Low-Dose Aspirin Not Protective Against Cardiovascular Events in Diabetics: Is a Paradigm Shift Imminent?

Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 2008;300:2134–41.

Study Overview

Objective. To determine whether low-dose aspirin is effective for primary prevention of cardiovascular events in patients with type 2 diabetes mellitus.

Design. Randomized, open-label trial with blinded endpoint assessment (the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes [JPAD] trial).

Setting and participants. 2539 patients aged 30 to 85 years with type 2 diabetes and no history of atherosclerotic disease from 163 institutions in Japan. Patients were excluded if they had documented evidence of atherosclerotic disease, atrial fibrillation, pregnancy, use of antiplatelet or antithrombotic therapy, a history of severe gastric or duodenal ulcer, severe liver dysfunction, severe renal dysfunction, and allergy to aspirin. Participants were randomly assigned to either once-daily, low-dose aspirin (81 mg or 100 mg) or no aspirin. The nonaspirin group did not receive placebo.

Main outcome measures. The primary endpoint was a composite of atherosclerotic events, including sudden death, fatal or nonfatal aortic disease, fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease. Secondary endpoints were individual and combinations of components of the composite primary endpoint and death from any cause.

Main results. Mean age was similar in the aspirin and nonaspirin groups (65 vs. 64 years), and a slight majority of patients were male (56% and 53%, respectively). Most patients had well-controlled diabetes (mean hemoglobin A_{1c}, 7.1% and 7.0%) and hypertension (mean blood pressure, 136/77 and 134/76 mm Hg). Patients were followed for a mean of 4.37 years. Only 154 atherosclerotic events occurred, with no difference noted between the groups (68 events in the aspirin group vs. 86 events in the nonaspirin group; hazard ratio [HR], 0.80 [95% confidence interval, {CI}, 0.58–1.10]; $P = 0.16$). No difference was evident in death from any cause (HR, 0.90 [95% CI, 0.57–1.14]; $P = 0.67$), although fewer fatal coronary and cerebrovascular events occurred in the aspirin group (1 vs. 10 events; HR, 0.10 [95% CI, 0.01–0.79]; $P = 0.004$). In subgroup analyses, patients aged > 65 years treated with aspirin were significantly less likely to have an atherosclerotic event as compared with those < 65 years (45 vs. 59 events; HR, 0.68 [95% CI, 0.46–0.99]; $P = 0.047$). More patients taking aspirin had gastrointestinal bleeding, but only 4 patients required transfusion for the bleeding.

Conclusion. Aspirin was not effective for preventing primary cardiovascular events in diabetic patients.

Commentary

Use of aspirin for primary prevention of cardiovascular events in diabetic patients has long been accepted clinical practice. The U.S. Preventive Services Task Force (USPSTF) recommends consideration of aspirin as primary prevention among individuals with a 3% or higher 5-year risk of cardiovascular events, and the recommendations mention diabetic patients among the high-risk group [1]. The American Diabetes Association (ADA) recommends use of aspirin for primary prevention among diabetic patients aged 40 years and older or in patients who smoke or have comorbid conditions such as hypertension, hyperlipidemia, a family history of cardiovascular disease, or albuminuria [2]. The scientific basis for these recommendations comes in large part from several large randomized controlled trials (RCTs) of aspirin as primary prevention; however, these trials enrolled either healthy patients or those who were generally at high risk for coronary disease and did not specifically enroll diabetic patients. A meta-analysis of the 6 major primary prevention trials including over 90,000 patients found a significant benefit to aspirin therapy for reducing coronary heart disease, nonfatal myocardial infarction, and total cardiovascular events in the overall study population [3]. However, no separate estimate was made in this meta-analysis for diabetic patients. Another meta-analysis that included 9 RCTs evaluating the effect of antiplatelet versus control therapy in 4961 diabetic patients found no significant reduction in serious vascular events in patients treated with antiplatelet therapy [4].

The JPAD study was conducted because of the lack of evidence documenting the benefit of aspirin as primary prevention among diabetic patients. Because no difference was found in the composite primary outcome, the JPAD

trial perhaps calls the USPSTF and ADA recommendations, among others, into question. Patients taking aspirin had similar rates of primary cardiovascular events as those not taking aspirin. Some positive findings were noted in subgroup analyses and in 1 secondary outcome. Patients aged 65 years and older taking aspirin had fewer overall cardiovascular events. Additionally, there were fewer deaths from the combined endpoint of cardiovascular and cerebrovascular causes in the aspirin group. However, the number of deaths from these causes was exceedingly low (1 in the aspirin group vs. 10 in the nonaspirin group), limiting the interpretability of this finding.

This study is especially provocative because similar results were found in a recent study of 1276 Scottish adults aged 40 years and older with type 1 or type 2 diabetes and at least mild, asymptomatic peripheral arterial disease [5]. In this double-blind, placebo-controlled trial (median follow-up, 6.7 years), no difference was evident in the aspirin or placebo groups in the primary endpoint of death from coronary heart disease or stroke and the primary composite endpoint that included fatal and nonfatal myocardial infarction, stroke, or above-the-ankle amputation for critical limb ischemia. No differences were found among secondary endpoints.

Although this study by Ogawa et al was not a placebo-controlled trial (due to prohibition against the use of placebo in Japan), it was well-conducted. Fewer than 100 patients were lost to follow-up in each arm. Furthermore, limited crossover occurred between groups; more patients switched from aspirin to no aspirin than the reverse. Approximately 10% of patients (123 patients) in the aspirin arm stopped taking aspirin, while only 9 patients in the nonaspirin arm started taking aspirin or another antiplatelet therapy. Although small, this differential crossover could bias the results toward a null finding.

The major limitation of the study was the lack of statistical power to detect a difference in cardiovascular events, a limitation that was also present in the POPADAD study [5]. Ogawa et al used prior Japanese studies of incident cardiovascular events in diabetic patients to predict the event rate, but the event rate in this trial was much lower than expected, leading to the trial being underpowered. A true difference could emerge in a large study. Additionally, patients had well-controlled diabetes and high blood pressure, and aspirin may be more beneficial in patients who do not have ideal control over their chronic conditions. The inclusion of only Japanese patients limit the applicability of these results to other populations; however, the finding from POPADAD using a Scottish population reinforces the results.

Ultimately, the JPAD results should not compel clinicians to forego aspirin for primary prevention in diabetic patients quite yet, especially because of the power issues in this trial and the results of the POPADAD trial. The results of 2 large RCTs of aspirin for primary prevention among diabetic patients are pending and should provide helpful information.

Applications for Clinical Practice

Clinicians should consider the risks and benefits of prescribing aspirin for primary prevention of cardiovascular events in diabetic patients. Benefits of aspirin are perhaps most evident for diabetic patients aged 65 years and older. Ongoing trials should provide helpful information to guide recommendations.

—Review by Jason P. Block, MD, MPH

References

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