



# Kidney Disease and Related Findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study

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## OBJECTIVE

Kidney disease manifests clinically as elevated albumin excretion rate (AER), impaired glomerular filtration rate (GFR), or both, and is a cause of substantial morbidity and mortality in type 1 diabetes (T1D). The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study tested whether intensive diabetes therapy (INT) aimed at lowering glucose concentrations as close as safely possible to the normal range reduces the risks of kidney disease and other diabetes complications.

## RESEARCH DESIGN AND METHODS

In the DCCT, 1,441 participants with T1D were randomly assigned to INT or conventional diabetes therapy (CON) for a mean duration of 6.5 years. Subsequently, participants have been followed for 18 years in the ongoing observational EDIC. Standardized longitudinal measurements of AER, estimated GFR, and blood pressure were made throughout the DCCT/EDIC.

## RESULTS

During the DCCT, INT reduced the risks of incident microalbuminuria (AER  $\geq 40$  mg/24 h) and macroalbuminuria (AER  $\geq 300$  mg/24 h) by 39% (95% CI 21–52%) and 54% (29–74%), respectively. 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% (39–73%) and 84% (67–92%), respectively. Beneficial effects of INT on the development of impaired GFR (sustained estimated GFR  $< 60$  mL/min/1.73 m<sup>2</sup>) and hypertension became evident during combined DCCT/EDIC follow-up, with risk reductions of 50% (18–69%) and 20% (6–21%), respectively, compared with CON.

## CONCLUSIONS

In the DCCT/EDIC, INT resulted in clinically important, durable reductions in the risks of microalbuminuria, macroalbuminuria, impaired GFR, and hypertension.

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Kidney disease manifests clinically as elevated albumin excretion rate (AER), impaired glomerular filtration rate (GFR), or both, and is a cause of substantial morbidity and mortality in type 1 diabetes (T1D). In early cohort studies, up to 40% of patients with T1D developed macroalbuminuria (AER  $\geq 300$  mg/24 h), and up to 75% of these patients progressed to end-stage renal disease (ESRD) within 10 years (1,2). Moreover, the presence and severity of kidney disease have been consistently and strongly associated with increased risks of cardiovascular disease (CVD) and death (3,4).

A large body of evidence demonstrates that hyperglycemia contributes to the damage of target organs, including the kidney (5). Moreover, poor glycemic control has been consistently associated with increased risk of developing kidney disease in T1D (2,6). The Diabetes Control and Complications Trial (DCCT) tested the hypothesis that intensive diabetes therapy (INT) aimed at lowering glucose concentrations as close as safely possible to the normal range would reduce the risk of developing microalbuminuria (AER  $\geq 40$  mg/24 h), macroalbuminuria, and other complications of T1D, compared with conventional therapy (CON) (7). The Epidemiology of Diabetes Interventions and Complications (EDIC) study—the observational study following the DCCT—has examined and continues to examine the extent to which the effects of INT observed during the DCCT are durable (8). In addition, the EDIC has examined the long-term effects of INT on related outcomes, such as impaired GFR and hypertension, as well as the evolving clinical course of kidney disease in T1D. This article summarizes the most important published DCCT/EDIC findings related to kidney disease.

## RESEARCH DESIGN AND METHODS

The DCCT enrolled 1,441 people with T1D from 1983–1989 to determine the effects of INT on the long-term complications of diabetes (7,9). The trial included two cohorts. The primary prevention cohort was characterized by diabetes duration 1–5 years, AER  $< 40$  mg/24 h, and no retinopathy by fundus photography. The secondary intervention cohort was characterized

by diabetes duration 1–15 years, AER  $\leq 200$  mg/24 h, and at least one microaneurysm in either eye (but no more than moderate nonproliferative retinopathy). For both cohorts, serum creatinine  $< 1.2$  mg/dL or creatinine clearance  $> 100$  mL/min/1.73 m<sup>2</sup> was required for eligibility. Hypertension, defined as systolic blood pressure  $\geq 140$  mmHg, diastolic blood pressure  $\geq 90$  mmHg, or treatment with antihypertensive medications, was an exclusion criterion.

