Glomerular Filtration Rate, Cardiorenal End Points, and All-Cause Mortality in Type 2 Diabetic Patients

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OBJECTIVE — Chronic kidney disease (CKD) predicts cardiovascular disease (CVD) in the general population. We investigated the effects of stages of renal function using the estimated glomerular filtration rate (eGFR) on all-cause mortality and cardiovascular end points in a prospective cohort of Chinese type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — Between 1995 and 2000, 4,421 patients without macrovascular disease or end-stage renal disease were recruited. Renal function was assessed by eGFR, as calculated by the abbreviated Modification of Diet in Renal Disease Study Group formula. Clinical end points included all-cause mortality, cardiovascular end point (cardiovascular death, new admissions due to angina, myocardial infarction, stroke, revascularization, or heart failure), and renal end point (reduction in eGFR by >50%, progression of eGFR to stage 5, or dialysis or renal death).

RESULTS — After a median follow-up period of 39.4 months (interquartile range 20.3–55), all-cause mortality rate increased from 1.2% (95% CI 0.8–1.7) to 18.3% (9.1–27.5) (*P* for trend <0.001) as renal function deteriorated from stage 1 (eGFR ≥90 ml/min per 1.73 m^2) to stage 4 (15–29 ml/min per 1.73 m^2). The respective rate of new cardiovascular end points also increased from 2.6% (2.0–3.3) to 25.3% (15.0–35.7) (*P* for trend <0.001). After adjustment for covariates (age, sex, albuminuria, use of renin-angiotensin-aldosterone system [RAAS] inhibitors, lipids, blood pressure, and glycemic control), hazard ratios across different stages of eGFR (≥90, 60–89, 30–59, and 15–29 ml/min per 1.73 m^2) for all-cause mortality were 1.00, 1.27, 2.34, and 9.82 (*P* for trend <0.001), for cardiovascular end points were 1.00, 1.04, 1.05, and 3.23 (*P* for trend <0.001), and for renal end points were 1.00, 1.36, 3.34, and 27.3 (*P* for trend <0.001), respectively.

CONCLUSIONS — Chinese type 2 diabetic patients with reduced eGFR were at high risk of developing cardiovascular end points and all-cause mortality, independent of albuminuria and metabolic control.

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Abbreviations: ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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In the general population, chronic kidney disease (CKD) predicts occurrence of cardiovascular disease (CVD), but similar information in the diabetic population is limited (1–3). Diabetes is the most common cause of end-stage renal disease, accounting for nearly 50% of all new cases of renal replacement therapy in most developed countries (3,4). Asians have a high risk of developing nephropathy, which affects 60% of hypertensive type 2 diabetic patients (5). In the World Health Organization Multinational Study of Vascular Disease in Diabetes (4), 10–15% of diabetic patients in China and Japan died from end-stage renal disease in contrast to <5% in North America and Europe, possibly due to genetic influence (6), environmental factors yet to be identified, and limited access to renal replacement therapy. Although large-scale studies have suggested that Asians might have a lower risk of developing CVDs compared with Caucasians (7), given their predilection for renal complications and the intimate relationships between CKD and CVD, there is a need to document the impact of renal function on cardiovascular morbidity and mortality in this growing population of diabetic patients. In this study, we investigated the effects of renal function on new-onset cardiorenal end points and all-cause mortality rates in a large prospective cohort of Chinese type 2 diabetic patients.

