Development and Progression of Renal Insufficiency With and Without Albuminuria in Adults With Type 1 Diabetes in the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications Study

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OBJECTIVE — This multicenter study examined the impact of albumin excretion rate (AER) on the course of estimated glomerular filtration rate (eGFR) and the incidence of sustained eGFR <60 ml/min/1.73 m^2 in type 1 diabetes up to year 14 of the Epidemiology of Diabetes Interventions and Complications (EDIC) study (mean duration of 19 years in the Diabetes Control and Complications Trial [DCCT]/EDIC).

RESEARCH DESIGN AND METHODS — Urinary albumin measurements from 4-h urine collections were obtained from participants annually during the DCCT and every other year during the EDIC study, and serum creatinine was measured annually in both the DCCT and EDIC study. GFR was estimated from serum creatinine using the abbreviated Modification of Diet in Renal Disease equation.

RESULTS — A total of 89 of 1,439 subjects developed an eGFR <60 ml/min/1.73 m^2 (stage 3 chronic kidney disease on two or more successive occasions (sustained) during the DCCT/EDIC study (cumulative incidence 11.4%). Of these, 20 (24%) had AER <30 mg/24 h at all prior evaluations, 14 (16%) had developed microalbuminuria (AER 30–300 mg/24 h) before they reached stage 3 chronic kidney disease, and 54 (61%) had macroalbuminuria (AER >300 mg/24 h) before they reached stage 3 chronic kidney disease. Macroalbuminuria is associated with a markedly increased rate of fall in eGFR (5.7%/year vs. 1.2%/year with AER <30 mg/24 h, $P < 0.0001$) and risk of eGFR <60 ml/min/1.73 m^2 (adjusted hazard ratio 15.3, $P < 0.0001$), whereas microalbuminuria had weaker and less consistent effects on eGFR.

CONCLUSIONS — Macroalbuminuria was a strong predictor of eGFR loss and risk of developing sustained eGFR <60 ml/min/1.73 m^2. However, screening with AER alone would have missed 24% of cases of sustained impaired eGFR.

Diabetes Care **33:1536–1543, 2010**

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Received 30 June 2009 and accepted 6 April 2010. Published ahead of print at http://care.diabetesjournals.org on 22 April 2010. DOI: 10.2337/dc09-1098. Clinical trial registry no. NCT00360815, NCT003608933, www.clinicaltrials.gov. *A complete list of participants in the DCCT/EDIC research group can be found in *Archives of Ophthalmology* 2008;126:1707–1715.

It has generally been thought that increases in urine albumin excretion rate (AER) precede a fall in glomerular filtration rate (GFR) in patients developing diabetic chronic kidney disease (1). Some large studies in patients with type 2 diabetes (2–4) and a few smaller studies in individuals with type 1 diabetes (5–9), however, have demonstrated that a substantial proportion of diabetic individuals with decreased GFR levels do not have increased AER.

In this article, we examine the effects of prior and current levels of AER on the rate of decline in estimated GFR (eGFR) and on the risk of decreased levels of eGFR (<60 ml/min/1.73 m^2) in subjects with type 1 diabetes in the Diabetes Control and Complications Trial (DCCT) and/or the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study.

RESEARCH DESIGN AND METHODS

The multicenter DCCT/EDIC study started with 1,441 participants (10). Two participants were lost to follow-up before developing end-stage renal disease (ESRD). Because neither AER nor eGFR were measured during this period, these two subjects were not included in the analyses herein. At DCCT baseline, the remaining 1,439 participants had normal GFR (serum creatinine ≤1.3 mg/dl and/or creatinine clearance >100 ml/min/1.73 m^2). At baseline, the AER was <40 mg/24 h for the primary prevention cohort and <200 mg/24 h for the secondary intervention cohort.

Renal function and blood pressure

Urine was collected over 4 h yearly during the DCCT and every other year in the EDIC study (one-half of the cohort each year) (10). Serum creatinine levels were

measured annually during the DCCT and EDIC study (10). The GFR was estimated using the abbreviated Modification of Diet in Renal Disease formula (11). ACE inhibitors were proscribed during the DCCT (angiotensin II receptor blockers [ARBs] were not yet available), and their use was recorded only during the EDIC study.

The DCCT/EDIC Central Biochemistry Laboratory measured serum creatinine using an automated kinetic modification of the Jaffe reaction on a Beckman Synchron CX3 Clinical C System (12). Urine microalbumin was measured using a solid-phase noncompetitive double-antibody fluorescent immunoassay (13). The respective coefficients of variation were 2.3 and 9.4%, and the coefficients of reliability for both were 94% from masked split duplicate collections originating at the study sites.

An abnormal eGFR was defined as a sustained value <60 ml/min/1.73 m^2 on at least two successive collections. Parallel analyses using a single eGFR <60 ml/min/1.73 m^2 are presented in an online appendix, available at http://care.diabetesjournals.org/cgi/content/full/dc09-1098/DC1. A value <60 ml/min/1.73 m^2 (stage 3 chronic kidney disease) has been used in other studies to indicate significant impairment of GFR (2–9). ESRD was defined as stage 5 chronic kidney disease, which includes dialysis or kidney transplant. The eGFRs for individuals who reached ESRD were imputed as 15 ml/min/1.73 m^2 thereafter in longitudinal analyses.

