ORIGINAL ARTICLE

Association of albuminuria and reduced estimated glomerular filtration rate with incident stroke and coronary artery disease in patients with type 2 diabetes

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It is unclear whether albuminuria and reduced glomerular filtration rate (GFR) independently increase the risk of incident stroke and coronary artery disease (CAD) in Japanese patients with diabetes. We investigated the independent effects of albuminuria and estimated GFR (eGFR) on the first occurrence of stroke and CAD in patients with type 2 diabetes mellitus (T2DM). We studied 1002 T2DM patients with eGFR (ml min^{-1} per 1.73 m^2) ≥ 15 and had no previous cardiovascular disease (CVD) history. GFR was estimated using the modified three-variable equation for the Japanese. Patients were divided into four eGFR categories: ≥ 90 , 60–89, 30–59 and 15–29. The end point was an incident stroke and CAD events. The Cox proportional hazard model was used to calculate hazard ratio and 95% confidence interval. During a mean follow-up period of 5.2 ± 2.1 years, 72 episodes of stroke and 90 of CAD were observed. Multivariate Cox analysis revealed no significant association between the eGFR category and incident stroke. The stroke hazard ratio (95% confidence interval) in reference to patients with an eGFR ≥ 90 was 0.78 (0.40–1.56) for patients with an eGFR of 60–89, 1.47 (0.70–3.10) for patients with an eGFR of 30–59 and 1.14 (0.39–3.35) for patients with an eGFR of 15–29. Reduced eGFR was a significant risk factor for CAD, with hazard ratios (95% confidence interval) for patients with an eGFRs of 60–89, 30–59 and 15–29 at 1.81 (1.01–3.57), 2.03 (1.04–4.40) and 3.01 (1.13–8.02), respectively. Reduced eGFR is independently associated with incident CAD but not stroke in Japanese patients with T2DM.

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INTRODUCTION

Chronic kidney disease (CKD)¹ has been recognized as an independent risk factor for cardiovascular disease (CVD) mortality and morbidity both in the Japanese² and Western populations.^{3,4} It has also been demonstrated that decreased estimated glomerular filtration rate (eGFR) is an independent risk factor for cardiovascular events and all-cause-mortality in patients with type 2 diabetes mellitus (T2DM).⁵ Observational analyses from the Action in Diabetes and Vascular Disease: preterAx and diamicroN-MR Controlled Evaluation study⁶ indicated that albuminuria and reduced eGFR, important components of CKD, are separately and independently associated with incident CVD. Similar findings were observed in patients with T2DM; however, there are no available data regarding whether albuminuria and reduced GFR are, independently of each other, associated with incident CVD in Japanese patients with T2DM.

A *post hoc* analysis from the Prevention of Renal and Vascular End-Stage Disease study⁷ showed that a category of subjects with a

decreased eGFR but normoalbuminuria was not at increased risk of CVD, and the impact of reduced GFR was shown by PROSPER (Prospective study of Pravastatin in the Elderly at Risk) to be greater for coronary artery disease (CAD) than for stroke in elderly people.⁸ We have recently shown that albuminuria, but not reduced eGFR, is associated with not only incident symptomatic stroke⁹ but also prevalent silent cerebral infarction¹⁰ in patients with T2DM. These findings^{8–10} may indicate the different impact of reduced GFR on incident stroke and CAD. In the present study, we aimed to examine the independent association of albuminuria and reduced eGFR, with incident stroke and CAD in Japanese patients with T2DM.

METHODS

Study population

This prospective hospital-based observational cohort study was conducted in accordance with the Declaration of Helsinki. The study comprised consecutive patients with T2DM who were admitted to the Department of Medicine,

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Diabetes Center, Tokyo Women's Medical University Hospital in Tokyo, Japan between 1 January 2002 and 31 December 2003. Patients were 20 years of age or older, and were admitted for glycemic control and for the evaluation of diabetic complications. Patients undergoing renal replacement therapy, pregnant women, and patients with infectious and malignant diseases were excluded. T2DM was diagnosed according to criteria from the World Health Organization.¹¹ We have previously studied 1300 type 2 diabetic patients who had no history of symptomatic stroke and the eGFR was $\geq 15 \text{ ml min}^{-1}$ per 1.73 m^2 , regardless of the degree of urinary albumin excretion in the same period to evaluate the association between CKD components and incident stroke.⁹ From the same cohort, we selected patients who had no history of symptomatic stroke, CAD or peripheral artery disease in the present study.