RESEARCH DESIGN AND METHODS

— Since 1995, all newly referred diabetic patients to the Prince of Wales Hospital in Hong Kong underwent comprehensive assessments of complications and risk factors based on the European DiabCare protocol (8). All type 2 diabetic patients with no history of macrovascular disease, as defined by history of myocardial infarction, stroke, peripheral vascular disease, and revascularization procedure, were included for analysis in this study. Patients with dialysis or estimated glomerular filration rate (eGFR) stage 5 (<15 ml/min per 1.73 m^2 as explained below) or those with type 1 diabetes, defined as presentation with diabetic ketoacidosis, acute symptoms with

Table 1—*Clinical and metabolic characteristics of 4,421 Chinese type 2 diabetic patients without macrovascular disease and end-stage renal disease (eGFR <15 ml/min per 1.73 m^2) at baseline*

		eGFR (ml/min per 1.73 m^2)				
	Total cohort	≥90	60–89	30–59	15–29	*P* for trend
n	4,421	2,257	1,636	457	71	
Men (%)	43.2	40.5	47.2	42.5	38.0	0.044
Age (years)	57.6 ± 13.3	51.4 ± 12.0	62.3 ± 11.5	69.3 ± 9.9	69.3 ± 9.5	<0.001
Duration of diabetes (years)	6.9 ± 6.3	5.6 ± 5.5	7.2 ± 6.2	11.2 ± 7.8	12.9 ± 6.8	<0.001
Smoking (ex and current) (%)	26.7	24.2	28.9	31.3	25.7	0.001
BMI (kg/m^2)						
Women	25.1 ± 4.0	25.1 ± 4.2	25.1 ± 3.9	25.3 ± 3.8	25.1 ± 3.3	0.905
Men	25.0 ± 3.9	25.1 ± 4.3	25.0 ± 3.5	25.0 ± 3.5	24.1 ± 2.8	0.837
Waist (cm)						
Women	83.2 ± 9.9	82.2 ± 10.2	83.9 ± 9.6	85.2 ± 9.5	85.4 ± 8.9	<0.001
Men	88.0 ± 9.8	87.5 ± 10.4	88.3 ± 9.2	89.6 ± 9.0	85.6 ± 8.4	0.026
Systolic blood pressure (mmHg)	134 ± 21	130 ± 19	137 ± 20	147 ± 22	158 ± 26	<0.001
Diastolic blood pressure (mmHg)	77 ± 11	77 ± 11	77 ± 11	78 ± 12	80 ± 12	0.193
A1C (%)	7.75 ± 1.85	7.69 ± 1.88	7.78 ± 1.83	7.96 ± 1.81	7.65 ± 1.69	0.080
Fasting plasma glucose [mmol/l (mg/dl)]	8.80 ± 3.35 (158.6 ± 60.4)	8.72 ± 3.14 (157.1 ± 56.6)	8.86 ± 3.44 (159.6 ± 62.0)	8.96 ± 3.90 (161.4 ± 70.3)	8.58 ± 3.90 (154.6 ± 70.3)	0.091
Total cholesterol [mmol/l (mg/dl)]	5.37 ± 1.17 (207.7 ± 45.2)	5.28 ± 1.14 (204.2 ± 44.1)	5.43 ± 1.14 (210.0 ± 44.1)	5.58 ± 1.25 (215.8 ± 48.3)	5.91 ± 1.71 (228.5 ± 66.1)	<0.001
HDL cholesterol [mmol/l (mg/dl)]	1.27 ± 0.36 (49.1 ± 13.9)	1.29 ± 0.36 (49.9 ± 13.9)	1.27 ± 0.36 (49.1 ± 13.9)	1.18 ± 0.37 (45.6 ± 14.3)	1.18 ± 0.39 (45.6 ± 15.1)	<0.001
LDL cholesterol [mmol/l (mg/dl)]	3.35 ± 0.96 (129.5 ± 37.1)	3.27 ± 0.92 (126.5 ± 35.6)	3.40 ± 0.97 (131.5 ± 37.5)	3.46 ± 1.01 (133.8 ± 39.1)	3.69 ± 1.39 (142.7 ± 53.8)	<0.001
Triglycerides [mmol/l (mg/dl)]	1.33 (0.93–2.01); 117.7 (82.3–177.9)	1.23 (0.86–1.87); 108.8 (76.1–165.5)	1.37 (0.96–2.03); 121.2 (85.0–179.6)	1.77 (1.21–2.60); 156.6 (107.1–230.1)	1.84 (1.14–2.55); 162.8 (100.9–225.7)	<0.001
Serum creatinine [μmol/l (mg/dl)]	73 (61–89); 0.83 (0.69–1.01)	61 (54–72); 0.69 (0.61–0.81)	83 (72–93); 0.94 (0.81–1.05)	123 (101–142); 1.39 (1.14–1.61)	221 (195–259); 2.5 (2.21–2.93)	<0.001
Urinary albumin excretion (mg/24 h)	17 (9–77)	13 (8–37)	19 (9–72)	146 (30–923)	1,674 (521–3,337)	<0.001
Spot urinary ACR (mg/mmol)	1.74 (0.75–7.66)	1.36 (0.68–3.92)	1.85 (0.77–8.65)	13.44 (2.10–98.37)	222.58 (42.39–416.35)	<0.001
Microalbuminuria (%)	26.3	24.0	27.4	35.0	18.8	<0.001
Macroalbuminuria (%)	12.7	5.3	12.4	41.3	78.3	<0.001
eGFR (ml/min per 1.73 m^2)	91 (74–108)	107 (99–120)	79 (71–85)	50 (41–55)	24 (20–26)	<0.001
Presence of retinopathy (%)	22.5	15.5	23.6	46.4	66.2	<0.001
Use of antihypertensive drugs (%)	48.3	36.6	54.2	79.0	87.3	<0.001
Use of RAAS inhibitors (%)*	37.8	27.7	42.5	68.7	53.5	<0.001
Use of lipid-lowering drugs (%)	22.3	18.0	22.4	39.6	47.9	<0.001

