



Making a Difference With Diabetes Research and Care

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Diabetes Care 2016;39:1309–1310 | DOI: 10.2337/dci16-0016

Type 1 and type 2 diabetes are serious diseases because they can cause a wide variety of health consequences that may reduce both the quality and/or length of life. Almost every body system can be adversely affected by diabetes, including the eyes, kidneys, nerves, skin, heart, brain, liver, circulatory system, skeleton, and reproductive system (1). Type 1 and type 2 diabetes are clearly caused by different processes and have different risk factors and natural histories. Regardless of these differences, both diseases share the same glycemic thresholds for diagnosis (2) and manifest a similar relationship between the extent of hyperglycemia and the risk to the integrity of the organ systems listed above (1). Moreover, for both diseases many of these long-term risks can be mitigated by chronically reducing the degree of hyperglycemia (3,4), by detection and treatment of other risk factors for many of these consequences (e.g., hypertension, smoking, and dyslipidemia), and by appropriate screening and aggressive therapy of early evidence of these consequences (e.g., retinal, renal, neurological, and cardiovascular disease) (5,6).

The Diabetes Control and Complications Trial (DCCT) and its long-term follow-up study (Epidemiology of Diabetes Interventions and Complications [EDIC]) comprise the most definitive body of evidence regarding the short- and long-term benefits of managing hyperglycemia in people with type 1 diabetes (7). The

DCCT recruited 1,441 individuals of mean age 27 years with 1–15 years' duration of type 1 diabetes who had no cardiovascular disease, hypertension, or dyslipidemia and randomly allocated them to more versus less intensive glycemic control. During a mean of 6.5 years of follow-up, the average HbA_{1c} levels achieved in the intensive and conventional groups were 7% and 9%, respectively. By that time, participants who had been allocated to the intensive group had a much lower incidence of retinal, renal, and neurological disease compared with those allocated to the conventional group. Despite a subsequent average HbA_{1c} of 8% in both groups, those who were initially allocated to the intensive group continued to experience less retinal, renal, and cardiovascular disease (8–10) and a 33% lower hazard of death during a total follow-up period of 27 years (11).

In this issue of *Diabetes Care*, Lachin and colleagues (12) extend these findings by comparing the total mortality rates in the DCCT/EDIC participants to that of the general population of the U.S. These elegant analyses showed that individuals who had been allocated to the intensive group had a mortality rate that was similar to that of a matched American population. Conversely, individuals who had been allocated to the conventional group had a mortality rate that was approximately 30% higher than that of the general population. Their analyses also

reported a 49% higher mortality rate for participants formerly in the conventional versus intensive group and showed that this effect was similar in men and women.

The small number of deaths ($N = 125$) limits the ability to assess the intervention's effect on mortality across study subgroups (e.g., those with vs. without retinopathy at baseline) and represents the major, yet unavoidable, weakness of the study (12). However, the large effect size and the fact that these findings are based on an intention-to-treat analysis of participants in a randomized controlled trial for whom long-term follow-up vital status was available in more than 97.5% are clear strengths that highlight the clinical importance and relevance of these findings.

Clinical trial findings such as these clearly reflect the long-term effect of intensive insulin therapy on mortality. Conversely, observational (i.e., epidemiological) data can only describe the relationship between risk factors such as HbA_{1c} levels and mortality; unless effect sizes are high (e.g., >fourfold) and are based on large samples of people with many incident deaths (e.g., >1,000), observational studies are unlikely to provide guidance regarding the effect of therapy. Thus, previously reported population-based epidemiological analyses comprising thousands of people with type 1 diabetes showing that those with HbA_{1c} levels <7% have higher mortality rates than people without any diabetes

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See accompanying article, p. 1378.

(13) provide no information regarding the effect of glucose-lowering in response to that HbA_{1c} level. This is clearly illustrated by the data reported by Lachin and colleagues (12). Despite the clear benefit of allocation to the intensive group described above, when the authors conducted an epidemiological analysis (i.e., without accounting for the intervention) using the same data, they found that people with an HbA_{1c} <7% have a higher mortality than the general population (which includes people with diabetes). This highlights the peril of making therapeutic inferences based on epidemiological analyses.