AER was classified into three categories: no elevation, microalbuminuria (30–300 mg/24 h), or macroalbuminuria (>300 mg/24 h) based either on the current value at each visit or the history of values up to a visit.

Statistical methods

Analyses used all AER and eGFR values from the 1,439 participants over the 23 years of the DCCT/EDIC study. The Kruskal-Wallis or Wilcoxon rank-sum test for differences among groups was used for quantitative or ordinal data and the χ^2 test for categorical data.

The general linear mixed model was used to estimate the rate of change in log-transformed eGFR during each of the three AER states adjusted for medication use and mean arterial pressure at the current visit, all as time-dependent covariates (14). This random coefficient model used the log of eGFR as the dependent variable with a random time effect, an AER group effect (normal, micro-, or macroalbuminuria), time by AER group interaction, and other covariate effects. Information sandwich empirical variance estimates for the fixed effects were used to ensure valid inferences, even if the covariance structure was mis-specified (14). The model estimated the change in log eGFR per year (slope) for each subject while that subject was in one or more of the three AER categories. The percent change in eGFR per year was obtained as $100 \times [\exp(\text{slope}) - 1]$, a negative value representing a decrease. The distribution of rates of change in eGFR among subjects (the random effects) were depicted using Kernel-smoothed density estimates (15). The model also provided estimates of the mean level of eGFR over time for subjects then in each category of AER.

The Cox proportional hazard model assessed the effect of the AER state (category) as a time-dependent covariate on the risk of sustained abnormal eGFR <60 ml/min/1.73 m^2 (16).

Additional models included interactions between DCCT treatment group (intensive versus conventional) and AER categories to determine whether the same relationships applied within each group.

RESULTS

— Characteristics of the 1,439 participants at DCCT entry are shown in Table 1; 156 (11%) had an AER ≥30 mg/24 h but <200 mg/24 h. During the mean follow-up of 19 years in the DCCT/EDIC study, 580 participants (40%) developed microalbuminuria on at least one occasion and 164 (11%) developed macroalbuminuria on at least one occasion. During the DCCT/EDIC study, 202 participants developed an eGFR <60 ml/min/1.73 m^2. Among the 178 subjects with a subsequent visit, 108 had at least one other eGFR <60 ml/min/1.73 m^2, and 89 had sustained (two or more consecutive) eGFR levels <60 ml/min/1.73 m^2. Twenty of these 89 participants who had macroalbuminuria when they developed sustained eGFR <60 ml/min/1.73 m^2 subsequently developed ESRD.

Figure 1*A* shows that the proportion with normal AER up to the last visit among those who never developed a sustained eGFR <60 ml/min/1.73 m^2 was greater than the proportion who had normal AER up to the time that an initial eGFR <60 ml/min/1.73m^2 was first observed, as were the proportions with a history of microalbuminuria. Conversely, the proportion of subjects with a history of macroalbuminuria was markedly higher among individuals with sustained eGFR <60 ml/min/1.73 m^2 versus not.

Figure 1*B* shows that the cumulative incidence of sustained eGFR <60 ml/min/1.73 m^2 rose exponentially over the 23 years of observation from 1.1% at 10 years, to 7.3% at 20 years, and 11.4% at 23 years after the start of the DCCT.

Table 1 compares the characteristics of individuals with no abnormal eGFR versus those who developed sustained eGFR <60 ml/min/1.73 m^2 according to the history of prior albuminuria (none versus micro- versus macroalbuminuria). As would be expected, numerous differences were observed including lipids, use of ACE inhibitors and ARB medications, and history of hyperglycemia (A1C), but not blood pressure or hypertension.

Table 2 presents the Cox proportional hazard model analyses of the risk of sustained abnormal eGFR <60 ml/min/1.73 m^2 as a function of having microalbuminuria or macroalbuminuria either at the current visit at which an eGFR has been measured (the current albuminuria model) or at any visit up to the present visit (the history of albuminuria model). In the current albuminuria model, among individuals with normal AER at the current visit, 30 experienced sustained eGFR <60 ml/min/1.73 m^2 corresponding to a crude rate of 1.1 subjects per 1,000 patient-years. Among individuals with microalbuminuria at the current visit, the rate was 4.4 per 1,000 patient-years. Adjusted for other factors, patients with microalbuminuria had a 3.3-fold increased risk (hazard ratio) compared with patients with normal AER ($P < 0.0001$). Among individuals with current macroalbuminuria, the rate was 46.7 per 1,000 patient-years, with an adjusted 15.3-fold increased risk (hazard ratio) compared with individuals with normal AER ($P < 0.0001$).

