Diabetes journals

The edict from DCCT/EDIC: Reducing the risk of cardiovascular disease in people with type 1 diabetes

Vinod Patel
Principal Teaching Fellow, Warwick Medical School, University of Warwick, and Honorary Consultant in Diabetes and Endocrinology, George Eliot Hospital NHS Trust, Nuneaton

Diabetes care has improved substantially in the UK, and we can congratulate ourselves on many of the care processes and clinical outcomes achieved. Unfortunately, the main successes have been in people with type 2 diabetes, with National Diabetes Audit data revealing worse care in people with type 1 versus type 2 diabetes.

Type 1 diabetes carries a high risk of cardiovascular disease (CVD) and is the most common cause of premature CVD morbidity and mortality (Lind et al, 2011; Harding et al, 2014). The DCCT (Diabetes Control and Complications Trial) showed that an average 6.5 years of intensive diabetes treatment achieving a mean HbA_{1c} of 56 mmol/mol (7.2%) substantially reduced microvascular complications compared with conventional treatment achieving an HbA_{1c} of 76 mmol/mol (9.1%; DCCT Research Group, 1993). After study closure and an additional 11 years of observational follow-up in the EDIC (Epidemiology of Diabetes Interventions and Complications) study, the risk of major adverse cardiac events (MACE; cardiovascular death, non-fatal myocardial infarction [MI] or non-fatal stroke) was reduced by 58%, and aggregate CVD (MACE plus confirmed angina, silent MI, revascularisation or congestive heart failure) by 42%, in the original intensive treatment group (Nathan et al, 2005).

In the article summarised alongside, the DCCT/EDIC Research Group report their 30-year follow-up data (mean follow-up, 26 years). A substantial 86% of the original cohort were included in this latest analysis. Despite comparable treatment for more than 25 years and near equalisation of achieved HbA_{1c} levels, the benefits of what the authors termed "metabolic memory" were apparent. In the intensive treatment group, 147 cardiovascular events were reported in 82 people, significantly less than the 217 events in 102 people observed in the conventional treatment group. This is equivalent to a rate of 0.81 cardiovascular events per 100 person-years in the intensive group versus 1.18 events per 100 person-years in the conventional group. The average age was only 55 years. This 30% reduction in any CVD was similar to the 32% reduction in MACE that was observed.

The UKPDS (UK Prospective Diabetes Study) showed a similar effect in people with type 2 diabetes, a phenomenon termed the "legacy effect" of good initial glycaemic control (Holman et al, 2008). However, it is important to differentiate this from good control in older people with high CVD risk; in these subjects, implementing very tight glycaemic control in fact resulted in increased mortality and mortality in some studies (Hayward et al, 2015).

A second DCCT/EDIC report (summarised on the facing page) is a detailed analysis of the overall risk factors for CVD at the 30-year follow-up point. Multivariate Cox proportional hazard models were used to assess traditional and novel risk factors for MACE and all CVD. Age and HbA_{1c} were strongly associated with MACE and all CVD. For each 11-mmol/mol (1.0%) increase in mean HbA_{1c}, the risk of all CVD and MACE rose by 31% and 42%, respectively. CVD and MACE were associated with seven other conventional risk factors but not with gender. This makes the point that in type 1 diabetes, the usual protective effect of female gender is lost. The other main significant risk factors were baseline age, mean pulse rate, raised triglyceride levels, systolic blood pressure, smoking, baseline diabetes duration and current LDL-cholesterol level. Current use of an angiotensin-converting enzyme (ACE) inhibitor was protective.

To conclude, people with type 1 diabetes may be the lost tribe caught in the maelstrom of the type 2 diabetes epidemic. Care for this <10% of the diabetes population as always been problematic. The edict? Blood pressure control, ACE inhibitor use and lipid control are all important in reducing CVD risk. However, we must re-focus our attention on achieving early good glycaemic control and maintaining it. ■

References on opposite page

Diabetes Care

30-year follow-up of DCCT/EDIC: CV outcomes

Readability	✓✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓✓✓

1 This article presents the 30-year cardiovascular (CV) outcomes of EDIC (Epidemiology of Diabetes Interventions and Complications), the observational follow-up of the DCCT (Diabetes Control and Complications Trial).

2 While earlier EDIC follow-up showed an equalisation of HbA_{1c} between the two groups, at the 30-year follow-up (mean follow-up, 26 years), mean HbA_{1c} was once again lower in the original intensive therapy group (61 vs 66 mmol/mol [7.8% vs 8.2%]).

3 In the intensive treatment group, 149 CV events occurred in 82 people, compared to 217 events in 102 people in the conventional treatment group (event rate, 0.81 vs 1.18 per 100 person-years; P=0.06).

4 Intensive therapy reduced the risk of any CV disease by 30% (95% confidence interval [CI], 7–48), a smaller reduction than in the previous follow-up (in 2004), but one that is still statistically significant (P=0.016).

5 Similarly, the risk reduction for major adverse cardiac events fell from 57% in 2004 to 32% (95% CI, –3 to 56), the latter difference now being of borderline significance (P=0.07).

6 The lower HbA_{1c} levels achieved during DCCT statistically account for all of the observed treatment effect on CV risk.

7 These results confirm that the effects of "metabolic memory" persist long after the active period of intensive therapy in people with T1D.

Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group (2016) Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: The DCCT/EDIC study 30-year follow-up. *Diabetes Care* **39**: 686–93

Diabetes

Risk factors for CVD in DCCT/EDIC

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓✓✓✓

1 The 30-year follow up of DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications) has provided data on a sufficient number of cardiovascular (CV) events to conduct an analysis of risk factors for CV disease (CVD) in people with T1D.

