The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 Years: The "Gift" That Keeps on Giving!

William T. Cefalu[1] *and Robert E. Ratner*[2]

Diabetes Care 2014;37:5–7 | DOI: 10.2337/dc13-2369

There are events that occur during our lives that because of the significance or enormity of the event we vividly remember the time, place, and what we were doing at the time! Clearly, events related to our family life would be good examples as we all remember the time, place, and emotion surrounding the birth of a child, a marriage, or perhaps the untimely death of a parent or other loved one. We also seem to recall with uncanny details where we were and what we were doing when we first heard news of a remarkable achievement, a human tragedy, or natural disaster. For example, most people today will easily recall their circumstances on the morning of 11 September 2001. Those in our generation vividly remember when we first heard of the assassination of John F. Kennedy or watched the first lunar landing on our black-and-white televisions. With this in mind, we can vividly recall when the initial results of the Diabetes Control and Complications Trial (DCCT) were presented in Las Vegas in 1993 at the American Diabetes Association (ADA) Scientific Sessions. During the session, the significance of the findings was quite apparent. We realized there was no more guessing on what our standards of treatment were to be. . .now we had data! But, to be honest, we clearly did not appreciate the fact that 20 years later, we would be reflecting on that moment as just the beginning of a long and rewarding story. We agreed that the initial results at the time ushered in a new paradigm of treatment, but not one of us in attendance that day could have predicted what was to come of the DCCT and that the study would be as relevant today as it was then and continue to inform and provide new information (1). In short, the study continues to evolve to the point that 20 years later the "gift" of new information continues. Thus, in celebration of the 30th anniversary of the DCCT and follow-up study, Epidemiology of Diabetes Interventions and Complications (EDIC), our editorial team is honored to feature the summary findings to date of the DCCT/EDIC in this issue.

Articles from DCCT/EDIC featured in this issue provide an excellent overview, background, and outcomes of the study and are based on presentations made at both the 2013 ADA Scientific Sessions and the 2013 European Association for the Study of Diabetes Annual Meeting (2–8). The contributions summarize results to date from the DCCT/EDIC for the major complications of neuropathy, nephropathy, retinopathy, and cardiovascular disease. Collectively, both the DCCT and the follow-up observational EDIC (as elegantly outlined in the overview provided by Zinman et al. [2]) have provided clear and consistent messages. First and foremost, 20 years after initial data were released, chronic hyperglycemia, as measured by HbA_{1c}, remains the primary modifiable mediator of the long-term complications of type 1 diabetes (T1D) (2). We have learned that intensive diabetes therapy (INT) with the goal of achieving glucose control as close to normal as safely possible will reduce both the development and progression of diabetic retinopathy, nephropathy, and neuropathy (2). The original DCCT, involving 1,441 patients with T1D, demonstrated that intensive glycemic control reduced the risk for retinopathy, nephropathy, and neuropathy by 76%, 50%, and 60%, respectively (1). However, glycemic control following DCCT converged for both the INT and conventionally treated groups to around an HbA_{1c} of 8%. Yet the groups continued to have a durable effect based upon initial therapy assignment. For example, as part of this issue, Aiello (4) reports on the retinopathy findings, demonstrating significantly lower incidence of further progression of clinical diabetic retinopathy in the INT group (4).

[1]*Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, LA*
[2]*Scientific and Medical Division, American Diabetes Association, Alexandria, VA*

Corresponding author: William T. Cefalu, cefaluwt@pbrc.edu.

See accompanying articles, pp. 8, 9, 17, 24, 31, 39, and 44.

Additionally, severe retinal outcomes and procedures to treat them were reduced by 50% in the original INT group (4). An update on the nephropathy findings was provided by de Boer (5). During EDIC years 1–8, participants previously assigned to DCCT INT continued to experience lower rates of incident microalbuminuria and macroalbuminuria, with risk reductions of 59% and 84%, respectively (5). Beneficial effects of INT on the development of impaired glomerular filtration rate and hypertension became evident during combined DCCT/EDIC follow-up, with risk reductions of 50% and 20%, respectively, compared with conventional treatment (4). Thus, intensive glycemic treatment resulted in clinically important, durable reductions in the risks of microalbuminuria, macroalbuminuria, impaired glomerular filtration, and hypertension (5). Martin et al. (6) report neuropathic findings and show that the prevalence and incidence of diabetic peripheral neuropathy and cardiovascular autonomic neuropathy remained significantly lower in the prior INT group compared with the prior conventional therapy group through EDIC year 13/14. Further, they report persistent effects of prior INT on neuropathy measures through 14 years of EDIC, largely mirroring those observed for other diabetes complications. As was the case for the other complications of diabetes, DCCT/EDIC provided important information on the influence of glycemic control, the clinical course of diabetic neuropathy, and, most important, on how to prevent neuropathy in T1D (6).

