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Abstract

Background and objectives In trials of people with type 2 diabetes, albuminuria reduction with renin-angiotensin system inhibitors is associated with lower risks of cardiovascular events and CKD progression. We tested whether progression or remission of microalbuminuria is associated with cardiovascular and renal risk in a well characterized cohort of type 1 diabetes.

Design, setting, participants, & measurements We studied 1441 participants in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Albumin excretion rate (AER) was quantified annually or biennially for up to 30 years. For each participant, albuminuria status was defined over time as normoalbuminuria (AER continuously <30 mg/d), sustained microalbuminuria (AER, 30–299 mg/d on two consecutive visits), macroalbuminuria (AER≥300 mg/d), or remitted microalbuminuria (transition from sustained microalbuminuria to AER<30 mg/d on two consecutive visits). We tested associations of time-updated albuminuria status with adjudicated clinical cardiovascular events, the development of reduced GFR (<60 ml/min per 1.73 m^2 on two consecutive visits), and subclinical cardiovascular disease.

Results At least one cardiovascular event occurred in 184 participants, and 98 participants developed reduced eGFR. Compared with normoalbuminuria, sustained microalbuminuria, remitted microalbuminuria, and macroalbuminuria were each associated with higher risk of cardiovascular events (adjusted hazard ratios [HRs] and 95% confidence intervals [95% CIs]: 1.79 [1.13 to 2.85], 2.62 [1.68 to 4.07], and 2.65 [1.68 to 4.19], respectively) and reduced eGFR (adjusted HRs [95% CIs], 5.26 [2.43 to 11.41], 4.36 [1.80 to 10.57], and 54.35 [30.79 to 95.94], respectively). Compared with sustained microalbuminuria, remission to normoalbuminuria was not associated with reduced risk of cardiovascular events (adjusted HR, 1.33; 95% CI, 0.68 to 2.59) or reduced eGFR (adjusted HR, 1.75; 95% CI, 0.56 to 5.49). Compared with normoalbuminuria, sustained microalbuminuria, remitted microalbuminuria, and macroalbuminuria were associated with greater carotid intima-media thickness, and macroalbuminuria was associated with a greater degree of coronary artery calcification.

Conclusions In type 1 diabetes, microalbuminuria and macroalbuminuria are associated with higher risks of cardiovascular disease and reduced eGFR, but achieving a remission of established microalbuminuria to normoalbuminuria does not appear to improve outcomes.

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Introduction

Albuminuria is strongly associated with the progression of CKD as well as cardiovascular disease (CVD) (1). However, urine albumin excretion is not static. For example, microalbuminuria (albumin excretion rate [AER] of 30–299 mg/d) can progress to macroalbuminuria (AER≥300 mg/d) or remit to normoalbuminuria (AER<30 mg/d), with or without renin-angiotensin system (RAS) inhibition (2–4). Similarly, macroalbuminuria can remit to microalbuminuria and even normoalbuminuria (3).

In clinical trials, changes in albuminuria correlate with renal and cardiovascular risk (5–8), supporting the viewpoint that albuminuria be considered a therapeutic target in clinical care and surrogate outcome in clinical trials (9–11). However, the predominant evidence supporting this argument comes from trials of people with type 2 diabetes and very high baseline urine albumin excretion treated with RAS inhibitors. It remains unclear whether changes in albumin are associated with improved clinical outcomes in other populations, at lower levels of urine albumin excretion, or outside the setting of RAS blockade.

We tested whether changes in urine albumin excretion were associated with differences in renal and cardiovascular risk in a well characterized cohort of type 1 diabetes. Up to 60% of patients with type 1 diabetes develop microalbuminuria, among whom similar proportions remit to normoalbuminuria or progress to more advanced stages of CKD (4,12). We

hypothesized that progression and remission of microalbuminuria would be associated with higher and lower long-term risks, respectively, of adverse cardiovascular and renal outcomes.