Participants were randomly assigned to receive INT or CON, as described in detail elsewhere (7,9). The DCCT ended in 1993 after a mean duration of 6.5 years. Subsequently, all surviving participants were invited to join the observational EDIC, which continues today. During EDIC, mean HbA<sub>1c</sub> levels, which were separated by  $\sim 2\%$  during DCCT, became similar for the two original DCCT treatment groups (8).

AER was measured yearly during DCCT and every other year during EDIC using supervised 4-h urine collections (10,11). Water intake was encouraged to maintain urine output throughout the collection period. Urine albumin was measured at the DCCT/EDIC Central Biochemistry Laboratory (CBL) at the University of Minnesota using a fluoroimmunoassay (interassay coefficient of variation 8.4%).

Serum creatinine was measured annually throughout DCCT/EDIC at the CBL (interassay coefficient of variation  $< 3\%$ ). All results were calibrated to National Institute of Standards and Technology isotope dilution mass spectrometry assigned values (12). The Chronic Kidney Disease Epidemiology Collaboration equation was used to estimate GFR from calibrated serum creatinine, age, sex, and race (13).

Blood pressure was measured every 3 months during DCCT and yearly during EDIC. Hypertension was defined as two consecutive study visits with systolic blood pressure  $\geq 140$  mmHg, diastolic blood pressure  $\geq 90$  mmHg, or the use of antihypertensive medications (14).

The effects of DCCT INT on AER, estimated GFR, and hypertension were tested according to intention to treat. Hazard ratios (HRs) were estimated

using Cox proportional hazards models, which incorporated death as a competing risk when evaluating impaired GFR as the outcome (12). Risk reduction associated with INT was calculated as  $(1 - \text{HR of INT vs. CON}) \times 100\%$ . Proportion of effect explained by DCCT HbA<sub>1c</sub> was the proportion of INT effect explained by statistical adjustment for the treatment group difference in DCCT mean HbA<sub>1c</sub>. Cumulative incidence of microalbuminuria or macroalbuminuria by diabetes duration was quantified using a nonparametric estimator that allows for interval-censored observations (15,16).

## RESULTS

### Baseline Characteristics

Of the 1,441 DCCT participants, 680 (47%) were female and 1,390 (96%) were Caucasian. At DCCT baseline, mean (SD) age was 26.8 (7.1) years and mean (SD) duration of diabetes was 5.9 (4.2) years. Measures of kidney disease were predominantly normal: median (interquartile range) AER was 11.5 (7.2–18.7) mg/24 h and mean (SD) serum creatinine concentration was 0.68 (0.14) mg/dL. AER was  $< 40$  mg/24 h for 1,365 participants (95%) and 40–200 mg/24 h for 76 participants (5%).

### Microalbuminuria

During the DCCT, among the 1,365 participants with baseline AER  $< 40$  mg/24 h at baseline, INT reduced the risk of developing incident microalbuminuria (AER  $\geq 40$  mg/24 h) by 39% (95% CI 21–52%) (Table 1) (7). Significant effects were observed for participants in both the primary and secondary intervention cohorts, with risk reductions of 34% (2–56%) and 43% (21–58%), respectively (17). These effects were strongest beginning 4 years after randomization.

During EDIC years 1–8, among participants who did not develop microalbuminuria during the DCCT, participants previously assigned to DCCT INT continued to experience a lower risk of incident microalbuminuria (risk reduction 59% [95% CI 39–73%]) (8). The effects of INT on microalbuminuria during the DCCT and EDIC were largely explained by group differences in mean DCCT HbA<sub>1c</sub> (Table 1).

**Table 1—Effects of INT on the development of microalbuminuria and macroalbuminuria during the DCCT and during EDIC years 1–8**

	n (events)		Risk reduction with INT	Proportion of effect explained by DCCT HbA <sub>1c</sub>
	INT	CON		
<b>Microalbuminuria (AER ≥40 mg/24 h)</b>				
DCCT	110	166	39% (21–52%)	99%
EDIC years 1–8	39	87	59% (39–73%)	91%
<b>Macroalbuminuria (AER ≥300 mg/24 h)</b>				
DCCT	18	37	54% (29–74%)	98%
EDIC years 1–8	9	59	84% (67–92%)	99%

Risk reduction associated with INT was calculated as  $(1 - \text{HR of INT vs. CON}) \times 100\%$  and presented with 95% CI. Proportion of effect explained by DCCT HbA<sub>1c</sub> is the proportion of INT effect explained by statistical adjustment for the treatment group difference in DCCT mean HbA<sub>1c</sub>.