A history of macroalbuminuria (previously or currently) was likewise associated with an 8.6-fold increased risk of sustained abnormal eGFR over normal AER, but the risk among patients with a history of microalbuminuria was not different from patients with normal AER. These risk ratios may be lower than those using the current AER categories in part because 90% of the 580 subjects with a history of microalbuminuria reverted to normal AER on at least one later visit. Likewise, 19% of 164 subjects with a history of macroalbuminuria reverted to normal AER, and 56% reverted to mi-

Table 1—*Characteristics of the 1,439 DCCT/EDIC participants within each AER category (based on the history of AER values) at the last visit for subjects with no sustained eGFR <60 ml/min/1.73 m² and at the initial abnormal eGFR visit for subjects with sustained eGFR <60 ml/min/1.73 m²*

	No sustained eGFR <60 ml/min/1.73 m² (*n* = 1,350)				Sustained eGFR <60 ml/min/1.73 m² (*n* = 89)			
Clinical characteristics	AER ≤30	AER >30–300	AER >300	Total	Total	AER ≤30	AER >30–300	AER >300
n	675	566	109	1,350	89	21	14	54
Primary cohort (%)	59	43	39*	50	52	67	79	39*
Intensive therapy (%)	54	50	28*	50	38†	57	43	30
Female (%)	43	53	34*	47	55	81	64	43*
DCCT baseline								
Age (years)	28 ± 7	26 ± 7	25 ± 7*	27 ± 7	28 ± 8	30 ± 7	33 ± 5	26 ± 7*
Diabetes duration (years)	5.3 ± 4.1	6.4 ± 4.3	6.2 ± 3.9*	5.8 ± 4.2	5.8 ± 3.8	4.0 ± 3.0	4.3 ± 3.8	6.9 ± 3.8*
BMI (kg/m²)	23 ± 3	23 ± 3	24 ± 3	23 ± 3	24 ± 3	23 ± 3	25 ± 3	24 ± 3
MAP (mmHg)	87 ± 9	86 ± 8	87 ± 9	86 ± 9	87 ± 8	84 ± 9	86 ± 9	88 ± 7
Hypertension (%)‡	32	30	37	31	30	19	14	39
AER (mg/24 h) [median (Q1, Q3)]	9 (6, 13)	14 (9, 27)	16 (9, 29)*	12 (7, 19)	12 (7, 19)	7 (4, 10)	12 (8, 19)	14 (7, 22)*
Clinical neuropathy (%)§	6	6	11	6	10	5	7	13
HDL (mg/dl)	51 ± 13	50 ± 12	48 ± 13*	51 ± 12	50 ± 13	55 ± 14	50 ± 13	49 ± 13
LDL (mg/dl)	110 ± 30	109 ± 29	111 ± 28	109 ± 29	114 ± 26†	108 ± 30	118 ± 25	116 ± 25
Triglyceride (mg/dl)	76 ± 42	83 ± 47	97 ± 72*	80 ± 48	94 ± 44†	70 ± 27	98 ± 38	102 ± 48*
eGFR (ml/min/1.73 m²)	108 ± 23	118 ± 28	121 ± 28*	113 ± 26	108 ± 33†	85 ± 20	94 ± 23	121 ± 33*
Diabetes duration at first sustained eGFR <60 ml/min/1.73 m² or last GFR visit (years)‖	24.0 (5.7)	25.9 (5.6)	25.7 (5.0)*	24.9 (5.7)	21.0 (5.4)	20.0 (5.6)	19.5 (4.8)	21.8 (5.4)
Take ACE inhibitors in EDIC study (%)¶	44	53	81*	51	82†	43	93	94*
Take ARBs at EDIC year 13/14 (%)¶	6.4	8.0	12.8	7.6	23.6†	14.0	21.4	27.8
DCCT mean A1C	7.8 ± 1	8.3 ± 1	9.4 ± 1*	8.1 ± 1	9.3 ± 2†	7.8 ± 1	8.9 ± 2	10.0 ± 1*
EDIC mean A1C up to year 13/14	7.7 ± 1	8.2 ± 1	8.9 ± 1*	8.0 ± 1	8.7 ± 1†	7.7 ± 1	8.7 ± 1	9.1 ± 1*
DCCT/EDIC follow-up (years)	19.0 ± 4	19.6 ± 3	19.8 ± 3*	19.3 ± 4	19.7 ± 3	19.7 ± 2	19.4 ± 2	19.8 ± 3

Data are means ± SD for quantitative variables unless noted otherwise. No sustained eGFR includes subjects with all eGFR >60 ml/min/1.73 m² and subjects with a history of single eGFR <60 ml/min/1.73 m², but no sustained eGFR <60 ml/min/1.73 m². *$P < 0.05$ from a multiple-group comparison among the three AER groups within the no sustained eGFR <60 ml/min/1.73 m² and sustained eGFR <60 ml/min/1.73 m² group, respectively, based on a 2 df Kruskal-Wallis test for quantitative variables and a χ^2 test for categorical variables. †$P < 0.05$ from a between-group comparison between the no sustained eGFR <60 ml/min/1.73 m² and sustained eGFR <60 ml/min/1.73 m² group as a whole, based on Wilcoxon rank-sum test for quantitative variables and a χ^2 test for categorical variables. ‡Hypertension: systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg. §Clinical neuropathy: a definite diagnosis of peripheral diabetic neuropathy by clinical examination based on the presence of at least two of the following: physical symptoms, abnormalities on sensory examination, and absent or decreased deep-tendon reflexes. ‖Diabetes duration up to the time of first reported sustained eGFR <60 ml/min/1.73 m² or up to the last GFR visit for subjects with no sustained eGFR <60 ml/min/1.73 m². No statistical test was conducted comparing subjects with no sustained eGFR <60 ml/min/1.73 m² versus sustained eGFR <60 ml/min/1.73 m² groups as a whole. ¶Use of ARBs was not collected before EDIC year 13/14. ACE inhibitor use was proscribed during the DCCT.

croalbuminuria transiently at some visit later.

