

Aspirin Therapy in Diabetes

AMERICAN DIABETES ASSOCIATION

People with diabetes have a two- to fourfold increase in the risk of dying from the complications of cardiovascular disease. Both men and women are at increased risk. Atherosclerosis and vascular thrombosis are major contributors, and it is generally accepted that platelets are contributory. Platelets from men and women with diabetes are often hypersensitive in vitro to platelet aggregating agents. A major mechanism is increased production of thromboxane, a potent vasoconstrictor and platelet aggregant. Investigators have found evidence in vivo of excess thromboxane release in type 2 diabetic patients with cardiovascular disease. Aspirin blocks thromboxane synthesis by acetylating platelet cyclooxygenase and has been used as a primary and secondary strategy to prevent cardiovascular events in nondiabetic and diabetic individuals. Meta-analyses of these studies and large-scale collaborative trials in men and women with diabetes support the view that low-dose aspirin therapy should be prescribed as a secondary prevention strategy, if no contraindications exist. Substantial evidence suggests that low-dose aspirin therapy should also be used as a primary prevention strategy in men and women with diabetes who are at high risk (over age 40 or with other CVD risk factors) for cardiovascular events (1–3). Despite its proven efficacy, aspirin therapy is underutilized in patients with diabetes. Available data suggest that less than half of eligible patients are being treated with aspirin.

EFFICACY

Secondary prevention trials

A meta-analysis of 145 prospective controlled trials of antiplatelet therapy in men and women after myocardial infarction, stroke or transient ischemic attack, or

positive cardiovascular history (vascular surgery, angioplasty, angina, etc.) has been reported by the Anti-Platelet Trialists (APT) (4). Reductions in vascular events were about one-quarter in each of these categories, and diabetic subjects had risk reductions that were comparable to nondiabetic individuals. There was a trend toward increased risk reductions with doses of aspirin between 75 and 162 mg/day. It was estimated that 38 ± 12 vascular events per 1,000 diabetic patients would be prevented if they were treated with aspirin as a secondary prevention strategy. Comparable results were seen in males and females.

Primary prevention trials

Two studies have examined the effect of aspirin in primary prevention and have included patients with diabetes. The U.S. Physicians' Health Study (5) was a primary prevention trial in which a low-dose aspirin regimen (325 mg every other day) was compared with placebo in male physicians. There was a 44% risk reduction in the treated group, and subgroup analyses in the diabetic physicians revealed a reduction in myocardial infarction from 10.1% (placebo) to 4.0% (aspirin), yielding a relative risk of 0.39 for the diabetic men on aspirin therapy.

These results are supported by the Early Treatment Diabetic Retinopathy Study (ETDRS), a mixed primary and secondary prevention trial (6). This population consisted of type 1 and type 2 diabetic men and women, about 48% of whom had a history of cardiovascular disease. The study, therefore, may be viewed as a mixed primary and secondary prevention trial. The relative risk for myocardial infarction in the first 5 years in those

randomized to aspirin therapy was lowered significantly to 0.72 (CI 0.55–0.95).

The Hypertension Optimal Treatment (HOT) Trial examined the effects of 75 mg/day of aspirin vs. placebo in 18,790 hypertensive patients who were randomized to achieve diastolic blood pressure goals of 90, 85, or 80 mmHg (7). Aspirin significantly reduced cardiovascular events by 15% and myocardial infarction by 36%. This study provides further evidence for the efficacy and safety of aspirin therapy in diabetic patients with systolic blood pressure less than 160 mmHg.

SAFETY

— A major risk of aspirin therapy is gastric mucosal injury and gastrointestinal hemorrhage. Aspirin increases the relative risk of major gastrointestinal bleeding (relative risk 1.6), even with relatively low doses. Enteric coating does not appear to reduce such risk. Minor bleeding episodes (epistaxis, bruising, etc.) are also increased. A well-conducted meta-analysis of primary and secondary prevention trials found a moderately increased relative risk of hemorrhagic stroke in aspirin users. Absolute risk was approximately 1 event per 1,000 users over 3–5 years. Risk did not appear to differ significantly by dosage, but power to detect such differences was limited. Contraindications to aspirin therapy include allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease.

