Update on Cardiovascular Outcomes at 30 Years of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study

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OBJECTIVE

To describe the beneficial long-term effects of an average of 6.5 years of intensive diabetes therapy (INT) in type 1 diabetes on measures of atherosclerosis, cardiac structure and function, and clinical cardiovascular events observed in the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study.

RESEARCH DESIGN AND METHODS

The DCCT was a randomized clinical trial of 1,441 participants assigned to receive INT or conventional therapy (CON). It was conducted between 1983–1993 with an average follow-up of 6.5 years. EDIC (1994–present) is an observational follow-up of the DCCT cohort. Cardiovascular events have been recorded throughout. During EDIC common carotid intima-media thickness (IMT) was measured with ultrasound, coronary artery calcification with computed tomography, and cardiac structure and function with cardiac magnetic resonance imaging.

RESULTS

DCCT INT and lower levels of HbA_{1c} during DCCT/EDIC were associated with thinner carotid IMT, less coronary calcification, and a lower incidence of clinical cardiovascular events including myocardial infarction, stroke, and cardiac death. While there were no significant differences in cardiac structure and function between the former INT and CON groups, they were significantly associated with higher HbA_{1c} during DCCT/EDIC.

CONCLUSIONS

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.

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The Diabetes Control and Complications Trial (DCCT) has documented the profound beneficial effects of intensive diabetes therapy (INT) compared with conventional therapy (CON) on the development and progression of microvascular and neuropathic complications during the DCCT, mediated by the separation of HbA_{1c} levels between the two treatment groups (1). In addition, the further separation of

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these outcomes during the Epidemiology of Diabetes Interventions and Complications (EDIC) study, despite the disappearance of the differences in HbA_{1c} seen in the DCCT (metabolic memory), has been described (2). The long-term benefits of INT versus CON are almost completely explained by the differences between the two groups in the mean level of HbA_{1c} during the mean of 6.5 years of treatment in the DCCT (3,4).

While retinal, renal, and neurological complications of diabetes are a major source of morbidity among patients with type 1 disease, cardiovascular disease (CVD) also causes substantial morbidity and excess mortality compared with similar aged, nondiabetic people. However, the incidence of CVD events is less clearly associated with HbA_{1c} in a number of observational studies, as recently reviewed (5–7). The DCCT was not designed or powered to assess the difference between INT and CON on the risk of cardiovascular events. The mean age of the cohort at baseline was only 27 years, and subjects with prior CVD, hypertension, or dyslipidemia were excluded. The risk of macrovascular events was therefore very low over the mean 6.5 years of the DCCT. However, due to increasing age of the cohort with EDIC follow-up, the major risk factor for CVD, it became possible to examine whether the original DCCT interventions would have a long-term effect on atherosclerosis and CVD and to explore glycemia as a risk factor. Assessments of atherosclerosis and further ascertainment of CVD events were performed during EDIC to address these critical issues.

RESEARCH DESIGN AND METHODS

During the DCCT/EDIC, all CVD events were reported, and all were adjudicated, masked to the assigned DCCT therapy and HbA_{1c} levels (8,9).

At years 1, 6, and 12 of EDIC, common carotid intima-media thickness (IMT) was evaluated with carotid ultrasonography (10–12). During EDIC year 8, coronary artery calcification (CAC) was assessed using computed tomography to determine whether CAC was present (13), and, if so, the degree of calcification measured by Agatston score, with >200 being used as an outcome. The Agatston score is the product of the cardiac artery area of calcification times the density that is a strong predictor of CVD risk. Cardiac structure and function were assessed by cardiac magnetic resonance imaging (MRI) at EDIC year 15 (14,15). Electrocardiograms (ECGs) were obtained annually throughout DCCT/EDIC. All of these outcome assessments were read centrally, masked to therapy.

