Published in final edited form as:

Lancet Diabetes Endocrinol. 2014 October ; 2(10): 793–800. doi:10.1016/S2213-8587(14)70155-X.

Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: long-term follow-up of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study

The DCCT/EDIC research group

Summary

Background—Intensive diabetes treatment reduces the risk of developing albuminuria in individuals with type 1 diabetes. Effects on the long-term clinical course of kidney disease remain to be defined. We aimed to compare the long-term effects of intensive versus conventional treatment on incident albuminuria.

Methods—For this long-term follow-up study of the Diabetes Control and Complications Trial (DCCT) we assessed the effect of intensive diabetes treatment on albuminuria during 18 years after the completion of the trial. During the DCCT (1983–1993), 1441 participants with type 1 diabetes were randomly assigned to receive either intensive treatment (with the goal of achieving levels of glycaemia as close to the non-diabetic range as safely possible) or conventional treatment (aimed at prevention of symptoms of hyperglycaemia and hypoglycaemia). At the end of the DCCT, all participants were instructed in intensive treatment, and all participants were invited to join the observational Epidemiology of Diabetes Interventions and Complications (EDIC) study. Mean HbA_{1c} during the EDIC study was similar in the two groups of patients who differed in their treatment assignment during the DCCT. Albumin excretion rate was measured every other year during the EDIC study. Microalbuminuria was defined as an albumin excretion rate of 30 mg per 24 h or higher on two consecutive study visits and macroalbuminuria as an albumin excretion rate of 300 mg per day or higher. We estimated glomerular filtration rate from annual serum creatinine measurements throughout DCCT and the EDIC study. The DCCT is registered with ClinicalTrials.gov, number NCT00360815, and the EDIC study, with number NCT00360893.

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Contributors

IHD designed the study, did statistical analyses, and wrote the report. WS and SG did statistical analyses and reviewed the report. JML directed the statistical analyses and reviewed and edited the report. PAC, MEM, MWS, and BZ reviewed the analyses and edited the report.

Declaration of interests

We declare no competing interests.

Findings—During years 1–18 of EDIC, we noted 191 new cases of microalbuminuria (71 in the group receiving intensive treatment during DCCT and 120 in the group receiving conventional treatment during DCCT; risk reduction 45%, 95% CI 26–59) and 117 new cases of macroalbuminuria (31 intensive, 86 conventional; 61%, 41–74). At year 17–18 of EDIC, the prevalence of albumin excretion rate of 30 mg per 24 h or higher was 18.4% in participants assigned to intensive treatment during the DCCT, compared with 24.9% in participants assigned to conventional treatment ($p=0.02$). During years 1–18 of EDIC, we recorded 84 cases of sustained estimated glomerular filtration rate lower than 60 mL/min per 1.73m^2 (31 intensive, 53 conventional; risk reduction 44%, 95% CI 12–64).

Interpretation—In individuals with type 1 diabetes, intensive diabetes treatment yields durable renal benefits that persist for at least 18 years after its application. Ultimately, such benefits should result in fewer patients requiring renal replacement therapy.

Funding—National Institute of Diabetes and Digestive and Kidney Disease.

Introduction

Kidney disease is a common complication of diabetes. Albuminuria (increased urine albumin excretion) is a hallmark of diabetic kidney disease and is often the earliest clinical sign of kidney damage. During their life, up to 40% of people with type 1 diabetes develop urine albumin excretion that is persistently greater than the normal limit (30 mg per 24 h).^{1–5} Moreover, albuminuria is strongly associated with cardiovascular disease.^{6,7} People with type 1 diabetes and albuminuria are at markedly increased risk of premature death, whereas those with persistently normal urine albumin excretion have little or no excess mortality risk compared with the general population.^{8,9} Similarly, in type 2 diabetes, kidney disease is common and is strongly associated with adverse health outcomes.^{10–12} Therefore, the prevention of kidney disease, including albuminuria, is a major therapeutic goal in the care of patients with diabetes.^{13,14}

The Diabetes Control and Complications Trial (DCCT) had a 6.5 year mean follow-up, and its findings showed that intensive diabetes treatment (aimed at lowering glycaemia as close to the non-diabetic range as safely possible) reduced the risk of developing albuminuria in patients with type 1 diabetes in comparison with conventional treatment (aimed at prevention of symptoms of hyperglycaemia and hypoglycaemia).^{15,16} Specifically, intensive treatment reduced incident microalbuminuria (defined as albumin excretion rate ≥ 40 mg per 24 h during the DCCT) by 39%, and incident macroalbuminuria (albumin excretion rate ≥ 300 mg per 24 h) by 54%, compared with conventional treatment.