Participants underwent a routine medical history, physical examination and blood sampling. Information regarding smoking and family history of CVD was obtained using a standard questionnaire. Smoking habits were classified as current or not. Physical examination included blood pressure measurement and anthropometry; laboratory examinations included hemoglobin A1C, serum lipids and creatinine using fasting blood samples; and urinary albumin was measured in the first morning urine specimen.

Past history of CVD was defined as stroke/transient ischemic attack, CAD and peripheral artery disease. Past history of stroke and transient ischemic attack was obtained from medical records. Clinical evidence of CAD was defined from the following: angina pectoris diagnosed by coronary angiography or myocardial scintigraphy and a history of myocardial infarction or previous coronary revascularization. Past history of peripheral artery disease was defined as lower extremity peripheral artery disease according to American College of Cardiology/American Heart Association 2005 guidelines.¹²

Measurements

Serum creatinine was initially measured by Jaffé's method in the hospital laboratory. From January 2003, this method was replaced by an enzymatic method, and measurements were adjusted using a regression equation obtained from the correlational analysis between both measurements of serum creatinine analysis in 10 132 samples from diabetic patients: serum creatinine (enzymatic method, mg dl^{-1}) = $0.972 \times \text{serum creatinine (Jaffé's method, mg dl}^{-1}) - 0.224$ ($r=0.9992$, $P<0.001$).

GFR was estimated using the following modified three-variable equation for the Japanese, as has recently been proposed by the Japanese Society of Nephrology:¹³ $\text{GFR} = 194 \times \text{SCr}^{-1.094} \times \text{age}^{-0.287}$ ((if female) $\times 0.739$), where $\text{SCr} = \text{serum creatinine in mg dl}^{-1}$, measured by an enzymatic method. Patients were divided into four eGFR categories: eGFR ≥ 90 , 60–89, 30–59 and $15\text{--}29 \text{ ml min}^{-1}$ per 1.73 m^2 . Classification of the degree of urinary albumin was assessed according to the American Diabetes Association criteria, on the basis of the albumin-to-creatinine ratio (ACR) in the first morning urine specimen.¹⁴ Urinary ACR was calculated from urinary albumin, as determined using the latex agglutination method, and urinary creatinine concentrations. Normoalbuminuria, microalbuminuria and macroalbuminuria were defined as an ACR <30 , 30–299 and $\geq 300 \text{ mg g}^{-1}$, respectively.

Hemoglobin A1C was determined using the high-performance liquid chromatography (normal range: 4.3–5.8%). Total cholesterol and high-density lipoprotein cholesterol were determined enzymatically. Low-density lipoprotein cholesterol was calculated using the Friedewald's equation, when serum triglycerides level was $<4.57 \text{ mmol l}^{-1}$.¹⁵

Outcomes

Patients were followed up until September 2009. The primary end point was an incident first stroke and CAD event, information on which was obtained by direct reference to medical records by a single investigator (RB). Stroke was defined as an acute focal neurological deficit lasting longer than 24 h or resulting in death within 24 h of the onset of symptoms, and was diagnosed as being due to cerebral lesions of vascular origin (*International Classification of Diseases*, 9th Revision (ICD-9), codes of cerebrovascular diseases). Most stroke cases were diagnosed by computed tomography, MRI including diffusion image, magnetic resonance angiography of the brain and carotid duplex imaging. CAD was defined as myocardial infarction, angina pectoris of which patients received treatment in hospital for ischemic discomfort and diagnosed

by coronary angiography, coronary revascularization and sudden death. Coronary revascularization was achieved when a patient underwent percutaneous coronary intervention (for example, angioplasty, stenting, atherectomy and laser ablation) or coronary artery bypass graft.