### Macroalbuminuria

During the DCCT, INT reduced the risk of macroalbuminuria (AER ≥300 mg/24 h) by 54% (95% CI 29–74%) (Table 1) (7).

This effect was significant among participants in the secondary prevention cohort (15 vs. 36 cases, risk reduction 56% [95% CI 18–76%]) but not in the primary prevention cohort, where few cases were observed (3 vs. 6 cases, risk reduction 44% [95% CI –124 to 86%]) (17).

During EDIC years 1–8, among participants who did not develop macroalbuminuria during the DCCT, participants previously assigned to DCCT INT had an 84% lower risk of developing incident macroalbuminuria (95% CI 67–92%) (8). As with microalbuminuria, the effects of INT on

macroalbuminuria were largely explained by group differences in mean DCCT HbA<sub>1c</sub> (Table 1).

### Impaired GFR

From DCCT baseline through EDIC year 16, 70 participants developed impaired GFR, defined as a sustained estimated GFR <60 mL/min/1.73 m<sup>2</sup> on two consecutive study visits (12). Sixty-six of these (94%) occurred during EDIC. Cumulative incidence curves by treatment assignment began separating 10 years after DCCT randomization (Fig. 1). Over combined DCCT/EDIC follow-up, participants assigned to DCCT INT had a 50% lower risk of developing impaired GFR (95% CI 18–69%).

Adjustment for DCCT mean HbA<sub>1c</sub> fully explained the effect of INT on impaired

GFR. In parallel, adjustment for updated mean AER explained 90% of the effect of INT on impaired GFR (12). Relative risk reductions for more advanced stages of GFR loss were similar in magnitude to those for estimated GFR <60 mL/min/1.73 m<sup>2</sup> (Table 2). However, these risk reductions were not all statistically significant, likely due to small numbers of events. INT reduced the risk of a composite outcome of impaired GFR or death, demonstrating that beneficial effects on impaired GFR were not attributable to a possible competing risk of death.