Data are means ± SD or median (interquartile range). Parameters were age and sex adjusted, except for age, sex, and smoking. *RAAS, including ACE inhibitors or angiotensin receptor antagonist

Table 2—*All-cause mortality and renal, cardiovascular, and composite end points in 4,421 Chinese type 2 diabetic patients without macrovascular disease and end-stage renal disease*

	Total cohort	eGFR (ml/min per 1.73 m^2)				*P* for trend
		≥90	60–89	30–59	15–29	
n	4,421	2,257	1,636	457	71	
All-cause mortality (%)	2.5 (2.0–2.9)	1.2 (0.8–1.7)	2.6 (1.9–3.4)	5.5 (3.3–7.6)	18.3 (9.1–27.5)	<0.001
Cardiovascular end points (%)	4.8 (4.2–5.5)	2.6 (2.0–3.3)	5.4 (4.3–6.5)	10.3 (7.5–13.1)	25.4 (15.0–35.7)	<0.001
Renal end points (%)	4.8 (4.1–5.4)	1.7 (1.1–2.2)	3.0 (2.1–3.8)	16.5 (12.9–20.1)	68.2 (56.6–79.7)	<0.001
Composite end points (%)	9.6 (8.7–10.5)	5.0 (4.1–6.0)	9.0 (7.6–10.5)	23.9 (19.8–28.0)	75.8 (65.1–86.4)	<0.001

Data are percent (95% CI). Cardiovascular end points were defined as hospitalizations due to ischemic heart disease, congestive heart failure, stroke, and revascularization procedures. Renal end points were defined as reduction in eGFR by >50% or progression to eGFR <15 ml/min per 1.73 m^2 (stage 5) or renal dialysis or death secondary to renal causes. Composite end points were that of all-cause mortality and cardiovascular and renal end points.

heavy ketonuria (≥3), or continuous requirement of insulin within 1 year of diagnosis (9), were excluded. Informed consent was obtained from all patients for data analysis and research purpose at the time of assessment. The study was approved by the Chinese University of Hong Kong Clinical Research Ethics Committee.