Statistical analyses

Data were expressed as percentage, arithmetic mean $\pm$ s.d. or geometric mean with 95% confidence interval, as appropriate, according to data distribution. Triglycerides and ACR were logarithmically transformed owing to skewed distributions. For statistical analyses, one-way analysis of variance was used for between-group comparisons for continuous variables and the Cochran–Armitage test for categorical variables. The cumulative incidence of the end point was estimated using the Kaplan–Meier method. Risk estimates for reaching the end point were calculated using univariate and multivariate Cox proportional hazard model analyses. The following variables were incorporated as covariates: age, sex, duration of diabetes, presence of proliferative diabetic retinopathy, smoking status, body mass index, systolic and diastolic blood pressures, usage of renin–angiotensin system inhibitors (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), anti-platelet agents and statins, hemoglobin A1C, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, hemoglobin, uric acid, eGFR and urinary ACR at baseline. All statistical analyses were performed using the Statistical Analysis System (SAS Institute, Cary, NC, USA) version 9.13. A P -value <0.05 was considered significant.

RESULTS

A total of 1002 T2DM patients had sufficient baseline and follow-up data to qualify for inclusion in the study, including 452 women and 550 men with a mean ($\pm$ s.d.) age of 61 ± 12 years (range: 21–90 years). At baseline, the mean eGFR was $76.6 \pm 26.6 \text{ ml min}^{-1}$ per 1.73 m^2 (range: 16.6–216.1), and 283, 469, 203 and 47 patients were classified into eGFR groups ≥ 90 , 60–89, 30–59 and $15\text{--}29 \text{ ml min}^{-1}$ per 1.73 m^2 , respectively. Demographic and characteristic patient data in four eGFR categories are listed in Table 1.

Compared with patients with an eGFR $\geq 90 \text{ ml min}^{-1}$ per 1.73 m^2 , those with lower eGFRs were likely to be older, have exhibited a longer duration of diabetes and have higher systolic but lower diastolic blood pressure, yielding a higher pulse pressure. Furthermore, reduced eGFR was significantly associated with a higher prevalence of diabetic retinopathy. Medications and laboratory data according to eGFR levels are shown in Tables 1 and 2, respectively.

During the mean follow-up period of 5.2 ± 2.1 years (median = 6.1 years; maximum = 7.8 years; overall = 5247 patient-years), 72 first episodes of stroke were observed, yielding an incidence rate of 13.7 episodes per 1000 patient-years. The stroke cases were classified as 65 with cerebral infarction, 6 with cerebral bleeding and 1 with subarachnoid hemorrhage. In all, 90 first episodes of CAD (17.2 episodes per 1000 patient-years), including 12 myocardial infarctions, 63 angina pectoris and 15 sudden deaths, were also observed. Of 51 coronary interventions, 40 cases were percutaneous coronary intervention and 11 were coronary artery bypass graft. As shown in Figure 1a, the 5-year cumulative incidence of stroke in patients with an eGFR ≥ 90 , 60–89, 30–59 and $15\text{--}29$ were 3.9, 5.4, 13.6 and 18.3%, respectively ($P<0.001$ by the log-rank test). Those of CAD were 3.6, 6.1, 12.0 and 27.4%, respectively (Figure 1b; $P<0.0001$ by the log-rank test). When incident stroke and CAD events were combined as a composite end point (total CVD), the 5-year cumulative incidence of total CVD in patients with an eGFR ≥ 90 , 60–89, 30–59 and $15\text{--}29$ were 7.2, 10.6, 20.8 and 41.6%, respectively (Figure 1c; $P<0.0001$ by the log-rank test).