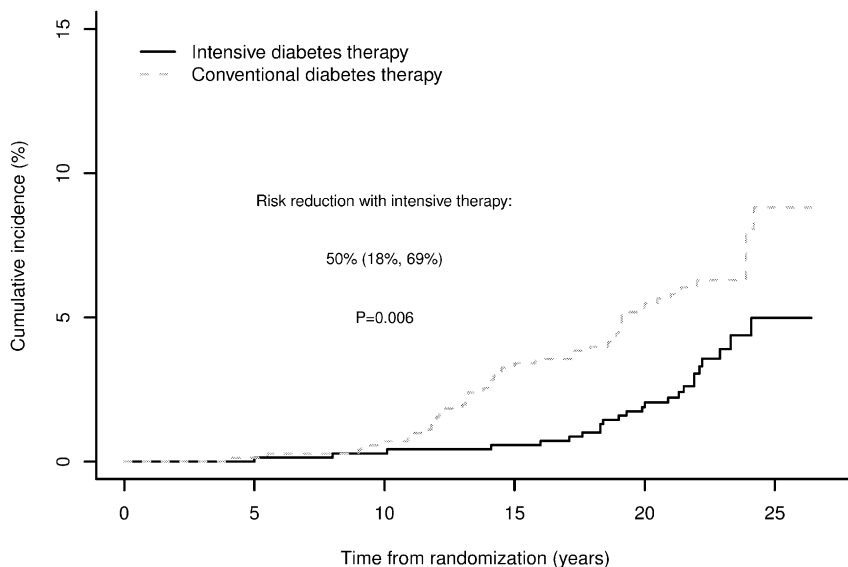
### Hypertension

From DCCT baseline through EDIC year 12, 630 participants developed incident hypertension (Fig. 2) (14). During DCCT, the incidence of hypertension was similar in INT and CON treatment groups. However, INT during the DCCT reduced the risk of incident hypertension during EDIC follow-up. Over combined DCCT/EDIC follow-up, INT reduced the risk of hypertension by 20% (95% CI 6–21%). Adjustment for treatment group differences in DCCT mean HbA<sub>1c</sub> fully explained the effect of INT on incident hypertension. Parallel analyses suggested that AER explained a smaller portion of the effect of INT on hypertension and that weight gain with INT slightly blunted the effect on hypertension that would have otherwise been seen (14).

### Clinical Course

The detailed long-term data collected during DCCT/EDIC have enabled assessment of the clinical course of kidney disease in T1D. These analyses suggest that INT has modified the clinical course of kidney disease and have allowed further characterization of disease progression in this population.

Thirty years after diabetes diagnosis, the cumulative incidences of microalbuminuria and macroalbuminuria were lower among participants assigned to INT versus CON. The 30-year cumulative incidence of microalbuminuria, defined for the observational analyses as sustained AER ≥30 mg/24 h to be consistent with recent guidelines (18,19), was 25 or 38% among participants assigned to INT or CON, respectively (Fig. 3) (15). Similarly,



**Figure 1—**Cumulative incidence of impaired GFR (sustained estimated GFR <60 mL/min/1.73 m<sup>2</sup>) by DCCT treatment group, accounting for death as a competing risk. Reproduced with permission from de Boer et al. (12).

**Table 2—Effects of INT on the development of impaired GFR during the DCCT/EDIC**

	n (events)		Relative risk	
	INT	CON	Risk reduction	P
Sustained estimated GFR <60 mL/min/1.73 m <sup>2</sup>	24	46	50% (18–69%)	0.006
Estimated GFR <45 mL/min/1.73 m <sup>2</sup>	24	39	40% (1–64%)	0.045
Estimated GFR <30 mL/min/1.73 m <sup>2</sup>	13	23	44% (–9 to 72%)	0.088
ESRD	8	16	51% (–14 to 79%)	0.098
Combined outcome of estimated GFR <60 mL/min/1.73 m <sup>2</sup> or death	53	80	37% (10–55%)	0.011

Separate models were created to assess the effect of DCCT INT on risk of each outcome, based on Cox proportional hazards models with Lin-Wei variance estimates robust to departure from the proportional hazards assumption, adjusting for DCCT baseline estimated GFR. Sustained estimated GFR <60 mL/min/1.73 m<sup>2</sup>, the primary outcome, was defined as an estimated GFR <60 mL/min/1.73 m<sup>2</sup> on two consecutive study visits, usually 1 year apart. Risk reduction associated with INT was calculated as (1 – HR of INT vs. CON) × 100% and presented with 95% CI.

the 30-year cumulative incidence of macroalbuminuria or worse, defined for this analysis as AER ≥300 mg/24 h or serum creatinine ≥2 mg/dL, was 9 or 25%, respectively (16).

Renal outcomes after developing microalbuminuria were variable in the DCCT/EDIC. Ten years after developing persistent microalbuminuria, 28, 15, and 4% of participants went on to develop macroalbuminuria, impaired GFR, and ESRD, respectively (Fig. 4) (15). However, 40% of participants with incident microalbuminuria regressed to persistent AER <30 mg/24 h. Lower

HbA<sub>1c</sub> was associated with more favorable renal outcomes after microalbuminuria diagnosis.

Macroalbuminuria was more strongly associated than microalbuminuria with GFR loss in the DCCT/EDIC. Mean rate of change in estimated GFR was 5.7% per year (95% CI 4.5–6.8%) in subjects who developed macroalbuminuria, compared with 1.2% per year (1.2–1.3%) with AER <30 mg/24 h and 1.8% per year (1.6–1.9%) in subjects with microalbuminuria (20). Moreover, macroalbuminuria was associated with a more than a 15-fold increase in

risk of developing impaired GFR (HR 15.3 [95% CI 8.9–26.3]). Sixty-one percent of participants who developed impaired GFR first developed macroalbuminuria.