The general linear mixed model in Table 2 also shows that while subjects had normal AER, either currently or by history, the eGFR declined on average by 1.2% per year. However, the eGFR declined by 1.8%/year while subjects currently had microalbuminuria, or 1.4%/year with a history of microalbuminuria (each $P < 0.0001$ vs. normal AER). The eGFR declined by 5.7% per year while subjects currently had macroalbuminuria, or 5.1% with a history of macroalbuminuria, each significantly higher than with microalbuminuria, or with normal AER ($P < 0.001$).

Figure 2*A* presents the model-estimated average decline in eGFR while subjects currently had normal AER versus microalbuminuria or macroalbuminuria. Whereas the slopes in eGFR over visits with normal AER and microalbuminuria are significantly different, the estimated levels of eGFR are similar over time owing to slightly higher values early in the DCCT for subjects with microalbuminuria. The subjects with macroalbuminuria had a much more rapid rate of decline over time. A decline of 5.7% per year over 10 years equates to $100 \times (1 - 0.943^{10}) = 44.4\%$ decline. The analysis based on a history of AER identifies an almost identical trend.

Figure 2*B* presents the smoothed distribution of the model-estimated patient-specific percent change in eGFR per year (slope) within each current AER category. While subjects had normal AER or microalbuminuria, there was little variation around the respective mean percent change shown in Table 2 (i.e., a narrow range from the highest to lowest values). Conversely, while subjects had macroalbuminuria, the distribution is flattened and skewed to the left with much more variation among subjects, with some subjects having as much as a 20% reduction per year in eGFR.

Although the incidence of change in eGFR or AER was significantly higher in the DCCT conventional than the intensive treatment group, the relationships between AER and eGFR described above in the combined cohort applied to both treatment groups. Tests of the interaction between DCCT treatment group and AER

