Aspirin Therapy in Diabetes

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People with diabetes have a two- to fourfold increase in the risk of dying from the complications of cardiovascular disease (1). Atherosclerosis and vascular thrombosis are major contributors. In type 2 diabetes, the increased risk is present before fasting hyperglycemia is seen. These individuals often have a sedentary lifestyle, poor physical conditioning, insulin resistance, centripetal obesity, hypertension, and dyslipidemia, and are in a prothrombotic state. Chronic hyperglycemia is then added to these risk markers. Microalbuminuria may precede hyperglycemia in type 2 diabetes, occurs in 30–40% of those individuals after diabetes is established, and is a predictor of cardiovascular events. In type 1 diabetes, microalbuminuria is a predictor of renal failure and cardiovascular events. An all-inclusive approach that focuses on early risk factor (or marker) identification and management to prevent or delay accelerated atherosclerosis and thrombosis in diabetes is an attractive strategy (2).

PLATELET FUNCTION IN DIABETES

— Platelets from people with diabetes are often hypersensitive in vitro to platelet aggregating agents (3). A major mechanism is increased production of thromboxane, a potent vasoconstrictor and platelet aggregant (4). Investigators have found evidence in vivo of excess thromboxane release in type 2 diabetic patients with cardiovascular disease (5). 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 large-scale collaborative trials in people with diabetes support the view that low-dose aspirin therapy should be prescribed as a secondary prevention strategy in diabetic subjects if no contraindications exist (6). Substantial evidence suggests that low-dose aspirin therapy should also be used as a primary prevention strategy in diabetic patients who are at high risk for cardiovascular events (7,8).

PHARMACOLOGY OF ASPIRIN'S ACTION ON PLATELETS

— It has long been recognized that aspirin will induce a long-lasting platelet defect that is characterized by a prolonged bleeding time. The major mechanism is aspirin's permanent inactivation of prostaglandin G/H synthase, the enzyme that catalyzes the conversion of arachidonic acid to prostaglandins G2 and H2. These are the precursors of thromboxane, which is a potent platelet proaggregant. Aspirin has been shown to selectively acetylate the hydroxy group of a serine residue at position 529 in the polypeptide chain of platelet G/H synthase, leading to an irreversible loss of cyclo-oxygenase activity (9,10).

Aspirin leads to an immediate inhibition of thromboxane synthesis in normal subjects and in diabetic individuals. The effect is rapid and probably begins in the hepatic portal system as soon as aspirin is absorbed from the gastrointestinal tract. Because platelets do not have the synthetic machinery to make new protein, there is no enzyme recovery in exposed platelets during their life span, which averages 8–10 days. Each day, new platelets enter the bloodstream at a rate of ~10% per day. This rate may be accentuated in people with diabetes (11), leading to special considerations about aspirin therapy in these patients.

A trial of repeated low-dose aspirin therapy (25 or 100 mg aspirin every 6 h) on platelet thromboxane release in type 1 and 2 diabetic patients with micro- or macroangiopathy has been reported by DeMinno et al. (11). Probably because of an accelerated platelet turnover, there were time gaps between doses in which platelets from diabetic patients would produce thromboxane. This was apparently due to the rapid turnover of platelets in people with diabetes and angiopathy. While the absolute amount of thromboxane released by platelets was less than 2% of that released before aspirin therapy, it was greater than that released by platelets from nondiabetic control subjects under the same dosing conditions. To overcome this issue, these authors recommended that low-dose slow-release preparations of aspirin be used to produce steady blood levels and continuous suppression of platelet aggregation and thromboxane formation.

The effect of repeated daily doses of aspirin of <100 mg/day has been shown to be cumulative. Thus 30–50 mg of aspirin leads to complete inhibition of platelet thromboxane synthesis after 7–10 days. Larger doses of aspirin have similar cumulative effects and, if given as a loading dose, will result in immediate inhibition of thromboxane synthesis. Doses of 300 mg/day or more may have other effects, including decreased thrombin formation, increased plasminogen activation, and increased hemorrhagic complications. In this article, we will review results from primary and secondary prevention trials and will comment on safety, dosage, and special considerations regarding aspirin therapy. Based on these considerations, we will make recommendations for aspirin therapy in diabetes.