2 In this analysis of DCCT/EDIC data, the authors used multivariate Cox proportional hazard models to determine risk factors for major adverse cardiac events (MACE; CV death, non-fatal myocardial infarction [MI] or non-fatal stroke) and all forms of CVD (MACE plus subclinical MI, confirmed angina, revascularisation or congestive heart failure).

3 In the multivariate model, increasing age at baseline had the strongest association with all CVD (hazard ratio [HR] per 5-year increase, 1.54) and MACE (HR, 1.77). This was followed by HbA_{1c} (HR per 11-mmol/mol [1.0%] increase, 1.31 for all CVD; 1.42 for MACE).

4 In addition, CVD was associated with seven other risk factors, including mean pulse rate (HR, 1.60 per 10-bpm increase), current triglyceride level (HR, 1.78 per logarithmic increase), mean systolic blood pressure (HR, 1.39 per 10-mmHg increase), current smoking (HR, 1.87), baseline diabetes duration (HR, 1.33 per 5-year increase) and current LDL-cholesterol level (HR, 1.07 per 0.6-mmol/L increase). Use of an angiotensin-converting enzyme inhibitor was protective (HR, 0.58).

5 With a mean age of 55 years in 2013, the cohort is still young, and subsequent follow-up may shed more light on risk factors for CVD.

Diabetes Control and Complications Trial (DCCT)-Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group (2016) Risk factors for cardiovascular disease in type 1 diabetes. *Diabetes* **65**: 1370–9

Diabet Med

Aspirin for primary CVD prevention: Meta-analysis

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓

1 This systematic review and meta-analysis assessed the benefits of aspirin treatment for the primary prevention of cardiovascular disease (CVD) in people with diabetes.

2 Ten randomised controlled trials comparing aspirin with placebo or no treatment met the inclusion criteria and were analysed.

3 Pooled analysis of 15 988 people showed a significant reduction in risk of a major adverse cardiac event (MACE) with aspirin (relative risk [RR], 0.90; 95% confidence interval [CI], 0.81–0.99). However, exclusion of the largest trial, ETDRS (Early Treatment Diabetic Retinopathy Study), in which a small proportion of participants had previous CVD, made the difference non-significant.

4 Stratified analysis showed that aspirin reduced MACE risk in men (RR, 0.79; 95% CI, 0.64–0.98) but not women (RR, 0.95; 95% CI, 0.77–1.16).

5 Aspirin therapy was not associated with reductions in risk of myocardial infarction, coronary heart disease, stroke, CVD mortality or all-cause mortality.

6 The number needed to treat to prevent one MACE was estimated to be 109.

7 Given these findings and the potential for increased risk of bleeding events associated with aspirin, the authors conclude that aspirin treatment for primary prevention of CVD in this population is not justified. This is in keeping with the latest NICE guidelines for T1D and T2D.

Kunutsor SK, Seidu S, Khunti K (2016) Aspirin for primary prevention of cardiovascular and all-cause mortality events in diabetes: updated meta-analysis of randomized controlled trials. *Diabet Med* 17 Apr [Epub ahead of print]

Diabetes Care

ACCORD follow-on: Nine-year CV effects of intensive glycaemic control

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓✓
WOW! Factor	✓✓✓

1 The glycaemic control part of the ACCORD (Action to Control Cardiovascular [CV] risk in Diabetes) trial was stopped after 3.7 years owing to an increased mortality rate in the intensive treatment arm.

2 In the ACCORDION (ACCORD Follow-On) study, the surviving participants were followed for a further 5 years, with both arms continuing with standard glycaemic control.

3 A total of 8601 people with T2D, representing 98% of those who did not have a major adverse cardiac event or death during the original trial, were followed for a median of 8.8 years.

4 Intensive treatment in the active phase of the trial had a neutral effect on the primary outcome (a composite of CV death, non-fatal myocardial infarction and non-fatal stroke) at final ACCORDION follow-up.

5 Furthermore, the increased risk of all-cause death observed in ACCORD was no longer significant at the final follow-up.

6 However, the increased risk of CV death, while attenuated, remained significant (hazard ratio, 1.20; 95% confidence interval, 1.03–1.40). This corresponds to an absolute risk difference of 1.3% over 10 years

7 Product-limit estimates of the time to event for these outcomes suggested that any differences in incidence were confined to the active treatment period.

8 A large reduction in retinopathy risk was also observed (see page 75 of this journal).

ACCORD Study Group (2016) Nine-year effects of 3.7 years of intensive glycemic control on cardiovascular outcomes. *Diabetes Care* **39**: 701–8

"These results confirm that the effects of "metabolic memory" persist long after the active period of intensive therapy in people with type 1 diabetes."

References from commentary

Diabetes Control and Complications Trial Research Group (1993) 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* **329**: 977–86

Harding JL, Shaw JE, Peeters A et al (2014) Mortality trends among people with type 1 and type 2 diabetes in Australia: 1997–2010. *Diabetes Care* **37**: 2579–86

Hayward RA, Reaven PD, Wiitala WL et al (2015) Follow-up of glycemic control and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* **372**: 2197–206

Holman RR, Paul SK, Bethel MA et al (2008) 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* **359**: 1577–89

Lind M, Bounias I, Olsson M et al (2011) Glycaemic control and incidence of heart failure in 20,985 patients with type 1 diabetes: an observational study. *Lancet* **378**: 140–6

Nathan DM, Cleary PA, Backlund JY et al (2005) Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* **353**: 2643–53