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Multifactorial Aspects of the Treatment of the Type II Diabetic Patient

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People with type II diabetes have a twofold to fourfold increased risk of dying from the complications of cardiovascular disease. Atherosclerosis and vascular thrombosis are major contributors. The increased risk is present before fasting hyperglycemia is seen. These individuals often have a sedentary life-style, poor physical conditioning, insulin resistance, centripetal obesity, hypertension, dyslipidemia, and a prothrombotic state. Chronic hyperglycemia is then added to these risk markers. Microalbuminuria may precede hyperglycemia in type II diabetes, occurs in 30% to 40% of these individuals after diabetes is established, and is a predictor of cardiovascular events. Early intervention in high-risk individuals may delay or prevent fasting hyperglycemia. An all-inclusive approach that focuses on early risk factor (or marker) identification and management to prevent or delay accelerated atherosclerosis and thrombosis in type II diabetes is an attractive strategy. However, the database to support this strategy is limited. In particular, large-scale prospective trial data are not available to support the concept of intensive glycemic regulation to prevent progression of macrovascular disease in type II diabetes. This is in contrast to the situation regarding microvascular disease of the eyes and kidneys. Recently, indirect data of a correlative nature have emerged, and short- and long-term prospective trials at early and late stages of type II diabetes are now being reported. These studies are analyzed and interpreted in this report. In contrast, the database to support an intensive antiplatelet regimen to prevent vascular thrombotic events in people with type II diabetes is large, and these studies are reviewed. They are of a type and magnitude to allow definite recommendations for aspirin therapy in type II diabetes. Aggressive therapy directed at hypertension, hyperlipidemia, and elevated urinary albumin in people with type II diabetes appears to be indicated. Increased attention to the multifactorial aspects of treatment of the type II diabetic patient is needed. Our present challenge is to translate these findings for patients and primary health care providers so that effective actions may be implemented.
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THE LEADING CAUSE of mortality and morbidity in people with type II diabetes is cardiovascular disease. People with diabetes have a twofold to fourfold increased risk of dying of heart disease, and the addition of classic risk factors (hypertension, elevated serum cholesterol, and cigarette smoking) increases this risk substantially—perhaps to a greater extent than in nondiabetic individuals.[1] In addition, there are a number of other cardiovascular risk markers that appear to contribute to the pathogenesis of atherosclerosis and thrombosis in diabetes mellitus. The purpose of this report is to review clinical research data that will allow us to make general recommendations for cardiovascular preventative strategies for people with type II diabetes. The emphasis is on large-scale clinical trials that address intensive glycemic management and antiplatelet medication in diabetes.

HYPERGLYCEMIA

Table 1 summarizes studies[2-8] that have indicated a relationship between hyperglycemia and cardiovascular disease. Many of these studies are of recent origin. In all, they indicate that hyperglycemia may contribute to macrovascular disease in diabetes.

Four collaborative clinical trials on the effect of intensive glycemic regulation on macrovascular endpoints in type II diabetes have been undertaken. Three trials[9-11] have studied intensive management in type II diabetes from the time of first diagnosis of diabetes[9,10] or shortly after diagnosis.[11] Rates of major cardiovascular event in patients studied at this early stage of type II diabetes are approximately 1% to 3% per year. These rates do not appear to be modified by intensive insulin therapy, and the results with oral sulfonylurea agents are controversial. When chronic type II diabetes patients are studied (after failure of glycemic control with oral agents), insulin therapy is

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Table 1. Hyperglycemia and Cardiovascular Disease: Type II Diabetes

- Hemoglobin A_{1c} predicts coronary heart disease mortality and events.[2]
- Average blood glucose values correlate with mortality from ischemic heart disease and other cardiovascular events.[3,4]
- Postprandial glycemia is correlated with deaths from coronary heart disease.[5]
- Autopsy studies in young individuals (ages 15-34) who died of external causes show a correlation between glycohemoglobin and fatty streaks and raised lesions in the coronary artery.[6]
- Glucose contributes to atherosclerosis and thrombosis, as well as to vascular wall changes by many mechanisms, including protein glycation.[7]
- Hyperglycemia correlates with increased intimal and medial thickness of the carotid artery.[8]

associated with a very high rate of cardiovascular events. Preexisting cardiovascular disease is the major contributor.

It is apparent from these data that the effect of insulin therapy on the progression of macrovascular disease in type II diabetes is not clear. The United Kingdom Prospective Diabetes Study[10] is a multicenter trial in which newly diagnosed type II diabetic patients are randomly assigned to treatment with diet alone or more intensive glycemic regulation with oral agents or insulin. The final report will be published in 1998, after a median duration from randomization of 11 years. The study has an 81% power at a level of 1% significance of detecting whether a strategy of intensive glycemic regulation causes a 15% decrease (or increase) in the incidence of major vascular complications. For this primary analysis, advanced microvascular and macrovascular endpoints will be pooled. Thus, an effect of more intensive glycemic regulation on macrovascular endpoints alone will depend on subgroup analysis, and the study may not have the power to detect a significant difference between the treatment groups. Nevertheless, it is clear that this trial will provide guidance on strategies to use in newly diagnosed type II diabetic patients.