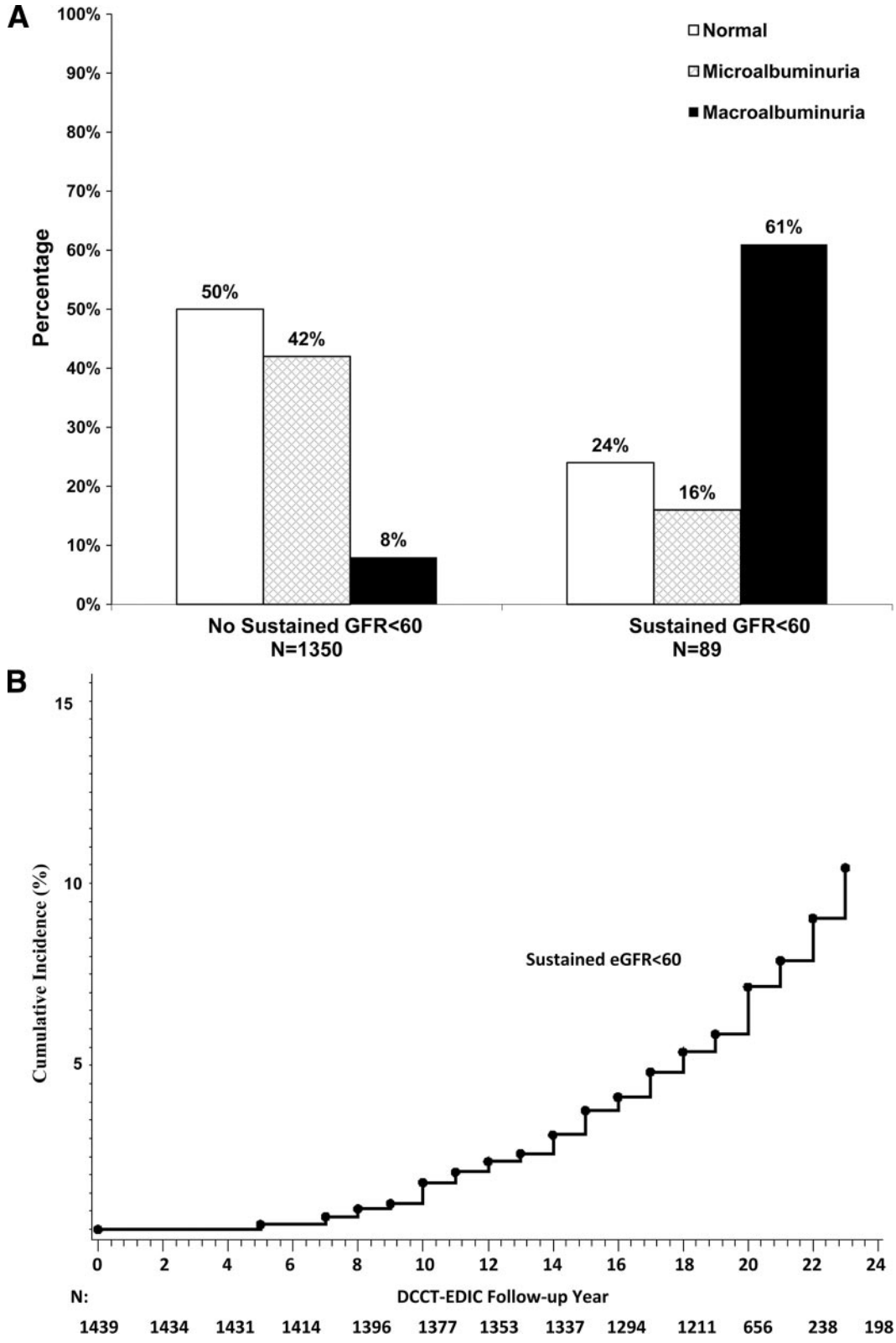

Figure 1—A*: The proportions of subjects with a history of normal AER (AER ≤30 mg/24 h), microalbuminuria (AER >30 and ≤300 mg/24 h), and macroalbuminuria (AER >300 mg/24 h or ESRD) among subjects who never developed a sustained eGFR <60 ml/min/1.73 m^2 by the time of their final visit, or at the visit where a subject first presents with a sustained eGFR <60 ml/min/1.73 m^2.* B*: Cumulative incidence of sustained eGFR <60 ml/min/1.73 m^2 during the DCCT/EDIC follow-up among the 1,439 DCCT/EDIC participants.*

Table 2—*Progression of eGFR as a function of the category of AER in the DCCT/EDIC study (n = 1,439) based on the current AER value or the history of AER values*

Models	Effect	Number with event (n = 89)†	Patient-years‡	Rate per 1,000 patient-years	Cox proportional hazard model*		GLMM§	
					Hazard ratio (95% CI)	Pair-wise P value	% Decrease per year (95% CI)	Pair-wise P value
Current albuminuria model	Normal (N)	30	28,123	1.1	1	M vs. N <0.0001	1.2% (1.2–1.3)	M vs. N <0.0001
Albuminuria category defined from the AER value at the time of estimated GFR assessment	Microalbuminuria (M)	18	4,041	4.4	3.3 (1.8–6.1)	A vs. M <0.0001	1.8% (1.6–1.9)	A vs. M <0.0001
	Macroalbuminuria (A)	41	837	46.7	15.3 (8.9–26.3)	A vs. N <0.0001	5.7% (4.5–6.8)	A vs. N <0.0001
History of albuminuria model	Normal (N)	21	21,069	1.0	1	M vs. N 0.281	1.2% (1.2–1.3)	M vs. N 0.0007
Albuminuria category defined from the highest AER value observed before or at the time of estimated GFR assessment	Microalbuminuria (M)	14	10,492	1.3	0.7 (0.4–1.4)	A vs. M <0.0001	1.4% (1.3–1.4)	A vs. M <0.0001
	Macroalbuminuria (A)	54	1,440	36.1	8.6 (5.0–14.7)	A vs. N <0.0001	5.1% (4.0–6.2)	A vs. N <0.0001

Crude risk of developing sustained estimated GFR <60 ml/min/1.73 m^2 (or ESRD) and the relative risk (hazard ratio) estimated from the Cox proportional hazards model are shown. Mean of the rate of decline (% decrease per year) in estimated GFR was obtained from the general linear mixed model. *Cox proportional hazard model of the time from DCCT randomization to the initial sustained eGFR <60 ml/min/1.73 m^2 through EDIC year 14, after adjustment for mean arterial pressure and ACE inhibitor use versus not at each visit as time-dependent covariates. For those with a missing covariate value at a visit, the prior observed value was carried forward. Mean arterial pressure was computed as (2/3 diastolic blood pressure + 1/3 systolic blood pressure). ACE inhibitor use was proscribed during DCCT (1983–1993). †The 89 patients with events are subjects with sustained eGFR <60 ml/min/1.73 m^2. ‡For each patient, patient-years is calculated as the elapsed whole years from randomization into the DCCT to either the visit at which a sustained eGFR <60 ml/min/1.73 m^2 was first observed or the last visit at which the eGFR was measured if a patient had no event during the time. §Percent decrease in eGFR per year while in each category of albuminuria obtained from the generalized linear mixed model of log-transformed levels of eGFR as a function of time, with heterogeneous random intercept, random slope over time, and residual errors among the time-dependent AER categories, after adjustment for time-dependent use of ACE inhibitor and time-dependent mean blood pressure at each DCCT-EDIC visit. For subjects with a missing covariate (AER, ACE inhibitor use, or mean blood pressure) at a visit, the prior observed value was carried forward. For subjects reaching ESRD, an eGFR value of 15 ml/min/1.73 m^2 was assigned thereafter for annual visits.

category in these models were not statistically significant (adjusted for two tests per model).

Additional analyses of a single eGFR <60 ml/min/1.73 m^2 showed a similar but less significant trend (see the online appendix).

CONCLUSIONS — It is generally believed that microalbuminuria serves as a marker for individuals who may develop diabetic nephropathy and likely reflects its earliest manifestation (1). However, only 30–45% of individuals with microalbuminuria have been found to progress to more advanced stages of kidney disease in recent studies (17). Furthermore, many patients with microalbuminuria often revert to normal AERs, as we have shown here and as has been shown previously (18). Only part of this reversion can be explained by good glycemic control and/or use of antiproteinuric medications (18).

The assumption that patients first pass through states with increasing levels of AER before eventually showing a decline in GFR (1) has been challenged by several studies which showed that a substantial proportion of adults with type 2 diabetes developed eGFR levels <60 ml/min 1.73m^2 had normal urinary AER (2–4).

