ■

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