EFFICACY

Primary prevention trials: U.S. Physicians' Health Study

There is one trial in which aspirin therapy was compared with placebo in patients with diabetes and no apparent vascular disease: the U.S. Physicians' Health Study (8). This was a randomized double-blind placebo-controlled trial in adult men to determine whether low-dose aspirin (325 mg every other day) would decrease car-

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Abbreviations: APT, Antiplatelet Trialists' Collaboration; ECG, electrocardiogram; ETDRS, Early Treatment Diabetic Retinopathy Study; PAI-1, plasminogen activator inhibitor 1; RR, relative risk.

Table 1—*Meta-analysis: 29 antiplatelet trials in high-risk patients (secondary prevention)*

Patients	Patients with vascular events/patients with no events		Vascular events prevented/1,000 patients	
	Control	Antiplatelet treatment	Antiplatelet treatment	*P*
Nondiabetic	3,466/21,197	2,700/21,136	36 ± 3 (SD)	<0.00001
% of patients	16.4	12.8	—	—
Diabetic	502/2,254	415/2,248	38 ± 12 (SD)	<0.002
% of patients	22.3	18.5	—	—

diovascular mortality. Results from 22,071 participants, with an average follow-up time of ~5 years, have been reported. There was a 44% reduction in the risk of myocardial infarction in the entire group (relative risk [RR] 0.56; 95% CI 0.45–0.70, $P < 0.00001$). There was no reduction in mortality from cardiovascular causes. There was a suggestion of an increase in stroke in the aspirin group, which, however, was not statistically significant.

Subgroup analyses were done in a group of 533 diabetic individuals randomized to aspirin or to placebo. Myocardial infarction occurred in 11/275 (4.0%) of diabetic men assigned to aspirin therapy and in 26/258 (10.1%) diabetic men assigned to placebo therapy. In nondiabetic men, 231/10,763 (2.0%) had myocardial infarction on placebo therapy, while 128/10,750 (1.2%) had this event on aspirin therapy. Although the diabetic men were at substantially higher risk for infarction than the nondiabetic men, the relative risk of myocardial infarction for the diabetic individuals on aspirin therapy was 0.39, while it was 0.60 in the entire cohort. The difference between these risk reductions was not significant ($P = 0.22$), indicating that aspirin therapy was as effective in diabetic men as in nondiabetic men (8).

Primary and secondary prevention trial: Early Treatment Diabetic Retinopathy Study (ETDRS)

The largest study of aspirin prophylaxis in diabetes is the Early Treatment Diabetic Retinopathy Study (ETDRS) (7). In this study, 3,711 male and female diabetic patients, 30% of whom had type 1 diabetes, were randomly assigned to aspirin (650 mg/day) or to placebo therapy. Mean follow-up time was 5 years. There was an insignificant reduction in total mortality in aspirin-treated patients (RR 0.91, 99% CI 0.75–1.11). Larger differences were noted in fatal and nonfatal myocardial infarctions. There were 289 myocardial infarctions in the aspirin group (16%) and 336 in the placebo group (18%, $P = 0.038$). When results for the first 5 years of the study were analyzed, the event rates were 9.1% (aspirin) and 12.3% (placebo). The relative risk for myocardial infarction in the aspirin group was 0.72 (99% CI 0.55–0.95).

The patients in this trial may be viewed as a group at high risk for cardiovascular disease. Of the patients, 84% were on insulin therapy, 83% had a known duration of diabetes of over 10 years, 42% had HbA_{1c} >10%, 36% had cholesterol levels >240 mg/dl, and 48% had a positive cardiovascular history.

