Proteinuria and clinical outcomes after ischemic stroke

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ABSTRACT

Objectives: The impact of chronic kidney disease (CKD) on clinical outcomes after acute ischemic stroke is still not fully understood. The aim of the present study was to elucidate how CKD and its components, proteinuria and low estimated glomerular filtration rate (eGFR), affect the clinical outcomes after ischemic stroke.

Methods: The study subjects consisted of 3,778 patients with first-ever ischemic stroke within 24 hours of onset from the Fukuoka Stroke Registry. CKD was defined as proteinuria or low eGFR (<60 mL/min/m^2) or both. The study outcomes were neurologic deterioration ($\geq$2-point increase in the NIH Stroke Scale during hospitalization), in-hospital mortality, and poor functional outcome (modified Rankin Scale score at discharge of 2 to 6). The effects of CKD, proteinuria, and eGFR on these outcomes were evaluated using a multiple logistic regression analysis.

Results: CKD was diagnosed in 1,320 patients (34.9%). In the multivariate analyses after adjusting for confounding factors, patients with CKD had significantly higher risks of neurologic deterioration, in-hospital mortality, and poor functional outcome ($p <0.001$ for all). Among the CKD components, a higher urinary protein level was associated with an elevated risk of each outcome (p for trend < 0.001 for all), but no clear relationship between the eGFR level and each outcome was found.

Conclusions: CKD is an important predictor of poor clinical outcomes after acute ischemic stroke. Proteinuria independently contributes to the increased risks of neurologic deterioration, mortality, and poor functional outcome, but the eGFR may not be relevant to these outcomes. *Neurology*® 2012;78:1909–1915

GLOSSARY

CKD = chronic kidney disease; **eGFR** = estimated glomerular filtration rate; **FSR** = Fukuoka Stroke Registry; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale.

Chronic kidney disease (CKD) is a worldwide public health problem with an estimated prevalence of 10% to 15% of adults in developed countries.[1,2] Recent studies have revealed that an impaired kidney function is associated with an increased risk for the development of cardiovascular disease, including stroke.[3–6] Previous studies have suggested that CKD may be a marker of adverse clinical characteristics and independently associated with adverse outcomes in patients with acute coronary syndrome.[7–9] The reports on the impact of CKD on the clinical characteristics and acute outcomes in patients with ischemic stroke have been conflicting.[10–14] Moreover, it is unclear how proteinuria and a low estimated glomerular filtration rate (eGFR) affect the short-term clinical outcomes in patients with acute ischemic stroke.

We designed a large-scale multicenter hospital-based study to elucidate whether CKD, proteinuria, and a low GFR affect the clinical outcomes after acute ischemic stroke.

Supplemental data at
www.neurology.org

Supplemental Data

METHODS **Standard protocol approvals, registration, and patient consent.** The Fukuoka Stroke Registry (FSR) is an epidemiologic and observational study of acute stroke involving 7 stroke centers in Fukuoka, Japan.[15] The hospitals participating in the FSR were as follows: Kyushu University Hospital, National Hospital Organization Kyushu Medical Center, National Hospital Organization Fukuoka Higashi Medical Center, Fukuoka Red Cross Hospital, St. Mary's Hospital, Nippon Steel Yawata Memorial Hospital, and Japan Labor Health and Welfare Organization Kyushu Rosai Hospital. The local ethics committee of Kyushu University and each participating hospital approved this study. The FSR consists of 2 database systems, i.e., prospective and retrospective databases. At admission, we explained the objectives, study design, risks, and benefits in detail to each patient or surrogate family member and obtained written informed consent. About 88% of all potentially eligible patients consented to participate in this registry.