Table 3 shows the estimated hazard ratios of stroke, CAD and total CVD relative to the category of an eGFR $\geq 90 \text{ ml min}^{-1}$ per 1.73 m^2 for other categories of eGFR in patients with T2DM based on

Table 1 Clinical characteristics and concomitant medication in type 2 diabetic patients according to eGFR levels

Characteristic	eGFR (ml min ⁻¹ per 1.73 m ²)				P-value ^a
	≥ 90 (n=283)	60–89 (n=469)	30–59 (n=203)	15–29 (n=47)	
Age (years)	54 ± 14	62 ± 11	67 ± 11	64 ± 13	<0.001
Sex (male, %)	56.5	54.2	55.2	51.1	0.595
Family history of CVD (%)	27.6	37.3	29.6	25.5	0.904
Current smoker (%)	29.7	23.7	19.7	21.3	0.014
Diabetes duration (years)	11 ± 8	14 ± 9	17 ± 10	16 ± 10	<0.001
Body mass index (kg m ⁻²)	24.7 ± 5.0	24.2 ± 4.3	24.4 ± 3.9	24.9 ± 4.4	0.288
Systolic blood pressure (mm Hg)	128 ± 11	130 ± 19	135 ± 23	147 ± 28	<0.001
Diastolic blood pressure (mm Hg)	77 ± 11	75 ± 12	73 ± 13	79 ± 16	0.007
Pulse pressure (mm Hg)	51 ± 16	54 ± 17	62 ± 19	68 ± 23	<0.001
Proliferative diabetic retinopathy (%)	22.6	30.9	43.8	63.8	<0.001
Atrial fibrillation (%)	3.2	5.5	4.9	4.3	0.429
<i>Anti-diabetic agents (%)</i>					
Oral agents	44.5	43.5	35.5	21.3	0.002
Insulin	39.2	43.9	54.2	70.2	<0.001
<i>Anti-hypertensive agents (%)</i>					
Calcium channel blockers	19.1	25.4	38.4	76.6	<0.001
ACEIs	13.8	18.6	25.2	21.3	0.004
ARBs	13.8	22.4	37.4	51.2	<0.001
β-Blockers	3.5	3.2	7.4	8.5	0.020
α-Blockers	0.7	3.2	2.5	12.8	0.001
Diuretics	1.1	5.2	21.2	38.3	<0.001
Anti-platelet agents (%)	13.4	22.6	32.0	23.4	<0.001
Statins (%)	20.9	24.7	34.0	23.4	0.012

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin type 1-receptor blocker; CVD, cardiovascular disease.
Data are expressed as mean ± s.d. or as percentage.

^aANOVA or Cochran–Armitage test.

Table 2 Laboratory data in type 2 diabetic patients according to eGFR levels

Characteristic	eGFR (ml min ⁻¹ per 1.73 m ²)				P-value ^a
	≥ 90 (n=283)	60–89 (n=469)	30–59 (n=203)	15–29 (n=47)	
HbA _{1c} (%)	9.1 ± 1.9	8.6 ± 1.6	8.1 ± 1.8	7.6 ± 1.9	<0.001
Triglycerides (mmol l ⁻¹) ^b	1.4 (1.3–1.5)	1.4 (1.3–1.5)	1.5 (1.4–1.6)	1.6 (1.4–1.8)	0.029
HDL cholesterol (mmol l ⁻¹)	1.3 ± 0.4	1.3 ± 0.4	1.2 ± 0.4	1.2 ± 0.7	<0.001
LDL cholesterol (mmol l ⁻¹)	3.0 ± 0.9	3.0 ± 0.8	3.1 ± 1.0	3.2 ± 1.2	0.075
Hemoglobin (g l ⁻¹)	140 ± 15	135 ± 16	126 ± 15	107 ± 20	<0.001
ACR (mg g ⁻¹) ^b	20 (18–24)	28 (24–31)	108 (79–147)	953 (567–1602)	<0.001
<30 (%)	70.3	63.1	35.0	6.4	<0.001
30–299 (%)	25.1	25.4	25.1	12.8	0.306
≥300 (%)	4.6	11.5	39.9	80.8	<0.001
Serum creatinine (μmol l ⁻¹)	47.4 ± 8.6	62.9 ± 11.2	93.1 ± 22.4	182.7 ± 44.0	<0.001
eGFR (ml min ⁻¹ per 1.73 m ²)	108.0 ± 17.7	74.9 ± 8.7	48.7 ± 8.2	23.4 ± 3.8	<0.001

Abbreviations: ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; HDL/LDL, high/low density-lipoprotein.

Data are expressed as mean ± s.d., geometric mean (95% CI) or percentage.