It is of interest that there is evidence that intensification of insulin therapy will improve short-term mortality (<1 year) in patients with diabetes and acute myocardial infarction, perhaps by inhibiting free fatty acid release. The DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study[12] showed that a group of people with type II diabetes who were randomized to an acutely administered insulin and glucose infusion shortly after an acute myocardial infarction and subsequently treated with multiple-dose insulin therapy had a decreased mortality rate after 1 year (18.6%) compared with those who did not receive this therapy (26.1%, $P = .027$). The effect was particularly apparent in low-risk subjects (8.6% *v* 18.0%, $P = .02$). Thus, insulin-glucose infusion followed by multiple-dose insulin administration will improve the short-term prognosis in diabetic patients after an acute myocardial infarction. On the other hand, the early mortality rates are high, and surviving patients are at a high risk for multiple future cardiovascular events while on insulin therapy.[13]

In conclusion, associations and correlations between hyperglycemia and cardiovascular disease are present, and a role for hyperglycemia in the pathogenesis of atherosclerosis is postulated. However, long-term clinical trials at various stages of type II diabetes to assess the relative benefits and risks of intensive glycemic regulation on cardiovascular endpoints are badly needed to guide clinical management.

PROTHROMBOTIC STATE

There are many changes in the intrinsic coagulation system, platelet function, and fibrinolysis that have been described in diabetes.[14] Therapeutically, the best case can be made for considering agents that affect platelet function. Since the clinical trial database is unusually robust in this area, a thorough consideration is given.

Altered platelet function in diabetes has been recognized for over 20 years.[15] Platelets in diverse groups of diabetic subjects have been found to be more adhesive than normal and to be hypersensitive in vitro to a variety of aggregating agents.[16,17] Platelet-plasma interactions with fibrinogen, immune complexes, low-density lipoprotein (LDL), glycated LDL, and von Willebrand factor may increase sensitivity to aggregating agents or increase platelet adhesiveness.[15,18-20] One major reason for platelet hypersensitivity to aggregating agents is increased production of arachidonic acid metabolites, including thromboxane, a potent vasoconstrictor and platelet aggregating agent.[20] Aspirin acetylates platelet cyclo-oxygenase and blocks thromboxane synthesis and the second phase of platelet aggregation.

There is one primary prevention trial in which aspirin therapy was compared with placebo in patients with diabetes and no apparent vascular disease, The US Physicians' Health Study.[21] 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 cardiovascular mortality. Results from 22,071 participants with a mean follow-up time of about 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% confidence interval [CI], 0.45 to 0.70, $P < .00001$). There was no reduction in mortality from cardiovascular causes. There was a suggestion of an increase in stroke in the aspirin group, which was not statistically significant.

Subgroup analyses were performed in a group of 533 diabetic individuals randomized to receive aspirin or placebo. Myocardial infarction occurred in 11 of 275 (4.0%) diabetic men assigned to aspirin therapy and in 26 of 258 (10.1%) diabetic men assigned to placebo therapy. The RR of myocardial infarction for the diabetic individuals on aspirin therapy was 0.39, whereas it was 0.58 for the entire cohort.

The largest study of aspirin prophylaxis in diabetes is the Early Treatment Diabetic Retinopathy Study (ETDRS).[22] In this investigation, 3,711 male and female diabetic patients, 30% of whom had type I diabetes, were randomly assigned to aspirin (650 mg/d) or placebo therapy. The 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 to 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%, $P = .038$). When results for the first 5 years of the study were analyzed, the RR for myocardial infarction in the aspirin group was 0.72 (99% CI, .55 to .95).

The patients in this trial were a group that was at high risk for cardiovascular disease. This trial was a study of aspirin use in a heterogeneous group of type I and type II 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 of 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 significantly increased gastrointestinal (GI) bleeding or hemorrhagic stroke in the study.

Prolonged aspirin therapy has been shown to offer significant protection against myocardial infarction, stroke, and vascular death in patients with clinically apparent vascular disease.[23] In a meta-analysis of 145 secondary prevention trials of antiplatelet therapy, 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 fourth 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 about one sixth in vascular deaths. There was no increase in nonvascular deaths.

Doses of 75 to 325 mg 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 2.