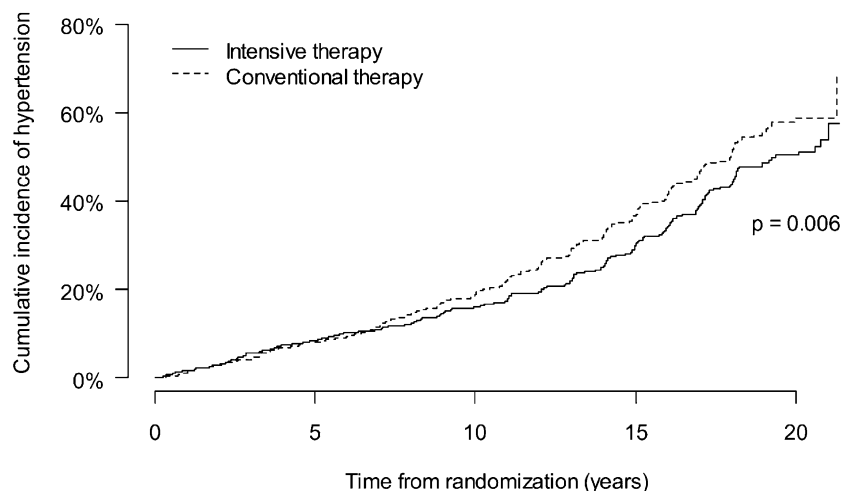
Additional work has identified genetic predisposition, male sex, obesity, blood pressure, inflammation, vitamin D deficiency, and dyslipidemia as risk factors for the development and progression of kidney disease in DCCT/EDIC (15,21–28).

**Kidney and CVD**

In EDIC, higher AER and higher blood pressure were associated with greater common and internal carotid intima-media thickness, a greater prevalence and severity of coronary artery calcium, reduced compliance of the aorta, and greater left ventricular mass (29–32). Moreover, during the combined DCCT/EDIC, microalbuminuria and macroalbuminuria were associated with nearly threefold increased risks of clinical CVD events (HR 2.93 [95% CI 1.85–4.65] and 2.57 [1.36–4.88], respectively) (33). Adjustment for treatment group differences in microalbuminuria and macroalbuminuria explained a minority of the beneficial effect of INT on risk of clinical CVD events.

**CONCLUSIONS**

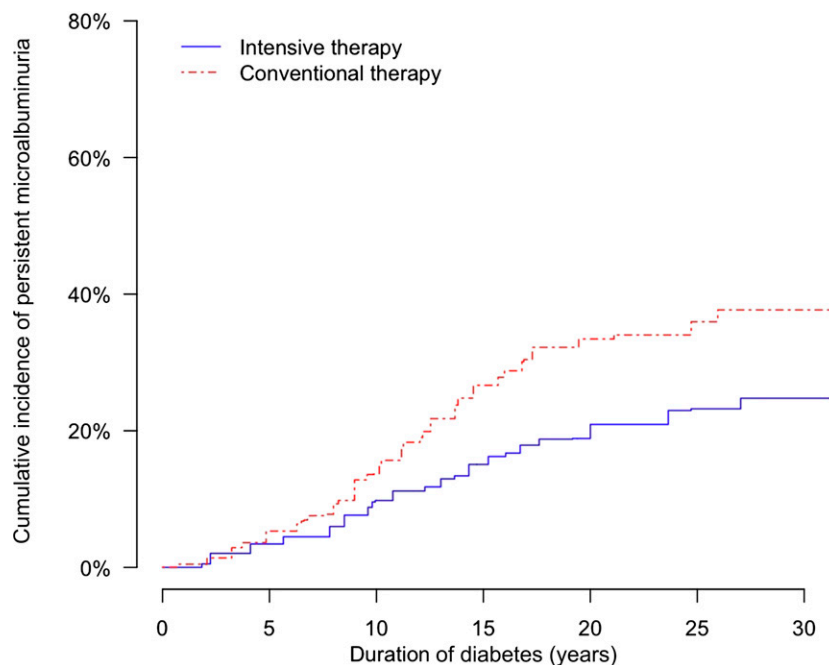
In the DCCT/EDIC, INT resulted in substantial, durable reductions in the risks of microalbuminuria, macroalbuminuria, impaired GFR, and hypertension. For microalbuminuria and macroalbuminuria, beneficial effects were observed during the DCCT. Moreover, during EDIC follow-up, the incidences of microalbuminuria and macroalbuminuria continued to be lower among participants previously assigned to DCCT INT, with risk reductions during EDIC years 1–8 that were even greater than those observed during the DCCT itself. For impaired GFR and hypertension, beneficial effects of INT were not observed during the DCCT, but significant effects became apparent during long-term EDIC follow-up. The cumulative incidences of microalbuminuria and macroalbuminuria 30 years after diagnosis of diabetes were substantially lower among participants assigned to INT versus CON, providing further



