In Brief

Although aspirin has been empirically used to prevent cardiovascular disease since the 1940s, there remains disagreement regarding the specific use of aspirin in people with diabetes. Despite this disagreement, several organizations have provided guidelines and recommendations concerning patient selection when considering aspirin use for this purpose. This review provides a brief overview of currently available recommendations related to aspirin use in the prevention of cardiovascular events in people with and without diabetes.

Aspirin Therapy in Patients With Diabetes: An Update on Current Recommendations

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Editor’s note: This article is an update to a previous published article (White J: Primary prevention of cardiovascular events with aspirin in patients with diabetes. Diabetes Spectrum 24:47–49, 2011).

Although aspirin was made available commercially in 1899 by the Bayer pharmaceutical company and is one of our oldest pharmacological agents, the precise role of aspirin as a preventive measure for cardiovascular disease (CVD) is still widely debated. Aspirin clearly conveys benefits in terms of reducing the risk of CVD, but questions remain regarding safety and appropriate patient selection when using aspirin for CVD prevention. Because of the established relationship between diabetes and CVD, the role of aspirin in CVD prevention is of particular importance to this patient population.

This article reviews the use of aspirin in people with diabetes as a primary and secondary CVD preventive measure. It summarizes current position statements related to the use of aspirin in this population and outlines the potential benefits and risks.

Mechanism of Action and Potential Role in Diabetes Management

Salicin, a natural precursor of aspirin found in willow bark and leaves, was used during the time of Hippocrates (400 BC) as a pain reliever and antipyretic. Aspirin was synthesized from the spirea plant (which is rich in salicin) in the 1800s and marketed by Bayer to physicians for use in their patients in 1899. Aspirin was used for its analgesic, antipyretic, and anti-inflammatory properties, as it still is today. Interestingly, Dr. Lawrence Craven noted in 1948, based on his empirical observations, that his patients treated with aspirin did not suffer heart attacks. Accordingly, Dr. Craven routinely prescribed aspirin to his patients as a preventive measure for myocardial infarction (MI).

Today, aspirin-induced inhibition of cyclooxygenase (COX)-1 leading to impaired platelet aggregation is considered the most likely cause of aspirin’s cardioprotective effect. Aspirin’s role as a cardioprotective medication was solidified with the publication of the Physician’s Health Study in 1989. This randomized, double-blinded, placebo-controlled trial in 22,000 physicians demonstrated a 44% reduction in the risk of MI in subjects taking 325 mg aspirin every other day. A plethora of studies have been conducted since then, and although questions regarding particular details such as dose are still being evaluated, it is widely accepted that low-dose aspirin can reduce the risk of both MI and stroke.

This pharmacotherapeutic modality has been, and remains, of great interest to providers managing patients with diabetes. Although the burden of CVD in the United States is significant, it is particularly heavy for people with diabetes, who are at a two- to fourfold greater risk of CVD than those without diabetes.
individuals with diabetes who are > 65 years of age, 68% of deaths are the result of coronary heart disease, and ~16% are secondary to stroke. Accordingly, measures that potentially convey CVD risk reduction are of great importance when managing people with diabetes.

Safety Considerations
Whenever discussing preventive therapy, it is important to consider the potential risks associated with a given treatment. As is true with other nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin treatment does place people at risk for bleeding events. The most important risk factors associated with aspirin-induced gastrointestinal (GI) bleeding are generally considered to be age and sex, with increased age and male sex conveying increased risk. Other important risk factors and symptoms include upper GI tract pain, history of GI ulceration, and concomitant NSAID use. In fact, the use of aspirin in combination with other NSAIDs approximately quadruples the risk for serious GI bleeding compared to aspirin use alone. Uncontrolled hypertension and the use of anticoagulant therapies (such as warfarin) additionally increase the risk.

Regarding the use of aspirin in primary CVD prevention, the Women’s Health Study provided data on potential adverse outcomes of treatment. Adverse outcomes that were significantly more common in women receiving aspirin therapy included GI bleeding, peptic ulcers, hematuria, bruising, and nosebleeds. Serious GI bleeding events were more common in women receiving aspirin (risk ratio 1.40, 95% CI 1.07–1.83). Because aspirin therapy is not without its risks, a prudent evaluation of the potential risks and benefits of therapy are crucial and discussed within the clinical guidelines briefly outlined below.

Overview of Current Recommendations
Given the evident impact of CVD in people with diabetes, several organizations have provided guidance related to CVD prevention in this population. As discussed previously, although efficacious in preventing CVD events, aspirin treatment is not without its risks. As described below, recommendations are often made in light of CVD risk using calculators such as the Framingham 10-year CVD Risk Calculator and the Framingham risk score for stroke.