Study design. The prospective database started June 1, 2007, and recruited consecutive patients with acute stroke within 7 days from the onset of the stroke to attending one of the centers. The prospective database collected data on patient demographics and medical history, and prehospital, emergency, and in-hospital interventions and outcomes. The retrospective database collected the data from all consecutive patients with acute stroke within 24 hours from the onset of the stroke to attending one of the centers from June 1, 1999, to May 31, 2007, and the data included medical information identical to that included in the prospective database. The database also included data from the patients who did not consent to participate in prospective data collection. There were no remarkable differences in the background characteristics, such as age (retrospective, 70.0 ± 11.7 years vs prospective, 70.0 ± 12.2 years) and gender (male, retrospective 61% vs prospective 62%) in these databases, whereas the prevalence of risk factors or treatment was changed as medical care improved.

As of February 28, 2011, 9,862 patients (5,547 patients from a retrospective and 4,315 patients from a prospective database) who were admitted to the participating medical centers were registered in the FSR databases and 4,782 patients (3,207 patients from a retrospective and 1,575 patients from a prospective database) met the following inclusion criteria: 1) admission within 24 hours of the onset of ischemic stroke, 2) no history of previous stroke, and 3) no impairment of the activities of daily living before onset. After excluding 1,004 patients whose urinary protein data were not obtained during hospitalization, 3,778 patients (2,463 patients from a retrospective and 1,315 patients from a prospective database) were finally included in the present analysis (figure).

Determination of ischemic stroke and its subtype. Stroke was defined as a sudden onset of nonconvulsive and focal neurologic deficit persisting for more than 24 hours and was classified into ischemic stroke, brain hemorrhage, subarachnoid hemorrhage, or other types by means of brain imaging, including CT or MRI. We further classified ischemic stroke into cardioembolic and noncardioembolic subtypes (i.e., lacunar, atherothrombotic, and unclassified).

Risk factors. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic pressure ≥90 mm Hg in the chronic stage of stroke or as current treatment with antihypertensive drugs. Diabetes mellitus was determined by either a 75 g oral glucose tolerance test according to the diagnostic criteria of the World Health Organization in 1998[16] or a medical history of

Figure   Flow chart showing the patient selection
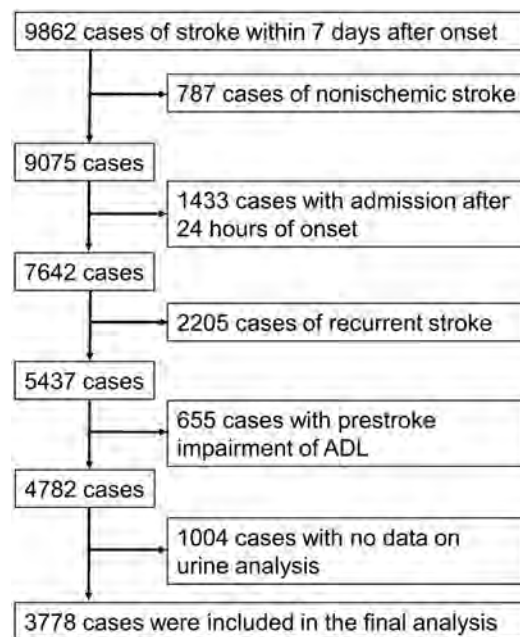
ADL = activities of daily living.

diabetes. Dyslipidemia was defined as a cholesterol level ≥220 mg/dL, low-density lipoprotein cholesterol level ≥140 mg/dL, high-density lipoprotein cholesterol level <40 mg/dL, or current treatment with a lipid-lowering drug. Atrial fibrillation was diagnosed based on electrocardiographic findings. Thrombolytic therapy was defined as IV or intra-arterial administration of thrombolytic agents, such as recombinant tissue plasminogen activator and urokinase. Infectious complications included clinically diagnosed infections in any organs, such as pneumonia and urinary tract infection, during hospitalization.