No. at risk					
Intensive	711	642	570	442	72
Conventional	730	665	563	411	40

**Figure 2—**Cumulative incidence of hypertension (two consecutive study visits with systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or the use of antihypertensive medications) by DCCT treatment assignment. Reproduced with permission from de Boer et al. (14).





No. at risk							
Intensive	710	698	654	577	389	183	67
Conventional	729	706	632	507	310	149	48

**Figure 3**—Cumulative incidence of persistent microalbuminuria (AER  $\geq$ 30 mg/24 h on two consecutive study visits) in the DCCT/EDIC, by duration of T1D and DCCT treatment assignment. Reproduced with permission from de Boer et al. (15).

evidence that early INT alters the clinical course of kidney disease in T1D.

The term “metabolic memory” has been used to describe the differences in outcomes that persist or even expand after the original separation in chronic glycemia, based on treatment assignment, has disappeared. The persistent effects of INT on microalbuminuria and macroalbuminuria during EDIC years 1–8 are striking examples of this phenomenon. The subsequent beneficial effects of INT on impaired GFR and hypertension represent the long-term consequences of INT. The biological basis of metabolic memory remains a matter of speculation. Clinically, the important implication is that INT applied early in the course of T1D has strong and long-lasting effects to reduce the long-term risks of kidney disease.

Importantly, the DCCT/EDIC evaluated the effects of INT on each of the two most important clinical features of diabetic kidney disease—albuminuria and impaired GFR. To our knowledge,

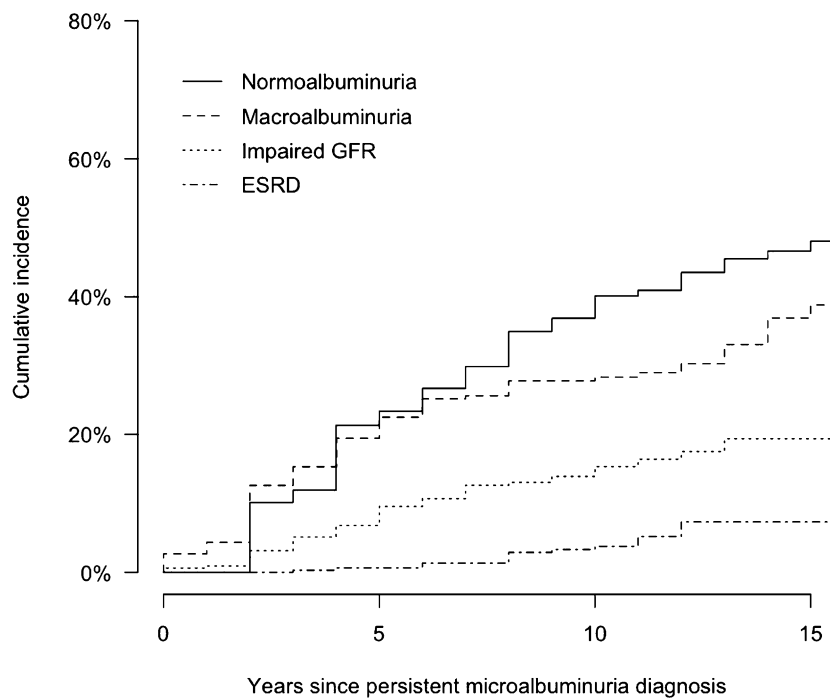
INT is the only intervention that has been demonstrated to reduce the risks of developing both albuminuria (microalbuminuria or macroalbuminuria) and impaired GFR in T1D. This emphasizes the importance of hyperglycemia in the pathophysiology of kidney disease in T1D and the primary role for glucose control in preventing both major manifestations of diabetic kidney disease in this population.

