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ORIGINAL ARTICLE

Increased risk of cardiovascular events and mortality among non-diabetic chronic kidney disease patients with hypertensive nephropathy: the Gonryo study

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To examine the clinical significance of hypertensive nephropathy (HN) among non-diabetic chronic kidney disease (CKD) patients. The study comprised 2692 CKD patients recruited from 11 outpatient nephrology clinics; these included 1306 patients with primary renal disease (PRD), 458 patients with HN, 283 patients with diabetic nephropathy (DN) and 645 patients with other nephropathies (ONs). All patients fulfilled the criteria of CKD, with a persistent low estimated glomerular filtration rate (eGFR) $<60\,ml\,min^{-1}$ per $1.73\,m^2$ or proteinuria as determined by a urine dipstick test. The risk factors for cardiovascular disease (CVD), such as ischemic heart disease, congestive heart failure and stroke; all-cause mortality; and progression to end-stage renal failure (dialysis induction) were analyzed using a Cox proportional hazards model in each group. During a mean follow-up period of 22.6 months from recruitment, 100 patients were lost to follow-up and 192 patients began chronic dialysis therapy. A total of 115 CVD events occurred (stroke in 37 cases), and 44 patients died. Regarding CVD events and death, there were significant differences in the hazard ratios (HRs) for the groups of patients with different underlying renal diseases as determined by both univariate and multivariate analysis adjusted for confounding factors including estimated glomerular filtration rate: PRD, 1.0 (reference); HN, 3.33 (95% confidence interval, 1.82–6.09); DN, 5.93 (2.80–12.52); and ON, 2.22 (1.22–4.05). However, there were no differences in the hazard ratio for dialysis induction for the groups of patients with different underlying renal diseases. HN is associated with an increased risk of CVD events and death among non-diabetic CKD patients, which highlights the clinical significance of HN.
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INTRODUCTION

Chronic kidney disease (CKD)[1] is a well-known independent risk factor for cardiovascular disease (CVD), including stroke, progression to end-stage renal failure and all-cause mortality in the general population.[2–8]

The relation between excess CVD morbidity and mortality, and decreased kidney function has been well demonstrated in diabetic patients[9,10] in specific sub-populations with preexisting heart disease,[11,12] hypertension[13] and dislipidemia,[14] and in the elderly.[15]

Patients with primary or secondary kidney diseases are exposed to several unique factors that increase the frequency of CVD events. These factors include hyperlipidemia and coagulopathy due to nephritic syndrome, systemic inflammation-associated vasculitides, underlying collagen or infectious disease, and the use of therapeutic agents such as steroids.[16–18] Even though patients with hypertensive nephropathy (HN, nephrosclerosis) are believed to be at high risk for progression to kidney failure,[19] the impact of HN on the frequency of CVD events compared with the impact of other nephropathies (ONs) has not been clearly demonstrated.

Accordingly, in terms of risk stratification of patients, it is crucially important to clarify the clinical outcomes of CKD with respect to the underlying renal diseases, especially for CKD cases that are not the result of diabetes. Only a few reports have examined this issue, including our preliminary report.[20–22]

The present study aimed to address this issue in a cohort of patients from nephrology clinics.

METHODS

Study population (Gonryo CKD cohort)

The Gonryo CKD project is a prospective survey of the patient characteristics and outcomes of individuals who visit outpatient nephrology clinics in the Miyagi Prefecture (Northeast area of Japan), the details of which have been

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reported elsewhere.[22] Eleven affiliated hospitals with Tohoku University, including one university hospital (Tohoku University Hospital), are participating in the project. Patient registration was originally requested for all patients who provided informed consent for participation in the project. The study protocol was approved by the institutional review board of the Tohoku University School of Medicine and by the respective participating hospitals.

Registration was conducted from May 2006 to November 2008, and 4015 patients were registered. Among the original registered patients, certain subjects were excluded from the present analysis—150 cases lacking data on serum creatinine levels and 241 cases with unknown underlying renal diseases. Among patients with essential hypertension and estimated glomerular filtration rates (eGFRs) above 60 ml min^{-1} per 1.73 m^2, those who did not have positive proteinuria findings at registration (n=836) and those lacking urinary testing results (n=96) were excluded. As a result, 2692 patients with complete CKD criteria were selected[1] and were subjected to analysis.

Patient classification and primary outcomes

Patients were classified according to one of four underlying renal diseases diagnosed by the attending physicians at the participating hospitals (Table 1): primary renal disease (PRD), defined by primary glomerulonephritis and tubulointerstitial nephritis, including biopsy-proven cases (81%); HN, defined by a history of hypertension and the absence of other possible disorders, including cases of biopsy-proven nephrosclerosis (20.8%); diabetic nephropathy, defined by a history of diabetes accompanying nephropathy and the absence of other possible renal disorders or presenting with nephropathy with diabetic retinopathy and the absence of other possible renal disorders, including biopsy-proven diabetic nephropathy (24.9%); and ONs, defined by ONs not included in the other three groups, including biopsy-proven cases (24.9%). The HN cases included in the present classification were in those patients who had an eGFR below 60 ml min^{-1} per 1.73 m^2 or positive proteinuria as determined by a dipstick test.

The primary outcomes of this survey included CVD events, such as angina pectoris, acute myocardial infarction, congestive heart failure, stroke (cerebral bleeding and infarction), and all-cause death before commencement of chronic dialysis therapy. Outcomes within 12 months after registration were surveyed using the medical records of the hospitals, death certificates and interviews with attending physicians at the time of annual checkups. An episode of CVD was defined as disease of the circulatory system (International Classification of Disease, 10th revision: I00 to I99), and the number of patients with angina pectoris or acute myocardial infarction included those who had received coronary stenting, angioplasty or bypass surgery, or who had a definite clinical course of acute myocardial infarction. In patients with congestive heart failure, only those who were admitted for treatment were counted. Diagnosis of stroke and stroke subtypes was based on the Classification of Cerebrovascular Diseases III by the National Institute of Neurological Disorders and Stroke,[23] and only cases confirmed by computed tomography or magnetic resonance imaging of the brain were counted.