Evaluation of urinary protein, eGFR, and CKD. We performed a urine analysis on admission. The level of urinary protein was examined using a urine dipstick in the absence of potential urinary tract infection and was classified into negative (dipstick reading of −), trace (±), mild (1+), and severe (≥2+) according to the classification described in a previous study[17] with minor modifications. The approximate amount of urine protein was estimated by the dipstick reading as follows: trace (15 mg/dL), mild (30 mg/dL), and severe (≥100 mg/dL). When a patient underwent a urinary test 2 times or more during hospitalization, in addition to on admission, the mildest result was adopted. The serum creatinine level was measured on admission, and the eGFR was determined using the equation proposed by the Japanese Society of Nephrology as follows: eGFR (mL/min/1.73 m²) = 194 × [serum creatinine (mg/dL)]$^{-1.094}$ × [age (year)]$^{-0.287}$ × 0.739 (if female).[18] We categorized the patients into 3 groups according to the classification by the National Kidney Foundation, with minor modifications[3,19,20]: eGFR ≥60, 45–59, and <45 mL/min/1.73 m². CKD was defined as proteinuria (mild or severe urinary protein) or a low eGFR (<60 mL/min/1.73 m²), or both.

Evaluation of neurologic severity and functional outcome. We evaluated the neurologic severity on admission and at discharge by the NIH Stroke Scale (NIHSS). Neurologic deterioration was defined as a ≥2-point increase in the NIHSS during

Table 1 The clinical characteristics of the patients with and without CKD

	Non-CKD (n = 2,458)	CKD (n = 1,320)	p
Age, y, mean ± SD	67.9 ± 11.7	74.0 ± 11.1	<0.001
Female, n (%)	946 (38.5)	523 (39.6)	0.50
Risk factors, n (%)			
Hypertension	1,700 (69.2)	1,072 (81.2)	<0.001
Diabetes	731 (29.7)	444 (33.6)	0.01
Dyslipidemia	947 (38.5)	493 (37.4)	0.48
Atrial fibrillation	504 (20.5)	473 (35.8)	<0.001
Stroke subtype, n (%)			
Cardioembolic stroke	561 (22.8)	507 (38.4)	<0.001
Blood pressure, mm Hg, mean ± SD			
Systolic	162 ± 28	164 ± 31	0.08
Diastolic	88 ± 17	87 ± 19	0.09
Thrombolytic therapy, n (%)	191 (7.8)	157 (11.9)	<0.001
Infectious complications, n (%)	437 (17.8)	410 (31.1)	<0.001
eGFR, mL/min/1.73 m², mm Hg, mean ± SD	83.4 ± 18.7	53.7 ± 19.3	<0.001
Urinary protein level, n (%)			
Negative	2,228 (90.6)	616 (46.7)	<0.001[a]
Trace	230 (9.4)	102 (7.7)	
Mild	0 (0)	338 (25.6)	
Severe	0 (0)	264 (20.0)	
NIHSS on admission, median (IQR)	4 (2–7)	5 (2–12)	<0.001

Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; IQR = interquartile range; NIHSS = NIH Stroke Scale.
[a] p for the trend among urinary protein levels.

hospitalization.[21] In-hospital mortality was defined as death from any cause during hospitalization. The functional outcome at discharge was graded using a modified Rankin Scale (mRS). A poor functional outcome was defined as death (mRS of 6) or dependency (mRS of 2 to 5).

Statistical analysis. The statistical analysis was performed using the JMP version 7 software program (SAS Institute Inc., Cary, NC). The clinical characteristics according to CKD status, urinary protein level, and eGFR level were compared using the χ^2 test or a logistic regression analysis for categorical variables, and the unpaired Student t test, Wilcoxon rank sum test, or analysis of variance for continuous or scoring variables, as appropriate. The age- and sex-adjusted or multivariate-adjusted odds ratios and 95% confidence intervals for the study outcomes were estimated by a logistic regression analysis. The multivariate model included all following potential confounding factors: age, sex, baseline NIHSS quartile, cardioembolic stroke, systolic blood pressure on admission, diabetes, hypertension, atrial fibrillation, thrombolytic therapy, and infectious complications. A p value <0.05 was considered to be significant.