The beneficial effects of INT on the risks of microalbuminuria, macroalbuminuria, and impaired GFR were fully attenuated by statistical adjustment for HbA<sub>1c</sub>. Interestingly, in parallel, the beneficial effects of INT on the risk of impaired GFR were also fully attenuated by statistical adjustment for AER. This suggests that a common set of disease mechanisms leading from hyperglycemia to both albuminuria and impaired GFR is interrupted by INT. Additional observations from the DCCT/EDIC suggest that other mechanisms also contribute to the development of microalbuminuria, macroalbuminuria, and impaired GFR, and that these

mechanisms may vary by disease manifestation. Most participants who developed microalbuminuria did not go on to develop impaired GFR, and most but not all participants who developed impaired GFR first developed macroalbuminuria. Blood pressure, obesity, and other metabolic factors appear to influence the development of kidney disease in T1D, in addition to hyperglycemia. These risk factors may offer additional treatment options to prevent and treat kidney disease in T1D, in addition to intensive glucose control.

Higher AER and blood pressure were associated with increased risks of CVDs, including carotid atherosclerosis, coronary atherosclerosis, stiffening of the aorta, and left ventricular hypertrophy. Taken together with similar observations in other cohorts (34,35), these results suggest a central role for kidney disease in the macrovascular complications of T1D. The beneficial effects of INT on kidney disease and blood pressure would therefore be expected to yield subsequent reductions in the risks of CVD. Statistical modeling suggested that reductions in AER explained a minority of the beneficial effects of INT on clinical CVD events, but such mediation analyses can underestimate the impact of covariates. Future studies will further evaluate the impact of kidney disease on CVD in the DCCT/EDIC, including the extent to which reductions in kidney disease with INT affect risk of CVD over long-term follow-up.

Strengths of the DCCT/EDIC include its randomized, controlled design with substantial separation in HbA<sub>1c</sub> achieved by treatment assignment; the detailed longitudinal characterization of diabetes complications; and the unusually long duration of follow-up, particularly for a clinical trial. These strengths were made possible by dedicated research staff, consistent sponsor support, and, most important, the invaluable contributions of the DCCT/EDIC participants. Low numbers of ESRD and CVD events have limited analyses of these outcomes to date. Continued follow-up of the DCCT/EDIC cohort will facilitate further examination of these events in the future.



No. at risk				
Normoalbuminuria	279	179	86	33
Macroalbuminuria	325	199	126	62
Impaired GFR	325	261	176	107
ESRD	325	292	219	131

**Figure 4**—Cumulative incidence of long-term renal outcomes after the development of persistent microalbuminuria (AER  $\geq 30$  mg/24 h on two consecutive study visits, defining time 0) among 325 participants in the DCCT/EDIC. Normoalbuminuria (AER  $< 30$  mg/24 h on two consecutive study visits), macroalbuminuria (AER  $\geq 300$  mg/24 h), impaired GFR (estimated GFR  $< 60$  mL/min/1.73 m<sup>2</sup> on two consecutive study visits), and ESRD are evaluated as parallel outcomes and are not mutually exclusive. Reproduced with permission from de Boer et al. (15).

In conclusion, INT applied early in the course of T1D resulted in clinically important, long-lasting reductions in the incidence of kidney disease. These benefits, combined with congruent reductions in the risks of retinopathy, neuropathy, CVD, and other diabetes complications, serve as a cornerstone of recommendations to control glycemia in T1D.

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**Author Contributions.** The DCCT/EDIC Research Group collected and analyzed the data. I.H.d.B. participated in data collection and analysis, and wrote the manuscript. I.H.d.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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