Table 1 Patient characteristics

	All	*PRD*	*ONs*	*HN*	*DN*
n	2.694	1.306	643	462	283
Age (years)	60.0 ± 16.2	55.7 ± 16.6	58.6 ± 15.7	70.3 ± 11.4	66.5 ± 12.6
Gender (male)	1441 (53.5%)	716 (54.8%)	275 (42.8%)	262 (56.7%)	188 (66.4%)
BMI	23.5 ± 3.8	23.4 ± 3.8	22.9 ± 3.7	24.2 ± 3.8	24.1 ± 3.8
Blood pressure (mmHg)					
Systolic	130.95 ± 16.2	129.21 ± 15.1	129.33 ± 15.8	134.68 ± 17.4	136.64 ± 17.5
Diastolic	76.7 ± 10.9	77.3 ± 10.4	76.7 ± 10.7	76.4 ± 11.8	74.0 ± 11.6
CKD stage (%)					
Stage 1+2	40.3	49.1	47.4	17.7	20.4
Stage 3	37.6	35.7	31.1	57.6	28.3
Stage 4	13.4	10.3	14.5	15.8	21.6
Stage 5	8.7	4.9	7.0	8.9	29.7
Comorbidities (%)					
Cardiac disease	12.8	7.5	12.3	21.2	24.7
Stroke	6.5	3.5	5.9	11.9	12.7
Diabetes	27.4	15.5	18.0	34.2	100.0
Hypertension	77.1	72.8	70.6	93.7	89.4
Hyperlipidemia	42.6	44.6	36.8	42.2	51.6
Pharmacotherapy (%)					
ARB/ACEI	62.7	62.1	52.6	70.1	76.3
Statin	34.7	36.1	30.0	32.3	43.1
ESA	6.5	3.6	4.8	7.8	21.9
Steroid	25.3	32.9	36.2	2.8	2.1
Proteinuria (%)	49.6	47.3	41.2	49.8	78.9
Hemoglobin (g dl^{-1})	12.8 ± 2.1	13.2 ± 1.9	12.6 ± 2.0	12.7 ± 2.1	11.6 ± 2.3
Total cholesterol (mg dl^{-1})	197.6 ± 38.7	198.7 ± 35.9	203.5 ± 41.3	190.99 ± 39.9	190.4 ± 41.4
Smoker (%)	16.2	15.8	14.6	16.2	21.6
Renal biopsy proven (%)	62.7	81.0	53.5	20.8	24.9
					mean ± s.d.

Abbreviations: ARB/ACEI, angiotensin receptor blocker/angiotensin-converting enzyme inhibitor; BMI, body mass index; DN, diabetic nephropathy; ESA, erythropoiesis stimulating agent; HN, hypertensive nephropathy; ONs, other nephropathies; PRD, primary renal disease.

Data collection

Serum creatinine levels were measured using the enzyme assay method. Kidney function was determined using the formula for eGFR for Japanese individuals.[24] Positive results for urinary protein were identified using the dipstick test for spot urine or an autoanalyzer. Patients were considered to be positive for macroalbuminuria when the dipstick result was positive or greater, corresponding to a urinary protein level $>30\,mg\,dl^{-1}$.[25] Blood pressure was measured at local medical centers in outpatient clinics using an automatic sphygmomanometer based on the Korotkoff sound technique with the subject in a seated position. Information on medications at baseline and each patient's history of CVD, diabetes mellitus, hypertension and hyperuricemia were obtained from the medical records or from the results of blood examinations at registration. Subjects receiving lipid-lowering drugs or displaying serum cholesterol levels $>220\,mg\,dl^{-1}$ were considered to have hypercholesterolemia. Subjects with fasting glucose levels $>126\,mg\,dl^{-1}$ or non-fasting glucose levels $>200\,mg\,dl^{-1}$ or who used insulin or oral antihyperglycemic drugs were defined as having diabetes mellitus.

Data analysis

Associations between primary outcomes and either baseline kidney function or underlying renal disease were examined using Cox proportional hazard model analysis adjusted for confounding factors.

Data are shown as means ± s.d. A *P*-value <0.05 indicated statistical significance. All statistical analyses were conducted using STATA version 10.0 software (StataCorp LP, College Station, TX, USA).

RESULTS

During an observation period of 22.6 ± 11.9 months, 100 patients were lost because of a switch to other medical services or to the patient quitting due to social reasons, and the follow-up of 192 patients was ended because of the initiation of maintenance dialysis therapy. There were 115 cases of CVD events (37 cases of stroke) and 44 cases of all-cause death (Table 2).

Table 2 Number of events

CKD stage	*CVD*	*Stroke*	*Death*	*ESRD*
Primary renal disease				
CKD1+2	2	1	1	—
CKD3	7	2	6	2
CKD4	2	1	2	8
CKD5	—	—	1	40
Hypertensive nephropathy				
CKD1+2	4	—	1	1
CKD3	12	8	6	—
CKD4	7	4	3	6
CKD5	3	2	3	24
Diabetic nephropathy				
CKD1+2	4	3	—	1
CKD3	7	1	3	1
CKD4	8	—	5	18
CKD5	10	3	4	54
Other nephropathies				
CKD1+2	2	7	2	—
CKD3	3	4	3	3
CKD4	6	1	4	9
CKD5	1	—	—	25

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; ESRD, end-stage renal disease (dialysis induction).

In terms of CVD events and all-cause mortality, significant increases in hazard ratios were seen with increasing CKD stage using univariate analysis (Figure 1); however, these trends disappeared after multivariate adjustment (Table 3a). Significant differences in hazard ratios were seen with respect to underlying renal diseases using univariate analysis, and these differences were significant even after adjusting for confounding factors including eGFR (Table 3b).