RESULTS Baseline characteristics. The mean ± SD age of the study subjects was 70.0 ± 11.9 years and 1,469 patients (38.9%) were female. A total of 2,772 patients (73.4%) had hypertension. There were 1,175 patients (31.1%) with diabetes and 1,440 patients (38.1%) with dyslipidemia. Atrial fibrillation

was documented in 977 patients (25.9%). The mean ± SD duration of hospitalization was 28 ± 24 days, and the median and interquartile range were 23 days and 15–34 days, respectively.

Among the study subjects, 1,320 (34.9%) patients had CKD. Table 1 shows the baseline characteristics of the patients with and without CKD. The patients with CKD were older than those without CKD. The patients with CKD had a higher frequency of hypertension, diabetes, and atrial fibrillation than those without CKD. The proportion of patients with cardioembolic stroke, thrombolytic therapy, and infectious complications were higher in the CKD group than in the non-CKD group. On admission, the NIHSS score of the patients with CKD was significantly higher than that of the patients without CKD. The baseline characteristics according to the urinary protein level and the eGFR level are shown in tables e-1 and e-2 on the *Neurology*® Web site at www.neurology.org, respectively.

The association between kidney functions and clinical outcomes. Table 2 shows the association between kidney functions and neurologic deterioration during hospitalization. The age- and sex-adjusted logistic regression analyses showed that CKD significantly increased the risk of neurologic deterioration (p <0.001). Among the CKD components, while a higher urinary protein level was associated with a higher risk of neurologic deterioration (p for trend <0.001), no clear relationship was observed between the eGFR level and neurologic deterioration. These findings were almost the same after adjustment for confounding factors, such as the baseline NIHSS, stroke subtype, systolic blood pressure, hypertension, diabetes, atrial fibrillation, thrombolytic therapy, and infectious complications.

Tables 3 and 4 show the impact of kidney functions on in-hospital mortality and a poor functional outcome, respectively. Similar to neurologic deterioration, proteinuria was a significant predictor for both outcomes in the age- and sex-adjusted and the multivariate analyses (p for trend <0.001 for all), but no clear relationships were found between the eGFR level and these outcomes.

DISCUSSION The present study has clearly shown that CKD is associated with more severe functional impairment and higher in-hospital mortality in patients with ischemic stroke. In patients with CKD, the NIHSS score was higher on admission and neurologic deterioration was more common. Consequently, CKD is an important predictor of a poor functional outcome in the acute stage of ischemic stroke. When ischemic stroke occurs in patients with CKD, the neurologic

Table 2 The odds ratios for neurologic deterioration[a] according to CKD status, urinary protein level, and eGFR level

	No. (%) of events	Age- and sex-adjusted		Multivariate-adjusted[b]	
		OR (95% CI)	p	OR (95% CI)	p
CKD status					
Non-CKD	171 (7.0)	1.00 (reference)		1.00 (reference)	
CKD	184 (13.9)	1.79 (1.43-2.25)	<0.001	1.49 (1.17-1.89)	0.001
Urinary protein level					
Negative	202 (7.1)	1.00 (reference)		1.00 (reference)	
Trace	43 (13.0)	1.88 (1.30-2.66)	0.001	1.42 (0.97-2.04)	0.07
Mild	60 (17.8)	2.69 (1.93-3.70)	<0.001	1.92 (1.35-2.70)	<0.001
Severe	50 (18.9)	3.12 (2.16-4.44)	<0.001	1.88 (1.27-2.74)	0.002
p for trend			<0.001		<0.001
eGFR level (mL/min/1.73 m^2)					
≥60	236 (8.6)	1.00 (reference)		1.00 (reference)	
45-59	66 (10.1)	0.85 (0.62-1.14)	0.27	0.89 (0.65-1.21)	0.46
<45	53 (14.4)	0.86 (0.60-1.22)	0.40	0.87 (0.60-1.25)	0.46
p for trend			0.25		0.36

Abbreviations: CI = confidence interval; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; NIHSS = NIH Stroke Scale; OR = odds ratio.

[a] Neurologic deterioration was defined as a ≥2-point increase in the NIHSS during hospitalization.