Apart from documentation of demographic data and clinical assessment of diabetes complications, fasting blood samples were taken for measurement of plasma glucose, HbA_{1c} (A1C), lipid profile (total cholesterol, HDL cholesterol, and triglycerides and calculated LDL cholesterol), and renal and liver functions. All patients had at least two urinary collections: a sterile, random spot-urine sample was used to measure the albumin-to-creatinine ratio (ACR) followed by a timed collection (4 or 24 h) for measurement of ACR and albumin excretion rate. Definition of albuminuria was based on the mean value of ACR from both the timed and spot-urinary samples. Normoalbuminuria was defined as a mean ACR ≤3.5 mg/mmol, microalbuminuria ACR between 3.5 and 25 mg/mmol, and macroalbuminuria ≥25 mg/mmol (10). Details of laboratory assays were reported previously (11). Albuminuria was defined as the presence of either micro- or macroalbuminuria. Renal function was assessed by serum creatinine and eGFR (expressed in ml/min per 1.73 m^2) and as calculated using the abbreviated Modification of Diet in Renal Disease formula (12): GFR = $186 \times [S_{CR} \times 0.011]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742, \text{if female}]$, where S_{CR} was serum creatinine expressed as μmol/l. Renal function was graded according to the Kidney Disease Outcomes Quality Initiative guidelines: stage 1, ≥90 ml/min per 1.73 m^2; stage 2, 60–89 ml/min per 1.73 m^2; stage 3, 30–59 ml/min per 1.73 m^2; stage 4, 15–29 ml/min per 1.73 m^2; and stage 5, <15 ml/min per 1.73 m^2 (13).

Outcome measures

All clinical end points were censored on 31 December 2000. Mortality data were obtained from the Hong Kong Death Registry and ascertained by review of case notes. Cardiovascular end points were defined as hospitalizations due to ischemic heart disease, congestive heart failure, stroke, and revascularization procedures (coronary arterial bypass grafting, percutaneous transluminal coronary angioplasty, or aorto-femoral bypass). Renal end points were defined as a reduction in eGFR by >50% or progression to eGFR <15 ml/min per 1.73 m^2 (stage 5) or renal dialysis or death secondary to renal causes. Composite end points included all-cause mortality and cardiovascular and renal end points.

Statistical analysis

The analysis was performed using SPSS (version 10.1) statistical package. Triglycerides, S_{CR}, ACR, and albumin excretion rate were logarithmically transformed due to skewed distributions. All data are expressed as means ± SD or median (interquartile range), as appropriate. The Student's *t* test or ANCOVA was used for between-group comparisons for continuous variables and the χ^2 test for categorical variables. Kaplan-Meier analysis was used to estimate the cumulative incidence of death and cardiorenal end points, and the log-rank test was used to demonstrate trend for survival. Multivariate Cox regression model was used to estimate the hazard ratio (HR) with 95% CI for clinical end points, with assumption that effects of the variables on survival are constant. A *P* value <0.05 (two tailed) was considered to be significant.

RESULTS

— Between 1995 and 2000, 5,426 consecutive patients underwent complication assessment. Patients with type 1 diabetes ($n = 252$), macrovascular complications at baseline ($n = 731$), and dialysis or stage 5 renal function ($n = 22$) were excluded. A total of 4,421 type 2 diabetic patients were included in the final analysis. The median follow-up time was 39.4 months (interquartile range 20.3–55).