Dialysis was started only for those patients who had a CKD stage 4 to 5 at the time of entry (Figure 2; CKD1+2: 0.2%, CKD3: 0.6%,

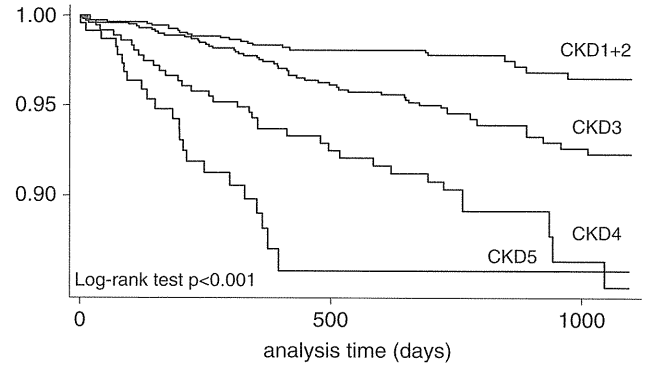

Figure 1 Event-free survival for cardiac disease, apoplexy and all cause of death for patients at different chronic kidney disease (CKD) stages.

Table 3a Risk for endpoints of CVD, stroke and death by CKD stage in all patients

				Univariate analysis		*Multivariate analysis*[a]	
CKD stage	*CVD*	*Stroke*	*Death*	*HR*	*95% CI*	*HR*	*95% CI*
CKD 1+2	12	11	4	1.00		1.00	
CKD 3	29	15	18	2.21	1.37–3.55	1.06	0.64–1.77
CKD 4	23	6	14	4.39	2.62–7.36	1.76	1.00–3.12
CKD 5	14	5	8	7.47	4.22–13.24	2.29	1.17–4.49

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease (such as angina pectoris, acute myocardial infarction and congestive heart failure); HR, hazard ratio.
[a]Adjusted for age, gender, hemoglobin, positive for proteinuria, systolic blood pressure, body mass index, presence of hyperlipidemia, presence of diabetes, prescription of steroid, smoker, history of cardiovascular disease or stroke, use of RAS (renin–angiotensin system) inhibitors.

Table 3b Risk for endpoints of CVD, stroke and death by underlying renal diseases in all patients

				Univariate analysis		*Multivariate analysis*[a]	
Underlying renal disease	*CVD*	*Stroke*	*Death*	*HR*	*95% CI*	*HR*	*95% CI*
PRD	11	4	10	1.00		1.00	
ONs	12	12	9	3.17	1.78–5.62	2.22	1.22–4.05
HN	26	14	13	7.12	4.18–12.14	3.33	1.82–6.09
DN	29	7	12	10.88	6.29–18.84	5.93	2.80–12.52

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DN, diabetic nephropathy; HN, hypertensive nephropathy; HR, hazard ratio; ONs, other nephropathies; PRD, primary renal disease.
[a]Adjusted for age, gender, hemoglobin, positive for proteinuria, systolic blood pressure, body mass index, presence of hyperlipidemia, presence of diabetes, prescription of steroid, smoker, history of cardiovascular disease or stroke, use of RAS (renin–angiotensin system) inhibitors and estimated GFR (glomerular filtration rate).

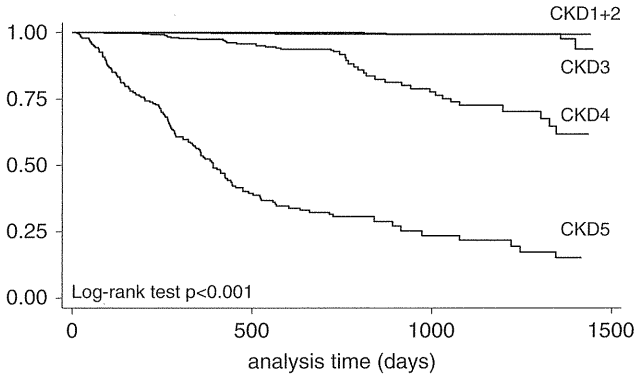

Figure 2 Event-free survival for progression to end-stage renal disease (dialysis induction) for patients at different chronic kidney disease (CKD) stages.

Table 4 Risk of progression to ESRD (dialysis induction) by underlying renal disease

Underlying		*Univariate analysis*		*Multivariate analysis*[a]	
Renal disease	*ESRD*	*HR*	*95% CI*	*HR*	*95% CI*
PRD	50	1.00		1.00	
ONs	37	1.43	0.94–2.19	1.11	0.70–1.76
HN	31	1.09	0.70–1.71	1.13	0.69–1.88
DN	74	5.25	3.66–7.53	1.25	0.68–2.28

Abbreviations: CI, confidence interval; DN, diabetic nephropathy; ESRD, end-stage renal disease; HN, hypertensive nephropathy; HR, hazard ratio; ONs, other nephropathies; PRD, primary renal disease.
[a]Adjusted for age, gender, hemoglobin, positive for proteinuria, systolic blood pressure, body mass index, presence of hyperlipidemia, presence of diabetes, prescription of steroid, smoker, history of cardiovascular disease or stroke, use of RAS (renin–angiotensin system) inhibitors and estimated GFR (glomerular filtration rate).

CKD4: 11.4%, CKD5: 61.1%), and no significant differences were observed with respect to underlying renal diseases after adjusting for confounding factors, including eGFR (Table 4).

DISCUSSION

This study aimed to clarify the impact of underlying renal diseases on CVD events and death before the initiation of dialysis treatment by analyzing the outcomes of 2692 CKD outpatients from 11 nephrology clinics. After 22.6 months of follow-up, there was a significant difference in the frequencies of CVD events and mortality among groups of patients with different underlying renal diseases, even after adjusting for possible confounding factors including kidney function. These findings showed that patients with HN represent a high-risk group, except for diabetic nephropathy patients, followed by ONs and PRD. In contrast, in terms of chronic dialysis induction, no significant differences were observed based on underlying renal diseases.

Both traditional and non-traditional mechanisms underlie the increased risk of CVD among CKD patients. Traditional factors include hypertension, diabetes, hyperlipidemia and smoking, whereas non-traditional factors include specific factors related to the uremic milieu, such as fluid overload, calcium/phosphate abnormalities, anemia, malnutrition, enhanced inflammation and oxidative stress, and the accumulation of uremic toxins.[26–34] Therefore, subjects with vasculopathy demonstrated by traditional factors are thought to undergo accelerated vascular damage along with progression of the CKD stage. Hypertension is a predominant risk factor for CVD in the general population, and it is logical that long-standing exposure to pathological conditions such as hypertension may have resulted in an increased frequency of CVD and mortality among non-diabetic subjects with HN. Several factors could have contributed to the better CVD outcomes in the group with PRD. First, half of the patients with PRD had immunoglobulin A nephropathy; glucocorticoid therapy does not increase the risk of CVD for these patients.[34] Blood pressure was also more adequately controlled in these patients than in patients in the other groups (Table 1). In addition, prevalent vasculopathy was not predominant in pre-dialysis PRD patients, as has been indicated for pediatric patients.[35,36] These results indicate that CKD staging cannot be applied on its own to predict which subjects are at high risk of CVD without taking into account the type of underlying renal disease. These results also suggest that individuals with HN should be the primary targets of CVD prevention measures among non-diabetic CKD patients.

