Although aspirin has been a cornerstone of the secondary prevention of ischemic events in cardiovascular medicine for more than 100 years, its role in primary prevention is still unknown. Several trials and meta-analyses have found a benefit in preventing cardiovascular events associated with the use of low doses of aspirin. However, the absolute benefits outweighed the risks of major extracranial bleeding and the low-risk nature of the majority of the participants in the earlier trials became the first critique of the lack in positive results among those trials. Common sense may say that aspirin might have greater benefit in populations with higher risk for cardiovascular events, such as those with high prevalence for cardiovascular risk factors. Given that trials of aspirin for primary prevention have enrolled too few patients with diabetes mellitus (DM), investigators have focused on this special population. Overall, the trials and a later meta-analysis also found no significant reduction in the risk of major cardiovascular events in DM-based populations. Although there were negative results again, the event rate in those trials was lower than-expected. Thus, should we continue searching in higher risk DM populations?

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Over the past decades the number of subjects with DM has been increasing due to population growth, aging, increasing prevalence of obesity and physical inactivity. Among adults the risk of DM ranges from approximately 25% to 55%, and is frequently associated with hypertension. Moreover, it has been clearly established that the coexistence of these pathological entities substantially increases the risk of developing cardiovascular disease (CVD). On the other hand, the American Diabetes Association and the American Heart Association jointly recommended that aspirin therapy (75–162 mg/day) should be used as a primary prevention strategy only in those patients with DM at increased cardiovascular risk (>10%) with low bleeding risk, and males older than 50 or females older than 60 years of age. However, this evidence is not supported by any trial thus far.

It is also true that despite the existence of multiple interventions to reduce the CVD risk, the majority of subjects with DM and/or hypertension still develop cardiovascular complications. This increased risk for cardiovascular events has led to considerable interest in identifying effective means of cardiovascular risk reduction. Furthermore, there is a strong level of evidence regarding the beneficial effect of a greater vs. a smaller blood pressure (BP) reduction in type 2 diabetic patients. Indeed, a recent meta-analysis suggests that lower BP may induce even greater cardiovascular benefits in diabetic patients than in non-diabetic subjects. According to this perspective and in order to maximize cardiovascular protection, it has been recommended that antihypertensive treatment should be more intense, and a goal BP <130/80 mmHg has been proposed for diabetic patients.

In this issue of the Journal, Soejima et al perform a sub-analysis of the Japanese primary prevention of atherosclerosis with aspirin for diabetes trial, JPAD, to assess the possible influence of BP level on the effectiveness of aspirin in preventing cerebrovascular events. They divided the main study population (2,539 patients with type 2 DM without a history of CVD) into 2 groups according to BP level (group 1: systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg and group 2: SBP <140 mmHg and DBP <90 mmHg). In this substudy, the authors found that the incidence of cerebrovascular events was similar in patients on aspirin regardless of their BP level, whereas among patients not taking aspirin the presence of higher BP confers a significantly higher risk for cardiovascular events. Based on these findings, the authors conclude that aspirin may reduce cerebrovascular events in diabetic patients with uncontrolled hypertension and suggest that this therapy could be an additional strategy as primary prevention for diabetic patients with higher BP. This report has raised the question of whether DM patients with uncontrolled BP may be an appropriate use of aspirin as primary prevention therapy.

However, we think that the decision to adjunctively administer aspirin to hypertensive patients should be taken in accordance with the total cardiovascular risk and/or the presence of organ damage. Evidence of the risk-benefit ratio of using low-dose aspirin in patients with hypertension was obtained from the HOT study. Overall, that study showed a 15% reduction in major cardiovascular events, and a 36% reduction...
in acute myocardial infarction, with no effect on stroke and no significant increased risk of intracranial hemorrhage but an associated 65% increased risk of major hemorrhagic events. However, subgroup analyses of the HOT study showed that patients with serum creatinine >1.3 mg/dl had a significantly greater reduction of cardiovascular events and myocardial infarction (13 and 7 events/1,000 patient-years respectively), while the risk of bleeding was not significantly increased. A favorable balance between the benefits and harm of aspirin was also found in patients at higher global baseline risk and higher baseline SBP or DBP (reduction of 3.1–3.3 cardiovascular events/1,000 patient-years vs. harm: 1.0–1.4 bleeds/1,000 patient-years), and in hypertensive patients at lower baseline risk the harm of aspirin counterbalanced the benefits. Of note, the benefits were observed among patients with effective BP control (all patients had DBP <90 mmHg) and it is possible that this control results in avoidance of an increase in intracranial hemorrhage, which has been reported in some studies.

In the light of the available evidence, it appears reasonable to suggest that when treating diabetic patients with uncontrolled hypertension the greatest effort should be made, not to add aspirin as a primary prevention strategy, but primarily to achieve the established goals for BP (<130/80 mmHg) and plasma glucose (HbA1c 7%, preprandial glucose 70–130 mg/dl and peak postprandial glucose <180 mg/dl), as well as for plasma lipids (low-density lipoprotein cholesterol <100 mg/dl, triglycerides <150 mg/dl and high-density lipoprotein-cholesterol >40 mg/dl in men and >50 mg/dl in women) and weight (body mass index 18.5–25 kg/m²). Unfortunately, the use of aspirin in primary prevention among DM patients warrants more evidence. We cannot encourage the use of a single therapeutic approach with related adverse (bleeding) events when the use of other (and safer) therapies could reduce the cardiovascular risk by almost the same amount. Ongoing trials, such as A Study of Cardiovascular Events in Diabetes (ASCEND; NCT00135226), the Japanese Primary Prevention Project With Aspirin (JPPP; NCT00225849) and the Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D; ISRCTN48110081), all of which plan to enrol high numbers of patients to ensure enough events, may address the real place of aspirin in primary prevention.

References