Materials and Methods

Study Population

The Diabetes Control and Complications Trial (DCCT) enrolled 1441 persons with type 1 diabetes from 1983 to 1989 to determine the effects of intensive diabetes therapy on the long-term complications of diabetes (13). The trial included two cohorts. The primary prevention cohort was characterized by diabetes duration of 1–5 years, AER<40 mg/24 h, and no retinopathy by fundus photography. The secondary intervention cohort was characterized by diabetes duration of 1–15 years, AER≤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 per 1.73 m^2 was required for eligibility.

Participants were randomly assigned to intensive diabetes therapy, aimed at lowering glucose concentrations as close as safely possible to the normal range, or to conventional therapy, aimed at preventing symptoms of hyperglycemia and hypoglycemia. In 1994, after completion of the DCCT, 1375 participants (96% of the surviving cohort) agreed to participate in the Epidemiology of Diabetes Interventions and Complications (EDIC) study. During the EDIC study, diabetes therapy and glycemic control as measured by hemoglobin A1c (HbA1c) became similar in the two original DCCT treatment groups, and yearly follow-up has continued through the present time (14). This study includes data from all participants collected through May 1, 2014 (EDIC study year 21).

Albuminuria

AER was measured yearly during the DCCT and every 2 years during the EDIC study. All assays were completed at the DCCT/EDIC Central Biochemistry Laboratory. From DCCT baseline through EDIC study year 18 (calendar year 2012), urine was collected for 4 hours during a water diuresis and albumin was measured by fluoroimmunoassay (coefficient of variation, 9.4%) (15). Starting in EDIC study year 19, spot urine samples were collected, urine albumin was measured using an immunoturbidimetric method, and a formula developed and validated in the EDIC study was used to estimate AER from urine albumin and creatinine concentrations (16).

For each participant, at the time of each urine collection, albuminuria status could be reclassified on the basis of their AER history into one of four mutually exclusive categories (normoalbuminuria, sustained microalbuminuria, remitted microalbuminuria, and macroalbuminuria), defined in a manner consistent with our prior work (Figure 1) (17). Participants were considered to have normoalbuminuria until they developed sustained microalbuminuria (two consecutive study visits with AER≥30 mg/d) or macroalbuminuria (AER≥300 mg/d in the absence of hematuria) (3,4). Sixty-eight participants with AER of 30–200 mg/d at baseline and ≥30 mg/d at their next DCCT visit were considered to have sustained microalbuminuria starting at

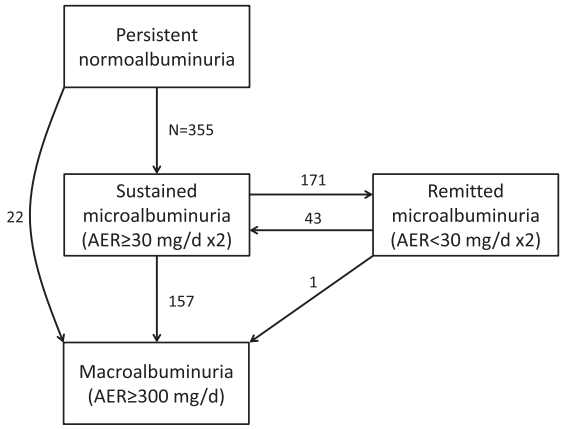

Figure 1. | Transitions in albuminuria status observed during the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study. The figure depicts the four albuminuria categories examined in primary analyses and the observed numbers of transitions between categories. Of 1441 participants included, 1373 entered the DCCT with normoalbuminuria and 68 entered the DCCT with persistent microalbuminuria. During subsequent follow-up, 355 participants with normoalbuminuria at baseline developed persistent microalbuminuria, 171 participants with persistent microalbuminuria regressed to persistent normoalbuminuria, and 180 participants developed macroalbuminuria. Some participants were observed to undergo multiple transitions in albuminuria status over time and were included in multiple counts in the figure. AER, albumin excretion rate.