The real benefit of such a long-range observation as outlined for DCCT/EDIC is the fact that a detailed view on natural history of cardiovascular findings can be obtained. It has been appreciated that longer-term clinical follow-up is needed to fully evaluate the progressive changes for atherosclerosis. In this regard, we have learned that over time, INT can have favorable effects to modulate cardiovascular disease in T1D. Specifically, Lachin et al. (7) report that the INT group with lower levels of HbA_{1c} during DCCT/EDIC was associated with thinner carotid intima-media thickness and less coronary calcification. Further, lower levels of HbA_{1c} were associated with a lower incidence of clinical cardiovascular events including myocardial infarction, stroke, and cardiac death. Although the authors report that there were no significant differences in cardiac structure and function between the former INT and conventionally treated groups, there was a significant association of these parameters with higher HbA_{1c} (7). Thus, "DCCT INT and the attendant 6.5 years of lower HbA_{1c} had long-term salutary effects on the development and progression of atherosclerosis and cardiovascular disease during the subsequent follow-up during EDIC" (7).

What appears very clear from the cumulative findings to date is that the long-term follow-up of DCCT/EDIC confirms the concept of "metabolic memory": "the benefits of INT versus conventional therapy persist even after the differences in glycemia achieved have disappeared" (2). Thus, it is clear that for benefits to be realized in the natural history of diabetes, INT should be initiated early in the course of T1D. Of course, with every gain in new information that benefits patients, we also learn of the limitations or concerns. In this case, we fully appreciate that although INT has incredible benefits, it does take effort by the patient and provider to implement and that weight gain and an increased risk of severe hypoglycemia are undesirable outcomes.

More important, the DCCT/EDIC is an outstanding example of how review of ongoing data and careful study and planning by investigators and sponsors can continue to reap benefits. In this case, the study continued to evolve and "reinvent" itself by proposing new studies to address relevant clinical questions. Specifically, as outlined in the summary and future directions narrative provided by Gubitosi-Klug (8), longitudinal follow-up of the DCCT/EDIC cohort provides the opportunity to continue monitoring the durability of INT as well as address lingering questions in T1D research. Future planned analyses are proposed to address additional questions regarding the microvascular triopathy (e.g., retinopathy, nephropathy, neuropathy), such as defining the relative time course of development and establishing evidence-based frequency of screening. Further, studies are planned to explore the effects of glycemic variability and nonglycemic risk factors on outcomes. Studies are also planned to evaluate long-term effects of INT on cognitive decline. Finally, studies are planned to evaluate the cost-effectiveness of the interventions. Three new proposed investigations include an examination of residual C-peptide secretion and its impact, prevalence of hearing impairment, and evaluation of gastrointestinal dysfunction. Thus, the comprehensive data collection to date and the remarkable participant retention over 30 years continue to allow the DCCT/EDIC to serve as an incredible resource for understanding T1D and its long-term complications (8).

Based on all stated above, the DCCT/EDIC has succeeded in continuing to provide and address major unanswered questions regarding the natural history of the long-range complications of diabetes and the role of glycemic control. We know without a doubt that 20 years after the report of the initial findings, and 30 years since the inception of the study, further follow-up of the cohort has demonstrated a consistent beneficial effect of INT on the development of complications. It is appreciated that although the risk reduction has decreased with time, there is a lingering beneficial effect nearly two decades after the study's end. The persistence of the investigators, together with the dedication of the participants, reminds us of the difficulties in generating evidence-based recommendations in the setting of a chronic disease. Only with prolonged observation can we see the impact of interventions on complications taking decades to develop. When the DCCT/EDIC and UK Prospective Diabetes Study (UKPDS) require over 20 years to demonstrate effects on cardiovascular disease, how can we expect reliable information from the ongoing cardiovascular outcome trials mandated by the U.S. Food and Drug Administration?

The DCCT/EDIC remains one of the most highly cited diabetes research trials and

one that has truly altered the course of diabetes management forever. Thus, it is our privilege and honor as the editorial team of *Diabetes Care* and representatives of ADA to feature the DCCT/EDIC. We acknowledge that such a study and the significant impact on human health could not have been possible without the dedication and collaboration between the DCCT/EDIC participants, the National Institutes of Health's National Institute of Diabetes and Digestive and Kidney Diseases as sponsor, the pharmaceutical donors, the DCCT/EDIC coordinators, and the investigators and collaborators. Collectively, these groups working together initiated a paradigm change in diabetes management and forever altered the diabetes landscape for the world's population affected by T1D. Again, who could have appreciated that two decades later, this study continues to provide new information and continues to evolve. We only hope that 10 years from now at the 40th anniversary the understanding of diabetes will be even deeper with this study. So, enjoy the series and let's honor all those who contributed to the DCCT/EDIC—clearly, DCCT/EDIC is the "gift" that keeps on giving!

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

1. 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
2. Zinman B, Genuth S, Nathan DM. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study: 30th anniversary presentations. Diabetes Care 2014;37:8
3. Nathan DM; DCCT/EDIC Research Group. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study at 30 years: overview. Diabetes Care 2014;37:9–16
4. 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
5. de Boer IH; DCCT/EDIC Research Group. Kidney disease and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Diabetes Care 2014;37:24–30
6. Martin CL, Albers JW, Pop-Busui R; DCCT/EDIC Research Group. Neuropathy and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Diabetes Care 2014;37:31–38
7. Lachin JM, Orchard TJ, Nathan DM; DCCT/EDIC Research Group. Update on cardiovascular outcomes at 30 years of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Diabetes Care 2014;37:39–43
8. Gubitosi-Klug RA; DCCT/EDIC Research Group. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study at 30 years: summary and future directions. Diabetes Care 2014;37:44–49