At the beginning of EDIC, the DCCT/EDIC Research Group, with the approval of the External Advisory Committee (EAC) appointed by National Institute of Diabetes and Digestive and Kidney Diseases, adopted a composite primary outcome of major CVD events for analysis. The composite CVD event was defined as the time to the first of any of the following component events: nonfatal myocardial infarction (MI) or stroke, cardiovascular death, confirmed angina, or revascularization (angioplasty, stent, or bypass), all adjudicated, or silent MI on an ECG read centrally. The secondary outcome of nonfatal MI or stroke or CVD death (major adverse cardiovascular event [MACE]) was also specified.

To avoid the statistical complications associated with repeated examinations of emerging data, the researchers, again with the approval of the EAC, adopted a policy that no analysis would be conducted of the differences between groups until at least 50 subjects in the CON group had experienced a primary composite CVD event. This "information-driven" policy provided 85% power to detect a 50% reduction in the risk of major CVD with INT versus CON using a two-sided test at the 0.05 level.

RESULTS

DCCT

During the DCCT, there were 21 major CVD events among 9 subjects in the CON group versus 3 events in 3 subjects in the INT group, including a total of 3 CVD deaths. The small number of participants with any event (12 total) was inadequate to conduct a conclusive analysis of the difference between treatment groups or of the role of glycemia (8).

EDIC

Due to the young age and good health of the cohort, it was anticipated that it might take a decade or more to reach the prespecified landmark of 50 CVD cases in the CON group. In the interim, the researchers conducted assessments of markers of atherosclerosis.

Carotid Artery IMT

We assessed carotid IMT by ultrasonography at EDIC years 1, 6, and 12 (12). At year 1, the results were largely within the age-matched, nondiabetic range with no difference between the DCCT INT and CON groups. Carotid ultrasonography was again repeated during EDIC year 6. During the ~5 year period between the two measurements, IMT increased within both groups, significantly more so in the former CON than INT group (Fig. 1). Ultrasonography was again conducted during year 12 (12). IMT increased even more in both groups, consistent with the recognized effects of aging. The magnitude of the increase between EDIC years 6 and 12 was slightly greater in the former INT than in the CON group, but the mean IMT remained significantly less at 12 years in the former INT group.

CAC

The CAC measured during EDIC year 8 (13) used an Agatston score >200, a level that is associated with an increased risk of future CVD, as the primary outcome. Calcification was only detectable in about 20% of this still relatively young population (mean age 43 years), and less than 10% had a score >200. Despite the low prevalence of calcification, there was a 50% reduction in the odds of a score >200 in the former INT versus CON groups ($P < 0.005$) (13).

HbA_{1c} and Atherosclerosis

Further analyses examined the estimated magnitude of the difference between groups in IMT (12) and CAC (13) after adjusting for the differences between groups in the mean HbA_{1c} during DCCT. In these analyses, the magnitude of the treatment group effect was substantially diminished—by 95% in IMT at year 6 and 96% at year 12, and by 85% for CAC >200—when adjusted for the DCCT HbA_{1c}. Thus, the initial DCCT therapy had effects on

