Aspirin for Primary Prevention of Cardiovascular Events in Diabetes

Aspirin is probably the most widely used and least expensive drug in existence. The value of extracts of willow bark in controlling pain and fever was recognized in 400 BC by Hippocrates. In the 19th century, salicylic acid was identified as the active principle, and in 1899, Felix Hoffman synthesized acetylsalicylic acid. Shortly thereafter, Heinrich Dreser, director of pharmacological research for Bayer and Company, led the clinical trials that demonstrated efficacy and named this new drug aspirin.

In the 20th century, aspirin attracted the attention of physicians interested in cardiovascular disease after it was found that platelet cyclooxygenase, the enzyme that converts arachidonic acid to prostaglandins G2 and H2, was irreversibly inhibited in man by very low doses of aspirin. This blockade would inhibit thromboxane production, platelet aggregation, and vasoconstriction. Meta-analyses of large-scale clinical trials have shown that aspirin will reduce the risk for major cardiovascular events by ~25% in high-risk individuals (1).

People with type 2 diabetes have a risk of myocardial infarction, stroke, and cardiovascular death that is at least two- to fourfold greater than that of age- and sex-matched control subjects. Individuals with diabetes have been shown to have platelets that are unusually sensitive to aggregating agents and manufacture prostaglandin metabolites and thromboxane in excess. Platelets from diabetic subjects also display increased adhesiveness via nonprostaglandin-mediated pathways. Two of these pathways are mediated by the ADP receptor and fibrinogen binding to the GPIIb/IIIa complex. Fibrinolytic activity is often suppressed in type 2 diabetes, predominantly via inhibitory actions of plasminogen activator inhibitor (PAI-1) on fibrinolysis. Approximately 90% of the PAI-1 in vivo is carried by the platelets. Thrombosis in diabetes is clearly a complicated issue.

It may seem optimistic to expect that aspirin, through its antiplatelet action, could change the risk for vascular events in people with diabetes. Nevertheless, there are three studies that have revealed positive results in diabetic individuals with high cardiovascular risk (2–4). These studies have formed the basis for the position statement from the American Diabetes Association, which recommends low-dose aspirin therapy as a secondary prevention strategy and as primary prevention strategy in adults with diabetes who are at high risk for cardiovascular events (5). Furthermore, the American Heart Association (6) and the U.S. Preventative Services Task Force (7) also recommend aspirin therapy for nondiabetic and diabetic individuals with a cardiovascular risk ≥10% in 10 years. Support for these recommendations has recently been provided by the Primary Prevention Project (PPP), an open-label study of the effect of aspirin or vitamin E on cardiovascular events in 4,495 high-risk individuals, including those with diabetes. The trial demonstrated a significant benefit of aspirin versus placebo in reducing the composite end point of cardiovascular deaths, stroke, or myocardial infarction (relative risk [RR] 0.59, 95% CI 0.37–0.94) (8).

Results in the diabetic subgroup of this study are reported by Sacco et al. (9) in this issue of Diabetes Care. There was not a significant reduction in the risk for the combined vascular end point in the 1,031 people with diabetes who were treated with aspirin when compared with those not treated with aspirin (RR 0.90; 95% CI 0.50–1.62).

Does this mean that the guidelines for aspirin therapy in people with diabetes should be abandoned? No. It is important to note that the substudy in diabetic patients was not adequately powered. The study group estimated that ~4,000 diabetic patients would be needed to detect a 25% reduction in risk over a 5-year period. The parent study was prematurely stopped after only 3.7 years because a significant effect was seen in the total population. The sample size of 4,000 subjects was predicted on the basis of an event rate of 4% per year, but the rate in the diabetic group was well short of that, at 1% per year. Although the study in diabetic individuals was greatly underpowered, a non-significant trend for an RR of 10% was seen, and the authors properly concluded that large-scale controlled trials of aspirin in the primary prevention of CVD in diabetic individuals are still indicated.