It is apparent, therefore, that this trial cannot be viewed solely as a primary prevention trial. Rather, it is a study of aspirin use in a heterogeneous group of type 1 and type 2 patients, some of whom had known cardiovascular disease and some of whom did not. Many had cardiovascular risk factors. All of these patients had diabetic retinopathy and/or maculopathy, and the majority had ocular findings that were more advanced than simple background retinopathy.

A very significant finding in this study was the observation that there was no increased risk of retinal or vitreous bleeding, even with relatively high-dose aspirin therapy in diabetic patients with established retinopathy. Further, there was no significant increase of gastrointestinal bleeding or hemorrhagic stroke in the study.

Secondary prevention trials

Prolonged aspirin therapy has been shown to offer significant protection against myocardial infarction, stroke, and vascular deaths in patients with clinically apparent vascular disease (6). In a landmark meta-analysis of 145 randomized trials of antiplatelet therapy in nondiabetic and diabetic people who had already had a major vascular event (6), prolonged therapy was definitely protective in four main high-risk categories: *1*) acute myocardial infarction, *2*) past history of myocardial infarction, *3*) past history of stroke or transient ischemic attack, and *4*) other relevant vascular history: angina, vascular surgery, angioplasty, and peripheral vascular disease. Reductions in vascular events were about one-quarter in each of these four categories and were separately statistically different in middle versus old age, hypertensive versus nonhypertensive patients, and diabetic versus nondiabetic patients. In all, reductions in nonfatal myocardial infarction and in stroke were about one-third, and the risk reduction was about one-sixth in vascular deaths. There was no increase in nonvascular deaths.

Doses of 75–325 mg of aspirin were most widely used. Doses in this range appeared to be similarly effective. Some advantage of an initial loading dose was present. These results are summarized in Table 1.

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 (9,10). 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. In the U.S. Physicians' Health Study (8), there was a nonsignificant trend of an increase in hemorrhagic stroke. In the ETDRS (7), fatal or nonfatal stroke occurred in 5% of the group randomized to aspirin and 4.2% of those assigned to placebo (NS). Aspirin therapy has been shown to be an effective therapeutic strategy following a stroke or transient ischemic attack, and no studies have implicated enteric-coated aspirin in low doses as increasing the risk for stroke. It is of interest that the majority of strokes in diabetic patients are thrombotic, not hemorrhagic, in nature (12). This fact makes aspirin prophylaxis particularly attractive in

patients with diabetes. 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 other than aspirin may increase the risk for chronic renal disease and may impair blood pressure control in hypertensive patients (10). 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 Antiplatelet Trialists' Collaboration (APT), a meta-analysis of 145 secondary prevention trials (6), found no evidence that higher doses of aspirin (up to 1,500 mg daily) were any more effective than low doses (75–325 mg daily). This is what would be expected if the decreased risk for a major vascular event is primarily the result of inhibition of thromboxane synthesis by platelets. This cyclo-oxygenase enzyme system is exquisitely sensitive to aspirin doses as low as 75 mg daily, and it has been demonstrated that endothelial prostacyclin release is not inhibited at these low doses (13). Further, more recent studies of low-dose aspirin therapy in patients with unstable coronary syndromes or transient ischemic attack support the efficacy and low risk of 75 mg of aspirin daily. Recent reviews and editorials from the cardiovascular community are supportive. These views are summarized in a recent paper by Patrono (10).

The APT meta-analysis (6) explored the results achieved with various doses of aspirin, alone or in combination with other antiplatelet agents, including dipyridamole and sulfinpyrazone. Whereas risk reductions of 21 ± 4% (SD) were seen in cardiovascular events in 30 trials in which doses of 500–1,500 mg/day were used, a trend was seen for greater risk reduction of 28 ± 3% in 12 trials of 160–325 mg/day and of 26 ± 11% in 7 trials in which aspirin doses of 40–150 mg/day were used. No evidence was found that combinations of aspirin with other antiplatelet drugs were any more effective than aspirin alone.