Since the end of the DCCT, consenting participants have been followed up in the observational Epidemiology of Diabetes Interventions and Complications (EDIC) study. During the first 8 years of the EDIC study, participants assigned to the intensive treatment group in the DCCT continued to have a decreased incidence of microalbuminuria and macroalbuminuria than did those assigned to conventional treatment, despite the decreased difference in mean HbA_{1c} between the two treatment groups during the DCCT. This phenomenon was named metabolic memory.¹⁷ These data suggested that early intensive treatment might have long-lasting benefits that fundamentally change the clinical course of

kidney disease in type 1 diabetes. We aimed to address this hypothesis by comparing the long-term effects of intensive versus conventional treatment during the DCCT on albuminuria during an additional 10 years of EDIC follow-up; 18 years post-trial assessment.

Methods

The DCCT and EDIC study

The DCCT was a multicentre randomised clinical trial done between 1983 and 1993.^{16,17} Between 1983 and 1989, 1441 participants aged 13–39 years with type 1 diabetes were enrolled and randomly assigned to receive either intensive or conventional diabetes treatment. Intensive treatment included three or more insulin injections per day or use of an insulin pump to achieve HbA_{1c} concentrations lower than 6.05%. The goal of conventional treatment was prevention of symptoms of hyperglycaemia and hypoglycaemia with one or two insulin injections per day. The trial included a primary prevention cohort with 726 participants (1–5 years duration of diabetes, albumin excretion rate of <40 mg per 24 h, and without retinopathy [assessed by fundus photography]) and a secondary intervention cohort with 715 participants (1–15 years duration; albumin excretion rate ≥200 mg per 24 h; and at least one microaneurysm in either eye, but no more than moderate non-proliferative retinopathy).

At the end of the DCCT, all participants who had received conventional treatment were instructed in intensive treatment, and all participants returned to their own healthcare providers to continue diabetes care. All DCCT participants were invited to join the EDIC study, an observational extension of the DCCT, and 1375 (96% of the surviving cohort) agreed to participate. During the EDIC study, mean HbA_{1c} concentrations, which had been separated by roughly 2% between conventional and intensive treatment groups during the DCCT, converged such that there was no significant difference in mean HbA_{1c} during the course of the EDIC study between the previous treatment groups.¹⁸ The DCCT and EDIC study procedures were approved by the institutional review boards of participating centres, and all participants provided written informed consent. We included data from the DCCT baseline through EDIC study years 17–18 (2010–12) in our analyses.

Procedures

Albumin excretion rate was measured every year during the DCCT and every 2 years during the EDIC study.¹⁹ In the EDIC study, 50% of participants were tested in odd study years and 50% in even study years to moderate participant burden and conserve resources. Urine was collected for 4 h, during which water consumption was encouraged, and albumin was measured by fluoro-immunoassay at the DCCT and EDIC study central biochemistry laboratory (University of Minnesota, MN, USA; coefficient of variation 9.4%).¹⁶ Albumin excretion rate was transformed to units of mg per 24 h to be consistent with clinical practice guidelines and previous DCCT and EDIC study reports.^{4,15–17,20} For earlier DCCT and EDIC study analyses, microalbuminuria was defined as an albumin excretion rate of 40 mg per 24 h or higher.^{15,17} To be consistent with contemporary guidelines, in the EDIC study microalbuminuria was defined as a sustained albumin excretion rate of 30 mg per 24 h or

higher on two consecutive study visits (usually 1 year apart during the DCCT and 2 years apart during EDIC) for more recent analyses,⁴ including our study. We defined macroalbuminuria as albumin excretion rate of 300 mg per 24 h or higher.