In contrast, the present study revealed that the differences among underlying renal diseases did not have any influence on the frequency of the induction of dialysis after adjusting for confounding factors, including eGFR. In addition, dialysis induction was limited to subjects with CKD5. This result may confirm the clinical notion that CKD5 is the primary criterion for dialysis induction, as recommended in published guidelines.[37–39]

In the present study, several clinical issues that might have biased the analytical results must be considered. First, because all of the included patients were recruited from nephrology clinics, our patient selection may have introduced a bias toward relatively better medical compliance among those patients with modifiable factors, including the uremic milieu and blood pressure. Second, among patients with hypertension or diabetes, patients who had presented with proteinuria before entry into the study and who had responded to medical treatment thereafter were excluded from the study unless their eGFR was $<60\,ml\,min^{-1}$ per $1.73\,m^2$. Thus, the patients with diabetes or HN included in the present study may have been relatively resistant to conventional therapies. This resistance may have made their outcomes relatively worse, even though we adjusted for positive findings for proteinuria. Finally, data on microalbuminuria were not available in the present study. Because the clinical significance of microalbuminuria has been well demonstrated, further study is needed to determine the effect of microalbuminuria in these patients.

In conclusion, the present study demonstrated that patients with HN are at increased risk of CVD events and death among non-diabetic CKD patients, which highlights the clinical significance of HN.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ORIGINAL ARTICLE

Different clinical outcomes for cardiovascular events and mortality in chronic kidney disease according to underlying renal disease: the Gonryo study

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Abstract

Purpose Chronic kidney disease (CKD) can result from a wide variety of diseases, but whether clinical outcomes differ in the same CKD stages according to the underlying renal disease remains unclear. Clarification of this issue is important for stratifying risk of cardiovascular disease (CVD) and death in patients before dialysis.

Patients and methods The study comprised 2,692 patients recruited from 11 outpatient nephrology clinics, classified by underlying disease of primary renal disease (PRD) ($n = 1{,}306$), hypertensive nephropathy (HN) ($n = 458$), diabetic nephropathy (DN) ($n = 283$), or other nephropathies (ON) ($n = 645$). Risks of events such as ischemic heart disease, congestive heart failure, stroke, and all-cause mortality within 12 months were examined by logistic regression analysis in each group.

Result During the 12-months' observation from recruitment, 200 cases were lost to follow-up, and 113 cases were introduced to chronic dialysis therapy. A total of 69 CVD events occurred (stroke in 27 cases), and 24 patients died. In total, increased odds ratios (OR) for the events by CKD stage (cf. CKD1 + 2: unadjusted) were CKD3, 1.29 [95% confidence interval (CI), 0.70–2.17]; CKD4, 2.73 (1.55–4.83); and CKD5, 4.66 (2.63–8.23). Regarding events in respective groups, no significant differences were seen by CKD stage except for the group with HN, but significant differences were seen by underlying diseases (cf. PRD: adjusted for confounding factors, including estimated glomerular filtration rate): HN, 2.57 (1.09–6.04); DN, 12.21 (3.90–38.20); and ON, 4.14 (1.93–8.89).

Conclusion Risk of CVD and mortality due to CKD needs to be stratified according to the underlying renal diseases.

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Keywords Chronic kidney disease · Cardiovascular disease · Nephritis · Hypertension · Diabetic nephropathy

Introduction

Chronic kidney disease (CKD) [1] is a well-known independent risk factor for cardiovascular disease (CVD), including stroke, progression to end-stage renal failure, and all-cause mortality in the general population [2–8]. CKD is thus a major public health and economic burden. Screening for CKD is thus recommended around the world [1] using estimated glomerular filtration rate (eGFR) and testing for urinary proteinuria. Conversely, excess CVD morbidity and mortality by decreased kidney function has been shown in specific subpopulations with pre-existing heart disease, e.g., myocardial infarction (MI), congestive heart failure (CHF) [9, 10], hypertension [11], diabetes [12], and the elderly [13]. Accordingly, CKD resulting from renal disorders associated with those underlying pathological conditions may thus contribute strongly to excess CVD events [14, 15].

In primary as well as systemic renal diseases, patients show increased atherogenic factors such as hyperlipidemia and coagulopathy due to proteinuria, systemic inflammation-associated vasculitides, collagen or infectious diseases, and administration of steroids. All these factors could potentially increase CVD risks [16–19] Nevertheless, as CKD can result from a wide variety of diseases [1], whether clinical outcomes within the same CKD stages differ according to the underlying renal disease has not been clearly addressed. As the prevalence of chronic glomerulonephritis, such as immunoglobulin (Ig)A nephritis, is known to vary by ethnic background and geographical area, clarification of this issue is crucially important with respect to risk stratification of CVD and death in patients before dialysis. However, only a limited number of reports examined this issue [20, 21]. The study presented here, therefore, aimed to address this issue in a cohort of nephrology clinics.

Patients and methods

Study population (Gonryo CKD cohort)

The Gonryo CKD project is a prospective survey of patient characteristics and outcomes for outpatient nephrology clinics in Miyagi prefecture (northeastern Japan). Eleven center hospitals, including one university hospital (Tohoku University Hospital), participated in the project, which covered almost the entire medical network of the area. Registration was originally requested for all patients who provided informed consent for participation in the project. The study protocol was approved by the institutional review board of Tohoku University School of Medicine and the respective attending hospitals. Registration was conducted from May 2006 to November 2008, and a total of 4,015 cases were registered. Among the original registered patients, the following were excluded from this analysis: 150 with lack of data on serum creatinine; 241 with unknown underlying renal diseases such as solitary microscopic hematuria ($n = 61$), or advanced renal failure or nephropathy of unknown origin ($n = 180$). Next, among patients with essential hypertension and eGFR > 60 ml/min, those who did not present positive proteinuria ($n = 836$) at registration or those lacking results of urinary testing ($n = 96$) were excluded. As a result, 2,692 patients were extracted as having complete CKD criteria [1] and were subjected to analysis.