The ETDRS (6) established that aspirin therapy was not associated with an increased risk for retinal or vitreous hemorrhage. Since the primary endpoint in this trial was retinopathy and maculopathy, these serial observations by ophthalmologists, using retinal photography in a group of diabetic subjects with retinopathy, established conclusively that aspirin therapy conveyed no increase in benefit or in risk regarding progression of diabetic retinopathy and maculopathy.

Regular use of nonsteroidal anti-

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Abbreviations: APT, Anti-Platelet Trialists; ETDRS, Early Treatment Diabetic Retinopathy Study.

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inflammatory drugs may increase the risk for chronic renal disease and may impair blood pressure control in hypertensive patients. However, a low dose of aspirin is a very weak inhibitor of renal prostaglandin synthesis and has no clinically significant effect on renal function or on blood pressure control.

DOSAGE — The platelet release reaction is exquisitely sensitive to inhibition by aspirin. In this regard, it has been shown that a dose as low as 75 mg of enteric-coated aspirin is just as effective as higher doses of either plain or enteric-coated aspirin in inhibiting thromboxane synthesis. When platelet turnover is rapid, as may be the case with diabetic vascular disease, the steady plasma aspirin concentration from enteric preparations theoretically allows for constant suppression of thromboxane synthesis.

The APT meta-analysis (4) explored the results achieved with various doses of aspirin, alone or in combination with other antiplatelet agents, including dipyridamole and sulfapyrazone. Whereas risk reductions of $21 \pm 4\%$ were seen in cardiovascular events in 30 trials in which doses of 500–1,500 mg/day were used, a trend for greater risk reductions of $29 \pm 7\%$ was seen in 5,000 patients in whom doses of 75 mg/day were used. Comparable risk reductions of $28 \pm 3\%$ were seen in 12 trials in which doses of 160–325 mg/day were used. No evidence was found that combinations of aspirin with other antiplatelet drugs were any more effective than aspirin alone. Because low-dose aspirin (75–162 mg/day) appears to be equally or more effective, and possibly to have lower risk than higher doses, low-dose aspirin should be recommended routinely.

SPECIAL CONSIDERATIONS — The meta-analysis of the secondary prevention trials provided sample sizes that were adequate to determine aspirin's efficacy in a wide variety of patients. Separate analyses were done in males and females, patients with or without diastolic hypertension, those over or under age 65 years, and in diabetic and nondiabetic subjects. Proportional benefits of aspirin therapy were seen in all subgroups studied. Abs-

olute benefit was greater among those at high risk (over age 65 years, diastolic hypertension, diabetes). Intervention trials in women are underway. Case-control studies have shown that the use of one to six aspirins a week is associated with a reduced risk for myocardial infarction in women. Further, the APT meta-analysis of secondary prevention trials showed no difference in responses in men and women, and the ETDRS included men and women in the trial. Diabetes appears to place women at high risk for myocardial infarction. For these reasons, recommendations in this article apply to men and women with diabetes.

Although data are limited in diabetic subjects, agents such as clopidogrel may be considered as a substitute in the case of aspirin allergy. In one large study (CAPRIE), clopidogrel (75 mg) was slightly more effective than aspirin (325 mg) in reducing the combined risk of stroke, myocardial infarction, or vascular death in diabetic and nondiabetic subjects (8). Other approaches, such as blocking a key platelet receptor (GPIIb/IIIa), are under study.

RECOMMENDATIONS

1. Use aspirin therapy (75–162 mg/day) as a secondary prevention strategy in diabetic men and women with a history of myocardial infarction, vascular bypass procedure, stroke or transient ischemic attack, peripheral vascular disease, claudication, and/or angina. (A)
2. Use aspirin therapy (75–162 mg/day) as a primary prevention strategy in men and women with type 2 diabetes at increased cardiovascular risk, including those over 40 years of age or who have additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, albuminuria). (A)
3. Use aspirin therapy as a primary prevention strategy in men and women with type 1 diabetes at increased cardiovascular risk, including those over 40 years of age or who have additional risk factors (family history of CVD, hypertension, smoking, dyslipidemia, albuminuria). (C)
4. People with aspirin allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease are not candidates for aspirin therapy. Other antiplatelet agents may be a reasonable alternative for patients with high risk. (E)
5. Aspirin therapy should not be recommended for patients under the age of 21 years because of the increased risk of Reye's syndrome associated with aspirin use in this population. People under the age of 30 have generally not been studied. (E)

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