Serum creatinine was measured every year throughout the DCCT and the EDIC study at the DCCT and EDIC central biochemistry laboratory. Results were calibrated to National Institute of Standards and Technology Isotope Dilution Mass Spectrometry assigned values²⁰ and used to estimate glomerular filtration rate with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.²¹ Impaired glomerular filtration rate was defined as an estimated glomerular filtration rate of less than 60 mL/min per 1.73m² on two consecutive study visits.²⁰ End-stage renal disease was defined as the initiation of maintenance haemodialysis or kidney transplantation.

HbA_{1c} was measured once every 3 months during the DCCT and every year during the EDIC study by high-performance liquid chromatography.²² Hyper tension was defined as a systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or use of antihypertensive drugs. Drug use was ascertained every year throughout the EDIC study. Angiotensin-converting enzyme (ACE) inhibitors were prohibited during the DCCT, and were analysed together with angiotensin 2 receptor blockers during EDIC as renin-angiotensin system (RAS) inhibitors. Hyper-lipidaemia was defined by a calculated low density lipoprotein cholesterol concentration of 130 mg/dL or higher, or the use of lipid-lowering drugs. Retinopathy was ascertained by fundus photography.²³ Confirmed clinical neuropathy was defined as signs and symptoms of distal symmetrical peripheral neuropathy on the basis of assessment by a board-certified neurologist, and was confirmed by abnormal nerve conduction findings in the DCCT; during the EDIC study, the assessment was done by a diabetes investigator at the participating centres without confirmatory nerve conduction studies.²²

Statistical analysis

We compared clinical characteristics with the Wilcoxon rank-sum test for quantitative or ordinal variables and the χ^2 test for categorical variables. We used Cox proportional hazards models with the Peto-Breslow adjustment for ties to assess the DCCT treatment effect on risk of renal outcomes during different study periods (ie, combined DCCT and EDIC, DCCT only, or EDIC only).²⁴ We adjusted all models for the albumin excretion rate or estimated glomerular filtration rate at the respective baseline (DCCT baseline for the combined DCCT and EDIC, and DCCT only; DCCT closeout for the EDIC only). We used Lin-Wei robust covariance estimate for all models, which is robust to departure from the assumption of proportional hazards.²⁴ Models that assessed albumin excretion rate outcomes in the EDIC study (or combined DCCT and EDIC study follow-up) were stratified by odd-year versus even-year schedule of albumin excretion rate visits during the EDIC study. Risk (hazard) reduction with intensive versus conventional treatment was calculated as (1-hazard ratio) times 100. We estimated the hazard rate (number per year) for the albumin excretion rate outcomes during an interval of the EDIC study with the Nelson-Aalen method. For analyses of albuminuria prevalence by EDIC study year, albumin excretion rate was classified as 30–299 mg per 24 h, more than or equal to 300 mg per 24 h, or end-stage renal disease.

Results

Table 1 shows baseline characteristics at DCCT baseline, DCCT closeout (EDIC study baseline), and year 18 of the EDIC study. Mean follow-up was 6.5 years during the DCCT, 17.2 years during EDIC, and 24.0 years during DCCT and EDIC combined.

1415 participants (98.2% of those randomly assigned) contributed renal outcome measurements at DCCT closeout, and 1220 (84.7% of those randomly assigned, 90.8% of survivors) contributed renal outcome measurements at year 17 or 18 of the EDIC study. During years 1–18 of the EDIC study, among participants who did not develop microalbuminuria during the DCCT, we noted more new cases of microalbuminuria among participants who were assigned to the conventional treatment group than in those assigned to the intensive treatment group (table 2). Cumulative incidence curves by DCCT treatment assignment showed progressive separation through years 7–8 of the EDIC study (figure 1A). Thereafter, the curves increased in parallel through year 17–18 with no further separation. The underlying hazard rate of incident micro albuminuria was substantially higher during EDIC years 1–8 for participants assigned to conventional treatment during DCCT than for those assigned to intensive treatment. The hazard rate for the previous conventional treatment group then fell during EDIC years 9–18 to levels similar to the previous intensive treatment group, during which time there was no significant difference in risk (figure 1C). Risk reduction for intensive versus conventional therapy during the DCCT was 58% (95% CI 40–71; $p<0.001$) during EDIC years 1–8 and 10% (–46 to 44; $p=0.68$) during EDIC years 9–16.