Patient classification and primary outcomes

Patients were classified according to the underlying renal diseases diagnosed by the attending physicians at the participating hospitals (Table 1): (1) primary renal diseases (PRD), defined by primary glomerulonephritis and tubulointerstitial nephritis, including cases not proven by biopsy; (2) hypertensive nephropathy (HN), defined by preceding history of hypertension with absence of other possible disorders, including cases with biopsy findings of nephrosclerosis; (3) diabetic nephropathy (DN), defined by preceding history of diabetes accompanying nephropathy with absence of other possible renal disorders, including cases with biopsy findings of diabetic nephropathy or those who presenting nephropathy with diabetic retinopathy in the absence of other possible disorders; and (4) other nephropathies (ON), defined by other nephropathies not included in the other three groups: systemic or secondary renal disorders such as systemic vasculitis, collagen diseases, infectious diseases (e.g., hepatitis B or C), drugs, pregnancy, vascular disorders, urological disorders, and genetic disorders.

Primary outcomes of this survey included CVD such as angina pectoris (AP), acute AMI, CHF, stroke (cerebral bleeding and infarction), and all-cause death before commencement of chronic dialysis therapy. Outcomes by 12 months after registration were surveyed using hospital medical records, death certificates, and interviews with attending physicians at the time of annual checkups. An episode of CVD was defined as disease of the circulatory system (*International Classification of Disease*, 10th Revision: I00–I99), and the number of patients with AP or AMI included those who had received coronary stenting, angioplasty, or bypass operation or had definite clinical course of AMI. In cases with CHF, only those who needed

Table 1 Patients characteristics

	All	PRD	HN	DN	ON
Number	2,692	1,306	458	283	645
Age (years)[a]	60.0 ± 16.2	55.6 ± 16.6	70.2 ± 11.5	66.5 ± 12.6	58.6 ± 15.7
Gender (male)	1,439 (53.5%)	716 (54.8%)	261 (57.0%)	188 (66.4%)	274 (42.5%)
Body mass index[a]	23.5 ± 3.8	23.4 ± 3.8	24.2 ± 3.7	24.1 ± 3.8	23.0 ± 3.8
Blood pressure (mmHg)[a]					
Systolic	131 ± 16	129 ± 15	136 ± 17	137 ± 18	129 ± 16
Diastolic	77 ± 11	77 ± 10	77 ± 12	74 ± 12	77 ± 11
CKD stage					
Stage 1+2	1,088 (40.4%)	641 (49.1%)	81 (17.7%)	58 (20.4%)	308 (47.7%)
Stage 3	1,010 (37.5%)	467 (35.8%)	264 (57.6%)	80 (28.3%)	199 (30.9%)
Stage 4	361 (13.4%)	135 (10.3%)	72 (15.7%)	61 (21.6%)	93 (14.4%)
Stage 5	233 (8.7%)	63 (4.8%)	41 (9.0%)	84 (29.7%)	45 (7.0%)
Comobidities					
Cardiac disease	334 (12.4%)	98 (7.5%)	98 (21.4%)	70 (24.7%)	68 (10.5%)
Stroke	175 (6.5%)	46 (3.5%)	55 (12.0%)	36 (12.7%)	38 (5.9%)
Diabetes	743 (27.6%)	202 (15.5%)	144 (31.4%)	283 (100.0%)	114 (17.7%)
Hypertension	2,092 (77.7%)	950 (72.7%)	451 (98.5%)	253 (89.4%)	438 (67.9%)
Hyperlipidemia	1,165 (43.3%)	582 (44.6%)	193 (42.1%)	146 (51.6%)	244 (37.8%)
Pharmacotherapy					
ARB/ACEI	1,702 (62.2%)	810 (62.0%)	338 (73.8%)	216 (76.3%)	307 (52.4%)
Statin	936 (34.0%)	471 (36.1%)	149 (32.5%)	122 (43.1%)	194 (30.1%)
ESA	175 (34.0%)	46 (3.5%)	36 (7.9%)	62 (21.9%)	31 (4.8%)
Steroid	683 (34.0%)	430 (32.9%)	14 (3.1%)	6 (2.1%)	233 (36.1%)
Proteinuria	1,318 (50.0%)	617 (47.4%)	224 (51.9%)	221 (78.9%)	256 (41.1%)
Hemoglobin (g/dl)[a]	12.8 ± 2.1	13.2 ± 1.9	12.7 ± 2.1	11.6 ± 2.3	12.6 ± 2.0
Total cholesterol (mg/dl)[a]	198 ± 39	199 ± 36	191 ± 39	190 ± 41	203 ± 41
Smoker	428 (16.1%)	205 (15.8%)	70 (15.7%)	60 (21.6%)	93 (14.6%)
Biopsy	1,412 (62.8%)	1,055 (81.0%)	61 (21.4%)	48 (24.9%)	248 (53.1%)

CKD chronic kidney disease, *PRD* primary renal disease, *HN* hypertensive nephropathy, *DN* diabetic nephropathy, *ON* other nephropathies, *ARB/ACEI* angiotensin receptor blocker/angiotensin converting enzyme inhibitor, *ESA* erythropoiesis stimulating agent, *PRD* primary renal disease, *HN* hypertensive nephropathy, *DN* diabetic nephropathy, *ON* other nephropathies

[a] Mean ± standard deviation

admission for treatment were counted. Diagnosis of stroke and stroke subtypes was based on the Classification of Cerebrovascular Diseases III by the National Institute of Neurological Disorders and Stroke [22], and only cases confirmed by computed tomography or magnetic resonance imaging of the brain were counted.