DCCT baseline and included in all analyses. Participants were considered to have sustained microalbuminuria until they were observed to have two consecutive AER values <30 mg/d (remission to normoalbuminuria) or an AER≥300 mg/d (macroalbuminuria). Participants who remitted to normoalbuminuria could subsequently develop and be reclassified as having sustained microalbuminuria or macroalbuminuria. Some participants who developed macroalbuminuria were subsequently observed to have two AER values <300 mg/d (remitted macroalbuminuria). Because insufficient numbers of events were observed for participants with remitted macroalbuminuria, they were included in the macroalbuminuria group for primary analyses but analyzed separately in secondary analyses.

Cardiovascular Outcomes

The primary study outcome, any CVD, was a composite of the time to the first occurrence of nonfatal myocardial infarction or stroke, death from CVD, subclinical myocardial infarction on electrocardiography ("silent" myocardial infarction), confirmed angina, or the need for coronary artery revascularization, consistent with published DCCT/EDIC study analyses (18). A secondary outcome, major adverse cardiovascular event (MACE), included only the time to the first of nonfatal myocardial infarction or stroke or death from CVD. CVD events were adjudicated by physician review through December 31, 2013. For secondary subclinical outcomes, we also examined coronary artery calcium (CAC) measured at EDIC study year 7–8 (November 22, 2000–March 21, 2003) and carotid intima-media thickness

(IMT) measured at EDIC study year 12 (January 5, 2004–August 17, 2005) (19,20).

Renal Outcomes

Serum creatinine was measured with highly reproducible methods annually throughout the DCCT and EDIC study at the DCCT/EDIC Central Biochemistry Laboratory. Most recently, results were calibrated to values traceable to isotope dilution mass spectrometry (14). The CKD-Epidemiology Collaboration equation was used to estimate GFR from calibrated serum creatinine (21). Reduced GFR was defined as eGFR<60 ml/min per 1.73 m^2 on two consecutive study visits, the initiation of maintenance dialysis, or kidney transplantation (14).

Covariates

Covariates were updated concurrently with updates in albuminuria status over time. Use of angiotensin-converting enzyme inhibitors and angiotensin 2 receptor blockers were combined as use of RAS inhibitors, and use of lipid-lowering medications (mostly hydroxymethyl glutaryl coenzyme A reductase inhibitors) were combined as lipid-lowering medications. Smoking status was ascertained by questionnaire. Body mass index and BP were measured in standardized fashions by trained research coordinators (22). HbA1c was measured by HPLC (23). The time-weighted updated mean HbA1c was computed up to each visit with quarterly HbA1c values during DCCT weighted by 1/4 and annual EDIC study values by 1.

Statistical Analyses

We quantified total time at risk by albuminuria status, with each participant able to contribute risk time to multiple albuminuria categories. We quantified the numbers of first cardiovascular and renal events and unadjusted incidence rates of these events by time-updated albuminuria status. We then used Cox proportional hazards models to test associations of albuminuria status as a time-dependent variable with time to first CVD event. We stratified the proportional hazards model by DCCT treatment assignment and adjusted for covariates that were anticipated to potentially confound the associations of primary interest based on current understanding of pathophysiology. Model 1 was adjusted for age, sex, and attained duration of diabetes, and model 2 was additionally adjusted for renin-angiotensin inhibitor use, smoking, and updated weighted mean HbA1c as time-dependent covariates. A secondary time-to-event analysis designed to account for duration of exposure to microalbuminuria was restricted to participants who developed microalbuminuria or macroalbuminuria and used time since development of microalbuminuria or macroalbuminuria (whichever occurred first) as the unit of time.

We tested associations of albuminuria status with the presence of CAC (Agatston score >0 versus ≥0) using multivariable logistic regression and with the presence and extent of CAC using Tobit regression (19). We used multiple linear regression to test associations of albuminuria status with carotid IMT. We used albuminuria status concurrent with or immediately preceding each subclinical CVD measurement as exposure for these analyses. All analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC).