During EDIC years 1–18, among participants who did not develop macroalbuminuria during the DCCT, we noted almost three times as many new cases of macroalbuminuria in the group of participants assigned to the conventional therapy group in the DCCT than in the group assigned to intensive treatment (table 2). As for incident microalbuminuria, cumulative incidence curves for macroalbuminuria by DCCT treatment assignment showed separation during EDIC years 1–8, followed by roughly parallel increasing curves during EDIC years 9–18 (figure 1B). The hazard of incident macroalbuminuria in the group assigned to conventional treatment during DCCT fell during years 9–18 in the EDIC study to levels similar to that in the group assigned to intensive treatment group during DCCT (figure 1D). Risk reduction for intensive versus conventional therapy during the DCCT was 79% (95% CI 58–89; $p<0.001$) during EDIC years 1–8 and 31% (–20 to 61; $p=0.19$) during EDIC years 9–16.

Among participants assigned to conventional treatment during the DCCT, the prevalence of albuminuria (albumin excretion rate ≥ 30 mg per 24 h or end-stage renal disease) peaked at 26.4% in EDIC years 7–8 and was subsequently slightly lower but generally stable (figure 2). Of participants assigned to receive intensive treatment during the DCCT, the prevalence of albuminuria peaked at years 17–18 of the EDIC study, and was consistently less than that noted in participants assigned to receive conventional treatment during the DCCT. At EDIC years 17–18, the prevalence of albuminuria was 18.4% in participants assigned to receive intensive treatment during the DCCT and 24.9% in participants assigned to conventional

treatment during the DCCT ($p=0.02$). We noted similar results for prevalent microalbuminuria and macroalbuminuria, which were assessed separately (appendix).

Models that assessed the treatment group effect after adjustment for the mean HbA_{1c} during the DCCT and the EDIC study showed that the time-averaged DCCT and EDIC mean HbA_{1c} explained 100% of the beneficial effect of intensive treatment on incident microalbuminuria and 93% of the effect on incident macroalbuminuria during EDIC years 1–18 (appendix). Adjustment for updated blood pressure, BMI, RAS inhibitor use, and antihypertensive drug use did not attenuate associations of treatment assignment during the DCCT with microalbuminuria or macroalbuminuria.

During combined DCCT and EDIC study follow-up, we recorded more new cases of incident impaired estimated glomerular filtration rate in the group assigned to conventional treatment during the DCCT than in the group assigned to intensive treatment during DCCT (table 2). All but five of these events arose during the EDIC study. We also noted more cases of end-stage renal disease through EDIC year 18 in the group assigned to conventional treatment during the DCCT than in the group assigned to intensive treatment during DCCT (table 2).

Discussion

In the DCCT and subsequent EDIC study, intensive treatment of patients with type 1 diabetes yielded large, durable reductions in the cumulative incidence of microalbuminuria and macroalbuminuria that have persisted through 18 years of follow-up after DCCT. Of the participants who had not developed microalbuminuria or macroalbuminuria during the DCCT, those assigned to intensive treatment during the DCCT continued to have decreased hazard rates for incidence of newly-reported microalbuminuria and macroalbuminuria during the first 8 years of follow-up in the EDIC study. During years 9–18 in the EDIC study, the hazard rates for microalbuminuria and macroalbuminuria in the conventional group decreased to levels similar to those in the intensive group, which remained low. As a result, cumulative incidence curves by DCCT treatment assignment progressively separated during the first 8 years of the EDIC study. Thereafter, the incidence curves increased in parallel. Consistent with these effects on cumulative incidence, we recorded persistent differences in the prevalence of albuminuria 17–18 years after the end of the DCCT. Additionally, we noted large differences in the incidence of impaired glomerular filtration rate by DCCT treatment assignment. These results show long-lasting renal benefits of intensive treatment and strongly suggest that early intensive treatment fundamentally changes the clinical course of kidney disease in patients with type 1 diabetes.

