Intensive Intervention Reduces Mortality in Type 2 Diabetes

Gaede P, Lund-Andersen H, Parving H, Pedersen H. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580–91.

Study Overview

Objective. To evaluate the effect of tight glucose regulation, renin-angiotensin system blockers, aspirin, and lipid-lowering agents on all-cause mortality and cardiovascular mortality in patients with type 2 diabetes mellitus and microalbuminuria.

Design. Prospective observational study.

Setting and participants. This was a follow-up to the Steno-2 study [1], in which 160 Danish patients who met the World Health Organization criteria for a diagnosis of type 2 diabetes and microalbuminuria were randomized to conventional or intensive therapy. Intensive therapy was based on recommendations from the American Diabetes Association and included focused behavior modification and targeted treatment goals of glycated hemoglobin (HbA_{1c}) < 6.5%, fasting total cholesterol < 175 mg/dL, fasting serum triglycerides < 150 mg/dL, systolic blood pressure < 130 mm Hg, and diastolic blood pressure < 80 mm Hg. After an initial (mean) 7.8 years in the Steno-2 study, all patients remaining in the trial (n = 130) were educated on the benefits seen in the intensive treatment arm, and patients then chose which therapy to continue on. They were subsequently followed for a mean 5.5 years.

Main outcome measures. The primary endpoint was time to death from any cause. Secondary endpoints included death from cardiovascular causes, nonfatal stroke, nonfatal myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention or revascularization for peripheral atherosclerotic arterial disease, and amputation due to ischemia. Tertiary endpoints included diabetic nephropathy, retinopathy, or neuropathy.

Main results. At the end of the Steno-2 study, the intensive therapy group had significantly improved HbA_{1c}, fasting serum levels of total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides, systolic and diastolic blood pressures, and rate of urinary albumin excretion relative to the conventional therapy arm. At the end of this follow-up study, none of these risk factors were statistically significantly different between the 2 groups. Over 13.3 years of follow-up (7.8 years for Steno-2 and 5.5 years for follow-up), 40 patients died in the conventional group and 24 died in the intensive therapy group, resulting in a 20% absolute risk reduction (P = 0.02). There were 19 deaths from cardiovascular causes in the conventional group and 9 in the intensive therapy group (P = 0.03). Occurrence of cardiovascular events was also significantly lower in the intensive therapy group. Diabetic nephropathy, retinopathy, and neuropathy occurred statistically significantly less often in the intensive therapy group.

Conclusion. An intensive intervention with behavior modification resulted in reduced all-cause and cardiovascular mortality as well as microvascular complications.

Commentary

Since the days of the Multiple Risk Factor Intervention Trial (MRFIT), trials of multifactorial interventions have been few and far between, in large part due to the difficulty in conducting these studies and interpreting results [2]. Despite knowledge of the many modifiable risks associated with diabetes, studies have often examined single risk factors rather than multifactorial modification, partly due to methodology concerns similar to those seen in MRFIT. Recently, several large trials have addressed various aspects of diabetes control, which gives the multifactorial approach of Steno-2 a stronger foundation. Specifically, the Diabetes Control and Complications Trial of patients with type 1 diabetes showed a decreased incidence of microvascular and cardiovascular complications with intensive therapy [3]. The United Kingdom Prospective Diabetes Study (UKPDS-33) study of patients with type 2 diabetes suggested a decreased incidence of microvascular disease with intensive therapy [4]. UKPDS-75 supported intensive glucose control as well as intensive blood pressure control for the optimal reduction in microvascular and macrovascular complications [5]. The composite risk reductions found in this Steno-2 follow-up study complement the results of these single risk factor modification trials.

At the end of the original Steno-2 trial, HbA_{1c}, total and LDL cholesterol, triglycerides, and systolic and diastolic blood pressures were statistically different between the intensive and conventional therapy groups. Over the

follow-up period, most of these risk factors improved in the (former) conventional treatment group and, as a result, there was no statistical difference in the risk factors between the 2 arms at the end of this study. However, on the Kaplan-Meier estimates, the cumulative incidence of death and the incidence of any cardiovascular event were statistically different and continued to diverge. Hence, the intervention and aggressive control of risk factors in Steno-2 may have played a key role in the long-term difference in cardiovascular and all-cause mortality. Gaede et al propose that hypercholesterolemia and hypertension are the most significant risk factors responsible for this long-term risk reduction, with glucose regulation and aspirin use contributing less to the overall decrease in risk.

Applications for Clinical Practice

During the same week this article was published, the *New York Times* reported the suspension of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, which examined multifactorial interventions to reduce cardiovascular events in over 10,000 high-risk patients with type 2 diabetes, due to an increased number of deaths in the intensive diabetes therapy arm [6,7]. Recently, the American Diabetes Association released interim results of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study [8], which did not support a mortality trend with intensive glucose control. Of importance when deciphering the results of these "conflicting" diabetes studies (prior and recent), intended and actual "intensive glucose control" varied widely, with intended (goal) HbA_{1c} levels as low as less than 6% but actual HbA_{1c} levels approaching 8% in some studies. In the ACCORD trial, the HbA_{1c} goal was less than 6%, with half the patients achieving HbA_{1c} values less than 6.4%. Hence, the achievement of strictly controlled HbA_{1c} is likely associated with other (as of yet unknown) factors that led to the discrepancy in results.

What is the take home message? Diabetic patients are more likely to die with their disease than directly from it. Cardiovascular events should remain a prime target for risk factor modification in patients with diabetes, as evidenced by the Steno-2 follow-up study. A carefully thought out, prioritized, multifactorial approach toward risk reduction can yield significant long-term benefits in clinically important outcomes.

—Review by Chhavi Bansal Kumar, MD (New York University School of Medicine, New York, NY) and Nirav R. Shah, MD, MPH

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