Table 1 compares the clinical and metabolic parameters of patients divided according to the stages of eGFR (13). In the whole cohort, the systolic and diastolic blood pressure was 134 ± 21 and 77 ± 11 mmHg, respectively, and mean A1C was 7.75 ± 1.85%, with 59.1% of patients having an A1C >7%. At recruitment, only 51.1% had normal renal function (stage 1: eGFR ≥90 ml/min per 1.73 m^2) and 37% had mild renal impairment with stage 2 renal function (60–89 ml/min per 1.73 m^2). Higher proportions of patients with stages 2–4 renal function were male subjects and smokers than those with stage 1 renal function. They also had longer duration of disease; had higher BMI, waist circumference, and blood pressure; had worse glycemic and lipid control; and were more likely to have diabetes complications, including retinopathy, than subjects with normal renal function. The use of medications including RAAS inhibitors (ACE inhibitors or angiotensin receptor blocker) and lipid-lowering drugs increased with declining renal function. For RAAS inhibitors, >90% were treated with ACE inhibitors. Its usage increased from 27.7% in patients with stage 1 renal function to 68.7% in patients with stage 3 renal function but dropped to 53.5% in patients with stage 4 renal function.

Table 2 summarizes the rates of all-cause mortality and cardiovascular, renal,

Table 3—*Adjusted HRs for all-cause mortality and cardiovascular, renal, and composite end point outcomes among 4,421 Chinese type 2 diabetic patients without macrovascular disease and end-stage renal disease at baseline*

	eGFR (ml/min per 1.73 m^2)				
	≥90*	60–89	30–59	15–29	*P*
Median eGFR (ml/min per 1.73 m^2)	107	78	50	24	
Cardiovascular end points					
Age and sex adjusted	1.00	1.18 (0.83–1.68)	1.66 (1.09–2.54)	5.15 (2.94–9.00)	<0.001
Multivariate-adjusted model 1	1.00	1.04 (0.72–1.48)	1.12 (0.71–1.76)	3.82 (2.13–6.86)	<0.001
Multivariate-adjusted model 2	1.00	1.04 (0.73–1.50)	1.05 (0.66–1.68)	3.23 (1.74–5.99)	<0.001
All-cause mortality					
Age and sex adjusted	1.00	1.20 (0.72–1.99)	1.83 (1.01–3.31)	8.34 (4.13–16.8)	<0.001
Multivariate-adjusted model 1	1.00	1.25 (0.73–2.14)	2.25 (1.12–4.52)	9.7 (4.47–21.1)	<0.001
Multivariate-adjusted model 2	1.00	1.27 (0.74–2.17)	2.34 (1.16–4.70)	9.82 (4.53–21.0)	<0.001
Renal end points					
Age and sex adjusted	1.00	1.91 (1.23–2.98)	11.4 (7.58–17.1)	120.9 (75.8–192.7)	<0.001
Multivariate-adjusted model 1	1.00	1.45 (0.92–2.28)	4.90 (3.08–7.80)	45.9 (26.5–79.6)	<0.001
Multivariate-adjusted model 2	1.00	1.36 (0.83–2.16)	3.34 (2.06–5.42)	27.3 (15.6–47.8)	<0.001
Composite end points					
Crude	1.00	1.28 (0.98–1.69)	2.93 (2.14–3.99)	15.2 (10.5–22.2)	<0.001
Multivariate-adjusted model 1	1.00	1.13 (0.85–1.50)	1.85 (1.32–2.60)	9.98 (6.68–14.9)	<0.001
Multivariate-adjusted model 2	1.00	1.13 (0.85–1.49)	1.63 (1.15–2.30)	7.54 (4.97–11.4)	<0.001

Model 1 adjusted for age, sex, duration of diabetes, smoking habit, BMI, systolic blood pressure, A1C, HDL and LDL cholesterol, triglycerides, diabetic retinopathy at baseline, and treatment with ACE inhibitors or angiotensin receptor blockers. Model 2 adjusted for albuminuria in addition to covariates as in model 1. *This group served as the reference group.

and composite (death, cardiovascular and renal end points) end points according to different categories of eGFR. For all-cause mortality, the rate increased from 1.2% (95% CI 0.8–1.7) to 18.3% (9.1–27.5) (*P* for trend <0.001) as renal function deteriorated from stage 1 to stage 4. The event rate of new cardiovascular end points also increased from 2.6% (2.0–3.3) to 25.3% (15.0–35.7) (*P* for trend <0.001) in patients with stage 1 and stage 4 renal function, respectively. The rate of renal end points followed the same trend (Table 2). During the median follow-up period of 39.4 months, 75.8% (65.1–86.4) of subjects with stage 4 renal function developed one or more of the clinical end points.