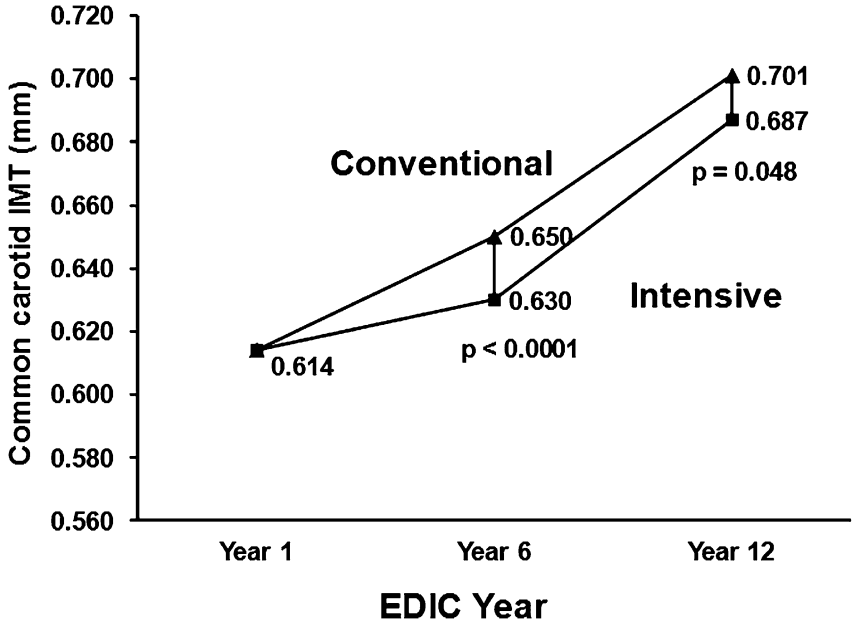

Figure 1—The mean level of the common carotid IMT within the INT and CON groups at EDIC year 1 and again at EDIC years 6 and 12. Reprinted with permission from Polak et al. (12).

atherosclerosis 6–12 years after the end of the DCCT, and virtually all of the long-term benefit of initial INT versus CON was explained by the difference between groups in mean HbA_{1c} during the DCCT.

Clinical CVD Events

The prespecified landmark of 50 former CON subjects with a defined clinical CVD event (composite primary outcome) was reached in 2004 (EDIC year 11) after an average of 18 years of follow-up in DCCT/EDIC (9). In aggregate, 98 CVD events occurred in 52 CON subjects versus 46 events in 31 INT subjects (P = 0.007). The risk of the primary composite CVD outcome was reduced by 42% (95% CI 9–63%, P = 0.016) (Fig. 2*A*) in the original DCCT INT versus CON group, and that of fatal or nonfatal MI or stroke (MACE) by 57% (25 vs. 11 subjects, 95% CI 12–79%, P = 0.018) (Fig. 2*B*). The numbers of each component type of event (including multiple events) and number of subjects with a given type of event were consistently less in the former INT compared with CON group, including the less clinically severe events of silent MI on ECG, angina, and revascularization.

As was observed with markers of atherosclerosis, 97% of the reduction in risk with INT versus CON was explained by the difference between the treatment group mean HbA_{1c} during the DCCT (9). While a decrease in the incidence of albuminuria during DCCT and EDIC with INT explained some of the decreased risk of CVD, the difference in CVD risk between treatment groups remained significant after adjusting for albuminuria. Overall, there was a 21% reduction in the risk of the composite primary CVD outcome per 10% lower mean HbA_{1c} during the DCCT (95% CI 9–30%, $P < 0.001$).

Cardiac MRI

In 2007–2009 (EDIC years 14–16), EDIC evaluated cardiac structure and function using cardiac MRI in 1,017 consenting subjects who could safely have an MRI, 81% of those available. Due to potential safety concerns regarding gadolinium, the gadolinium enhancement for detection of myocardial scars could only be conducted in the subset of 741 consenting subjects with estimated glomerular filtration rate >60 mL/min/1.73 m^2.

There were no differences between the former INT and CON groups in left ventricular structure or function (volumes, mass, or ventricular remodeling). Measures were generally