Data collection

Serum creatinine was measured using the enzyme assay method. Kidney function was determined using the estimation formula for Japanese [23]. Positive results for urinary protein were identified using the dipstick test for spot urine or an autoanalyzer. Positive macroalbuminuria was considered present for a dipstick result of + or more, corresponding to a urinary protein level of >30 mg/dl [24]. Blood pressure was measured at local medical centers in outpatient clinics using an automatic sphygmomanometer based on the Korotkoff sound technique with the patient in a seated position. Information on medications at baseline, as well as history of CVD, diabetes mellitus, hypertension, and hyperuricemia were obtained from the medical records or from results of blood examinations at registration. Patients receiving administration of lipid-lowering drugs or displaying serum cholesterol levels >220 mg/dl were considered to have hypercholesterolemia. Patients with fasting glucose levels >126 mg/dl or nonfasting glucose levels >200 mg/dl, or those who used insulin or oral antihyperglycemic drugs were defined as having diabetes mellitus.

Data analysis

Associations between primary outcomes and baseline kidney function as defined by CKD stage, positive for urinary proteinuria, and underlying renal diseases were examined using logistic regression analysis adjusted for age, gender, systolic blood pressure, body mass index (BMI), hemoglobin, serum albumin, presence of hyperlipidemia or diabetes, prescription of steroid, smoking habits, and history of CVD or stroke. Data are shown as means ± standard deviation (SD). Values of $p < 0.05$ were accepted as indicative of statistical significance. All statistical analyses were conducted using STATA version 10.0 software (Texas, USA).

Results

During the study period of 12 months observation, 200 cases were lost by changing to other medical services or stopping admission due to social reasons, and follow-up of 113 cases was stopped because of initiation of maintenance dialysis therapy. By 12 months, 69 cases of CVD events (27 cases of stroke) and 24 cases of all-cause death had been accumulated. Regarding primary events, significant increases in odds ratios (ORs) were seen by CKD stage under univariate analysis, but these trends disappeared under multivariate adjustment, and a significant lower risk was seen in stage 3 under multivariate analysis. In subanalysis excluding the ON group, there were significant increases in ORs by CKD stage under univariate analysis, but no significant changes were seen under multivariate analysis (Table 2).

Respective analyses by underlying renal disease are shown in Table 3. The same results were observed in the HN and DN groups but not in the PRD group.

ORs for primary events by underlying renal disease are shown in Table 4. Significant differences in ORs were seen in the HN, DN, and ON groups compared with the PRD group according to multivariate analysis.

Discussion

This study aimed to clarify the impact of differing underlying renal diseases on CVD events and death before initiation of dialysis treatment among 2,692 CKD outpatients from 11 nephrology clinics. By 12 months of follow-up, CKD stage was shown to be a significant risk factor for those events under univariate analysis but was not significant under multivariate analysis. However, the study confirmed significant differences in outcomes of CVD events and mortality according to underlying renal disease beyond CKD stage, even after adjusting for possible confounding factors, indicating a high-risk group of patients with HN or DN, and a low-risk group of patients with PRD. The exact mechanisms underlying increased risk of CVD in CKD have remained uncertain. Vascular dysfunctions developing in the uremic milieu may be involved with these pathologies. Associated factors could include fluid overload, calcium/phosphate abnormalities, anemia, malnutrition, chronic inflammation, oxidative stress, and accumulation of uremic toxins [25–32]. Patients with established vasculopathy might reasonably be expected to undergo accelerated vascular damage with progression of CKD stage.

Table 2 Risk of primary endpoints by chronic kidney diseae (CKD) stage

Events				Univariate analysis		Multivariate analysis[a]	
CKD stage	CVD	Stroke	Death	OR	95% CI	OR	95% CI
All patients							
CKD 1+2	14	10	4	1.00		1.00	
CKD 3	22	6	6	1.29	0.70–2.17	0.54	0.30–0.98
CKD 4	15	6	7	2.73	1.55–4.83	0.79	0.38–1.66
CKD 5	18	5	7	4.66	2.63–8.23	0.95	0.39–2.28
Patients with PRD, HN, and DN							
CKD 1+2	10	3	1	1.00		1.00	
CKD 3	19	3	4	1.60	0.82–3.11	0.63	0.30–1.34
CKD 4	11	5	4	3.42	1.66–7.05	0.82	0.33–2.05
CKD 5	16	5	7	7.15	3.60–14.21	1.11	0.40–3.12

Events: angina pectoris; acute myocardial infarction; congestive heart failure; stroke; all-cause mortality

CVD cardiovascular disease, *OR* odds ratio, *CI* confidence interval, *PRD* primary renal disease, *HN* hypertensive nephropathy, *DN* diabetic nephropathy, *ON*, other nephropathies

[a] Adjusted for age, gender, hemoglobin, positive for proteinuria, systolic blood pressure, body mass index, presence of hyperlipidemia, presence of diabetes, prescription of steroid, smoker, history of cardiovascular disease or stroke

Table 3 Risk of primary endpoints by chronic kidney disease (CKD) stage in respective underlying renal disease

Events				Univariate analysis		Multivariate analysis[a]	
CKD stage	CVD	Stroke	Death	OR	95% CI	OR	95% CI
Primary renal disease							
CKD 1+2	4	1	1	1.00		1.00	
CKD 3	5	1	1	1.29	0.41–4.04	0.32	0.07–1.41
CKD 4	1	0	1	0.72	0.09–6.02	0.11	0.00–1.38
CKD 5	0	0	1	1.54	0.18–13.03	0.14	0.00–2.98
Hypertensive nephropathy							
CKD 1+2	3	0	0	1.00		1.00	
CKD 3	8	2	1	1.16	0.31–4.30	0.21	0.03–1.32
CKD 4	5	3	1	3.70	0.95–14.27	0.32	0.04–2.37
CKD 5	4	2	3	4.48	1.05–19.03	0.20	0.01–2.18
Diabetic nephropathy							
CKD 1+2	3	2	0	1.00		1.00	
CKD 3	6	0	2	0.99	0.29–3.31	0.87	0.23–3.26
CKD 4	5	2	2	1.29	0.38–4.34	1.08	0.23–5.06
CKD 5	12	3	3	2.45	0.83–7.14	1.77	0.36–8.69
Other nephropathies							
CKD 1+2	4	7	3	1.00		1.00	
CKD 3	3	3	2	1.00	0.40–2.50	0.44	0.15–1.28
CKD 4	4	1	3	1.97	0.75–5.18	0.73	0.18–2.89
CKD 5	2	0	0	1.12	0.24–5.23	0.20	0.01–2.44