We have previously reported that participants assigned to intensive treatment in the DCCT continued to have lower rates of microalbuminuria and macroalbuminuria during years 1–8 in the EDIC study.¹⁷ This persistent beneficial effect, noted despite loss of separation in mean HbA_{1c} , has been attributed to so-called metabolic memory. Metabolic memory might be indicative of a lag time between the effects of intensive treatment on biological pathways initiating kidney damage and the clinical manifestations of that damage. For example, deposition of long-lived advanced glycation endproducts might initiate a slow cascade of

events leading to increased glomerular permeability.²⁵ Alternatively, intensive treatment might have effects on the biological pathways initiating kidney damage that persist beyond the period of peripherally measured glycaemic control—eg, through epigenetic regulation.²⁶

During years 9–18 in the EDIC study, the hazard rates for both microalbuminuria and macroalbuminuria in participants assigned to conventional treatment during the DCCT fell to levels similar to those in participants assigned to DCCT intensive treatment. As a result, cumulative incidence curves increased in parallel for the original intensive and conventional treatment groups during this period. The decreasing hazard rates in participants assigned to conventional treatment during the DCCT arose despite increases in weight and blood pressure. These decreasing hazard rates could be explained partly by increasing use of RAS inhibitors, which lower albumin excretion rate. However, during this same period, RAS inhibitor use also increased substantially in participants who had intensive treatment during the DCCT, and these patients did not have a decrease in hazards of microalbuminuria or macroalbuminuria.

The decreasing hazards of microalbuminuria and macroalbuminuria during years 9–18 in the EDIC study in participants assigned to conventional treatment during the DCCT might be due to improved glycaemic control during the EDIC study period. In this group, mean HbA_{1c} was 9.1% at the end of the DCCT and fell quickly during the EDIC study to nearly 8%. This improved glycaemic control during years 1–8 in the EDIC study might have had a delayed effect on incidence during years 9–18 in the EDIC study. Such a delay was noted during the DCCT, in which the effects of intensive treatment on the incidence of microalbuminuria and macroalbuminuria were not recorded until year 4 in the DCCT.¹⁶ This hypothesis suggests that, although early intensive treatment is ideal, later improvements in glycaemic control might also have a beneficial effect, albeit delayed. However, this hypothesis cannot be definitively tested because changes in diabetes treatment were not randomly assigned during EDIC.

Importantly, despite the convergence of the incidence hazard rates during years 9–18 in the EDIC study, the cumulative incidence curves for microalbuminuria and macroalbuminuria by DCCT treatment assignment did not converge during years 9–18 in the EDIC study. As a result, intensive treatment led to 49% and 66% lower risks of incident microalbuminuria and macroalbuminuria, respectively, averaged during a mean 24 years of follow-up in the DCCT and the EDIC study. Similarly, the prevalence of albuminuria at year 17–18 in the EDIC study, which accounts for regression of albuminuria as previously recorded in the DCCT and EDIC study, and in other cohorts,^{4,27} was substantially lower in participants assigned to intensive treatment during the DCCT. These long-term effects on albuminuria are congruent with the long-term reduction by intensive treatment in the incidence of impaired glomerular filtration rate, which was previously reported through year 16 in the EDIC study and was updated herein through year 18.²⁰ Together, these data provide strong evidence that intensive treatment favourably changes the long-term clinical course of kidney disease in type 1 diabetes (panel).

Panel: Research in context**Literature review**

Intensive diabetes treatment aimed at lowering glycaemia as close to the non-diabetic range as safely as possible reduces the risk of developing albuminuria (microalbuminuria and macroalbuminuria) and other microvascular diabetes complications. In type 1 diabetes, intensive treatment reduced risks of incident albuminuria during the DCCT and for 8 years after DCCT close-out, a phenomenon referred to as metabolic memory.¹⁷ Short-term benefits of intensive treatment on albuminuria have been shown in type 2 diabetes too.^{28–32} Microvascular benefits serve as a foundation for present recommendations on glycaemic control. However, it is now known how long the microvascular benefits of intensive treatment are maintained.