Results

Participant Characteristics

At baseline, mean participant age was 26.9 years; mean duration of diabetes was 5.6 years; 47% of participants were female; 96% of participants were white; and no participants were using RAS inhibitors (Table 1). Sustained microalbuminuria developed in 423 participants at a mean age of 33.9 years and a mean diabetes duration of 14.5 years. Of the 423 participants who developed microalbuminuria, 171 remitted to normoalbuminuria and 180 progressed to macroalbuminuria. At the time of remission or progression, 28% or 35%, respectively, were using RAS inhibitors.

Median follow-up times were as follows: after developing sustained microalbuminuria, 17.8 years (interquartile range [IQR], 10.0–24.0 years; range, 0–29.6 years); after remission of microalbuminuria, 15.7 years (IQR, 8.2–22.1 years; range, 1.0–27.1 years); and after developing macroalbuminuria, 12.0 years (IQR, 5.8–16.9 years; range, 0–28.4 years). Among the 168 who remitted to normoalbuminuria before a first CVD event, 127 (75.6%) persisted in normoalbuminuria until their follow-up time was censored, whereas 40 (23.8%) were reclassified to sustained microalbuminuria and one (0.6%) was reclassified to macroalbuminuria during follow-up.

Clinical Cardiovascular Events

During 24.6 mean years of follow-up (range, 0–30 years), an initial cardiovascular event (any CVD) was observed in 184 participants, including 88 with a MACE. Compared with normoalbuminuria, time-updated sustained microalbuminuria, remitted microalbuminuria, and macroalbuminuria were each associated with higher risks of any CVD event and MACE, after adjustment for age, sex, attained duration of diabetes, and DCCT treatment assignment: hazard ratios (HRs) and 95% confidence intervals (95% CIs) of 1.79 (1.13 to 1.85), 2.62 (1.68 to 4.07), and 2.65 (1.68 to 4.19), respectively (Table 2). With further adjustment for RAS inhibitor use, smoking, and HbA1c, remitted microalbuminuria and macroalbuminuria were associated with significantly higher risk of any CVD, but sustained microalbuminuria was not. Neither further adjustment for eGFR nor introduction of a 4-year time lag between assessment of albuminuria and CVD events substantially changed these results (Supplemental Tables 1 and 2). Compared with participants with sustained microalbuminuria, those with remission of microalbuminuria or macroalbuminuria were estimated to have higher risks of CVD events, but these associations were not statistically significant (Table 3).

Renal Outcomes

During 25.2 mean years of follow-up (range, 0–31 years), incident reduced eGFR was observed in 98 participants. Compared with normoalbuminuria, time-updated sustained microalbuminuria, remission of microalbuminuria, and particularly macroalbuminuria were each strongly associated with higher risk of reduced eGFR: HRs and 95% CIs of 5.26 (2.43 to 11.41), 4.36 (1.80 to 10.57), and 54.35

Table 1. Characteristics of participants in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study at baseline and at the time that albuminuria developed, remitted, or progressed