We further analyzed the independent relationship between stages of renal function and clinical outcomes, adjusting for conventional risk factors including age, sex, duration of diabetes, smoking status, BMI, systolic blood pressure, A1C, HDL cholesterol, LDL cholesterol, triglycerides, diabetic retinopathy, and albuminuria, as well as use of RAAS inhibitors. Table 3 shows the crude and multivariate-adjusted HR of all-cause mortality and cardiovascular and renal end points associated with different stages of renal function. Crude HRs of all-cause mortality and cardiovascular and renal end points increased with progressive decline in renal function. Compared with subjects with normal eGFR, subjects with stage 4 renal function had a 9.7-fold increase in HR for all-cause mortality and a 3.8-fold increased risk of developing cardiovascular end points after adjustment for all conventional cardiovascular risk factors, including albuminuria (Table 3).

Table 4 shows the additive effects of renal function and albuminuria in predicting clinical end points after adjustment of other factors. For cardiovascular and composite end points, the risk associations increased with declining renal function, while albuminuira conferred additional risk within the same stage of renal function. For example, patients with stage 1 renal function and albuminuira had similar cardiovascular event rates as those with stage 2 renal function but without albuminuira. In patients with stage 3 and 4 renal function, this additive effect was less evident (Table 4). Figure 1 shows the cumulative incidence of cardiovascular end points in patients stratified by different stages of renal function and albuminuric status. The survival curves separate early and continue to diverge throughout the follow-up period (log-rank test $P < 0.001$). For renal end points, there was also a progressive increase in risk associations with declining renal function (Table 3), which was mainly observed in the albuminuric group (Table 4).

CONCLUSIONS — In this prospective study, Chinese type 2 diabetic patients with reduced renal function were at high risk of early mortality and developing cardiovascular and renal end points. eGFR remained an independent and significant predictor after adjustment for conventional risk factors including age, sex, duration of diabetes, smoking, obesity, blood pressure, and glycemic and lipid control, as well as presence of diabetic retinopathy. More importantly, eGFR was an independent prognostic factor after adjusting for albuminuria and use of RAAS inhibitors. Compared with patients with stage 1 renal function and normoalbuminuria, stage 4 renal function and albuminuria at baseline conferred a 16-fold increased risk for composite end points, including all-cause mortality and cardiorenal end points.

Albuminuria is now considered a renal expression of endothelial dysfunction (14) and a powerful predictor for all-cause mortality, end-stage renal disease, and cardiovascular events (15,16). In a smaller set of patients recruited in the early phase of this cohort, we have reported the prognostic effect of albuminuria and protective role of RAAS inhibition (11). In this analysis, both eGFR and albuminuria

conferred independent risk for cardiovascular end points on both multivariate analysis (Table 3) and after stratification by albuminuric status (Fig. 1 and Table 4).

The risk association between CKD, defined as GFR <60 ml/min per 1.73 m^2, and adverse clinical outcomes had been reported in both epidemiological (1) and interventional (2,3) studies. Using pooled data from community-based studies, compared with subjects with preserved renal function, adjusted HRs for cardiovascular outcomes and all-cause mortality increased by 1.35 and 1.32, respectively, in patients with CKD (17). Despite their high risk for cardiorenal complications, there is a paucity of data on the impact of CKD on CVD in type 2 diabetic patients (18). In the U.S. Medicare population, the death rate of diabetic patients with CKD was 32%, mainly due to CVD, during a 2-year study period (19). Although this study involved 726,000 elderly Medicare enrollees carrying a clinical diagnosis of CKD, it was a telephone survey with self-reported prevalence of diabetes. Besides, important confounding factors including albuminuric status, blood pressure, and metabolic control were not adjusted for. In our prospective cohort with detailed documentation of risk factors at baseline, we have clearly demonstrated the inverse relationships between eGFR and clinical outcomes including all-cause mortality and cardiovascular and renal end points. This risk association was evident even in subjects with mild to moderate renal impairment, i.e., stage 2 CKD with eGFR between 60 and 89 ml/min per 1.72 m^2. Taken together, our findings are in agreement with the recent recommendation of the American Diabetes Association (20) to include albuminuria and renal function, as estimated by eGFR, to assess cardiovascular risk in diabetic patients.