American Diabetes Association recommendations
The American Diabetes Association (ADA) publishes guidelines for the use of aspirin for the primary prevention of CVD as a component of its annual Standards of Medical Care in Diabetes position statement. The most recent 2013 guidelines suggest aspirin therapy for primary prevention in patients with either type 1 or type 2 diabetes who have an increased risk of CVD (i.e., a 10-year risk of > 10%). They also state that this includes most men > 50 years of age and most women > 60 years of age who have at least one additional risk factor (i.e., family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). This effectively includes most patients with diabetes in this age range. They also state that aspirin therapy should not be recommended for CVD prevention in men < 50 years of age or most women < 60 years of age who are at low risk for CVD (i.e., 10-year risk < 5%) because the increased bleeding risk likely offsets the potential benefit of aspirin treatment. In the case of patients with diabetes and a history of CVD, however, the ADA recommends the use of aspirin therapy in all patients for secondary prevention.

The 2013 ADA Standards of Care statement also includes a short discussion regarding the notion of altered platelet function resulting in a resistance to the effects of aspirin in patients with diabetes. Some have suggested that this aberration might necessitate the use of higher-dose aspirin in this population. The guidelines conclude that, although there may indeed be a so-called “aspirin resistance” in the platelets of patients with diabetes, “these observations alone are insufficient to empirically recommend . . . that higher doses of aspirin be used in the diabetic patient at this time.”

Joint scientific statement
In 2010, the ADA, American Heart Association, and the American College of Cardiology Foundation released a joint position statement regarding the use of aspirin for primary prevention of CVD. This group completed a robust evaluation of the available data related to aspirin use for the primary prevention of CVD. Overall, the group concluded that “the effect of aspirin for primary prevention of CVD events in adults with diabetes is currently unclear,” but followed this overarching statement with the following opinions and recommendations for consideration by clinicians:

- The use of low-dose aspirin for primary prevention of CVD is “reasonable” for adults with diabetes with no previous history of vascular disease who are at increased risk of CVD (i.e., 10-year risk of > 10%) and who are not at increased risk of bleeding. They further define increased risk of CVD in a similar manner to the ADA guidelines discussed above as most men > 50 years of age and most women > 60 years of age who have at least one additional risk factor (i.e., family history of premature CVD, hypertension, smoking, dyslipidemia, or albuminuria). Increased risk of bleeding is defined as a history of GI bleeding, peptic ulcer disease, or the concurrent use of medications such as NSAIDs or warfarin, which might cause bleeding.

- Aspirin is not recommended for primary prevention of CVD in patients with diabetes who have a low risk of CVD, such as men < 50 years of age and women < 60 years of age who have no additional major risk factors (10-year risk of < 5%).

- Aspirin therapy might be considered (until further research is available) in those with intermediate risk of CVD, such as younger patients with one or more risk factors or older patients with no risk factors (10-year risk of 5–10%).

- Regarding dose, the group states that “the optimal dose of aspirin for the prevention of cardiovascular events is not clearly established from the outcomes literature.” They recommend a dose range of 75–162 mg daily.

U.S. Preventive Services Task Force recommendations
The U.S. Preventive Services Task Force (USPSTF), established by the U.S. Department of Health and Human Services, published in 2009 a Guide to Clinical Preventive Services, which included recommendations for the use of aspirin for the primary prevention of CVD. The task force recommended the use of aspirin for
primary prevention of CVD in men who are 45–79 years of age and women who are 55–79 years of age in whom the potential benefit (prevention of MI in men and stroke in women) outweighs the potential harm from increased risk of GI hemorrhage. The group also recommended against the use of aspirin in women <55 and men <45 years of age and did not make a recommendation for men or women ≥80 years of age because of insufficient evidence in this population (Table 1). Although the USPSTF recommendations provided clinically useful guidelines for the use of aspirin in primary CVD prevention, this statement included no special guidelines for patients with diabetes. It did not recommend a specific dose, but rather suggested that doses of 75–100 mg daily or 100–325 mg every other day have demonstrated effectiveness. It also stated that doses of ~75 mg daily seem as effective as higher doses and may be associated with a lower risk of GI bleeding.

Conclusion
Although aspirin has been empirically used to prevent CVD since the 1940s, there remains disagreement among opinion leaders and professional organizations regarding the specific use of aspirin in people with diabetes. Although there is strong evidence for the use of aspirin for secondary prevention of CVD (as noted in the 2013 ADA Standards of Care), aspirin use for primary prevention of CVD in patients with and without diabetes is less clear cut in light of the potential risks of therapy. Based on patients’ individual characteristics, family history, concomitant medications, and personal health beliefs, providers can use the available guidelines described here to make informed judgments regarding the use of aspirin in their patients.

References

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Table 1. USPSTF Recommendations for the Use of Aspirin for the Prevention of CVD

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Men 45–79 Years of Age</th>
<th>Women 55–79 Years of Age</th>
<th>Men &lt;45 Years of Age</th>
<th>Women &lt;55 Years of Age</th>
<th>Men and Women ≥80 Years of Age</th>
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<tr>
<td>Encourage aspirin use when potential CVD benefit (MI prevention) outweighs potential harm of GI hemorrhage</td>
<td>Grade A</td>
<td>Do not encourage aspirin use for MI prevention</td>
<td>Grade D</td>
<td>Do not encourage aspirin use for stroke prevention</td>
<td>Grade I (insufficient evidence)</td>
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