Preventing Cardiovascular Disease in Diabetes

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Cardiovascular disease is the leading cause of death in patients with diabetes. Risk of coronary heart disease is increased two to four fold in type 2 diabetes with the comparative increase being more pronounced for women and for hard endpoints, such as myocardial infarction (MI) and sudden death. Further, these patients continue to have poorer outcomes post-MI, and even after percutaneous intervention. Thus, preventive measures are of particular importance in diabetic patients.

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) was the first large-scale prospective randomized study that demonstrated the value of intensive glycemic control in preventing microvascular complications as well as cardiovascular disease in patients with type 1 diabetes. For type 2 diabetes, data from the United Kingdom Prospective Diabetes Study (UKPDS) and the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial have shown reduction in microvascular complications. However, the verdict is somewhat unclear for major cardiovascular events.

Conflicting reports

The randomized prospective UKPDS, ADVANCE and Action to Control Cardiovascular Risk in Diabetes (ACCORD) trials studied the effect of glucose control on cardiovascular outcomes in type 2 diabetes. UKPDS was a very long-term trial that studied intensive therapy with sulfonylurea, insulin, or metformin (in overweight patients) vs. conventional dietary restriction for 10 years in 5,102 newly diagnosed diabetic subjects, with an additional 10 year follow-up. The ADVANCE trial recruited 11,140 subjects and used gliclazide (modified release) plus other drugs in the intensive control arm (target HbA1c ≤ 6.5%) over a five year period. The ACCORD study enrolled 10,251 patients and used a variety of glucose lowering therapies for tight glucose control (target HbA1c < 6.0%). Unlike UKPDS, both ADVANCE and ACCORD only recruited older diabetics already on prior medication. Mean HbA1c levels were 7, 6.5, and 6.4 for intensive therapy and 7.9, 7.3, and 7.5 for standard therapy groups at the end of these trials, respectively. Each of these trials failed to show any significant benefits of intensive glycemic control on cardiovascular outcomes; although, a trend toward benefit was seen in UKPDS. In the ACCORD trial, there was actually an excess of total and cardiovascular mortality in the intensive glucose lowering arm. As a result, that arm was stopped prematurely (after three-and-a-half years instead of the planned four to eight years) in 2008 based on a recommendation by the Data Safety Monitoring Board. No increase, however, was seen in mortality in the ADVANCE trial.

Recent Evidence

In June 2008, results were presented from the seven-and-a-half year Veterans Affairs Diabetes Trial (VADT). This trial enrolled 1,791 "high-risk" veterans who had elevated HbA1c despite treatment with maximal doses of at least one oral hypoglycemic agent and/or insulin. Aggressive blood sugar control failed to significantly decrease cardiovascular events in these patients with established diabetes.

In September, the UKPDS investigators released the results of a 10 year post-trial follow-up to clarify the long-term effects of intensive glucose and blood pressure control on diabetes complications. After the initial 10 year trial period, the surviving patients received routine care over these 10 years, and no attempts were made to maintain therapies previously assigned to them during the actual randomized study.

Differences in HbA1c between the intensive and conventional glucose-lowering arms were lost within one year of trial completion. However, persistent reductions in microvascular complications continued to be evident in the entire original intensive therapy group at the end of follow-up. Interestingly, earlier nonsignificant reductions in MI and all-cause mortality seen within the sulfonylurea-insulin subgroup of the intensive therapy arm also achieved significance over this 10 year period. For the metformin subgroup, the initial reduction in MI and death were maintained.

Interestingly, in this same trial, they evaluated intensive blood pressure control as well. The initial UKPDS trial demonstrated a reduction in microvascular complications with tighter BP control compared with standard BP control. After trial completion, BP levels in both trial arms equalized within the first two years. But, in contrast to glycemic control, the benefits of tighter BP control did not last over the follow-up period. These findings suggest that, while early initiation of tight glucose control may reduce complications after several years, aggressive ongoing treatment for BP is essential for preventing more immediate adverse outcomes. The effect of hyperglycemia on atherosclerosis is a gradual and prolonged metabolic process, and it therefore has a "legacy effect." In contrast, the effects of BP on the endothelium are more physical and more short-term, thus, explaining the lack of this "legacy effect."

Currently, the best strategy for cardiovascular risk reduction in diabetes seems to be one of multiple risk factor controls (where lifestyle, lipids, and smoking habits are controlled in addition to blood glucose and BP). This follow-up analysis does provide evidence supporting early aggressive glucose control for preventing cardiovascular events. However, given that too aggressive glucose control leads to hypoglycemia, it appears that moderately aggressive glucose lowering seems to be a reasonable option based on the current data. The practical implementation of this is that, for now, I generally aim for a HbA1c of seven for my patients.

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