Cardiovascular and renal complications share common risk factors such as blood pressure, blood lipids, and glycemic control. Thus, the onset of CKD may indicate long duration and increased severity of these risk factors. This is evidenced by the inverse correlation between rates of diabetic retinopathy and stages of eGFR in our study. Besides, chronic inflammation may have a causative role for diabetes and associated complications (21,22). Apart from protein-energy malnutrition, which increases risk of sepsis, patients with CKD have retention of urotoxins, increased secretion and accumulation of cytokines such as C-

Table 4—*Multivariate-adjusted HRs (95% CI) of clinical end points in patients with type 2 diabetes stratified according to eGFR and albuminuria*

	eGFR (ml/min per 1.73 m^2)			
	≥90	60–89	30–59	15–29
Cardiovascular end points				
No albuminuria [HR (95% CI), *P* value]	1.00 (referent)	1.00 (0.59–1.72), *P* = 0.991	3.05 (1.51–6.15), *P* = 0.002	Not enough subjects
Albuminuria [HR (95% CI), *P* value]	1.85 (1.07–3.18), *P* = 0.03	1.89 (1.13–3.16), *P* = 0.016	1.35 (0.74–2.49), *P* = 0.33	5.46 (2.78–10.7), *P* < 0.001
Renal end points				
No albuminuria [HR (95% CI), *P* value]	1.00 (referent)	0.83 (0.35–1.96), *P* = 0.67	0.82 (0.12–6.22), *P* = 0.85	Not enough subjects
Albuminuria [HR (95% CI), *P* value]	2.62 (1.31–5.26), *P* = 0.007	4.13 (2.19–7.78), *P* < 0.001	10.27 (5.52–19.11), *P* < 0.001	90.29 (45.80–178.03), *P* < 0.001
Composite end points*				
No albuminuria [HR (95% CI), *P* value]	1.00 (referent)	1.21 (0.80–1.84), *P* = 0.36	2.98 (1.57–5.64), *P* = 0.001	Not enough subjects
Albuminuria [HR (95% CI), *P* value]	2.34 (1.58–3.50), *P* < 0.001	2.43 (1.64–3.59), *P* < 0.001	3.15 (2.06–4.82), *P* < 0.001	16.2 (10.0–26.0), *P* < 0.001

*Composite end points included all-cause mortality and cardiovascular and renal end points. Covariates included age, sex, duration of diabetes, smoking, BMI, systolic blood pressure, HDL and LDL cholesterol, triglycerides, A1C, RAAS inhibition and prevalent retinopathy.