One large study, the Second International Study of Infarct Survival (ISIS-2), has been used by some investigators to support a view that patients with diabetes may require a daily dosage >160 mg of an enteric-coated preparation (14). In this placebo-controlled study, 17,187 patients who entered the hospital up to 24 h after suspected acute myocardial infarction were randomly assigned to *1*) 1-h infusion of streptokinase, 2) 1 month of 160 mg/day enteric-coated aspirin, 3) both active treatments, or 4) neither active treatment. Streptokinase resulted in highly significant reduction in 5-week vascular mortality, and the combination of aspirin and streptokinase was superior to either agent alone. In patients who did not have diabetes, aspirin reduced nonfatal reinfarction and nonfatal stroke, and the differences in vascular mortality produced by aspirin were highly significant at a median follow-up of 15 months.

In this study (14), a subgroup of 645 patients with diabetes were given aspirin alone and 642 were given placebo. Vascular death (days 0–35) was equivalent in these two subgroups after admission for suspected myocardial infarction. Since streptokinase therapy was effective in the diabetic patients, some investigators have interpreted these data as suggesting that platelets from diabetic subjects are resistant to low doses of aspirin and that higher doses may be needed in diabetes. This is a generalization that is not warranted from this subgroup analysis. It gives no information on the key question of long-term low-dose aspirin use as a secondary preventive strategy. Most likely, in this acute clinical setting, a powerful prothrombotic tendency from diminished fibrinolytic activity was directly addressed by streptokinase therapy but not by inhibition of the platelet release reaction by aspirin. The study results should not be used as evidence in support of the use of high doses of aspirin as primary or secondary prevention strategy in people with diabetes.

SPECIAL CONSIDERATIONS — The meta-analysis of a large number of secondary prevention trials provided sample sizes that were adequate to determine aspirin's efficacy in a wide variety of patients (6). 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, with diastolic hypertension, with diabetes). 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 (15). 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 here apply to men and women with diabetes. Intervention trials of aspirin in women are now underway.

The majority of secondary prevention trials were done in people over the age of 30 years (6). The age range in the U.S. Physicians' Health Study (8) was 40–85 years, and 83% of the patients in the ETDRS (7) were >30 years of age. In view of this, and because the majority of people with diabetes under age 30 years have type 1 diabetes and appear to be at a relatively low risk for cardiovascular disease at that time, recommendations are confined to those age 30 years or greater.

Compliance with aspirin therapy does not appear to be a major issue in clinical trials (7,8). It can be taken once daily and is relatively inexpensive, and gastrointestinal side effects are minimized by low doses and enteric-coated preparations. Therefore, its use in clinical practice does not raise serious adherence issues.

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 (16). In this study, ticlopidine therapy was stopped in 13.2% of enrolled patients vs. 3.3% in the placebo group. Side effects from ticlopidine exceed those from aspirin therapy and include diarrhea, rash, and neutropenia as major problems.

Current research is underway on the effects of modifying the GPIIb/IIIa platelet receptor, which plays a critical role in

platelet aggregation and thrombus formation (17). Clinical trials are also in progress with agents such as ridogrel and picotamide, which combine blockage of thromboxane synthase and thromboxane receptors. While these are promising agents that affect different steps in platelet function, there are no large-scale trial data in diabetic patients. Indications for use must await the results of such trials.

DISCUSSION — In a recent series of studies (18,19), Yudkin has concluded that a low dose of enteric-coated aspirin is indicated as a preventive strategy in high-risk diabetic patients.

While this appears to be a sensible approach, it requires definition of a high-risk diabetic patient. There is general agreement that diabetic individuals who have had one major vascular event, such as a myocardial infarction, stroke, or transient ischemic attack, or have had vascular surgery are at high risk for future events. Further, the APT analysis of the secondary prevention trial data strongly supports the use of low-dose aspirin therapy in this group of patients. In addition, there is little controversy over the fact that addition of any of the classical risk factors (hypercholesterolemia, cigarette smoking, and/or hypertension) substantially magnifies the risk that people with diabetes have for cardiovascular events (1). Thus, patients in any of these groups could logically be defined as high risk and would therefore be candidates for aspirin therapy.

