Diabetes Management Update

How can we improve survival rates?

BY JOSHUA A. BECKMAN, MD, MS

The value of glucose lowering and cardiovascular event reduction has hit a lull. I am not discussing the treatment of hyperglycemia, per se, which has many new agents and new targets under development. I mean the (lack of) therapeutic value in reducing glycemia to reduce the primary cause of death in diabetes: cardiovascular disease. Indeed, recent data have been more consistent about solidifying our understanding of the lack of a role in hypoglycemic therapies in reducing cardiovascular events than finding new medications and procedures to do that.

Perhaps the area of greatest contention is the relationship of blood glucose reduction and cardiovascular outcomes. The initial United Kingdom Prospective Diabetes Study (UKPDS) suggested a reduction in nonfatal myocardial infarction (MI) but not stroke or death, with "tight" control (a hemoglobin A1c of approximately 7%) compared with standard control (hemoglobin A1c of approximately 8%), but the *P* value did not reach statistical significance.

Three randomized trials, larger than UKPDS, were conducted to determine whether even tighter control could reduce cardiovascular events. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, 10,251 patients with a median hemoglobin A1c of 8.1% were randomized to intensive therapy (a target of below 6%) or standard therapy (a target of 7%–7.9%).[1] With achieved levels of 6.4% and 7.5% in the intensive and standard therapy arms, respectively, the primary outcome of nonfatal MI, stroke, and cardiovascular death was not significantly different, but there was a 22% relative increase in death in the intensive arm.

Similarly, in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, 11,140 patients were randomized to standard or intensive glucose control, achieving mean hemoglobin A1c levels of 7.3% and 6.5%, respectively.[2] After 5-year follow-up, although intensive control reduced microvascular events (1.5% absolute risk reduction), there was no significant effect on nonfatal MI, stroke, death from cardiovascular cause, or all-cause death.

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Finally, in the Veterans Affairs Diabetes Trial (VADT), 1,971 veterans were randomized to standard or intensive therapy, achieving hemoglobin A1c levels of 8.5% and 6.9%, respectively. During a 5.6-year follow-up, there was no difference in the primary outcome of MI, stroke, cardiovascular death, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation as a composite or for any individual component. Moreover, there was no difference in all-cause death.

Despite the concordance of the results, some investigators and physicians still found trends and looked for areas to apply aggressive therapy.[3] To help flesh out the entirety of the data, Boussageon and colleagues performed a meta-analysis of the 13 randomized controlled trials in this area. The analysis included 34,553 patients and found that intensive treatment did not affect all-cause mortality or cardiovascular death but was associated with a 15% reduction in nonfatal MI. They noted that during a 5-year period, 117 to 150 patients would need to be treated to avoid one MI, whereas one severe hypoglycemic episode would develop for every 15 to 52 intensively treated patients.[4] The authors make clear that the data do not support more aggressive or intensive glucose-lowering therapy at this time. This conclusion is shared by the American Diabetes Association, American Heart Association, and American College of Cardiology.[5]

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Glucose lowering in the acute setting has also lost its luster. In the long-term follow-up of the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction 2 (DIGAMI-2) study, data were available for 1,145 of the 1,253 patients who were enrolled in the original trial.[6] With a median follow-up of 4 years, intensive therapy at the time of MI did not significantly affect mortality rates of 31% in either group. Of the deaths, 72% were cardiovascular in origin. Two other hypothesis-generating endpoints were noted: first, the intensively treated group had a higher rate of death from malignancy (hazard ratio, 1.77; confidence interval, 0.87–3.61), and second, metformin use was associated with a 35% reduction in mortality and 75% reduction in death from malignancy.

These results are buttressed by a meta-analysis of 21 trials of tight glucose control in intensive care settings by Kansagara and colleagues.[7] These investigators report that intensive insulin therapy reduced neither short- or long-term mortality, length of stay, rates of infection, or rates of renal replacement therapy in patients with MI. Thus, in both the acute and chronic settings, intensive treatment of glucose does not improve outcomes.

This past year has also seen the likely end of common use of the thiazolidinediones. These insulin sensitizers were first thought to have incredible potential and possible rivals with metformin as agents likely to improve cardiovascular outcomes because of their glucose-lowering, insulin-sensitizing, and lipid profile–improving properties. At first, the data looked promising. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE) study, 5,238 patients with type 2 diabetes and atherosclerosis were randomly assigned to oral pioglitazone titrated from 15 to 45 mg (n = 2,605) or matching placebo.[8] The group randomized to pioglitazone had a 16% reduction in the main secondary endpoint of death, MI, and stroke, although a primary composite endpoint including additional components did not meet statistical significance. However, the value of these agents began to be reevaluated.

First, rosiglitazone was associated with increased rates of MI.[9] This matched clinicians' assessments, because in a head-to-head analysis, pioglitazone has been shown to be superior.[10] However, more recently, chronic use of pioglitazone has been linked to bladder cancer.[11] Experts are now recommending switching patients to another class of hypoglycemic agents.[12]

Are there other therapies coming down the line that may be beneficial? Currently, it is unknown if any glucose-lowering therapy is going to reduce cardiovascular events. At this point, we should consolidate the use of tried and true therapies, such as statins, ACE inhibitors, and antiplatelet agents. ■

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