Among DCCT/EDIC participants with type 1 diabetes, only 34% of 202 participants who developed an eGFR <60 ml/min/1.73 m^2 had a history of macroalbuminuria, with 27% having only microalbuminuria. To reduce the effects of random variations in eGFR levels, analyses of 89 individuals who had sustained eGFR <60 ml/min/1.73 m^2 showed that 61% had a history of macroalbuminuria and 16% had microalbuminuria. Given that some patients were taking ACE inhibitors and ARBs, classification into these categories must be considered to be somewhat inexact. In a similar analysis of 71 subjects with type 1 diabetes who had only single measurements of eGFR <60 ml/min/1.73 m^2, Costacou et al. (8) found that 51 (72%) had prior macroalbuminuria and 15 (21%) had prior microalbuminuria.

A unique aspect of the DCCT/EDIC study was the ability to determine the effects of antecedent levels of AER on the risk and rate of progression to eGFR <60 ml/min/1.73 m^2. Using Cox proportional hazards models, subjects having microalbuminuria currently present at the time of the eGFR assessment had a 3.3-fold increased risk of having an eGFR <60 ml/min/1.73 m^2 (sustained) at that same visit compared with subjects with normal AER at the time of the eGFR assessment. The risk was increased 15.3-

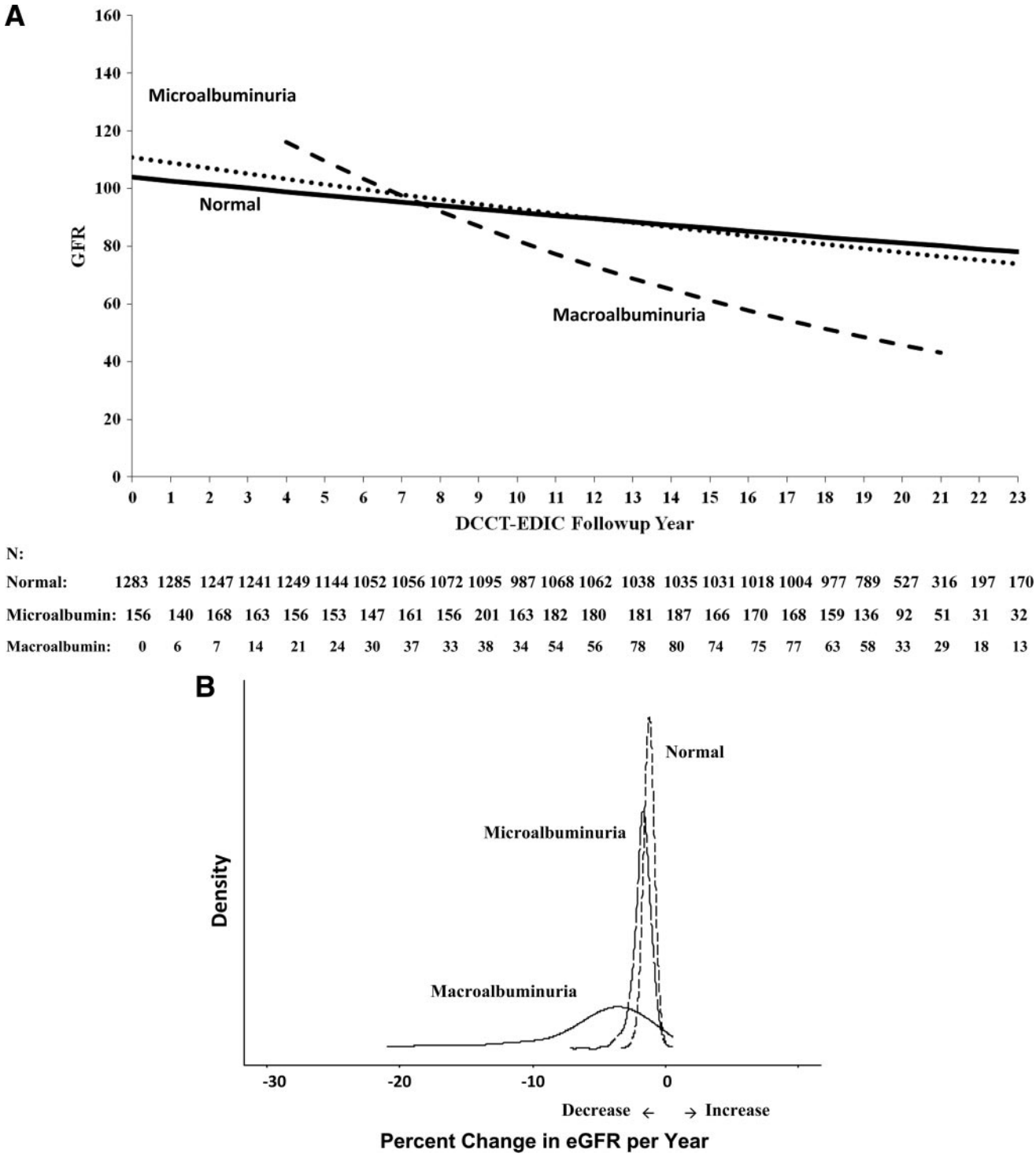

Figure 2—A*: Estimates of the mean levels of eGFR at each DCCT-EDIC follow-up year among subjects currently with normal AER, or microalbuminuria or macroalbuminuria at that time, obtained from the general linear mixed model in Table 2. Subjects may switch from one AER category to another depending on their current AER levels at each visit. For each AER category, the estimated mean levels of eGFR are shown for intervals during which at least 20 subjects had a visit.* B*: Smoothed estimates of the distribution of percent change in eGFR per year while subjects were in each current AER category. The* y*-axis is the probability density or the derivative of the probability distribution such that the integrated area under each curve equals 1. Each patient's rate of change in eGFR while currently in each AER category is estimated from the general linear mixed model in Table 2 (the current albuminuria model). Note the range of substantially increased rates of decline in eGFR while subjects had macroalbuminuria relative to those while having normal albuminuria or microalbuminuria.*

fold among individuals with current macroalbuminuria. The risk increases were not as great using a history of macroalbuminuria, in part because many subjects who developed microalbuminuria or macroalbuminuria later reverted to normal. Thus, transient elevations of AER did not appear to be as strongly associated with sustained effects on renal function.