Characteristic	At Baseline (*n*=1441)	During Follow-up		
		Time of Microalbuminuria Diagnosis (*n*=423)	Time of Microalbuminuria Remission (*n*=171)	Time of Macroalbuminuria Development (*n*=180)
Age, yr	26.9±7.1	33.9±11.2	36.7±11.2	38.3±10.2
Women	680 (47)	175 (41)	94 (55)	59 (33)
White patients	1390 (96)	404 (96)	168 (98)	166 (92)
DCCT treatment assignment (intensive therapy)	711 (49)	167 (39)	80 (47)	55 (30)
Duration of diabetes, mo	67.6±49.9	173.6±86.7	222.8±96.9	224.5±80.4
RAS inhibitor use				
Never	1441 (100)	358 (85)	116 (68)	108 (60)
Current	0	52 (12)	48 (28)	63 (35)
Prior	0	13 (3)	7 (4)	9 (5)
Lipid-lowering medication use	0	43 (10)	33 (19)	31 (17)
Current smoking	266 (18)	109 (26)	37 (22)	49 (27)
Body mass index, kg/m^2	23.5±2.8	25.9±4.3	27.2±5.3	27.0±4.5
Systolic BP, mmHg	114.5±11.4	121.7±14.2	119.5±14.8	131.9±17.3
Diastolic BP, mmHg	73.0±8.5	76.8±8.8	73.7±9.3	81.3±10.1
Updated mean hemoglobin A1c, %	8.9±1.6	9.2±1.4	8.5±1.3	9.7±1.3
Albumin excretion rate, mg/d	11.5 (7.2, 18.7)	46.1 (36.0, 69.1)	14.4 (11.5, 21.6)	534.2 (393.1, 796.3)
eGFR, ml/min per 1.73 m^2	126.1±14.2	117.8±18.2	110.5±18.1	106.0±22.4
LDL cholesterol, mg/dl	109.7±29.1	115.8±30.7	111.8±32.7	125.6±35.8

Data are mean±SD or *n* (%), except for albumin excretion rate, which is summarized as median (25th percentile, 75th percentile). DCCT, Diabetes Control and Complications Trial; RAS, renin-angiotensin system.

(30.79 to 95.94), respectively (Table 2). Among participants who developed microalbuminuria or macroalbuminuria, remission of microalbuminuria was associated with a non-significantly higher risk of reduced eGFR compared with sustained microalbuminuria, whereas progression to macroalbuminuria was significantly associated with higher risk of reduced eGFR (Table 3). When a 4-year time lag was introduced between assessment of albuminuria status and assessment of eGFR, remitted microalbuminuria was not significantly associated with risk of reduced eGFR (Supplemental Table 2).

Remission of Macroalbuminuria

Among participants who developed macroalbuminuria and subsequently remitted to persistent AER<300 mg/d, only seven developed a CVD event (including six with a MACE) and eight developed reduced eGFR (Supplemental Table 3). Compared with participants with normoalbuminuria, those with remitted macroalbuminuria had higher risks of CVD events and reduced eGFR. Compared with participants with sustained macroalbuminuria, those with remitted macroalbuminuria appeared to have similar risk of CVD events, with widely overlapping 95% CIs due to low numbers of event, but substantially lower risk of reduced eGFR.

Subclinical CVD

CAC was present in 339 of 1156 participants (29.3%). Macroalbuminuria was associated with higher risk of CAC compared with normoalbuminuria, but this was significant only in minimally adjusted models (Supplemental Table 4, Tables 4 and 5). Neither sustained nor remitted microalbuminuria was associated with CAC. Compared with normoalbuminuria, sustained microalbuminuria, remitted microalbuminuria, and macroalbuminuria were each associated with greater common carotid IMT.

Discussion

In this cohort study of type 1 diabetes spanning >30 years, the development of microalbuminuria or macroalbuminuria was associated with higher risks of clinical CVD and renal events, as expected. However, contrary to our hypothesis, remission from microalbuminuria to normoalbuminuria was not associated with reduced CVD or renal risk compared with sustained microalbuminuria. The lack of association of microalbuminuria remission with lower CVD and renal risk was robust in analyses adjusting for use of RAS inhibitors and accounting for time since microalbuminuria onset. Similarly, remission of microalbuminuria to normoalbuminuria was not associated with reduced subclinical CVD, quantified as CAC or carotid IMT.