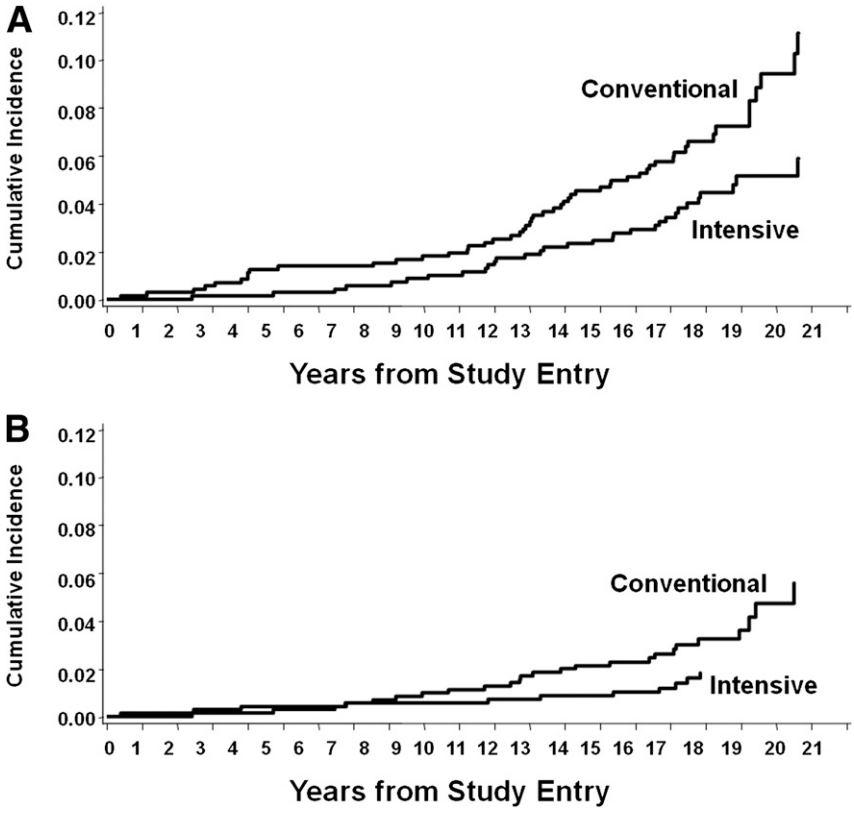

Figure 2—The cumulative incidence of clinical CVD outcomes during DCCT/EDIC. *A*: Any qualifying primary outcome event. *B*: MACE. Reprinted with permission from Nathan et al. (9).

Table 1—Association of the DCCT mean HbA_{1c} with cardiac MRI measures of left ventricular (LV) function and aortic distensibility

	Mean (SD)	Worse	β, SE	*P*
Ejection fraction, %	62 (6)	↓	−0.02, 0.15	0.90
LV mass, g/m^2	139 (33)	↑	1.57, 0.52	0.003
LV mass/EDV, mg/mL	1.0 (0.17)	↑	0.02, 0.004	<0.001
Ln aortic distensibility, mmHg-1 (inverse of stiffness)	0.60 (0.51)	↓	−0.05, 0.01	<0.001

EDV, end-diastolic volume; Ln, natural logarithm.

more abnormal among males and with increasing age and blood pressure and, after adjusting for these other risk factors, with higher mean HbA_{1c} over the DCCT/EDIC. Likewise, there were no treatment group differences in aortic stiffness, but the values were worse with increasing age and other factors and with higher DCCT/EDIC mean HbA_{1c} (15).

Myocardial scars were present in 32 of the 741 subjects who completed the gadolinium enhancement, 21 of whom had no prior history of a clinical MI. Of the 21 subjects with scars but no prior clinical history, 7 had typical ischemic scars and 14 had nonischemic-appearing lesions (14).

The cardiac MRI findings were associated with age and blood pressure and other traditional CVD risk factors. While there were no differences between the former DCCT therapy groups, the measures of cardiac structure and function were strongly associated with the mean HbA_{1c} over the period of the DCCT/EDIC and over the DCCT alone (Table 1) (16).

CONCLUSIONS

Compared with CON, the initial DCCT INT had beneficial effects on atherosclerosis (carotid IMT and CAC) 6–12 years after the end of the period of the randomized treatments. Furthermore, the benefit of INT increased with attained age. The benefits of INT versus CON were largely explained, statistically, by the difference between treatment groups in DCCT HbA_{1c} levels.

The salutary effects of INT on markers of atherosclerosis translated into long-term beneficial effects of DCCT INT versus CON on the incidence of clinical CVD events. Former INT reduced the aggregate CVD risk by 42% and that of the major CVD events (MI, stroke, and CVD deaths) by 57%. These long-term benefits were also statistically explained by the differences between the groups in the mean HbA_{1c} levels during the DCCT. While group differences in albuminuria explained some of these beneficial effects, the mean DCCT HbA_{1c} remained the stronger determinant of risk when the two were considered together. The magnitude of this beneficial effect of INT was far greater than usually seen in trials addressing blood pressure or cholesterol management. There were no differences between the former DCCT INT and CON groups in measures of cardiac structure and function on cardiac MRI. However, there were strong associations between the measures of structure and function with the mean HbA_{1c} during DCCT alone and over the entire period of the DCCT/EDIC prior to the MRI examination.

