FEATURE

Large Outcomes Trials Are Crucial for Understanding Diabetes

Written by Maria Vinall

Large outcomes trials are crucial to the understanding of how best to treat patients with diabetes, and the results from meta-analyses, administrative databases, and epidemiologic data from small trials are no replacement, according to Hertzel C. Gerstein, MD, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada. While the data from these trials are useful in that they can be used to identify risk factors, the relationship between risk factors and outcomes is not always clear.

The consequences of untreated diabetes are devastating. In addition to vascular disease, diabetes is associated with accelerated aging and premature death from several cancers, infectious diseases, external causes, intentional self-harm, and degenerative disorders, independent of several major risk factors [Emerging Risk Factors Collaboration et al. *N Engl J Med* 2011]. Diabetic patients aged 50 years die approximately 6 years earlier than their counterparts without diabetes. About 40% of the difference in survival is attributable to excess nonvascular deaths.

Although there are a number of risk factors for diabetes, 10 are potentially modifiable and, thus, the focus of many outcomes trials: dysglycemia, insulin level, blood pressure, lipids, abdominal obesity, albuminuria, smoking, genetics, inflammation, and fatty liver. Clinical outcomes trials have shown that long-term glucose lowering in young patients (mean age, 27 years) with type 1 diabetes leads to significant reduction in eye disease, albuminuria, nerve disease, and cardiovascular damage but has no effect on cognition [Gerstein HC, Werstuck GH. *Lancet Diabetes Endocrinol* 2013]. Similar reductions in eye disease, kidney disease, and nerve disease in older patients with type 2 diabetes have been reported. More intensive lowering among type 2 diabetes patients had a small effect on major cardiovascular events (a reduction of 9%), a nonsignificant effect on stroke, and no effect on hospitalization for fatal heart failure, but it did reduce myocardial infarction (MI) by 15% (HR, 0.85; 95% CI, 0.76 to 0.94) [Control Group et al. *Diabetologia* 2009]. There were increases in all-cause mortality and noncardiovascular death and significant increases ($p = .04$) in cardiovascular death in the group of patients receiving more intensive glucose lowering. The authors of the study suggested that glucose-lowering regimens should be tailored to the individual.

The Outcome Reduction With Initial Glargine Intervention trial [ORIGIN; ORIGIN Trial Investigators et al. *N Engl J Med* 2012] evaluated the use of basal insulin to normalize fasting plasma glucose levels; after 6 years, insulin glargine was shown to have a neutral effect on cardiovascular outcomes and cancers. However, a meta-analysis of 53 small randomized clinical trials suggested that the dipeptidyl peptidase-4 inhibitors (DPP4i) offer significant protection from negative cardiovascular events (overall OR, 0.69; 95% CI, 0.53 to 0.90; $p = .006$) [Monami M et al. *Curr Med Res Opin* 2011]. In the EXAMINE study, cardiovascular outcomes and death from all causes were no different in patients with type 2 diabetes who had had a recent acute coronary syndrome treated with alogliptin, a new DPP4i, compared with similar patients treated with placebo [White WB et al. *N Engl J Med* 2013]. Similar findings were reported for another DPP4i, saxagliptin, although the rate of hospitalization for heart failure was increased [Scirica BM et al. *N Engl J Med* 2013].

Another approach to control insulin levels is insulin sensitization therapy. In a randomized controlled trial in patients with type 2 diabetes and heart disease, no significant difference was noted in the rates of death and major cardiovascular events between patients undergoing prompt revascularization and those undergoing medical therapy or between strategies of insulin sensitization and insulin provision [BARI 2D Study Group et al. *N Engl J Med* 2009].

The Action to Control Cardiovascular Risk in Diabetes trial [ACCORD; ACCORD Study Group et al. *N Engl J Med* 2010] investigated whether targeting to systolic blood pressure of < 120 mm Hg

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compared with <140 mm Hg reduces major cardiovascular events in participants with type 2 diabetes at high risk for cardiovascular events. Primary composite outcome events (nonfatal MI, nonfatal stroke, or cardiovascular death) were not different between the 2 groups, although the annual rates of nonfatal (p=.03) and total stroke (p=.01) were significantly reduced in the intensive (<120 mm Hg) treatment group.

Combination therapy with a statin plus a fibrate (fenofibrate) to reduce cholesterol levels did not reduce the rate of fatal cardiovascular events, nonfatal MI, or nonfatal stroke, compared with simvastatin alone in patients with type 2 diabetes at high risk for cardiovascular events [ACCORD Study Group et al. *N Engl J Med* 2010]. Subgroup analyses suggested a benefit for men and possible harm for women (p=.001 for interaction) and a possible benefit for patients with both a high baseline triglyceride level and a low baseline level of high-density lipoprotein cholesterol (p=.057 for interaction).

In the final trial examined in the presentation—the multicenter randomized controlled Look AHEAD: Action for Health in Diabetes trial [Look AHEAD; Look AHEAD Research Group et al. *N Engl J Med* 2013]—5145 overweight or obese persons with type 2 diabetes were treated with intensive lifestyle intervention (weight loss and increased physical activity) or usual diabetic care over a 4- to 10-year period. The intervention group experienced significant weight reductions, greater reductions in glycated hemoglobin, and greater initial improvements in fitness as well as in all cardiovascular risk factors, except for low-density lipoprotein cholesterol levels. However, there were no differences in cardiovascular morbidity and mortality after 10 years (HR, 0.95; 95% CI, 0.83 to 1.09; p=.51), and the trial was halted early after a futility analysis.

Intensive glucose lowering in type 1 diabetes reduces most of its consequences and some of the consequences in type 2 diabetes, although it should be pursued with caution. Two commonly used strategies to lower glucose—insulin sensitization and provision—have similar effects on cardiovascular disease. Lowering systolic blood pressure to ~130 mm Hg has cardiovascular, retinal, and renal benefits, and lowering it further may reduce stroke risk. Although statins reduce cardiovascular events and mortality, adding fibrates to statins has no additional benefit. Metformin may have mortality benefits, but lifestyle intervention may not be better than drugs.

In concluding, Dr. Gerstein reiterated that the results of meta-analyses of small nonoutcomes trials for safety signals can be very misleading and that outcomes trials are central to physicians' ability to provide the best care to their patients with diabetes.