

Supplementary material for:

Albuminuria changes and cardiovascular and renal outcomes in type 1 diabetes: the DCCT/EDIC Study

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Supplementary Table 1. Associations of time-updated albuminuria status with cardiovascular and renal events in the DCCT/EDIC Study, without and with adjustment for estimated GFR.

		Model 2		Model 2 plus estimated GFR	
	N events	HR (95% CI)	p-value	HR (95% CI)	p-value
All cardiovascular events					
Normoalbuminuria	109	1 (ref)		1 (ref)	
Sustained microalbuminuria	23	1.3 (0.8, 2.1)	0.276	1.3 (0.8, 2.1)	0.272
Remitted microalbuminuria	27	2.2 (1.4, 3.5)	0.0004	2.2 (1.4, 3.5)	0.0004
Macroalbuminuria	25	1.8 (1.1, 2.9)	0.029	1.8 (1.1, 3.1)	0.026
Major adverse cardiac events					
Normoalbuminuria	48	1 (ref)		1 (ref)	
Sustained microalbuminuria	11	1.4 (0.7, 2.8)	0.335	1.4 (0.7, 2.8)	0.340
Remitted microalbuminuria	11	1.9 (0.9, 3.8)	0.074	1.9 (0.9, 3.8)	0.074
Macroalbuminuria	18	3.0 (1.5, 5.7)	0.0011	2.9 (1.4, 5.8)	0.0003

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, with or without adjustment for estimated GFR (as time-dependent eGFR <60 mL/min/1.73m²). Results with p<0.05 are highlighted in bold.

Supplementary Table 2. Associations of time-updated albuminuria status with cardiovascular and renal events in the DCCT/EDIC Study, introducing a time lag of 4 years between assessment of albuminuria and assessment of the cardiovascular or renal event ascertained.

			Model 1		Model 2	
	N events	Incidence rate (per 1000 person-years)	HR (95% CI)	p-value	HR (95% CI)	p-value
All cardiovascular events						
Normoalbuminuria	119	4.1	1 (ref)		1 (ref)	
Sustained microalbuminuria	28	10.9	2.3 (1.5, 3.5)	0.0002	1.8 (1.1, 2.8)	0.013
Remitted microalbuminuria	18	11.7	2.1 (1.3, 3.5)	0.005	1.8 (1.1, 3.1)	0.024
Macroalbuminuria	19	14.7	2.6 (1.5, 4.3)	0.0003	1.8 (1.1, 3.2)	0.031
Major adverse cardiac events						
Normoalbuminuria	52	1.8	1 (ref)		1 (ref)	
Sustained microalbuminuria	11	4.1	2.1 (1.1, 4.0)	0.034	1.6 (0.8, 3.1)	0.199
Remitted microalbuminuria	9	5.5	2.4 (1.1, 5.0)	0.022	2.0 (0.9, 4.2)	0.073
Macroalbuminuria	16	11.4	5.0 (2.7, 9.4)	<.0001	4.0 (2.1, 7.9)	<.0001
Sustained eGFR<60						
Normoalbuminuria	31	1.1	1 (ref)		1 (ref)	
Sustained microalbuminuria	25	9.4	8.8 (5.1, 15.2)	<.0001	3.7 (2.1, 6.8)	<.0001
Remitted microalbuminuria	4	2.4	1.9 (0.7, 5.4)	0.240	1.4 (0.5, 4.2)	0.495
Macroalbuminuria	38	33.8	26.7 (15.7, 45.6)	<.0001	11.8 (6.5, 21.3)	<.0001

In this sensitivity analysis, a time lag of four years between albuminuria status and outcome ascertainment was introduced. In other words, at any time that a CVD or renal event was being assessed, the albuminuria status four years earlier was used as exposure.

In Model 1, the proportional hazards model was stratified by 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.

Results with $p < 0.05$ are highlighted in bold.

Supplementary Table 3. Associations of time-updated albuminuria status with cardiovascular and renal events in the DCCT/EDIC Study, splitting participants with macroalbuminuria into those with sustained macroalbuminuria versus remitted macroalbuminuria.

			Model 1		Model 2	
	N events	Incidence rate (per 1000 person-years)	HR (95% CI)	p-value	HR (95% CI)	p-value
All cardiovascular events						
Normoalbuminuria	109	6.3	1 (ref)		1 (ref)	
Sustained microalbuminuria	23	13.2	1.8 (1.1, 2.9)	0.014	1.3 (0.8, 2.1)	0.275
Remitted microalbuminuria	27	23.9	2.6 (1.7, 4.1)	<.0001	2.2 (1.4, 3.5)	0.0004
Macroalbuminuria	18	27.6	2.8 (1.7, 4.8)	<.0001	1.8 (1.0, 3.1)	0.047
Remitted Macroalbuminuria	7	21.3	2.3 (1.0, 4.9)	0.043	1.7 (0.8, 3.8)	0.198
Major adverse cardiac events						
Normoalbuminuria	48	2.7	1 (ref)		1 (ref)	
Sustained microalbuminuria	11	6.2	2.0 (1.0, 3.9)	0.040	1.4 (0.7, 2.8)	0.346
Remitted microalbuminuria	11	9.2	2.3 (1.1, 4.5)	0.019	1.9 (0.9, 3.8)	0.071
Macroalbuminuria	12	17.2	4.1 (2.1, 8.0)	<.0001	2.7 (1.3, 5.6)	0.009
Remitted Macroalbuminuria	6	16.8	4.4 (1.8, 10.7)	0.001	3.7 (1.4, 9.4)	0.005
Sustained eGFR<60						
Normoalbuminuria	19	1.1	1 (ref)		1 (ref)	
Sustained microalbuminuria	10	5.6	5.3 (2.4, 11.5)	<.0001	2.9 (1.3, 6.5)	0.011
Remitted microalbuminuria	7	5.8	3.9 (1.6, 9.5)	0.003	3.0 (1.2, 7.4)	0.015
Macroalbuminuria	54	156.5	78.5 (44.1, 139.6)	<.0001	36.2 (18.6, 70.4)	<.0001
Remitted Macroalbuminuria	8	23.2	16.4 (6.8, 39.2)	<.0001	9.6 (3.8, 24.1)	<.0001

In Model 1, the proportional hazards model was stratified by 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.

Results with p<0.05 are highlighted in bold.

Supplementary Table 4. Associations of albuminuria status with mean coronary artery calcification, using left censored Tobit regression

			Model 1		Model 2	
Albuminuria Status	N evaluated	Mean CAC Score*	Geometric Mean Ratio (95% CI)	p-value	Geometric Mean Ratio (95% CI)	p-value
Normoalbuminuria	872	39.8 (177.6)	1.0 (ref)		1.0 (ref)	
Sustained microalbuminuria	102	45.6 (135.7)	1.88 (0.57, 6.20)	0.2954	0.93 (0.28, 3.17)	0.9180
Remitted microalbuminuria	94	114.1 (388.0)	3.53 (1.01, 12.29)	0.0473	2.07 (0.60, 7.10)	0.2492
Macroalbuminuria	88	109.8 (238.7)	12.36 (3.72, 41.08)	<.0001	3.49 (0.94, 12.95)	0.0619

Model 1 is adjusted for age, sex, and attained duration of diabetes, and 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.

*Mean CAC score is among those who have detectable levels of CAC.

Abbreviations: CAC = coronary artery calcium; CI = confidence interval

Results with $p < 0.05$ are highlighted in bold.