DCCT INT providing an average of 6.5 years of lower HbA_{1c} had long-term, major salutary effects on the progression of atherosclerosis and the development of clinical CVD during the subsequent EDIC follow-up. These results provide a clear demonstration of a benefit of glycemic control on CVD in type 1 diabetes. In contrast, demonstration of such an effect with trials in type 2 diabetes has been elusive (17,18). This likely reflects a number of factors including the much earlier stage of atherosclerosis and younger age in DCCT/EDIC than seen in the type 2 trials where many participants already had established CVD at the time of intervention. Follow-up was also shorter in the type 2 diabetes trials in which multiple glucose-lowering medications were also used. Of note, the one trial in type 2 diabetes that has demonstrated a benefit of intensive diabetes management on CVD outcomes, the UK Prospective Diabetes Study (19), recruited a relatively young population with new-onset diabetes, reduced HbA_{1c} to approximately 7%, and followed the subjects postintervention, similar to the DCCT/EDIC. Regardless of the putative benefits of INT in type 2 diabetes, DCCT/EDIC has demonstrated that INT benefits both microvascular disease and CVD in type 1 diabetes.

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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. Lachin J, Genuth S, Nathan D, Davis M; The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group.

Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000; 342:381–389

3. Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN; DCCT/EDIC Research Group. Effect of glycemic exposure on the risk of microvascular complications in the diabetes control and complications trial—revisited. Diabetes 2008;57:995–1001
4. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications 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
5. Orchard TJ, Costacou T, Kretowski A, Nesto RW. Type 1 diabetes and coronary artery disease. Diabetes Care 2006;29:2528–2538
6. Orchard TJ, Costacou T. When are type 1 diabetic patients at risk for cardiovascular disease? Curr Diab Rep 2010;10:48–54
7. Snell-Bergeon JK, Nadeau K. Cardiovascular disease risk in young people with type 1 diabetes. J Cardiovasc Transl Res 2012;5: 446–462
8. The Diabetes Control and Complications Trial Research Group. Effect of intensive diabetes management on macrovascular events and risk factors in the Diabetes Control and Complications Trial. Am J Cardiol 1995;75:894–903
9. 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
10. Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Effect of intensive diabetes treatment on carotid artery wall thickness in the Epidemiology of Diabetes Interventions and Complications. Diabetes 1999;48:383–390
11. Nathan DM, Lachin J, Cleary P, et al.; Diabetes Control and Complications Trial; Epidemiology of Diabetes Interventions and Complications Research Group. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. N Engl J Med 2003;348:2294–2303
12. Polak JF, Backlund JYC, Cleary PA, et al.; DCCT/EDIC Research Group. Progression of carotid artery intima-media thickness during 12 years in the Diabetes Control and Complications (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study. Diabetes 2011;60:607–613
13. Cleary PA, Orchard TJ, Genuth S, et al.; DCCT/EDIC Research Group. The effect of intensive glycemic treatment on coronary artery calcification in type 1 diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. Diabetes 2006;55: 3556–3565
14. Turkbey EB, Backlund JYC, Genuth S, et al.; DCCT/EDIC Research Group. Myocardial structure, function, and scar in patients with type 1 diabetes mellitus. Circulation 2011;124:1737–1746
15. Turkbey EB, Redheuil A, Backlund JY, et al.; DCCT/EDIC Research Group. Aortic distensibility in type 1 diabetes. Diabetes Care 2013;36:2380–2387
16. Genuth SM, Backlund J-YC, Bayless M, et al.; DCCT/EDIC Research Group. Effects of prior intensive versus conventional therapy and history of glycemia on cardiac function in type 1 diabetes in the DCCT/EDIC. Diabetes 2013;62:3561–3569
17. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
18. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
19. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–1589