Albuminuria has been consistently associated with higher CVD and renal risk across multiple cohorts with type 1 diabetes, including the DCCT/EDIC study, as well as cohorts with type 2 diabetes and the general population (1,18,24–26). Furthermore, albuminuria and other

Table 2. Associations of time-updated albuminuria status with cardiovascular and renal events in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study

Variable	Events, *n*	Person-Years at Risk	Incidence Rate (per 1000 Person-Years)	Model 1		Model 2	
				HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All cardiovascular events							
Normoalbuminuria	109	27,310	6.3	1 (reference)		1 (reference)	
Sustained microalbuminuria	23	2882	13.2	1.79 (1.13 to 2.85)[a]	0.01	1.31 (0.81 to 2.12)	0.28
Remitted microalbuminuria	27	2089	23.9	2.62 (1.68 to 4.07)[a]	<0.001	2.25 (1.44 to 3.51)[a]	<0.001
Macroalbuminuria	25	1899	25.5	2.65 (1.68 to 4.19)[a]	<0.001	1.76 (1.06 to 2.91)[a]	0.03
Major adverse cardiac events							
Normoalbuminuria	48	27,773	2.7	1 (reference)		1 (reference)	
Sustained microalbuminuria	11	2975	6.2	2.01 (1.03 to 3.90)[a]	0.04	1.41 (0.70 to 2.81)	0.34
Remitted microalbuminuria	11	2216	9.2	2.28 (1.15 to 4.53)[a]	0.02	1.88 (0.94 to 3.76)	0.07
Macroalbuminuria	18	2052	17.1	4.19 (2.34 to 7.52)[a]	<0.001	2.96 (1.54 to 5.67)[a]	0.001
Sustained eGFR<60 ml/min per 1.73 m^2							
Normoalbuminuria	19	27,292	1.1	1 (reference)		1 (reference)	
Sustained microalbuminuria	10	2976	5.6	5.26 (2.43 to 11.41)[a]	<0.001	2.68 (1.19 to 6.03)[a]	0.02
Remitted microalbuminuria	7	2246	5.8	4.36 (1.80 to 10.57)[a]	0.001	3.18 (1.31 to 7.77)	0.01
Macroalbuminuria	62	1710	67.6	54.35 (30.79 to 95.94)[a]	<0.001	25.50 (13.42 to 48.46)[a]	<0.001

In model 1, the proportional hazards model was stratified by Diabetes Control and Complications Trial (DCCT) treatment assignment and adjusted for age, sex, and attained duration of diabetes. In model 2, the proportional hazards model was stratified by DCCT treatment assignment, adjusted for age and sex as fixed covariates, and adjusted for attained duration of diabetes, renin-angiotensin inhibitor use, smoking, and updated weighted mean hemoglobin A1c as time-dependent covariates. HR, hazard ratio; 95% CI, 95% confidence interval.
[a]Results with $P<0.05$.

Table 3. Associations of albuminuria status with cardiovascular and renal events among participants who developed microalbuminuria

Variable	Events, *n*	Model 1		Model 2	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All cardiovascular events					
Sustained microalbuminuria	23	1 (reference)		1 (reference)	
Remitted microalbuminuria	27	1.33 (0.68 to 2.59)	0.40	1.69 (0.86 to 3.32)	0.13
Macroalbuminuria	25	1.46 (0.76 to 2.82)	0.26	1.05 (0.54 to 2.08)	0.88
Major adverse cardiac events					
Sustained microalbuminuria	11	1 (reference)		1 (reference)	
Remitted microalbuminuria	11	0.89 (0.34 to 2.33)	0.81	1.06 (0.41 to 2.75)	0.90
Macroalbuminuria	18	1.63 (0.70 to 3.82)	0.26	1.31 (0.54 to 3.15)	0.55
Sustained eGFR<60 ml/min per 1.73 m^2					
Sustained microalbuminuria	10	1 (reference)		1 (reference)	
Remitted microalbuminuria	7	1.75 (0.56 to 5.49)	0.34	2.21 (0.70 to 7.00)	0.18
Macroalbuminuria	62	5.07 (2.36 to 10.90)[a]	<0.001	5.11 (2.33 to 11.22)[a]	<0.001