Interpretation

In this long-term follow-up study of the DCCT, the separation in cumulative incidence of albuminuria achieved through 8 years of post-trial follow-up was maintained through an additional 10 years—a total 18 years after end of the DCCT. Consistent with this finding, participants assigned to intensive treatment had a lower prevalence of albuminuria 18 years after the end of the DCCT. Additionally, the risk of development of impaired glomerular filtration rate was reduced with intensive treatment. These data provide further evidence that early intensive diabetes treatment has long-lasting, durable renal benefits in individuals with type 1 diabetes.

Published data suggest that intensive diabetes treatment might have similar long-term renal benefits in type 2 diabetes, but do not conclusively address this question. In the UK Prospective Diabetes Study, pharmacological glucose-lowering treatment reduced microalbuminuria and proteinuria, and a persistent separation in cumulative incidence curves was noted for composite diabetes complications through 10 years of follow-up after the trial.^{28,29} However, specific long-term effects on estimated glomerular filtration rate and end-stage renal disease have not been published to our knowledge. In the ACCORD trial,³⁰ ADVANCE trial,³¹ and the VA Diabetes trial,³² intensive glucose-lowering reduced the incidence or progression of albuminuria. However, no beneficial effects on estimated glomerular filtration rate were noted during the active intervention periods, and long-term follow-up is not yet available. In ADVANCE,³³ fewer end-stage renal disease events were noted with intensive glucose-lowering, but the number of events was small and consistent changes in estimated glomerular filtration rate were not seen.

This study provides a unique investigation of the long-term effects of an important diabetes intervention. Characterisation of these effects was only possible with high participant retention and detailed, frequent, and carefully ascertained longitudinal outcome measurements, which are important strengths of the DCCT and the EDIC study. Limitations include the assessment of intermediate biomarkers rather than clinical end-stage renal disease events, which have been uncommon in the DCCT and EDIC study population up to now.

In conclusion, intensive diabetes treatment applied early in the course of type 1 diabetes has long-lasting beneficial effects on the clinical course of kidney disease that persist at least 18 years after its initial application.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was funded by the National Institute of Diabetes and Digestive and Kidney Disease. A complete list of participants in the DCCT and EDIC research group has been published previously.²⁰ The DCCT and EDIC studies have been supported by U01 Cooperative Agreement grants (1982–93, 2011–16), and contracts (1982–2011) with the Division of Diabetes Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Disease, and through support from the National Eye Institute, the National Institute of Neurologic Disorders and Stroke, the Genetic Clinical Research Centers programme (1993–2007), and Clinical Translational Science Center Program (2006–present), Bethesda, MD, USA. Industry contributors had no role in the DCCT and EDIC study, but provided free or discounted supplies or equipment to support participants' adherence to the study: Abbott Diabetes Care (Alameda, CA, USA), Animas (Westchester, PA, USA), Bayer Diabetes Care (North America Headquarters, Tarrytown NY, USA) Becton Dickinson (Franklin Lakes, NJ, USA), CanAm (Atlanta, GA, USA), Eli Lilly (Indianapolis, IN, USA), Lifescan (Milpitas, CA, USA), Medtronic Diabetes (Minneapolis, MI, USA), Omron (Shelton, CT, USA), OmniPod Insulin Management System (Bedford, MA, USA), Roche Diabetes Care (Indianapolis, IN, USA), and Sanofi-Aventis (Bridgewater NJ, USA). de Boer's effort was supported by grants R01DK087726 and R01DK088762 from the National Institute of Diabetes and Digestive and Kidney Disease.

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Figure 1. Cumulative incidence of microalbuminuria and macroalbuminuria during years 1–18 in the EDIC study

(A) Cumulative incidence of microalbuminuria (sustained albumin excretion rate ≥ 30 mg per 24 h). (B) Cumulative incidence of macroalbuminuria (albumin excretion rate ≥ 300 mg per 24 h). (C) Hazard rate of microalbuminuria. (D) Hazard rate of macroalbuminuria. *In units of number per patient-year.

