

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 cyclo-oxygenase 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 for cardiovascular events (1).

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). 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 of 325 mg/day or less. 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.

These results are supported by the Early Treatment Diabetic Retinopathy Study (ETDRS). 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 (2). There were 1,501 diabetic subjects in this trial. Aspirin significantly reduced cardiovascular events by 15% and myocardial infarction by 36%. The relative effects of aspirin were similar in nondiabetic and diabetic subjects. Fatal bleeding episodes including intracerebral bleeding were equal in the aspirin and placebo groups, while nonfatal minor bleeding episodes were more common in the aspirin group. This study provides further evidence for the efficacy and safety of aspirin therapy in diabetic patients with well-controlled hypertension.

Primary prevention trials

The U.S. Physicians' Health Study 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.

SAFETY— A major risk of aspirin therapy is gastric mucosal injury and gastrointestinal hemorrhage. These effects are dose related and are reduced to placebo levels when enteric-coated preparations of 75–325 mg are used once daily. Minor bleeding episodes (epistaxis, bruising, etc.) may occur at low doses, probably from the effect of aspirin to inhibit the platelet release reaction. In several prospective studies, a trend for an increase in hemorrhagic stroke has been seen, but has not reached statistical significance. Contraindications to aspirin therapy include allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease.

The ETDRS 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-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

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

icant 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 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.

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. Absolute 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 (3). Other approaches, such as blocking a key platelet receptor (GPIIb/IIIa), are under study.

Aspirin therapy has been shown in secondary analysis to lessen the beneficial effects of ACE inhibitors in patients with established CVD (e.g., prior myocardial infarction, angina, congestive heart failure) (4). Therefore, alternative antiplatelet agents should be considered in these patients until more definitive results are available.

RECOMMENDATIONS

1. Use aspirin therapy as a secondary prevention strategy in diabetic men and women who have evidence of large vessel disease. This includes 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.
2. In addition to treating the primary cardiovascular risk factor(s) identified, consider aspirin therapy as a primary prevention strategy in high-risk men and women with type 1 or type 2 diabetes. This includes diabetic subjects with the following:
 - A family history of coronary heart disease

- Cigarette smoking
- Hypertension
- Obesity ($>120\%$ desirable weight); BMI $>27.3 \text{ kg/m}^2$ in women, $>27.8 \text{ kg/m}^2$ in men
- Albuminuria (micro or macro)
- Lipids:
 - Cholesterol $>200 \text{ mg/dl}$
 - LDL cholesterol $\geq 100 \text{ mg/dl}$
 - HDL cholesterol $<45 \text{ mg/dl}$ in men and $<55 \text{ mg/dl}$ in women
 - Triglycerides $>200 \text{ mg/dl}$
- Age >30 years

Use of aspirin has not been studied in diabetic individuals under the age of 30 years.

3. Use enteric-coated aspirin in doses of 81–325 mg/day.
4. People with aspirin allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease are not candidates for aspirin therapy.
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.

References

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