^aANOVA or Cochran–Armitage test.

^bGeometric mean.

univariate and multivariate Cox regression analyses. Stroke hazard ratios for patients with an eGFR of 30–59 and 15–29 ml min⁻¹ per 1.73 m² were significant in the univariate Cox model; however, no statistical significance was evident from multivariate Cox analysis of hazard ratios for patients with an eGFR of 30–59 and 15–29 ml min⁻¹ per 1.73 m². In contrast, reduced eGFR was a significant risk factor

for CAD in both the univariate and multivariate Cox analyses including albuminuria as a covariate. When data were analyzed combining stroke and CAD events as total CVD events, there were also significant increases in total CVD risk in the eGFR of 30–59 and 15–29 ml min⁻¹ per 1.73 m² groups in multivariate Cox regression analysis.

Figure 1 Kaplan–Meier curve of cumulative incidence of first stroke (a), CAD (b) and total CVD including stroke and CAD (c) events in patients with type 2 diabetes stratified by eGFR: eGFR ≥ 90 , 60–89, 30–59 and 15–29 ml min^{−1} per 1.73 m².

Table 3 Hazard ratios of stroke, coronary artery disease and total cardiovascular disease in patients with type 2 diabetes stratified by eGFR categories

eGFR (ml min ^{−1} per 1.73 m ²)	Stroke			CAD			Total CVD		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
<i>Univariate analysis</i>									
≥90	1.00	(Reference)		1.00	(Reference)		1.00	(Reference)	
60–89	1.21	0.62–2.37	0.621	2.38	1.22–4.63	0.011	1.66	1.02–2.68	0.040
30–59	3.36	1.73–6.51	<0.001	4.35	2.16–8.74	<0.001	3.61	2.20–5.93	<0.001
15–29	4.00	1.60–10.03	<0.001	8.34	3.61–19.25	<0.001	5.88	3.10–11.14	<0.001
<i>Multivariate analysis</i>									
≥90	1.00	(Reference)		1.00	(Reference)		1.00	(Reference)	
60–89	0.79	0.40–1.56	0.494	1.81	1.01–3.57	0.049	1.23	0.75–2.02	0.407
30–59	1.47	0.70–3.10	0.312	2.03	1.04–4.40	0.042	1.66	1.01–2.89	0.045
15–29	1.14	0.39–3.35	0.810	3.01	1.13–8.02	0.027	1.86	1.07–3.97	0.040
Log ACR (mg g ^{−1})	1.85	1.36–2.53	<0.001	1.48	1.13–1.93	0.004	1.75	1.39–2.22	<0.001
Age (years)	1.06	1.03–1.08	<0.001	1.04	1.02–1.06	<0.001	1.05	1.04–1.07	<0.001
Family history of CVD	1.74	1.08–2.80	0.022	NS			NS		
Diastolic blood pressure (mm Hg)	1.03	1.01–1.06	0.012	NS			1.03	1.01–1.05	0.002
LDL cholesterol (mmol l ^{−1})		NS		1.39	1.05–1.58	0.039	NS		
Gender (male vs. female)		NS			NS		1.56	1.10–2.22	0.013
Body mass index (kg m ^{−2})		NS			NS		1.04	1.00–1.09	0.046

Abbreviations: ACR, albumin-to-creatinine ratio; CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LDL, low density-lipoprotein.

Figure 2 Kaplan-Meier curve of cumulative incidence of first stroke (a), CAD (b) and total CVD including stroke and CAD (c) events in patients with type 2 diabetes stratified by urinary ACR: ACR <30 mg g⁻¹, normoalbuminuria; 30–299 mg g⁻¹, microalbuminuria; ≥300 mg g⁻¹, clinical albuminuria.