Figure 2. Prevalence of albuminuria by DCCT treatment group and EDIC study year

Albumin excretion rate is classified into four mutually exclusive categories. End-stage renal disease was used for any participant who was treated with dialysis or underwent kidney transplantation irrespective of whether urine was collected or albumin excretion rate was measured. DCCT=Diabetes Control and Complications Trial. EDIC=Epidemiology of Diabetes Interventions and Complications. I=DCCT intensive diabetes treatment. C=DCCT conventional diabetes treatment. RAS=renin-angiotensin system.

Table 1

Participant characteristics at DCCT baseline, DCCT closeout (EDIC baseline), and EDIC year 18

	DCCT baseline (1983-89) (N=1441)		End of DCCT (1993) (N=1415)*		EDIC year 18 (2010-12) (N=1220)*	
	INT (n=711)	CONV (n=730)	INT (n=698)	CONV (n=717)	INT (n=622)	CONV (n=598)
Medical history						
Age (years)	27.2 (7.1)	26.7 (7.1)	33.6 (7.0)	33.0 (7.0)	52.3 (6.9)	51.3 (6.9) [‡]
Women	345 (49%)	335 (46%)	342 (49%)	329 (46%)	303 (49%)	274 (46%)
Diabetes duration (years)	5.8 (4.2)	5.5 (4.1)	12.3 (4.9)	11.9 (4.8)	30.7 (5.0)	30.2 (4.9)
Hypertension	22 (3%)	15 (2%)	31 (4%)	28 (4%)	415 (67%)	411 (69%)
Hyperlipidaemia	162 (23%)	171 (23%)	179 (26%)	213 (30%)	427 (69%)	407 (68%)
Present cigarette smoking	132 (19%)	134 (18%)	141 (20%)	142 (20%)	71 (11%)	64 (11%)
Medical treatment						
Glucose management						
Pump or multiple daily injections (three)	0 (0%)	0 (0%)	680 (97%)	36 (5%) [‡]	607 (98%)	584 (98%)
Glucose monitoring four times a day	0 (0%)	0 (0%)	368 (53%)	27 (4%) [‡]	422 (68%)	423 (71%)
Antihypertensive drug [§]						
Any	0 (0%)	0 (0%)	..	..	374 (60%)	374 (63%)
RAS inhibitor	0 (0%)	0 (0%)	..	..	352 (57%)	357 (60%)
Physical examination						
BMI (kg/m ²)	23.4 (2.7)	23.5 (2.9)	26.6 (4.2)	25.0 (3.1) [‡]	29.1 (5.7)	28.5 (5.1)
Obese (BMI ≥30 kg/m ²)	9 (1%)	14 (2%)	130 (19%)	40 (6%) [‡]	225 (36%)	198 (33%)
Systolic blood pressure (mm Hg)	114.5 (11.3)	114.6 (11.4)	116.3 (11.7)	115.3 (12.0)	122.4 (15.4)	121.8 (15.1)
Diastolic blood pressure (mm Hg)	73.1 (8.2)	72.9 (8.7)	74.4 (8.8)	74.3 (8.8)	71.5 (9.1)	71.3 (8.8)
Mean arterial pressure (mm Hg)	86.9 (8.2)	86.8 (8.6)	88.3 (8.9)	88.0 (8.9)	88.4 (9.8)	88.2 (9.6)
Laboratory values						
HbA1c [¶]	9.1 (1.6%)	9.1 (1.6%)	7.2 (0.9%)	9.1 (1.3%) [‡]	8.0 (1.0%)	8.0 (1.0%)
Diabetes complications						
Retinopathy				[‡]		[‡]