[b] Adjusted for age, sex, baseline NIHSS in quartile, cardioembolic stroke, systolic blood pressure on admission, diabetes, hypertension, atrial fibrillation, thrombolytic therapy, and infectious complications. In the multivariate model for the urinary protein level, the eGFR level was additionally adjusted. In the multivariate model for the eGFR level, the urinary protein level was additionally adjusted.

symptoms are more severe, and the functional outcome is poorer, even after hospitalization.

Previous studies showed controversial results concerning the effects of proteinuria and the eGFR on the clinical characteristics of stroke patients. Some studies suggested that reduced creatinine clearance or a low eGFR was associated with a poor outcome in ischemic stroke patients.[10–12,22] There have been con-

Table 3 The odds ratios for in-hospital mortality according to CKD status, urinary protein level, and eGFR level

	No. (%) of events	Age- and sex-adjusted		Multivariate-adjusted[a]	
		OR (95% CI)	p	OR (95% CI)	p
CKD status					
Non-CKD	44 (1.8)	1.00 (reference)		1.00 (reference)	
CKD	88 (6.7)	3.14 (2.16-4.62)	<0.001	2.38 (1.61-3.57)	<0.001
Urinary protein level					
Negative	46 (1.6)	1.00 (reference)		1.00 (reference)	
Trace	24 (7.2)	4.57 (2.70-7.56)	<0.001	2.96 (1.71-5.01)	<0.001
Mild	32 (9.5)	6.06 (3.72-9.76)	<0.001	3.98 (2.38-6.61)	<0.001
Severe	30 (11.4)	8.11 (4.85-13.41)	<0.001	4.53 (2.62-7.77)	<0.001
p for trend			<0.001		<0.001
eGFR level (mL/min/1.73 m^2)					
≥60	81 (2.9)	1.00 (reference)		1.00 (reference)	
45-59	27 (4.1)	0.85 (0.53-1.34)	0.50	0.89 (0.54-1.43)	0.65
<45	24 (6.5)	0.75 (0.44-1.24)	0.26	0.81 (0.47-1.37)	0.44
p for trend			0.21		0.38

Abbreviations: CI = confidence interval; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; NIHSS = NIH Stroke Scale; OR = odds ratio.

[a] Adjusted for age, sex, baseline NIHSS in quartile, cardioembolic stroke, systolic blood pressure on admission, diabetes, hypertension, atrial fibrillation, thrombolytic therapy, and infectious complications. In the multivariate model for the urinary protein level, the eGFR level was additionally adjusted. In the multivariate model for the eGFR level, the urinary protein level was additionally adjusted.

Table 4 The odds ratios for poor functional outcome[a] according to CKD status, urinary protein level, and eGFR level

	No. (%) of events	Age- and sex-adjusted		Multivariate-adjusted[b]	
		OR (95% CI)	p	OR (95% CI)	p
CKD status					
Non-CKD	1071 (43.6)	1.00 (reference)		1.00 (reference)	
CKD	788 (59.7)	1.55 (1.35–1.79)	<0.001	1.25 (1.05–1.48)	0.01
Urinary protein level					
Negative	1250 (44.0)	1.00 (reference)		1.00 (reference)	
Trace	202 (60.8)	2.02 (1.58–2.58)	<0.001	1.27 (0.94–1.71)	0.11
Mild	224 (66.3)	2.49 (1.94–3.21)	<0.001	1.69 (1.24–2.29)	<0.001
Severe	183 (69.3)	3.16 (2.36–4.25)	<0.001	1.66 (1.16–2.39)	0.006
p for trend			<0.001		<0.001
eGFR level (mL/min/1.73 m^2)					
≥60	1274 (46.2)	1.00 (reference)		1.00 (reference)	
45–59	354 (54.3)	0.95 (0.79–1.14)	0.56	0.98 (0.79–1.23)	0.89
<45	231 (62.8)	0.91 (0.71–1.17)	0.46	0.87 (0.64–1.19)	0.38
p for trend			0.35		0.42

Abbreviations: CI = confidence interval; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; NIHSS = NIH Stroke Scale; OR = odds ratio.