Longitudinal mixed models further demonstrate that eGFR levels declined at an accelerating rate as the AER levels progressed from normal, to microalbuminuria and to macroalbuminuria. The rate of decline in eGFR was significantly greater among individuals with macroalbuminuria by history or the current value (5.1, 5.7%) at a visit compared with individuals with normal AER (1.2%, 1.2%) or microalbuminuria (1.4, 1.8%). The rate of decline for individuals with microalbuminuria was closer to, but significantly different from, that of subjects with normal AER ($P < 0.001$). The 5.7% decline per year while subjects concurrently had macroalbuminuria translates into a substantial 44% loss of renal function over 10 years. In some, this rate of decline was in the range of 10–20% per year, corresponding to 65–89% loss of renal function over 10 years. A correlation of progressive decline in GFR with progressing stages of albuminuria has also been shown in the Joslin cohort (9).

The pathophysiology and clinical significance of the low GFR levels in patients without albuminuria is unclear. In eight type 1 diabetic patients with normal AER and decreased GFR, Lane et al. (5) found that their biopsy results were virtually indistinguishable from patients with similar decreases in GFR and elevated urinary AER. Similar biopsy findings were reported by Caramori et al. (7) in 23 type 1 diabetic patients with less severe decreases of GFR without elevations of urinary AER.

In patients with type 2 diabetes, one large study (4) showed that subjects with macroalbuminuria had a greater rate of fall of eGFR than subjects with microalbuminuria or normal albumin excretion, but this was not shown in a second smaller study (19). A third study of a mixed group of subjects with type 1 and type 2 diabetes found that subjects without albuminuria had a lower risk of worsening of GFR than subjects with albuminuria (20).

Undoubtedly, other causes of chronic kidney disease must also be present in some patients with decreased eGFR and normal AER, and some may just reside in the lowest part of the normal range of GFR. However, the limited number of biopsy studies of type 1 diabetic patients suggests that many have diabetic glomerulopathy (5,7). Although some studies have suggested that the standard immunoassay for urinary albumin underestimates urine albumin levels in the low range compared with a high pressure liquid chromatography method (21), others have not found this to be so (22). At present, immunoassay remains the standard methodology.

Limitations of our study include the use of the Modification of Diet in Renal Disease formula to estimate GFR rather than a direct measurement of GFR, a lack of kidney biopsies, and the use of a 4-h instead of a 24-h urine collection to assess albumin excretion status. None of these are routine in clinical practice. The 4-h urine collections for albumin have been used in the DCCT/EDIC study since 1983 and have been used previously by the Steno Study Group (23) and the Pittsburgh Epidemiology of Diabetes Complications Study (24). The Pittsburgh group also showed that the 4-h collection correlated highly ($r = 0.942$) with the 24-h collection and found a similar correlation with the albumin/creatinine ratio (0.940) (24).

Our studies have also shown that there is substantial within-subject variation in the 4-h estimated AER and in the excretion rate expressed per 24 h. Over the 23 years spanned by these data, adjusting for temporal trends, the intraclass correlation among repeated values within subjects was 0.49, for both the 4-h values and those extrapolated to 24 h. The intraclass correlation, however, is substantially higher (0.80) during the later years of the EDIC study (2004–2008) when the levels of AER were higher.

The albumin-to-creatinine ratio, measured annually during EDIC since 2004, had a lower intraclass correlation (0.685) than our 4-h AER data (0.803), and when used as an outcome in comparisons of the DCCT treatment groups, AER and ACR show similar results. Thus, we would expect that longitudinal measures of ACR would provide similar effects on longitudinal eGFR as those shown herein.

In summary, 24% of the 89 subjects with sustained eGFR levels <60 ml/min/1.73 m^2 in the DCCT/EDIC study did not have a history of microalbuminuria or macroalbuminuria on annual visits before developing sustained eGFR levels <60 ml/min/1.73 m^2. However, we also show that the course of renal function in the DCCT/EDIC subjects, based on eGFR levels, is substantially worse when macroalbuminuria is present. Our findings support the recommendations of Jerums et al. (25) that both eGFR and AER should be assessed in the evaluation of kidney disease in diabetic patients.

Acknowledgments— The DCCT/EDIC project was supported by contracts with the Division of Diabetes, Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases, National Eye Institute, National Institute of Neurological Disorders and Stroke, the General Clinical Research Centers Program and the Clinical and Translation Science Awards Program, National Center for Research Resources, and by Genentech through a Cooperative Research and Development Agreement with the National Institute of Diabetes and Digestive and Kidney Diseases.