The fact that the DCCT was not a blinded study precludes knowing whether the mortality benefit is due just to the degree of glycemic control or to all of the other things that a participant in the intensive group (or his/her providers) may or may not have done as a result of being in that group. Notwithstanding the explanation for the effect, this analysis clearly indicates that allocating young individuals with type 1 diabetes to at least 6.5 years of a therapeutic strategy that includes intensive glycemic control (and all of the activities required to achieve intensive glycemic control) essentially eliminates their excess risk of death compared with the general population. Note that this analysis only relates to mortality and does not account for the total burden of illness associated with type 1 diabetes.

The findings from DCCT/EDIC are extremely encouraging to patients with diabetes and their health care providers. They compellingly show that as little as 6.5 years of targeting good glucose levels can eliminate the excess mortality of type 1 diabetes over a 27–30-year window (Table 1). Coupled with other findings from this crucial trial that was conducted almost 40 years ago, the health benefits of managing type 1 diabetes are indisputable. However, these findings do not speak to all of the effort and costs borne by the patients, providers, and the health care system to achieve these findings. Indeed, good health outcomes are not guaranteed without these efforts and costs.

Hyperglycemia is clearly a risk factor for mortality in the general population (14) and we know from the DCCT/EDIC that

Table 1—Glycemic control and mortality in type 1 diabetes

People with recently diagnosed type 1 diabetes who are not intensively treated have a higher death rate than the general population
At least 6.5 years of intensive insulin therapy in people with type 1 diabetes reduces this risk to normal
Higher HbA _{1c} levels predict a higher risk of death in people with type 1 diabetes

it is clearly a modifiable risk factor in people with type 1 diabetes and that glucose lowering has health and mortality benefits. Science and technology continue to add new advances that make it easier to achieve these glycemic goals and that reduce the burden for both patients and providers. These include new forms of insulin delivery and glucose monitoring systems, innovative software that can regulate insulin delivery, islet cell transplantation or implantation, and other agents such as glucagon, incretins, and oral medications that may soon be added to insulin.

In 1921, 1 year before the “insulin era” (15), typical patients with type 1 diabetes died within 1 year of diagnosis. In 2016 (i.e., year 94 15), it is now clear that their mortality is as good as, if not better than, that of the general population. That is clear evidence of progress by any measure, but there is still so much more to do.

Duality of Interest. H.C.G. has received fees for advice and lectures related to diabetes from Abbot, AstraZeneca, Bayer, Berlin-Chemie, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Hoffmann-La Roche, Novo Nordisk, and Sanofi and has received grants from Sanofi, Lilly, AstraZeneca, and Merck. No other potential conflicts of interest relevant to this article were reported.

References

- Gerstein HC, Werstuck GH. Dysglycaemia, vasculopenia, and the chronic consequences of diabetes. *Lancet Diabetes Endocrinol* 2013; 1:71–78
- American Diabetes Association. Classification and diagnosis of diabetes. Sec. 2. In *Standards of Medical Care in Diabetes—2016*. Diabetes Care 2016;39(Suppl. 1):S13–S22

- American Diabetes Association. Glycemic targets. Sec. 5. In *Standards of Medical Care in Diabetes—2016*. Diabetes Care 2016;39(Suppl. 1):S39–S46
- Imran SA, Rabasa-Lhoret R, Ross S; Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Targets for glycemic control. *Can J Diabetes* 2013;37(Suppl. 1):S31–S34
- American Diabetes Association. Cardiovascular disease and risk management. Sec. 8. In *Standards of Medical Care in Diabetes—2016*. Diabetes Care 2016;39(Suppl. 1):S60–S71
- Stone JA, Fitchett D, Grover S, Lewanczuk R, Lin P; Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Vascular protection in people with diabetes. *Can J Diabetes* 2013;37(Suppl. 1):S100–S104
- The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986
- Nathan DM, Cleary PA, Backlund JY, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643–2653
- Aiello LP; DCCT/EDIC Research Group. Diabetic retinopathy and other ocular findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. *Diabetes Care* 2014;37:17–23
- Nathan DM, Zinman B, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications experience (1983–2005). *Arch Intern Med* 2009;169:1307–1316
- Orchard TJ, Nathan DM, Zinman B, et al.; Writing Group 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
- Diabetes Control and Complications (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Mortality in type 1 diabetes in the DCCT/EDIC versus the general population. *Diabetes Care* 2016;39:1378–1383
- Lind M, Svensson AM, Kosiborod M, et al. Glycemic control and excess mortality in type 1 diabetes. *N Engl J Med* 2014;371:1972–1982
- Seshasai SR, Kaptoge S, Thompson A, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med* 2011;364:829–841