Thus, the evidence is strong that aspirin is a wise and safe primary and secondary prevention strategy in many people with diabetes. A low dosage is preferred for many reasons. As already noted, the Antiplatelet Trialists' Collaboration, a meta-analysis of 145 secondary prevention trials, found no evidence that higher doses of aspirin (up to 1,500 mg daily) were any more effective than low doses (75 to 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.[24] Further, more recent studies of low-dose aspirin therapy in patients with unstable coronary syndromes or transient ischemic attacks support the efficacy and low risk of 75 mg aspirin daily. Recent reviews and editorials from the cardiovascular community are supportive. These views are summarized in a recent review by Patrono and Davi.[25]

One large study, ISIS-2 (Second International Study of Infarct Survival) has been used by some investigators to support a view that patients with diabetes may chronically require a daily dosage greater than 160 mg of an enteric-coated preparation.[26] In this placebo-controlled study, 17,187 patients who entered the hospital up to 24 hours after suspected acute myocardial infarction were randomly assigned to either (1) 1-hour infusion of streptokinase, (2) 1 month of 160 mg/d enteric-coated aspirin, (3) both active treatments, or (4) neither. Streptokinase resulted in a highly significant reduction in 5-week vascular mortality, and the combination of aspirin and streptokinase was superior to either agent alone. In patients without 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 period of 15 months.

In this study, a subgroup of 645 patients with diabetes were given aspirin alone and 642 were given placebo. Vascular death rates (days 0 to 35) were 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 to suggest 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 preventative strategy. Most likely, in this acute clinical setting, a powerful prothrombotic tendency resulting 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 chronic use of high-dose aspirin as a primary or secondary prevention strategy in people with diabetes.

GI side effects, including GI bleeding, may occur with aspirin therapy. Gastric mucosal injury can be seen with doses as low as 300 mg daily, and these effects are dose-related with higher doses.[25] The enteric coating reduces the gastric erosion from 300 mg aspirin to placebo levels. Low doses of plain aspirin (75 mg) are associated with low rates of adverse GI effects, and enteric-coated preparations of 75 mg produce no excess of GI symptoms compared with placebo. Minor bleeding (bruises, nosebleeds, etc.) can occur with 75 mg aspirin. This is expected, since this dose will inhibit the platelet release reaction and thromboxane production.

In the US Physicians' Health Study,[21] there was a nonsignificant trend of an increase in hemorrhagic stroke. In the ETDRS,[22] there was also a trend for an increase in stroke in type II patients, which did not reach significance. On the other hand, aspirin therapy has been shown to be an effective treatment strategy following a stroke or transient ischemic attack, and no studies have implicated enteric-coated aspirin at low doses in increasing the risk for stroke. Finally, the majority of strokes in diabetic patients are thrombotic, not hemorrhagic, in nature.

Based on this review, the following recommendations are made.

Table 2. Meta-Analysis: Antiplatelet Trials (secondary prevention)

Patients	Vascular Events		Vascular Events Prevented/1,000 Patients on Antiplatelet Rx	*P*
	Control	Antiplatelet Rx		
Nondiabetic	3,612/20,954 (17.2%)	2,874/20,910 (13.7%)	35 ± 4	<.00001
Diabetic	545/2,321 (23.5%)	434/2,247 (19.3%)	42 ± 14	<.01

Abbreviation: Rx, therapy.

1. Use aspirin therapy in all diabetic patients *except* the following:
   - Type I patients without any vascular risk factors except diabetes
   - Non-obese type II patients without any vascular risk factors except diabetes
   - People with aspirin allergy, GI bleeding, ulcer disease, hemorrhagic diathesis, or other clinical contraindication to aspirin therapy
2. In making these judgments, include any of the following as a vascular risk factor(s):
   - Obesity (>20% ideal body weight)
   - Hypertension (>140/90 mm Hg)
   - Cigarette smoking (past or present)
   - $HbA_{1c} > 8\%$
   - Urinary albumin $\geq$ 30 mg/24 h
   - LDL cholesterol > 130 mg/dL
   - Triglycerides > 250 mg/dL
   - High-density lipoprotein cholesterol < 40 mg/dL for men and < 50 mg/mL for women
   - Fibrinogen $\geq$ 25% above maximum normal level
   - PAI-1 $\geq$ 25% above maximum normal level
3. Use enteric-coated aspirin at a dose of 75 to 325 mg daily. This will provide a constant blood aspirin level to completely suppress platelet thromboxane synthesis. The low dose (75 mg) will not block endothelial prostacyclin synthesis.[24]

SUMMARY AND CONCLUSIONS

An aggressive approach to risk-factor control is indicated in people with type II diabetes. Multifactorial therapy is usually indicated and is supported by large-scale prospective clinical trials in nondiabetic individuals and by meta-analyses of many trials in the case of aspirin therapy. In this report, we have briefly reviewed the evidence in favor of intensive glycemic management and aspirin as a simple, safe, inexpensive antiplatelet agent. These measures appear to be greatly underused in the care of people with type II diabetes. Our present challenge is to translate these recommendations for patients to primary health care providers so that effective actions may be implemented.

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