What are some other reasons that the diabetic group appeared to be less responsive to aspirin therapy than other high-risk individuals? Compliance is one possibility because 28.2% of subjects assigned to aspirin had stopped this therapy by the conclusion of the trial. These figures, however, are comparable with those of the Early Treatment Diabetic Retinopathy Study (3), in which aspirin had a significant effect to reduce the risk of myocardial infarction. Another possibility is “aspirin resistance.” This is an entity that may be defined as the failure of aspirin therapy to prevent a major vascular event in an individual on aspirin therapy. This occurs in diabetic as well as nondiabetic individuals and may result from several mechanisms. First, there are platelet functions that may be involved in vascular thrombosis that are not sensitive to aspirin’s inhibition of platelet cyclooxygenase. ADP may cause platelet aggregation by stimulation of the ADP receptor, which then activates the GP IIb/IIIa receptor. There is evidence that this may occur in diabetes by ADP release from metabolically compromised erythrocytes. Plasma fibrinogen turnover is high in diabetes, and plasma fibrinogen levels are frequently elevated. Fibrinogen binding to platelets is increased in diabetes. It is accomplished via the GP IIb/IIIa receptor, and interplatelet bridging and agglutination may occur, which is independent of the thromboxane pathway.

There may be production and release of thromboxane precursors (PGG2, PGH2) from activated macrophages and damaged endothelium, and these may then be transported into platelets and...
serve as substrates for thromboxane. This could occur in the presence of aspirin’s blockade of cyclooxygenase. It has recently been shown that ibuprofen competes with aspirin for cyclooxygenase binding, and thereby inhibits aspirin’s effectiveness. Platelet PAI-1 release is binding, and thereby inhibits aspirin.

Recently been shown that ibuprofen competes with aspirin for cyclooxygenase binding, and thereby inhibits aspirin’s effectiveness. Platelet PAI-1 release is binding, and thereby inhibits aspirin.

Finally, there is one other issue that is particularly relevant to the study of Sacco et al. The trial had a 2 × 2 factorial design to investigate the effects of low-dose aspirin (100 mg/day) and vitamin E (300 mg/day) on cardiovascular events in patients with one or more cardiovascular risk factors. The vitamin E component of the study showed no effect on the pooled cardiovascular end point. The factorial design allowed for a comparison of the group treated with aspirin (aspirin alone or aspirin with vitamin E) with the group not treated with aspirin (vitamin E or no treatment). Vitamin E was chosen for the study because of its antioxidant properties. However, there is substantial literature documenting the antiplatelet actions of vitamin E. Vitamin E inhibits platelet phospholipase and results in decreased thromboxane production. These effects have been shown in diabetic animals as well as in diabetic patients (10). Thus, in the study of Sacco et al., vitamin E’s antplatelet effect may have adversely influenced the expected results of the aspirin trial by lowering thromboxane production in 50% of the control group but having little additional effect in the aspirin group. A double-blind, placebo-controlled design with aspirin but no vitamin E would overcome this issue.

In this study a question of “aspirin resistance” in diabetic patients is raised. More research on this issue is needed, including a precise definition and clinical trials. Logical therapeutic targets would include the platelet ADP receptor, the GPIIb/IIa receptors, and the sources responsible for elevated plasma PAI-1 levels in diabetes. In the meantime, the guidelines for aspirin therapy released by the American Diabetes Association (5), the American Heart Association (6), and the U.S. Preventive Services Task Force (7) are appropriate for primary prevention of cardiovascular events in high-risk individuals, including those with diabetes.

John A. Colwell, MD, PhD

From the Diabetes Center, Medical University of South Carolina, Charleston, South Carolina.

Address correspondence to John A. Colwell, MD, PhD, Diabetes Center, Medical University of South Carolina, 135 Rutledge Ave., Charleston, South Carolina 29425. E-mail: colwelja@musc.edu.

J.A.C. has been a committee member for Pfizer, has been on an advisory board for Takeda Pharmaceuticals America, and has received honoraria from Bayer and Pfizer.

© 2003 by the American Diabetes Association.

References


