Aspirin Therapy in Diabetes is Underutilized

In 1997, the American Diabetes Association (ADA) recommended low-dose aspirin therapy as a secondary prevention strategy in people with diabetes (1,2). There was nothing that was unique in this policy. It simply formalized recommendations that were supported by meta-analyses of all secondary prevention antiplatelet trials before 1994 (3). The ADA, however, agreed that this sole strategy was not sufficient for people with diabetes. Cardiovascular events are increased at least two- to fourfold in diabetes, and the major mode of death is a cardiovascular event. The cardiovascular risk for a person with type 2 diabetes who has not had a recognized myocardial infarction is the same as a non-diabetic individual who has already had a heart attack (4). People with diabetes have platelets that are hypersensitive to aggregating agents in vitro, and there is increased platelet thromboxane synthesis that is blocked by low doses of aspirin (5). It is generally accepted that the antithrombotic effect of aspirin is mediated by its inhibition of thromboxane synthesis. Results from primary and secondary prevention trials in people with diabetes support the final recommendation that adult diabetic individuals at high risk for vascular disease should be treated with 81–325 mg enteric-coated aspirin daily (1,2).

The definition of high vascular risk is of obvious importance. The ADA recommended that the presence of at least one of the following cardiovascular risk factors in a patient with diabetes confers eligibility for aspirin therapy: family history of heart attack, smoking, body weight in excess of 120% of normal, hypertension, macro- or microalbuminuria, or dyslipidemia. Important questions are 1) how many individuals with diabetes in the U.S. would qualify for aspirin therapy? and 2) of this number, how many are regularly taking aspirin therapy?

In this issue of Diabetes Care, Rolka et al. (6) have addressed these two questions. They have reviewed data from the Third National Health and Nutrition Examination Study (NHANES III), which was conducted between 1988 and 1994. There were 1,503 adults (≥21 years of age) with diabetes; 27% of these had a history of cardiovascular disease (CVD), and an additional 71% had at least one cardiovascular risk factor. Thus, according to ADA guidelines, virtually every adult diabetic individual in the study was eligible for aspirin therapy. However, only 20% (95% CI 16–23) gave a history of regular aspirin use. Aspirin was used regularly by 37% of those with CVD, but only by 13% with one or more risk factors. Clearly, an inexpensive and effective form of preventive therapy was not widely used by diabetic individuals.

Why should this be the case? The survey was completed 3 years before the ADA’s position statement, so a lack of appreciation of the evidence probably existed. However, data from other sources have also indicated that aspirin therapy is underutilized, even as a secondary prevention strategy in eligible individuals (6). There are other issues that may have influenced the results. Much of the early collaborative trial data was obtained primarily in men. Analysis of data in the Nurses Health Study showed a correlation between aspirin use and cardiovascular events, but intervention data have not yet appeared (7). However, it is clear that women with type 2 diabetes are at high risk for cardiovascular events. Recent studies of the NHANES I cohort have shown a 23% increase in cardiovascular mortality in diabetic women in comparison with a decrease of 27% in non-diabetic women between 1971 and 1984 (8). Two excellent prospective trials, the Early Treatment Diabetic Retinopathy Study (ETDRS) (9) and the Hypertension Optimal Treatment (HOT) study (10), contained many women with diabetes and showed significant reductions in the risk for the first myocardial infarction with aspirin therapy. The HOT study helped to reduce concern about cerebrovascular bleeding as a complication. In this study, there was a 15% reduction in the risk for major cardiovascular events and a 36% reduction in the risk for myocardial infarction in hypertensive diabetic individuals who were carefully treated with antihypertensive agents.

What is the optimal dosage of aspirin to prevent cardiovascular events and to avoid such complications as gastrointestinal or cerebrovascular bleeding? The platelet cyclooxygenase enzyme is exquisitely sensitive to low doses of aspirin, and virtually complete inhibition of thromboxane synthesis will occur with as little as 40 mg aspirin daily. In the meta-analysis of secondary prevention trials (3), efficacy was found at daily doses as low as 75 mg/day, and a range of 75–325 mg/day was equally effective. Because gastrointestinal and cerebrovascular hemorrhages are dose-related, and because no further cardioprotective benefit is seen with doses >325 mg/day, this dosage range was chosen by the ADA. To minimize stomach irritation, entericoated preparations were recommended.

Aspirin in low doses is a weak inhibitor of renal prostaglandin synthesis, so reduced renal function is not a complication of low-dose aspirin therapy. Platelet turnover may be increased in diabetes. When low doses of aspirin are used once daily, it has been shown that a small population of newly released platelets will manufacture thromboxane. In one study of low-dose aspirin, thromboxane release was suppressed 98%, and the residual 2% production was proaggregatory (11). However, this observation does not appear to be of clinical significance in view of the consistent cardiovascular risk reductions seen in controlled clinical trials in people with diabetes.

There are effects of high doses of aspirin on hemostasis that may not be due to inhibition of platelet thromboxane production. Enhanced fibrinolysis has been reported with 650 mg aspirin twice daily. High doses of aspirin may inhibit the release of plasminogen activator inhibitor 1 (PAI-1) from its storage site in the platelet α granules. Platelet PAI-1 accounts for ~90% of total body stores, and its storage and release are higher in type 2 diabetic subjects than in control subjects (12). In one study, a single 650-mg dose of aspirin inhibited arachidonic acid–induced release of PAI-1 by platelets and was associated
with a 60% fall in plasma PAI-1 levels (13). This area of research has received little attention to date; however, more studies of aspirin’s effects on fibrinolysis and platelet PAI-1 release are indicated.

Plasma levels of C-reactive protein, a marker of inflammation, may be elevated in people with diabetes. In the U.S. Physicians Health Study, C-reactive protein was a risk marker for cardiovascular events, and randomization to 325 mg aspirin every other day led to a 55% reduction in the risk for myocardial infarction in those with the highest C-reactive protein levels (14). An anti-inflammatory mechanism was suggested.

Rolka et al. (6) make the excellent suggestion that aspirin use should be incorporated in such programs as the Diabetes Quality Improvement Program (DQIP) and the Health Plan Employer Data and Information Set (HEDIS). Outcomes of diabetes education are currently under development by the National Diabetes Education Outcomes System (NDEOS). Incorporation of aspirin use as a measure used in this system could also encourage regular use of aspirin by people with diabetes. Low-dose aspirin therapy is a simple inexpensive medication with potential medical benefits that clearly outweigh its risks in people with type 2 diabetes.

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References