	DCCT baseline (1983–89) (N=1441)		End of DCCT (1993) (N=1415)*		EDIC year 18 (2010–12) (N=1220)*	
	INT (n=711)	CONV (n=730)	INT (n=698)	CONV (n=717)	INT (n=622)	CONV (n=598)
No Retinopathy	347 (49%)	378 (52%)	197 (28%)	124 (17%)	66 (11%)	28 (5%)
Microaneurysms only	249 (35%)	203 (28%)	277 (40%)	230 (32%)	230 (37%)	160 (27%)
Mild NPDR	82 (12%)	111 (15%)	148 (21%)	204 (29%)	132 (21%)	110 (18%)
Moderate NPDR	32 (5%)	37 (5%)	57 (8%)	102 (14%)	102 (16%)	117 (20%)
Severe PDR or worse	0 (0%)	1 (0%)	18 (3%)	56 (8%)	92 (15%)	183 (31%)
Neuropathy	48 (7%)	41 (6%)	64 (9%)	124 (18%)*	147 (24%)	195 (33%)*

Data are mean (SD) or N (%). DCCT=Diabetes Control and Complications Trial. EDIC=Epidemiology of Diabetes Interventions and Complications study. INT=intensive diabetes treatment. CONV=conventional diabetes treatment. RAS=renin-angiotensin system. ARB=angiotensin 2 receptor blocker. NPDR=non-proliferative diabetic retinopathy *Renal measurements (albumin excretion rate or expected glomerular filtration rate) were completed for 1415 participants at DCCT close-out and 1220 participants at EDIC year 17 or 18.

[†]p<0.05.

[‡]p<0.01.

[§]Drug data were not collected during the DCCT. Angiotensin-converting enzyme inhibitors were prohibited during the DCCT.

[¶]End of DCCT HbA1c values are time-averaged mean HbA1c throughout the DCCT; EDIC year 17–18 HbA1c values are time-averaged mean EDIC HbA1c.

Table 2

DCCT/EDIC renal outcomes through EDIC, year 18

	Total at risk	Event (N) (%)		Risk reduction (95% CI) [†]		p value [‡]
		Intensive (N=711)	Conventional (N=730)			
Number at risk during DCCT	1441	..	..	..	..	..
Sustained albumin excretion rate >30 mg per 24 h	1441	166 (23%)	263 (36%)	49 (32 to 62)		<0.0001
During DCCT	1441	95 (13%)	143 (20%)	49 (37 to 59)		<0.0001
During EDIC [*]	1172	71 (12%)	120 (21%)	45 (26 to 59)		<0.0001
Albumin excretion rate >300 mg per 24 h	1441	48 (7%)	121 (17%)	66 (50 to 78)		<0.0001
During DCCT	1441	17 (2%)	35 (5%)	62 (48 to 73)		<0.0001
During EDIC [*]	1350	31 (5%)	86 (13%)	61 (41 to 74)		<0.0001
Sustained expected glomerular filtration rate <60 mL per min per 1.73 m ²	1441	31 (4%)	53 (7%)	44 (12 to 64)		0.011
During DCCT	1441	1 (0%)	3 (0%)	..		..
During EDIC [*]	1398	30 (4%)	50 (7%)	45 (13 to 66)		0.010
Dialysis or kidney transplant [‡]	1441	10 (1%)	16 (2%)	40 (–33 to 73)		0.21
Dialysis	1399	10 (1%)	12 (2%)	..		..
Kidney transplant	1399	6 (1%)	12 (2%)	..		..

^{*} During EDIC, participants were deemed at risk if they were free of the event under consideration during the DCCT and underwent ascertainment of the outcome at least once during EDIC.

[†] Risk reduction and p value were derived from discrete Cox proportional hazards models, which assessed the associations of DCCT treatment group with risk of the respective renal complication in the combined DCCT and EDIC, the DCCT only, or EDIC only, adjusting for baseline albumin excretion rate or expected glomerular filtration rate (at DCCT baseline or DCCT close-out).

[‡] Some participants started dialysis and underwent kidney transplantation. Such participants are included for both dialysis and kidney transplant tallies but are included only once for the combined outcome of dialysis or kidney transplant. DCCT=Diabetes Control and Complications Trial. EDIC=Epidemiology of Diabetes Interventions and Complications study.