Events: angina pectoris; acute myocardial infarction; congestive heart failure; stroke; all-cause mortality

CVD cardiovascular disease, *OR* odds ratio, *CI* confidence interval

[a] Adjusted for age, gender, hemoglobin, positive for proteinuria, systolic blood pressure, body mass index, presence of hyperlipidemia, presence of diabetes, prescription of steroid, smoker, history of cardiovascular disease or stroke

Table 4 Risk of primary endpoints by underlying renal disease

Underlying renal disease	Events			Multivariate analysis[a]	
	CVD	Stroke	Death	OR	95% CI
PRD	10	2	4	1.00	
HN	20	7	5	2.87	1.37–6.02
DN	26	7	7	11.88	4.58–30.83
ON	13	11	8	3.59	1.81–7.09

Events: angina pectoris; acute myocardial infarction; congestive heart failure; stroke; all-cause mortality

CVD cardiovascular disease, *OR* odds ratio, *CI* confidence interval, *PRD* primary renal disease, *HN* hypertensive nephropathy, *DN* diabetic nephropathy, *ON* other nephropathies

[a] Adjusted for age, gender, hemoglobin, positive for proteinuria, systolic blood pressure, body mass index, presence of hyperlipidemia, presence of diabetes, prescription of steroid, smoker, history of cardiovascular disease or stroke

In this study cohort, all patients were recruited from nephrology clinics. This may have introduced a bias toward relatively better medical compliance in patients with modifiable factors, including uremic milieu and blood pressure. To note, the average blood pressure was well controlled as a whole in respective groups: 129/77 mmHg in PRD, 136/77 mmHg in HN, 137/74 mmHg in DN, and 129/77 mmHg in ON. On the other hand, patients with diabetes in this study may have been relatively resistant to conventional therapies, because most of them were originally introduced from diabetic clinics. Therefore, together with patient background, the findings of the study are not altogether surprising. Clinical outcomes of CVD and mortality differed significantly by underlying renal disease, such as relatively high CVD risk in DN and HN and relatively low risk in PRD. As hypertension, DM, and older age are all strong classic risk factors for predicting CVD in the general population, longstanding exposure to such pathological conditions may have resulted in increased CVD and mortality in HN and DN patients compared with patients with PRD with no clinical impact on CVD events of CKD staging.

As for the reasons for differing CVD outcomes in the group with PRD, several factors may have contributed. First, half of the patients showed IgA nephropathy in which glucocorticoid therapy does not increase the risk of CVD [33]. Blood pressure was also adequately controlled with angiotensin inhibitors, which may have improved patients'

clinical course, as shown in Japanese CKD patients [34]. In addition, we speculate that the uremic milieu for symptomatic CVD events may not be so clinically relevant in predialysis cases, instead starting to play a crucial role in the period of chronic dialysis, as has been indicated in pediatric patients in whom prevalent vasculopathy is not a dominant issue but who show high rates of CVD mortality and morbidity on dialysis [35, 36].

In this study, a significant lower risk was seen in stage 3 disease under the multivariate analysis compared with CDK stages 1+2 (Table 2). However, in subanalysis for groups excluding ON, no statistical difference was observed (Table 2), which implies the possible clinical significance of ON with stages 1+2 disease. The ON group consisted of various type of underlying diseases. In the ON group with stages 1+2, there were ten excess events in stroke or death, including patients with collagen diseases (four cases) and antineutrophil cytoplasmic autoantibody (ANCA)-related systemic vasculitis (one case). Therefore, we speculate that those types of underlying disorders might have increased the events in this group, and they predispose patients to high risks of death or vascular events independently of CKD stage. These results indicate that CKD staging cannot be simply applied to detect patients at high risk of CVD in the field of nephrology without taking into account differences in underlying renal disease, and those cases with prevalent hypertensive nephropathy or diabetic nephropathy should be the primary targets. Furthermore, as heart failure becomes dominant as CKD stage progresses, those cases should be managed with special attention to heart failure.

In this study, several clinical issues that might have biased the analytical results must be considered. First, angiotensin inhibitors were the leading agents prescribed to patients, whereas β-blockers, which benefit patients with heart failure, were the third-most prescribed agents. Second, hemoglobin levels among cases who developed heart failure were lower than those in their counterparts (data not shown), implying a need for anemia correction including induction of dialysis at an earlier time. Last, the study observation priod was relatively short—just 12 months—and therefore may not have been enough long to delineate the impact of CKD stage. This may, at least partly, account for the lack of significance of CKD stage for events by multivariate analysis. This should await further observations. In conclusion, risk of CVD and mortality due to CKD need to be stratified according to the underlying renal diseases.

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Conflict of interest statement None.

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厚生労働科学研究費補助金（腎疾患対策研究事業）

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腎臓病・糖尿病と上手に付き合うために!!

とき 平成23年 **7月31日(日)** 13:00～15:00（開場12:30）

ところ 石川県地場産業振興センター 新館コンベンションホール1階
※裏面会場案内図を参照の上、お越し下さい。

プログラム

●司　会	金沢大学 医薬保健研究域医学系 血液情報統御学 教授 和田　隆志 先生 名古屋大学大学院 医学系研究科 腎臓内科学 特任准教授 今井　圓裕 先生	
●開会挨拶	岡山大学大学院 医歯薬学総合研究科 腎・免疫・内分泌代謝内科学 教授 槇野　博史 先生	13:00～13:05
テーマ1	「変わる!糖尿病 ―糖尿病の最新治療―」 旭川医科大学 内科学講座 病態代謝内科学分野 教授 羽田　勝計 先生	13:05～13:25
テーマ2	「糖尿病性腎症の早期診断の最近の進歩」 藤田保健衛生大学医学部 腎内科学 教授 湯澤　由紀夫 先生	13:25～13:45
テーマ3	「メタボにならないライフスタイル ～メタボリック症候群を克服するために～」 岡山大学病院 新医療研究開発センター 教授 四方　賢一 先生	13:55～14:15
テーマ4	「危ない高血圧」 熊本大学大学院 生命科学研究部 腎臓内科学 教授 冨田　公夫 先生	14:15～14:35
●質問コーナー（質疑応答）		14:35～14:55
●閉会挨拶	金沢医科大学医学部　腎臓内科学　教授 横山　仁 先生	14:55～15:00

