PERSPECTIVES

Use of Aspirin Among Diabetics in the Primary Prevention of Cardiovascular Disease: Need For Reliable Randomized Evidence and Astute Clinical Judgment

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BACKGROUND: The American Heart Association Guidelines recommend aspirin for all apparently healthy individuals whose 10-year risk of a first coronary heart disease (CHD) event is >10%.

METHODS: The United States (US) Preventive Services Task Force (USPSTF) has recently updated its guidelines to encourage men 45 to 79 years and women 55 to 79 years to use aspirin when the potential benefit outweighs the potential harm. In addition, in some US guidelines, diabetes is considered to be a CHD risk equivalent.

RESULTS: Two recently published trials, the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) and the Prevention of Progression of Arterial Disease and Diabetes (POPADAD), concluded that aspirin did not reduce risks of CHD. Both JPAD and POPADAD had inadequate statistical power. Reliable randomized evidence is necessary to provide a sufficient totality of evidence about benefits and risks among diabetics.

CONCLUSION: At present, astute individual clinical judgments are necessary.

KEY WORDS: diabetes; cardiovascular disease; prevention; risk assessment; evidenced-based medicine.

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In randomized trials of the treatment of cardiovascular disease (CVD) and their meta-analyses, which include substantial numbers of diabetics, aspirin reduces the risks of myocardial infarction (MI) by about 1/3, stroke by about 1/4 and CVD death by about 1/6.[1,2] In primary prevention trials and their meta-analyses, which include far fewer diabetics, aspirin reduces the risk of a first MI by about 1/3, but there are nonsignificant effects on stroke and CVD death.[3] Unfortunately, virtually all the data in primary prevention have accrued in trials among subjects whose 10-year risk of a first coronary heart disease (CHD) event is <10%. Based on these trials, the American Heart Association Guidelines recommend aspirin for all apparently healthy individuals whose 10-year risk of a first coronary heart disease (CHD) event is >10%.[4] The United States (US) Preventive Services Task Force (USPSTF) has recently updated its guidelines to encourage men 45 to 79 years and women 55 to 79 years to use aspirin when the potential benefit outweighs the potential harm.[5] These guidelines are based on meta-analyses that suggest that the absolute benefits of aspirin on reducing the risk of a first MI exceed the absolute risks of major extracranial bleeding. In the latest version of the US Federal Guidelines, the National Cholesterol Education Adult Treatment Panel III (NCEP ATP III) elevated diabetes from a major risk factor to a CHD risk equivalent.[6] Thus, according to NCEP ATP III, patients with diabetes with no prior history of cardiovascular disease should be treated just as aggressively as secondary prevention patients. Further, the American Diabetes Association (ADA) has recommended aspirin in secondary prevention for all patients with diabetes and prior CHD and in primary prevention for all patients with diabetes at increased cardiovascular risk, including those over 40 years of age or who have additional risk factors.[7] Recently, two randomized trials, the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) [8] and the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) [9] trials, were published. Both tested low-dose aspirin in patients with diabetes without previous CVD and concluded that aspirin did not significantly reduce the risk. In this commentary, we review the data from JPAD and POPADAD in the context of the totality of evidence, emphasize the need for reliable randomized evidence on this question, and suggest clinical strategies for the use of aspirin in the primary prevention of CVD among diabetics.

The JPAD [8] trial enrolled 2,539 patients with type 2 diabetes and examined the efficacy of low-dose aspirin for prevention of atherosclerotic events. The investigators created a combined primary endpoint that included thrombotic events, such as fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease, which aspirin might be expected to reduce. The primary endpoint, however, also included atherogenic events such as angina, which low-dose aspirin might not affect.[10] In this randomized open-label design over 4.4 years, 154 atherosclerotic events occurred, 68 in the aspirin and 86 in the non-aspirin group. For the primary prespecified endpoint, the relative risk (RR) and 95% confidence intervals (CI) were 0.80 (0.58–1.10). These data are compatable with a possible but

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nonsignificant 20% reduction in risk of atherosclerotic events in the aspirin as compared to the non-aspirin group. The secondary endpoint of fatal coronary events and fatal cerebrovascular events occurred in one patient in the aspirin group and ten in the non-aspirin group (RR=, 0.10; 95% CI=0.01–0.79). Since a RR of 1.0 does not lie within this confidence interval, the finding is statistically significant (p=0.004). The investigators concluded that low-dose aspirin did not reduce the risk of CVD since the observed 20% reduction in the primary endpoint did not achieve statistical significance. If a 20% benefit were real, however, far more clinical CVD endpoints than the observed 154 events would have had to accrue to achieve statistical significance. Thus, this trial had inadequate statistical power to detect the most plausible effect sizes.[11] In fact, a 20% reduction is a plausible effect size because 15% of patients who achieved the primary endpoint developed stable angina, which aspirin may not affect.[10]