The following companies contributed free or discounted supplies and/or equipment: LifeScan, Roche, Aventis, Eli Lilly, OmniPod, Can-Am, B-D, Animas, Medtronic, Medtronic Minimed, Bayer (one-time donation in 2008), and Omron.

No other potential conflicts of interest relevant to this article were reported.

M.E.M. wrote the manuscript; M.S. reviewed and edited the manuscript; W.S. researched the data and performed the analysis; B.R. performed the analysis; P.C. researched data and reviewed/edited the manuscript; I.H.d.B. contributed to the discussion; B.Z. contributed to the discussion; and J.L. reviewed and edited the manuscript/rebuttal letter. We acknowledge the technical editorial assistance of Mary Hawkins.

This study was presented orally at the 66th Scientific Sessions of the American Diabetes Association, Washington, D.C., 9–13 June 2006.

References

1. American Diabetes Association. Standards of medical care in diabetes. Diabetes Care 2009;32(Suppl. 1):S13–S61
2. Kramer HJ, Nguyen QD, Curhan G, Hsu CY. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. JAMA 2003;289:3273–3277
3. Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR, UKPDS Study Group. Risk factors for renal dysfunction in type 2 diabetes: U.K. Prospective Diabetes Study 74. Diabetes 2006;55:1832–1839
4. So WY, Kong AP, Ma RC, Ozaki R, Szeto CC, Chan NN, Ng V, Ho CS, Lam CW, Chow CC, Cockram CS, Chan JC, Tong PC. Glomerular filtration rate, cardiorenal end points, and all-cause mortality in type 2 diabetic patients. Diabetes Care 2006; 29:2046–2052
5. Lane PH, Steffes MW, Mauer SM. Glomerular structure in IDDM women with low glomerular filtration rate and normal urinary albumin excretion. Diabetes 1992; 41:581–586
6. Tsalamandris C, Allen TJ, Gilbert RE, Sinha A, Panagiotopoulos S, Cooper ME, Jerums G. Progressive decline in renal function in diabetic patients with and

without albuminuria. Diabetes 1994;43:649–655
7. Caramori ML, Fioretto P, Mauer M. Low glomerular filtration rate in normoalbuminuric type 1 diabetic patients: an indicator of more advanced glomerular lesions. Diabetes 2003;52:1036–1040
8. Costacou T, Ellis D, Fried L, Orchard TJ. Sequence of progression of albuminuria and decreased GFR in persons with type 1 diabetes: a cohort study. Am J Kidney Dis 2007;50;721–732
9. Perkins BA, Ficociello LH, Ostrander BE, Silva KH, Weinberg J, Warram JH, Krolewski AS. Microalbuminuria and the risk for early progressive renal function decline in type 1 diabetes. J Am Soc Nephrol 2007;18:1353–1361
10. Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group: Epidemiology of Diabetes Interventions and Complications (EDIC). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. Diabetes Care 1999;22:99–111
11. Levey A, Bosch J, Breyer Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine. Ann Intern Med 1999;139:461–470
12. Fabiny DL, Ertingshausen G. Automated reaction-rate method for determination of serum creatinine with the CentrifiChem. Clin Chem 1971;17:696–700
13. Chavers BM, Simonson J, Michael AF. A solid-phase fluorescent immunoassay for the measurement of human urinary albumin. Kidney Int 1984;25:576–578
14. Fitzmaurice GM, Laird NM, Ware HH. *Applied Longitudinal Analysis.* New York, Wiley, 2004
15. Silverman BW. *Density Estimation for Statistics and Data Analysis.* London, U.K., Chapman and Hall, 1986
16. Cox DR, Oakes D. *Analysis of Survival Data.* New York, Chapman and Hall, 1984
17. Caramori ML, Fioretto P, Mauer M. The need for early predictors of diabetic nephropathy risk: is albumin excretion rate sufficient? Diabetes 2000;49:1399–1408
18. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. N Engl J Med 2003;348:2285–2293
19. MacIsaac RJ, Tsalamandris C, Panagiotopoulos S, Smith TJ, McNeil KJ, Jerums G. Nonalbuminuric renal insufficiency in type 2 diabetes. Diabetes Care 2004;27:195–200
20. Rigalleau V, Lasseur C, Raffaitin C, Beauvieux MC, Barthe N, Chauveau P, Combe C, Gin H. Normoalbuminuric renal-insufficient diabetic patients: a lower-risk group. Diabetes Care 2007;30:2034–2039
21. Comper WD, Osicka TM, Jerums G. High prevalence of immuno-unreactive intact albumin in urine of diabetic patients. Am J Kidney Dis 2003;41:336–342
22. Peters T Jr. How should we measure the albumin in urine? Clin Chem 2006;52;555–556
23. Steno Study Group. Effect of 6 months of strict metabolic control on eye and kidney function in insulin-dependent diabetics with background retinopathy. Lancet 1982;1:121–123
24. Ellis D, Coonrod BA, Dorman JS, Kelsey SF, Becker DJ, Avner ED, Orchard TJ. Choice of urine sample predictive of microalbuminuria in patients with insulin-dependent diabetes mellitus. Am J Kidney Dis 1989;13;321–328
25. Jerums G, Panagiotopoulos S, Premaratne E, MacIsaac RJ. Integrating albuminuria and GFR in the assessment of diabetic nephropathy. Nat Rev Nephrol 2009;5:397–406