Use of Aspirin to Reduce Risks of Cardiovascular Disease in Patients With Diabetes

Clinical and research challenges

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In their third version of U.S. federal guidelines, the National Cholesterol Education Program Adult Treatment Panel III elevated diabetes from a major risk factor to a coronary heart disease (CHD) risk equivalent (1,2). The rationale for this change derives, in part, from earlier observations that patients with diabetes have several-fold increased risks of CHD (3), which are even greater in women than men (4). In fact, it has been suggested that at any given age, diabetes eliminates the lower absolute risk of CHD in women compared with men. Specifically, a middle-aged woman with diabetes has an absolute risk of CHD approximately equal to her male counterpart without diabetes. Furthermore, in a prospective cohort study, nondiabetic subjects with prior CHD had a 7-year event rate of ~18.8%, whereas diabetic subjects without prior CHD had an event rate of ~20% (5). Whether such high absolute risks apply to patients with newly diagnosed diabetes is less clear. Nonetheless, current U.S. federal guidelines recommend that patients with diabetes be treated just as aggressively as secondary prevention patients without diabetes (i.e., those who have already experienced a CHD event).

With respect to secondary prevention, aspirin conclusively reduces risks of subsequent myocardial infarction (MI) by about one-third, stroke by about one-fourth, and vascular death by about one-sixth (6,7). In primary prevention, aspirin conclusively reduces the risk of a first MI by about one-third, but the numbers of strokes and vascular deaths in the five published primary prevention trials preclude firm conclusions. Nonetheless, based on meta-analyses of risks (8) and benefits (9), recent U.S. Preventive Services Task Force Guidelines recommend that aspirin also be considered for all apparently healthy individuals whose 10-year risks of a first CHD event are ≥6% (10). More recently, the American Heart Association (AHA) has recommended aspirin for all apparently healthy individuals whose 10-year risks of a first CHD event are ≥10% (11). Furthermore, the American Diabetes Association (ADA) has recommended aspirin (as a secondary prevention strategy) for patients with diabetes who have evidence of prior CHD and (as a primary prevention strategy) in patients with diabetes who have one other risk factor (12). Finally, the ADA emphasized that in patients with type 1 diabetes, cardiovascular disease (CVD) event rates may be <10% over 10 years. For these reasons they suggested that for patients with insulin-dependent or type 1 diabetes aspirin should be considered for those aged ≥40 years with one other risk factor.

These recommendations for patients with diabetes are based on a totality of evidence that includes randomized evidence from the Early Treatment Diabetic Retinopathy Study (13–14). This large-scale randomized trial demonstrated a significant benefit of aspirin on reducing risk of a first MI among patients with diabetes who had evidence of retinopathy. Two additional important issues from this trial merit consideration. First, the CHD event rates in these patients were high (i.e., ~15% over 5 years). Second, the randomized evidence was reassuring that aspirin did not increase risks of vitreous hemorrhage, even in this high-risk population (15).

The clear benefits of aspirin must be weighed in the context of side effects. The chief side effects of clinical concern are gastrointestinal (GI) upset and significant GI bleeding. The perception by patients that aspirin causes GI upset is reflected in the finding from the U.K. Transient Ischemic Attack (UK-TIA) trial (16) over 5 years of treatment and follow-up. Among over 800 patients assigned to aspirin placebo, 25% reported GI upset. Patients were also randomized in approximately equal numbers to aspirin at 300 mg daily and aspirin at 1,200 daily. In each of these categories of patients the corresponding

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rates were 29 and 39%. Thus, the rates of GI upset attributable to aspirin were 4% for the 300-mg/day group and 14% for the 1,200-mg/day group. With respect to GI bleeding the corresponding rates were 1.6, 2.6, and 4.9%, so the rates attributable to aspirin were 1.0% for the 300-mg/day group and 3.3% for the 1,200-mg/day group. In the most recent meta-analysis of the Antithrombotic Trialists (ATT) Collaboration (7), bleeding rates were dose related but did not reach statistical significance for those receiving 75 or 325 mg daily. In addition, the benefits of aspirin on CVD were apparently lower and not statistically significant at doses <75 mg daily, so the recommended dosage for patients not suffering an acute coronary syndrome is 75–325 mg/day.

All drugs that decrease clotting increase bleeding. In the overview of the randomized trials there is about a 60% statistically significant excess of major bleeds attributable to aspirin, over 5 years. This includes a very small increase (0.3 per 1,000) in cerebral hemorrhage in the long-term trials. Although the benefits are similar across a wide range of doses from 75 to >1,500 mg daily, the side effects appear to increase with dose, especially at ~325 mg/day. With respect to benefits and risks, for high-risk patients whose 10-year risk of a CHD event is >20%, the benefits of aspirin clearly outweigh any risks, and for moderate-risk patients whose 10-year risk of CHD event is >10% the benefits of aspirin are likely to outweigh any risks. As the side effects of aspirin are similar across a wide range of patients, the absolute risk of the individual is likely to be more important than the proportional reduction in serious events.

Despite an emerging totality of evidence and guidelines from several organizations there remains underutilization of and mismedication with aspirin (17). Specifically, in these survey data <50% of individuals prescribed aspirin are actually taking it. Further, among those who believe they are taking aspirin for cardiovascular prophylaxis, 10% are taking other nonsteroidal anti-inflammatory drugs (NSAIDs) and an additional 11% are taking acetaminophen. Aspirin irreversibly inhibits platelet-dependent cyclooxygenase for the life of the platelet (18) Other NSAIDs will have beneficial effects on platelets but only while their metabolites are in the bloodstream. Further, some but not all recent observational epidemiological data suggest a deleterious interaction between aspirin and other NSAIDs, principally ibuprofen (19–21). Specifically in two of the four published observational studies the clinical benefit of aspirin was negated in the presence of concomitant ibuprofen use. Finally, acetaminophen would be expected to have no effect on platelets.

Subgroup data of relatively recently diagnosed patients with diabetes from randomized trials of primary prevention are suggestive of benefits, but direct randomized evidence on this question should emerge over the next several years. One major randomized trial, A Study of Cardiovascular Events in Diabetes (ASCEND), which is about to begin, is being conducted by the Clinical Trial Services Unit (CTSU) in Oxford, U.K. In this trial, patients with recently diagnosed type 2 diabetes will be randomized in a double-blind, placebo-controlled design to 75 mg of aspirin or placebo daily (J. Armitage, personal communication). Nonetheless, nonfatal MI, nonfatal stroke, and fatal CVD occurred at a rate of >20% for 10 years in the U.K. Prospective Diabetes Study (UKPDS), which randomized patients with newly diagnosed non–insulin-dependent or type 2 diabetes (22).

In the meanwhile, clinicians should follow the ADA and AHA guidelines for the use of aspirin to reduce risks of CVD in patients with diabetes. The ADA guidelines recommend aspirin for all patients with diabetes who have had a prior CHD event as well as a primary prevention strategy among those with at least one other risk factor (12). The AHA recommends aspirin for all apparently healthy individuals whose 10-year risk of first event is 10% or greater (11). The more widespread and appropriate utilization of aspirin in patients with diabetes would avoid many premature deaths from CVD in secondary prevention and first MI in primary prevention (6–9).

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References

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References
Commentary


