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MANAGEMENT TO DECREASE CARDIOVASCULAR DISEASE IN PATIENTS WITH TYPE 2 DIABETES

BRUCE R. ZIMMERMAN

Endocrinology & Internal Medicine. Mayo Clinic. Minnesota. USA.

Cardiovascular disease accounts for over 70% of the mortality related to diabetes. Although epidemiological studies show a strong relationship between hyperglycemia and cardiovascular disease, no large prospective study has yet demonstrated that treatment of hyperglycemia reduces cardiovascular disease in people with diabetes. In contrast, multiple studies demonstrate that an early aggressive approach to risk factor reduction is beneficial. In spite of these findings, persons with diabetes have not experienced the same steady decline in heart disease mortality as those without diabetes[1], perhaps because most care provides do not take an aggressive approach to risk factor reduction. I hope to convince you that there is value in a comprehensive approach to risk factor management in type 2 diabetes.

Smoking

Of course, I don't believe anyone should smoke but smoking has as especially bad effect in those with diabetes[2]. Studies have shown that if the medical record contains a reminder to the physician that the patient smokes and the physician discusses stopping smoking frequently the success rate in discontinuing smoking is higher. This must be done in all people with diabetes.

Hyperglycemia

Postprandial glucose elevations before fasting glucose reaches levels diagnostic for diabetes are associated with increased cardiovascular disease. Endothelial dysfunction has been found to be associated with the insulin resistance syndrome[3]. It appears that the stage is set for the development of vascular complications in people at risk of developing type 2 diabetes. Data from the Insulin Resistance Atherosclerosis Study (IRAS) show that insulin resistance is associated with carotid artery intimal-medial thickness, a marker of subclinical atherosclerosis[4]. An issue that has become prominent in the US with the development of new medications is the value of early targeting of treatment of patients with postprandial glucose elevations. There is no question in my mind that nonpharmacologic treatment with life style modification, weight reduction and regular exercise, will be of benefit. The benefits of pharmacologic therapy remain unknown. In particular the hypothetical benefits of reducing insulin resistance with a thiazolidinedione have not yet been proven. The United Kingdom Prospective Diabetes Study (UKPDS)[5] data strongly suggest metformin therapy may offer special benefit in reducing cardiovascular disease. It should be remembered that the UKPDS did not demonstrate any adverse influence of insulin or sulfonylurea treatment.

Hypertension

The UKPDS convincingly demonstrated that reducing blood pressure also reduces cardiovascular morbidity and mortality[4]. In addition, multiple studies have demonstrated that control of hypertension reduces the microvascular complications of diabetes particularly nephropathy. Hypertension occurs in ~50% of people with type 2 diabetes and is part of the insulin resistance syndrome. Hypertension may exist prior to the onset of hyperglycemia and is often labeled essential hypertension. In contrast, hypertension in people with type 1 diabetes is usually a marker of diabetic nephropathy. Because of the importance of hypertension in people with diabetes, most authorities recommend treatment goals of Bp <130/85 which is more rigorous than the recommendations in people without diabetes. These recommendations can be very difficult to achieve in the elderly or in those with long-standing diabetes and very sclerotic arteries. With isolated systolic hypertension and sclerotic vessels the goals may need to be modified.

When treating hypertension in people with diabetes non-pharmacological measures should not be neglected. Reduction of excessive alcohol intake, reduction of di-

etary salt, weight reduction, and regular exercise may all offer substantial benefit. Some aspects of the pharmacological therapy have been controversial and the presence of diabetes should influence the drug choices. It is now well established that ACE inhibitors have reno-protective effects that may offer benefit over and above the benefits of blood pressure control alone. In patients with overt proteinuria or increased microalbuminuria, ACE inhibitors should be the first line of antihypertensive therapy and their use should be considered in younger patients even if they are not hypertensive. The HOPE Study demonstrated cardioprotective effects of the ACE inhibitor ramipril above those of Blood pressure control alone[7]. Balancing these findings against those of the UKPDS, which found no special benefit of ACE inhibitors, is difficult. If an ACE inhibitor is not tolerated, angiotensin II receptor blockers may offer the same renal benefits although studies have not been definitive yet. Even without these medications substantial renal protection is achieved by hypertension control alone. Beta-blockers were in disfavor for the treatment of hypertension in people with diabetes for awhile. The UKPDS demonstrated that these concerns were unjustified. Atenolol was as effective as an ACE inhibitor in reducing mortality, at least in people with a low incidence of nephropathy. Calcium channel blockers have been controversial. The weight of evidence now suggests that nondihydropyridine calcium channel blockers have significant beneficial effects. High dose thiazide diuretics can worsen hyperglycemia and dyslipidemia and for awhile diuretics were avoided in people with diabetes. Low dose thiazides are effective antihypertensives particularly in combination therapy and don't have these adverse effects[8]. They are inexpensive and should be used more frequently. Adequate control of hypertension in people with diabetes can be difficult. The UKPDS found that 2 or 3 drug therapy is frequently necessary. By balancing the benefits and potential risks in people with diabetes, safe and effective drug therapy can usually be achieved.

Dyslipidemia

The characteristic dyslipidemia of type 2 diabetes is hypertriglyceridemia and low HDL-cholesterol. Generally in the US the trend had been to ignore triglycerides and concentrate on LDL-cholesterol. Total LDL-cholesterol is generally not increased in patients with type 2 diabetes. It is now known that the hypertriglyceridemia of type 2 diabetes is associated with an increase in the very atherogenic small dense LDL_cholesterol. Even though increases in normal size LDL are not a feature of type 2 diabetes the Scandinavian Simvastatin Survival Study (4S) found a 37% reduction in any CVD event in the simvastatin arm compared to placebo in a sub analysis of those with diabetes[9]. Similar results were found with pravastatin therapy among diabetic subjects in the secondary prevention Cholesterol and Recurrent Events (CARE) Trial[10]. Many years ago the Helsinki Heart Study[11] and more recently the VA HIT trial[10] demonstrated the benefit of gemfibrozil therapy which more directly targets the lipid abnormalities found in type 2 diabetes. Based on these results stringent targets for LDL-cholesterol are recommended in people with diabetes. Triglyceride targets remain controversial. Nicotinic acid (Niacin) therapy unfortunately increases hyperglycemia and is not recommended in people with type 2 diabetes. The unfortunate risk of myopathy with statin and fibrate therapy makes combination therapy more difficult.

Coagulopathy

People with diabetes have enhanced platelet aggregability and adhesion and an increase in coagulation factors such as fibrinogen and PAI-1 that may also contribute to the increased atherosclerosis. Low dose aspirin therapy in all high-risk patients with diabetes is recommended and unfortunately often neglected.

Other Issues

Space and time do not permit a detailed discussion of some other issues that should be mentioned. The DIGAMI Study demonstrated that intensive insulin therapy the time of and after a myocardial infarction reduced cardiovascular mortality. The BARI study showed that 5-year mortality was greater for diabetic patients who had PTCA rather then CABG. Both of these study results require confirmation in additional studies that are planned.

One of the difficult clinical issues in people with diabetes is that their coronary disease is often "silent" and it is difficult to know in whom and how to screen for CVD without symptoms. AN ADA consensus conference attempted to develop some recommendations in this regard[12, 13].

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