

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).

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 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 $20 \pm 4\%$ were seen in cardiovascular events in 29 trials in which doses of

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

500–1,500 mg/day were used; a trend for greater risk reduction of $28 \pm 11\%$ was seen in seven trials in which aspirin doses of 40–150 mg/day were used. Intermediate results were seen in 12 trials in which 160–325 mg/day was 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 or 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, antiplatelet agents such as ticlopidine may be considered as a substitute in the case of aspirin allergy. One large-scale collaborative trial (Ticlopidine Microangiopathy of Diabetes [TIMAD]) showed that ticlopidine may slow progression of retinopathy. Other approaches, such as blocking a key platelet receptor (GPIIb/IIIa), are under study.

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 >28 in women, >27.3 in men
- Albuminuria (micro or macro)
- Lipids:
 - Cholesterol >200 mg/dl
 - LDL cholesterol >130 mg/dl
 - HDL cholesterol <40 mg/dl
 - Triglycerides >250 mg/dl

3. The following may not be candidates for aspirin therapy:

- Diabetic individuals under the age of 30 years without cardiovascular risk factors listed above.
- People with aspirin allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding, and clinically active hepatic disease.

4. Use enteric-coated aspirin in doses of 81–325 mg/day.

References

1. Colwell JA: Aspirin therapy in diabetes (Technical Review). *Diabetes Care* 20:1767–1771, 1997