Table 4 Hazard ratios of stroke, coronary artery disease and total cardiovascular disease in patients with type 2 diabetes stratified by urinary ACR levels

ACR (mg g ⁻¹)	Stroke			CAD			Total CVD		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
<i>Univariate analysis</i>									
<30	1.00	(Reference)		1.00	(Reference)		1.00	(Reference)	
30–299	2.06	1.56–3.69	0.014	2.56	1.34–3.80	0.002	2.15	1.46–3.27	<0.001
≥300	3.59	2.07–6.22	<0.001	3.93	2.39–6.44	<0.001	3.67	2.50–5.41	<0.001
<i>Multivariate analysis</i>									
<30	1.00	(Reference)		1.00	(Reference)		1.00	(Reference)	
30–299	2.02	1.11–3.65	0.021	1.97	1.16–3.34	0.012	2.33	1.52–3.57	<0.001
≥300	4.60	2.31–9.13	<0.001	2.70	1.46–4.99	0.002	3.70	2.21–6.23	<0.001
eGFR (ml min ⁻¹ per 1.73 m ²)	1.00	0.99–1.01	0.541	0.99	0.98–1.00	0.008	0.99	0.98–1.00	0.013
Age (years)	1.06	1.04–1.09	<0.001	1.03	1.01–1.05	0.003	1.06	1.04–1.07	<0.001
Family history of CVD	1.69	1.05–2.71	0.030	NS			NS		
Diastolic blood pressure (mm Hg)	1.03	1.01–1.06	0.011				1.03	1.01–1.05	0.001
LDL cholesterol (mmol l ⁻¹)		NS		1.41	1.06–1.61	0.032	1.29	1.03–1.48	0.029
Gender (male vs. female)		NS			NS		1.50	1.06–2.14	0.024
Body mass index (kg m ⁻²)		NS			NS		1.05	1.01–1.09	0.024
Atrial fibrillation		NS			NS		1.81	1.01–3.24	0.047
RAS inhibitors		NS			NS		0.69	0.48–0.99	0.047

Abbreviations: ACR, albumin-to-creatinine ratio; CAD, coronary artery disease; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LDL, low density-lipoprotein; RAS, rennin-angiotensin system.

When participants were classified by urinary ACR at baseline, the 5-year cumulative incidences of stroke in patients with normoalbuminuria, microalbuminuria and clinical albuminuria were 4.3, 8.8 and 14.0%, respectively (Figure 2a; $P < 0.001$ by the log-rank test). As well as stroke, the five-year cumulative incidence of CAD (Figure 2b; $P < 0.001$ by the log-rank test) and total CVD (Figure 2c; $P < 0.001$ by the log-rank test) significantly increased with an increase in urinary

ACR in patients with T2DM. Table 4 shows the hazard ratios of stroke, CAD and total CVD in patients with T2DM stratified by urinary ACR categories in univariate and multivariate Cox regression analyses. Compared with patients with normoalbuminuria ($n=569$), the hazard ratios of stroke, CAD and total CVD events for those with microalbuminuria ($n=247$) and clinical albuminuria ($n=186$) were significant in both univariate and multivariate Cox model analyses.

Figure 3 Hazard ratio of stroke (a), CAD (b) and total CVD (c) in patients with type 2 diabetes in the multivariate Cox model in six subgroups stratified by eGFR (≥ 60 ml min⁻¹ per 1.73 m² or less) and degree of albuminuria. The multivariate model included covariates listed in the Methods section other than urinary ACR and eGFR.

Finally, hazard ratios were calculated in six subgroups classified according to eGFR (≥ 60 ml min⁻¹ per 1.73 m² or less) and category of albuminuria to determine the simultaneous effect of these CKD manifestations on the risk of stroke and CAD events (the subgroup with an eGFR ≥ 60 ml min⁻¹ per 1.73 m² and normoalbuminuria was used as the reference group). As shown in Figure 3a, reduced eGFR was not predictive of incident stroke events except for patients with clinical albuminuria, whereas a stepwise increase in hazard ratios was identified as albuminuria increase, regardless of eGFR levels. In contrast, the impact of reduced eGFR on CAD was observed in patients with microalbuminuria and clinical albuminuria (Figure 3b). As well as stroke, a stepwise increase in hazard ratios was identified as albuminuria increase independent of eGFR levels. Similar findings were observed for total CVD events (Figure 3c). Compared with the reference group, patients with clinical albuminuria and an eGFR < 60 ml min⁻¹ per 1.73 m² were at the highest risk for each cardiovascular event, whereas those with normoalbuminuria and an eGFR < 60 ml min⁻¹ per 1.73 m² were not at significantly increased risk for stroke, CAD or total CVD events (Figure 3).