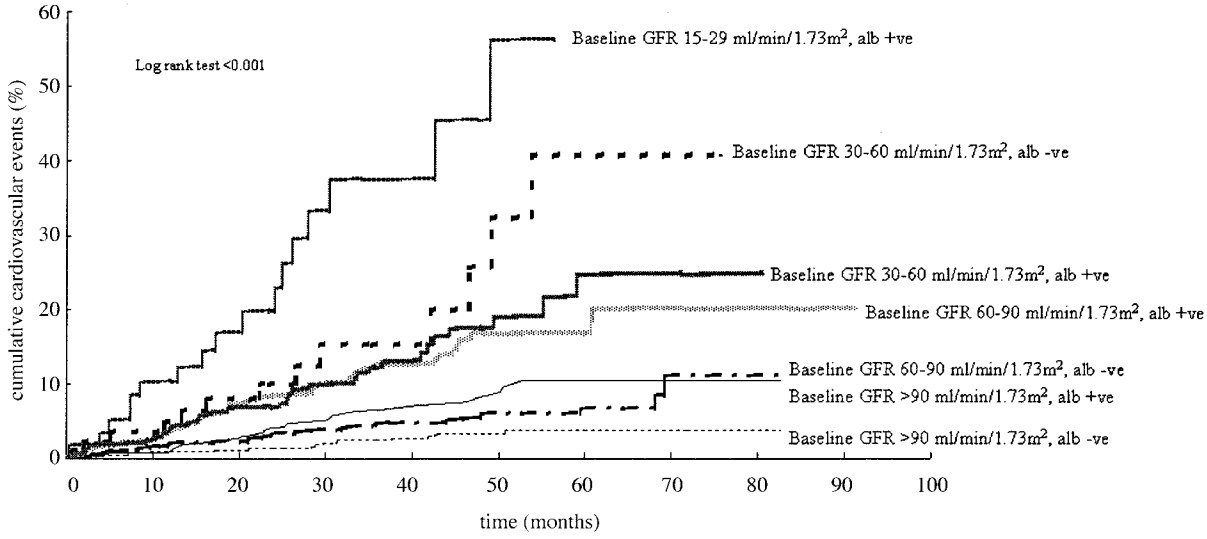

Figure 1—*Kaplan-Meier survival curves for new cardiovascular events in 4,421 Chinese type 2 diabetic patients without macrovascular disease and end-stage renal disease (estimated GFR <15 ml/min per 1.73 m²) at baseline categorized according to GFR estimated by the modified Modification of Diet in Renal Disease equation and albuminuric status.*

reactive protein, tumor necrosis factor-α, and tumor growth factor-β. This abnormal metabolic mileau can lead to chronic inflammation and increased oxidative stress, resulting in atherosclerosis (23,24). The latter can be further accelerated by CKD-associated anemia and abnormal bone metabolism, resulting in left ventricular hypertrophy and vascular calcification (17,25,26).

In agreement with other authors (27), the risk association between eGFR and renal end points was mainly observed in patients with albuminuiria (Table 4). However, treatment effects including use of RAAS inhibitors might have confounded the definition of the latter. In the multivariate analysis, eGFR remained an independent risk factor for renal end points when RAAS inhibition and albuminuria were included. Apart from albuminuria, other factors such as atherosclerosis, inflammation, and oxidative stress that worsen with deteriorating renal function especially in diabetic patients may set up a vicious cycle and contribute to the progressive decline in renal function (23,24).

Our study has several limitations. First, our study cohort was hospital based, making selection bias a potential confounding factor. Second, the use of baseline values as predictors might underestimate risk association secondary to regression dilution during the follow-up period. On the other hand, the fact that a single biochemical value was predictive of outcome further emphasizes their usefulness as a clinical tool in identifying high-risk patients for surveillance or intervention. Third, we only adjusted for drug use at baseline but not during study period. Often, these drugs are prescribed to patients at high risk or with complications as evidenced by the increased proportion of patients with CKD receiving RAAS inhibitors. This might lead to a paradoxical association between the use of these drugs and adverse clinical outcome in an observational study. Last, we have not examined the prognostic value of novel cardiovascular risk factors such as C-reactive protein or homocysteine (23,24), which are not routinely measured in our daily clinical practice.

In conclusion, in Chinese patients with type 2 diabetes, reduction in eGFR, even of mild degree, was associated with increased risk of all-cause mortality and cardiovascular and renal end points. These findings highlight the importance of regular surveillance and monitoring of renal function for intensive therapy (28).

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