The POPADAD trial [9] enrolled 1,276 patients with type 1 or type 2 diabetes and asymptomatic peripheral arterial disease, but no symptomatic CVD, and used a 2×2 factorial design to test low-dose aspirin and antioxidant therapy. The two hierarchical composite primary endpoints were: death from CHD or stroke, nonfatal MI or stroke, or amputation above the ankle for critical limb ischemia; and death from CHD or stroke. After an average of about 6 years of treatment and follow-up, 233 CVD events occurred, 116 in the aspirin and 117 in the placebo group (RR=0.98; 95% CI=0.76–1.26). As regards death from CHD or stroke, 43 occurred in the aspirin and 35 in the placebo group (RR=1.23; 95% CI=0.79–1.93). The authors concluded that aspirin was not effective in the primary prevention of cardiovascular events in patients with diabetes and asymptomatic peripheral arterial disease. In fact, this trial was far more uninformative than statistically null. This is because the numbers of endpoints are low and, in addition, after 5 of the 8 years of follow-up about 50% of patients were not taking their assigned drug. The statistical power of a trial to detect a postulated difference between treatment groups, if one truly exists, is dependent not simply on the sample size, but more specifically on two factors: (1) the total number of endpoints experienced by the study population and (2) the difference in compliance between treatment groups.[11]

The only other published large-scale randomized trial of aspirin among diabetics that accrued a large number of CVD endpoints was the Early Treatment Diabetic Retinopathy Study (ETDRS).[12] ETDRS enrolled 3,711 patients. Of 446 incident MIs, there were 204 in the aspirin and 242 in the placebo group. The authors concluded that aspirin significantly reduced the risk of a first MI by 17% in a population at high risk of a CHD event of about 15% over 5 years due, in part, to enrollment of high risk patients as evidenced by moderate retinopathy at baseline, as well as perhaps 10% of patients with prior CHD. There was, however, no significant modification of the benefit of aspirin among those with and without prior CHD.

Randomized trials among diabetics without prior occlusive cardiovascular disease events of sufficient size and duration that maintain high adherence rates are necessary to provide reliable evidence upon which to draw firm conclusions about the balance of benefits and risks of aspirin in the primary prevention of CVD. The potentially most informative trial, A Study of Cardiovascular Events in Diabetes (ASCEND), is enrolling at least 10,000 patients with diabetes (either type 1 or type 2) who do not have known vascular disease. ASCEND subjects are randomly allocated to take 100 mg aspirin daily or placebo in a double-blind design.[13] If ASCEND meets its recruitment goal, maintains high adherence and follow-up, and accrues a sufficient number of clinical endpoints, this trial will provide the most reliable evidence about the effects of aspirin in diabetes without prior CVD. The Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D) is an open label trial assessing whether 100 mg of daily aspirin prevents cardiovascular events in 5,170 diabetic patients without clinically manifest vascular disease who are treated with simvastatin. ACCEPT-D is planned to accrue 515 first events.[14]

Until reliable evidence emerges from these two ongoing and perhaps other planned trials, individual clinical judgments that weigh the absolute risk of CVD of the diabetic against the risk of major extracranial bleeding seem the most prudent course of action. While aspirin increases risks of intracranial bleeding, based on reliable evidence from the secondary prevention trials [2], the magnitude of the excess risk is unlikely to exceed 3 per 10,000 per year. The need for astute clinical judgment derives from the fact that there are far more uncertainties concerning aspirin in primary compared to secondary prevention of CVD. Moreover, the primary prevention trials were mainly in people who were not taking statins, which would have reduced myocardial infarction, stroke and cardiovascular deaths with little hazard. If the risk of occlusive vascular disease is approximately halved by statins or other measures, then the further absolute benefit of adding aspirin could well be only about half as large as was suggested by the primary prevention trials, but the main bleeding hazards could well remain. While reliable evidence is more important than clinical judgment, in the meanwhile it seems prudent to consider aspirin only for those in whom the expected benefits on a first occlusive vascular event substantially exceed the risks of major extracranial bleeding. In the context of secondary prevention, where the risk of a serious vascular event generally exceeds 20% per 10 years, the benefits of aspirin clearly exceed the risks, irrespective of gender.[15] The major unmet clinical and public health challenges are reflected in data from the Third National Health and Nutrition Examination Survey (NHANES III) that show that only 20% of diabetic patients with prior CHD are using aspirin regularly.[16] This underutilization of aspirin in secondary prevention is particularly unfortunate because the totality of evidence is so persuasive. For primary prevention among diabetics, based on the currently available inadequate totality of evidence, the clinical challenge for the health-care provider of patients with diabetes is to identify those at a sufficiently high risk of a first CHD event for which aspirin reliably prevents a first MI but may have more limited effects on stroke.

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