

Results of the Epidemiology of Diabetes Interventions and Complications Trial

Reviewed by Eugene E. Wright, Jr.

Study

Article A. Writing Team for the DCCT/EDIC Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 2003;290:2159–2167

Article B. Writing Team for the DCCT/EDIC Research Group. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. *JAMA* 2015;313:45–53

The results of the Epidemiology of Diabetes Interventions and Complications (EDIC) study are in, and the results are very interesting.

Historically, type 1 diabetes was associated with an increased risk of early or premature mortality compared with the general population. In the pre-insulin era, 50% of patients died within the first 20 months of diagnosis. After the discovery of insulin in 1922, patients with diabetes lived longer. However, they still had a 20-year reduction in life expectancy compared with the general population. In the second half of the 20th century and the beginning of the 21st century, advances have narrowed the survival gap to <4 years. EDIC, the long-term observational follow-up of the Diabetes Control and Complications Trial (DCCT) (1), has sought to help us understand

the key factors that have contributed to narrowing this gap.

Summary

Design and Methods

The DCCT was the first major interventional trial in type 1 diabetes patients and was conducted between 1983 and 1993. The study included 1,441 participants with type 1 diabetes who were 13–39 years of age with a diabetes duration of 1–15 years. Participants had no early microvascular complications of diabetes, hypertension, cardiovascular disease (CVD), or other potentially life-threatening diseases at enrollment. This permitted observations of disease progression to complications in participants who were free of complications at the start of the study.

The patients were randomly assigned to intensive ($n = 711$) or conventional ($n = 730$) therapy. Those in the intensive treatment group were treated to glycemic targets as close to the nondiabetic range as safely possible, whereas those in the conventional treatment group had goals of avoiding symptomatic hypo- or hyperglycemia. All the patients were followed in academic clinical centers in the United States and Canada for a mean of 6.5 years, after which intensive therapy was taught to those in the conventional treatment group. All participants were advised to follow an intensive therapy regimen and were returned to the care of their personal physicians.

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At the end of the DCCT, there was an A1C difference of ~2 percentage points (7.2 vs. 9.1%) between the two groups. However, this did not persist throughout the first 7–8 years of follow-up in the EDIC (8.0 vs. 8.2%). One criticism of the DCCT was that its patient population lacked diversity and was not representative of the general population.

The EDIC was the observational follow-up of the original DCCT groups through 31 December 2012. The EDIC time period, plus the initial 6.5 years of the DCCT, yielded a mean 27 years of total follow-up. During the EDIC, annual contact with DCCT participants was maintained, and vital status was ascertained for 1,429 (99.2%) of the original participants. The main outcomes of the EDIC were total and all-cause mortality.

Results

The results were quite interesting, but not surprising. Despite an equalizing of glycemic control as determined by the mean A1C between the groups during the EDIC study, there was and has continued to be a persistent effect of early intensive treatment.

In the course of the study, there were 107 deaths, with 43 from the intensive group and 64 from the conventional group. Sixty-eight deaths were in men, and, of those, 27 were from the intensive treatment group. Restated, 1.5 times as many men in the conventional treatment group died as did men in the intensive treatment group (27 vs. 41). A sim-

ilar effect was noted for women (16 vs. 23).

The primary causes of death were as one might imagine. Of all deaths, CVD accounted for 24 (22.4%), cancer for 21 (19.6%), acute diabetes complications for 19 (17.8%), and accidents, including suicide, for 18 (16.8%). In the intensive treatment group, there were fewer deaths from diabetic renal disease (1 vs. 6), CVD (9 vs. 15), and cancer (7 vs. 14).

Higher A1C levels and the development of albuminuria were associated with all-cause mortality. Those who developed macroalbuminuria (≥ 300 mg/24 hours) had the greatest risk (2). Other contributors to increased mortality were older age, smoking, and higher baseline blood pressure, cholesterol, and A1C levels.

Interestingly, it took ~15 years to detect a difference in mortality between the two groups. This is graphically demonstrated in Figure 1 of the 2015 EDIC article in the *Journal of the American Medical Association* (3). Hypoglycemia was more common in the intensive treatment group and has been associated with an increased risk for mortality.

Commentary

The conclusion one might draw from this long-term observational study is that implementing 6.5 years of intensive treatment in type 1 diabetes does not incur increased mortality over time, despite an increase in the risk for hypoglycemia.

Of note, the DCCT was conducted three decades ago, when many of the current therapeutic and

management options were not yet available. Options such as analog insulin formulations, insulin pumps, accurate and reliable blood glucose meters, and continuous glucose monitoring devices were not yet available. Despite this, there still seemed to be a slight beneficial effect of early intensive treatment compared to conventional treatment of type 1 diabetes that may explain the observation of a lower early or premature mortality rate in patients treated intensively.

It seems plausible that, given the new tools (therapy and management options) available today, we should be able to improve on the reported results of the EDIC to the benefit of our patients.

Duality of Interest

E.E.W. has served on advisory boards of Abbott Diabetes Care and Eli Lilly and Company and as an advisor/consultant to the Boehringer Ingelheim Lilly Alliance. No other potential conflicts of interest relevant to this article were reported.

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