In this time-to-event model, time is evaluated since the development of microalbuminuria or macroalbuminuria (whichever occurred first). In model 1, the proportional hazards model was stratified by Diabetes Control and Complications Trial (DCCT) treatment assignment and adjusted for age, sex, and attained duration of diabetes. In model 2, the proportional hazards model was stratified by DCCT treatment assignment, adjusted for age and sex as fixed covariates, and adjusted for attained duration of diabetes, renin-angiotensin inhibitor use, smoking, and updated weighted mean hemoglobin A1c as time-dependent covariates. HR, hazard ratio; 95% CI, 95% confidence interval.
[a]Results with $P<0.05$.

manifestations of diabetic kidney disease accounted statistically for all the excess mortality in two large type 1 diabetes cohorts (23,24). Our observed associations of microalbuminuria and macroalbuminuria with higher risks of clinical and subclinical CVD as well as reduced eGFR are consistent with these reports and support the concept that preventing albuminuria may help improve long-term health in type 1 diabetes.

Once developed, microalbuminuria is known to commonly regress to normoalbuminuria, a phenomenon documented first and most clearly in type 1 diabetes (2–4). In the present study, we confirmed frequent remission from microalbuminuria to normoalbuminuria using standardized, longitudinal measurements of AER. We required that microalbuminuria and normoalbuminuria be persistent over time (each present on two consecutive study visits spanning at least 1–2 years), generating confidence that we observed true changes in AER status. As previously reported, remission to normoalbuminuria occurred both with and without RAS inhibitor treatment (4).

The new finding in this study is that remission from microalbuminuria to normoalbuminuria was not associated with reduced risk of subsequent CVD or renal events. We were concerned that the lack of improved outcomes with remission to normoalbuminuria may be due to confounding by duration of preceding microalbuminuria.

Table 4. Association of albuminuria status with subclinical cardiovascular disease (coronary artery calcium)

Variable	Patients Evaluated, *n*	Patients with CAC, *n* (%)	Model 1		Model 2	
			Adjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Normoalbuminuria	872	237 (27)	1 (reference)		1 (reference)	
Sustained microalbuminuria	102	32 (31)	1.12 (0.68 to 1.86)	0.28	0.90 (0.53 to 1.53)	0.26
Remitted microalbuminuria	94	31 (33)	1.47 (0.86. 2.49)	0.82	1.24 (0.72 to 2.15)	0.66
Macroalbuminuria	88	39 (44)	2.32 (1.37 to 3.92)[a]	0.01	1.47 (0.81 to 2.66)	0.24

Model 1 is adjusted for age, sex, and attained duration of diabetes, and Diabetes Control and Complications Trial (DCCT) treatment assignment, plus scan site for coronary artery calcium or reader and machine type for carotid intima-media thickness. Model 2 is adjusted for age, sex, DCCT treatment assignment, attained duration of diabetes, renin-angiotensin inhibitor use, smoking, and updated mean hemoglobin A1c, plus scan site for coronary artery calcium or reader and machine type for carotid intima-media thickness. CAC, coronary artery calcium; OR, odds ratio; 95% CI, 95% confidence interval.
[a]Results with $P<0.05$.

Table 5. Association of albuminuria status with subclinical cardiovascular disease (common carotid intima-media thickness)

Variable	Patients Evaluated, *n*	Mean IMT±SD, mm	Model 1		Model 2	
			Adjusted Difference (95% CI), mm	*P* Value	Adjusted Difference (SEM), mm	*P* Value
Normoalbuminuria	821	0.67±0.12	0 (reference)		0 (reference)	
Sustained microalbuminuria	91	0.74±0.17	0.06 (0.04 to 0.09)[a]	<0.001	0.05 (0.02–0.08)[a]	<0.001
Remitted microalbuminuria	105	0.68±0.14	0.03 (0.01 to 0.01)[a]	0.02	0.03 (0.00–0.05)	0.06
Macroalbuminuria	94	0.74±0.19	0.07 (0.05 to 0.1)[a]	<0.001	0.06 (0.03–0.09)[a]	<0.001