It is important to recognize that this is a very large group of individuals. Depending on the population studied, close to 50% of people with type 2 diabetes will have evidence of cardiovascular disease or will have one or more cardiovascular risk factors at the time of diagnosis of the disease. Thus, in the University Group Diabetes Program (UGDP), a study of type 2 patients who entered within 1 year of the diagnosis of diabetes (20), 46% had vascular disease or one or more cardiovascular risk factors (hypertension, digitalis use, angina, significant electrocardiogram [ECG] changes, and/or cholesterol >300 mg/dl). Cardiovascular disease at the time of diagnosis was seen in the recent data from the U.K. Prospective Diabetes Study (UKPDS) in patients with recently diagnosed type 2 diabetes (21). In this study, an abnormal ECG was seen in 18%, absent foot pulses in 13%, and hypertension in 35%, and myocardial infarction, claudication, or stroke was present in 1–3% at entry into the study. In Finland, a country with a high prevalence of coronary artery disease, newly diagnosed type 2 diabetic patients had an 18% prevalence of myocardial infarction (22). By ECG criteria, 32% of men and 42% of women with diabetes had some evidence of coronary artery disease.

These findings at the time of diagnosis of type 2 diabetes should not be surprising. Autopsy studies have provided evidence that histopathologic characteristics of early atherosclerosis are present in the right coronary artery of young individuals (ages 15–34 years) who have elevated HbA_{1c} levels (23). Many studies have documented that individuals in the prediabetic or impaired glucose tolerance stage of type 2 diabetes have a high cardiovascular risk and often have cardiovascular risk factors other than glycemia that are operative (i.e., hypertension, insulin resistance, hyperlipidemia, and elevated plasminogen activator inhibitor 1 [PAI-1] levels). For instance, diabetic individuals in the San Antonio Heart Study had an atherogenic mix of risk factors (elevated total and LDL cholesterol, triglycerides, glucose, insulin, BMI, blood pressure, and low levels of HDL cholesterol) when compared with control nondiabetic individuals (24). As these authors note, the clock for coronary heart disease probably starts ticking before the onset of clinical diabetes in many patients.

Micro- and macroalbuminuria are predictors of vascular death in individuals with type 2 diabetes (25) and predict renal failure and vascular events in people with type 1 diabetes (26). Microalbuminuria may be present before the diagnosis of type 2 diabetes is made (27). Thus, albuminuria, even in small amounts, is viewed as a risk marker for cardiovascular disease in type 1 and type 2 diabetes.

There are other risk markers that are predictors of cardiovascular events in people with diabetes. These include elevated PAI-1 levels (28,29) and high plasma fibrinogen concentrations (30).

When one reflects on these findings, it is likely that a majority of patients with type 2 diabetes in the U.S. are at high risk for cardiovascular disease. This view is supported by studies of type 2 diabetic patients of long duration, who were found to be candidates (on glycemic-control grounds) for insulin therapy. In one recent study of insulin therapy in type 2 diabetes, 38% of these patients had clear historical evidence of cardiovascular disease. This included prior myocardial infarction, angina, claudication, cerebrovascular accident, and history of coronary artery bypass graft. When more sensitive methods were used (including ambulatory ECG and low left ventricular ejection fraction by MUGA scan), 82% of this group had evidence of cardiovascular disease (31). At this stage of type 2 diabetes, a high yield of subsequent cardiovascular events was seen, and these events were best predicted by a previous finding of cardiovascular disease. In the ETDRS, baseline characteristics for those patients categorized as having type 2 diabetes included 70% with a cardiovascular disease history (7).

Thus, it is evident that people with type 2 diabetes are at high risk for cardiovascular events from the time of diagnosis, and this risk is often present in the prediabetic phase of the disease. On balance, it may be more difficult to define which patients are not at high risk and who, therefore, would not be candidates for aspirin therapy. This probably can be best defined as type 1 or type 2 diabetic patients with the absence of a previous cardiovascular event, who also do not have evidence of large vessel disease or of cardiovascular risk factors, except for diabetes.

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