DISCUSSION

Although CKD has been recently identified as a potent risk factor for cardiovascular events,^{3,5,16} independent effects of the manifestations of CKD, albuminuria and reduced GFR are largely unknown, particularly in diabetic patients who carry a high risk of developing stroke and CAD. To the best of our knowledge, this is the first study to determine the independent effect of albuminuria and eGFR on the incidence of CVD, mainly focusing on stroke and CAD events in patients with T2DM. In this hospital-based prospective cohort study of Japanese diabetic patients, we have demonstrated that reduced eGFR is see-

mingly associated with a higher risk of incident stroke and CAD in patients with T2DM. This association remained statistically significant for CAD and total CVD even after adjusting for cardiovascular risk factors and urinary ACR; however, the association between reduced eGFR and stroke disappeared. In contrast, albuminuria, another renal manifestation of diabetic kidney disease, was robustly predictive of both stroke and CAD events even after adjusting for covariates including eGFR.

Previous studies^{5,6} have indicated the significant association of reduced eGFR with incident CVD in patients with T2DM even if albuminuria was included as a covariate. Our present findings are compatible with these observations.^{5,6} Reduced GFR has numerous effects on the cardiovascular system, including inhibition of erythropoiesis and platelet function,^{17,18} and induction of volume overload,¹⁹ dyslipidemia, hypertension²⁰ and vascular calcification.²¹ Therefore, reduced GFR is not only a marker of the presence of conventional cardiovascular risk factors but may also have an important role in the pathogenesis of CVD, particularly CAD.

On the other hand, although patients with reduced eGFR had a higher incidence of stroke in the present study, reduced eGFR was not associated with incident stroke events in T2DM patients except those with clinical albuminuria. The higher incidence of stroke in patients with reduced eGFR may be partly due to confounding factors including higher age and diastolic blood pressure (Table 3). In fact, the statistical significance between reduced eGFR and incident stroke disappeared after adjustment for these covariables including albuminuria. Stroke events were less common than coronary events, possibly because of lower associated power to detect a significant association; however, our data were in agreement with those of a pooled analysis of community-based studies.¹⁶ Bos *et al.*²² from the Rotterdam Study

also reported that low GFR was not associated with incident ischemic stroke. Furthermore, secondary analysis from PROSPER⁸ indicated that elderly people with reduced GFR were at significantly increased risk of incident CAD but not stroke. These findings suggest that reduced eGFR has less predictive value of incident stroke than CAD. Further studies are required to clarify the different pathogenesis of stroke and CAD associated with reduced eGFR and/or albuminuria.

In contrast to reduced eGFR, albuminuria was confirmed to be a strong and independent predictor of CAD as well as stroke in the present study. This association has been well recognized in previous studies.^{23–26} As discussed previously, albuminuria and CVD share numerous risk factors that may explain this relationship.⁹

The limitations of this study first include an ethnically and socially homogeneous population because of a hospital-based study; therefore, the generalization of our findings may be limited. Second, we only studied diabetic patients without a previous history of CVD to determine the effects of renal parameters in T2DM patients on the first event of stroke or CAD. Our results should therefore be reviewed with caution when extrapolating incidences of secondary stroke or CAD events. Third, we defined patients without CVD by a routine medical history, and procedures such as cranial MRI or myocardial scintigraphy were not performed in all patients in the present study. Therefore, we were unable to rule out the possibility that some of type 2 diabetic patients in the present study may have a history of CVD. Fourth, albuminuria was determined from a single measurement of urinary ACR, possibly leading to improper categorization because of marked day-to-day variability in albumin excretion. Although we did not obtain multiple measurements of urinary ACR, we restricted the timing of urine collection to the first morning urine to minimize exercise-induced and diurnal variation.²⁷

CONCLUSION

This prospective hospital-based observational cohort study has demonstrated that albuminuria and reduced eGFR are independent of each other, associated with CAD but not stroke in Japanese patients with T2DM.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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