Model 1 is adjusted for age, sex, and attained duration of diabetes, and Diabetes Control and Complications Trial (DCCT) treatment assignment, plus scan site for coronary artery calcium or reader and machine type for carotid intima-media thickness. Model 2 is adjusted for age, sex, DCCT treatment assignment, attained duration of diabetes, renin-angiotensin inhibitor use, smoking, and updated mean hemoglobin A1c, plus scan site for coronary artery calcium or reader and machine type for carotid intima-media thickness (IMT). 95% CI, 95% confidence interval

[a]Results with $P<0.05$.

However, results were robust in sensitivity analyses using microalbuminuria onset as the beginning of time at risk. Incidence rates of cardiovascular events were actually higher among participants with remitted microalbuminuria than those with sustained microalbuminuria. However, this comparison was made using small numbers of events, and differences were not significant in adjusted analyses. Our data therefore suggest that remission of microalbuminuria to normoalbuminuria is associated with neither higher nor lower risk of cardiovascular or renal events in type 1 diabetes. Similar results were observed in analyses of subclinical CVD, which had substantially more power: Remission of microalbuminuria to normoalbuminuria was associated with neither higher nor lower CAC or carotid IMT.

Our results suggest that the manner through which albuminuria is reduced or the albuminuria range over which reduction occurs may affect the association of changes in albuminuria with CVD and renal risk. Most participants who remitted from microalbuminuria to normoalbuminuria in our study did so without the use of RAS inhibitors, whereas prior studies assessing the health impact of changes in albuminuria have focused on albuminuria changes induced by RAS blockade (5–8). In addition, we primarily assessed remission from microalbuminuria to normoalbuminuria, whereas prior studies assessing the health impact of changes in albuminuria have often focused on populations with higher levels of baseline albuminuria (8). For example, in the Reduction in End Points in Noninsulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan study, all participants had macroalbuminuria at baseline, and RAS inhibitor–induced reductions in albuminuria were associated with lower subsequent CVD and renal risk (5,6). Interestingly, in our study, associations of macroalbuminuria with reduced eGFR were very strong, consistent with prior DCCT/EDIC reports (14). Moreover, regression of macroalbuminuria to AER<300 mg/d was associated with reduced risk of reduced eGFR compared with sustained macroalbuminuria, and regression of microalbuminuria appeared to be associated with lower risk of reduced eGFR compared with sustained microalbuminuria, when a 4-year lag time was introduced. These results confirm dose-response relationships between established albuminuria and GFR loss and are more consistent with prior studies evaluating albuminuria reductions starting from the macroalbuminuric range.

Strengths of our study include the long period of time over which to ascertain AER status and subsequent cardiovascular and renal outcomes, the frequent and standardized assessment of AER, and the evaluation of complementary clinical CVD events, subclinical CVD outcomes, and eGFR outcomes. Limitations include an inability to fully ascertain the cause of remission from microalbuminuria to normoalbuminuria (or its absence) and the relatively small number of observed clinical events. By design, our data do not directly evaluate the effects of any treatment on albuminuria reduction or related cardiovascular or renal risk, nor do they address whether treatment-induced changes in albuminuria are suitable as surrogate end points in clinical trials.

In conclusion, our results confirm the associations of the onset of microalbuminuria and macroalbuminuria with adverse cardiovascular and renal outcomes in type 1 diabetes. This supports the general practice of preventing the development of microalbuminuria through such interventions as intensive glycemic control and preventing progression of microalbuminuria to macroalbuminuria through such interventions as RAS inhibition and BP control. However, remission of established microalbuminuria to normoalbuminuria was not associated with improved cardiovascular or renal outcomes.

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A complete list of participants in the DCCT/EDIC Research Group can be found in de Boer *et al.* (14).

Disclosures

None.

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