共催 厚生労働科学研究費補助金腎疾患対策研究事業
（糖尿病性腎症の病態解明と新規治療法確立のための評価法の開発）
（CKDの早期発見、予防、治療標準化、進展阻止に関する調査研究）
日本慢性腎臓病対策協議会（J-CKD I）

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厚生労働科学研究費補助金
難治性疾患克服研究事業「進行性腎障害に関する調査研究」
腎疾患対策研究事業「ＣＫＤの早期発見、予防、治療標準化、進展阻止に関する調査研究」

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あなたの腎臓大丈夫？

日時：平成23年9月18日(日)13:00～15:00
（開場12:30）
場所：名古屋大学医学部附属病院
医系研究棟1号館　地下1階会議室

13:00	「進行性腎障害に関する調査研究」班　研究代表者挨拶 松尾　清一　先生（名古屋大学大学院医学系研究科 腎臓内科　教授）
13:05	IgA腎症 川村　哲也　先生（東京慈恵会医科大学 腎臓・高血圧内科　准教授）
13:20	急速進行性糸球体腎炎 山縣　邦弘　先生（筑波大学大学院人間総合科学研究科腎臓病態医学分野　教授）
13:35	難治性ネフローゼ症候群 今井　圓裕　先生（名古屋大学大学院医学系研究科 腎臓内科　特任教授）
13:50	多発性嚢胞腎 堀江　重郎　先生（帝京大学医学部 泌尿器科　教授）
	休憩
14:15	「ＣＫＤの早期発見、予防、治療標準化、進展阻止に関する調査研究」班　研究代表者挨拶 今井　圓裕　先生（名古屋大学大学院医学系研究科 腎臓内科　特任教授）
14:20	CKDについて 安田　宜成　先生（名古屋大学大学院医学系研究科 慢性腎臓病地域連携システム寄附講座　寄附講座准教授）
14:35	Q&A

◆◇◆先着100名◆◇◆
事前のお申し込みは
不要です

主催：厚生労働科学研究費補助金難治性疾患克服研究事業「進行性腎障害に関する調査研究」班
　　厚生労働科学研究費補助金腎疾患対策研究事業「ＣＫＤの早期発見、予防、治療標準化、進展阻止に関する調査研究」班
後援：中部日本放送株式会社
お問い合わせ先：名古屋大学医学部附属病院　腎臓内科　052-741-2111(代表)
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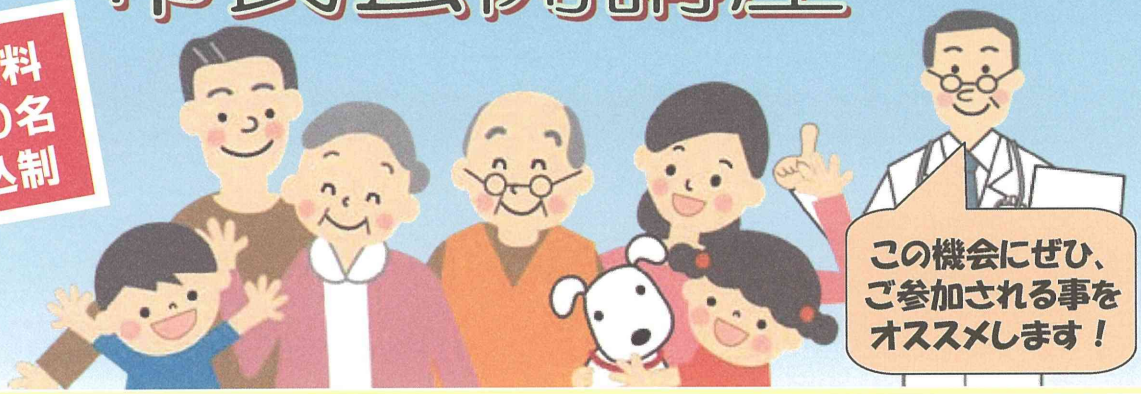

あなたは大丈夫？
糖尿病と慢性腎臓病（CKD）

とき 平成23年 **12月11日**（日） **13:30-16:30**（開場：13:00）

ところ **ミッドランドホール**
名古屋市中村区名駅4-7-1ミッドランドスクエア５階
※裏面会場案内図をご参照の上、お越し下さい。

プログラム

●開会挨拶　名古屋大学大学院医学系研究科　腎臓内科学　教授　松尾　清一 先生

●講　演

司　会　名古屋大学大学院医学系研究科　腎臓内科学　特任教授　今井　圓裕 先生
金沢大学医薬保健研究域医学系　血液情報統御学　教授　和田　隆志 先生

13:35-14:05
1．「糖尿病腎症の診断と病態」
新潟大学　保健管理本部 保健管理センター　教授　鈴木　芳樹 先生

14:05-14:35
2．「糖尿病腎症に対する治療」
金沢医科大学　糖尿病・内分泌内科学　教授　古家　大祐 先生

14:45-15:15
3．「高血圧とCKD」
琉球大学医学部附属病院　血液浄化療法部　准教授　井関　邦敏 先生

15:15-15:45
4．「高尿酸血症・メタボリック症候群とCKD」
東京慈恵会医科大学　腎臓・高血圧内科　教授　大野　岩男 先生

15:50-16:30
●パネルディスカッション

司　会　名古屋大学大学院医学系研究科　腎臓内科学　教授　松尾　清一 先生

「糖尿病、腎臓病なんでもQ＆A」

パネリスト　講師全員

●閉会挨拶

共催　厚生労働省科学研究費補助金腎疾患対策研究事業
（CKDの早期発見、予防、治療標準化、進展阻止に関する調査）
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日本慢性腎臓病対策協議会（J-CKDI）

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