[a] Poor functional outcome was defined as modified Rankin Scale score ≥2 at discharge.

[b] Adjusted for age, sex, baseline NIHSS in quartile, cardioembolic stroke, systolic blood pressure on admission, diabetes, hypertension, atrial fibrillation, thrombolytic therapy, and infectious complications. In the multivariate model for the urinary protein level, the eGFR level was additionally adjusted. In the multivariate model for the eGFR level, the urinary protein level was additionally adjusted.

flicting results regarding the association between the eGFR and the clinical outcomes after thrombolytic therapy in patients with acute ischemic stroke.[13,14] A recent study with a limited sample size of 251 patients with ischemic stroke indicated that proteinuria, but not eGFR, was related to the discharge outcome.[23] In the present study, we demonstrated the detrimental effects of proteinuria on the acute outcomes of ischemic stroke in a much larger population. After adjusting for possible confounding factors, patients with urinary protein have an approximately 1.3 to 1.7 times higher risk of poor functional outcome and a 3.0 to 4.5 times higher risk of in-hospital mortality according to the severity of proteinuria compared with patients with negative urinary protein. In contrast, we found that the eGFR was not clearly associated with the clinical outcome in patients with ischemic stroke. The increased risk of CKD may not be due to the decreased eGFR, but predominantly to the presence of proteinuria.

Proteinuria is a strong and independent predictor for the risk of cardiovascular events and mortality.[24–26] The mechanisms by which proteinuria is independently associated with short-term mortality and poor functional outcome after ischemic stroke are currently unclear. Various factors such as kidney disease, hypertension, hyperlipidemia, systemic inflammation, thrombotic factors, coronary artery calcification, and vascular endothelial growth factor have been suggested to be involved in the mechanisms by which proteinuria increases the risk of cardiovascular events.[26] In the present study, fibrinogen, high-sensitivity C-reactive protein, thrombin-antithrombin complex, and D-dimer levels tended to increase in the presence of proteinuria (data not shown). Since inflammation and coagulation states may be detrimental to ischemic brain damage, proteinuria may affect the outcome via these factors. Another possibility is that proteinuria may be associated with hemorrhagic transformation in ischemic stroke. Previous studies suggested that albuminemia was associated with hemorrhagic transformation after ischemic stroke.[27] In the present study, symptomatic hemorrhagic infarction was more common in patients with proteinuria compared to those without it (data not shown).

There were some limitations to this study. Among the 4,782 patients who met the inclusion criteria, 1,004 patients were excluded because of a lack of data on their urine analysis. In this study, the number of patients with an eGFR ≥60 and proteinuria was comparable to that of those with an eGFR <60 and proteinuria. However, the absolute number of patients with eGFR ≥60 was much larger than that

of those with eGFR <60. Therefore, such a distribution of patients appears not to be different from that observed in noninstitutionalized adults.[28] Patients on hemodialysis or peritoneal dialysis were generally excluded from the study because of anuria. However, the proportion of dialysis patients was estimated to be small (1.8%) among the overall studied subjects. In addition, hemodialysis appears to be associated with a poor outcome after stroke.[29] Therefore, the odds ratios of proteinuria for poor clinical outcomes may have been little affected, because these patients would likely have been categorized in the severe proteinuria group. The urinary protein analyses using a dipstick were quasi-quantitative, and not standardized among the participating hospitals, and the assessments of urinary protein and the eGFR were based on a single measurement. In addition, we cannot exclude the possibility that the amount of urine protein and the serum creatinine level may have been affected by stroke, although they were assessed on admission. A prestroke evaluation would be desirable to exclude the influence of stroke on these factors. Therefore, misclassifications in the urinary protein level and the eGFR level were possible, and these might have resulted in the observed conservative results in terms of the risk estimations. In the present study, we investigated the effects of CKD, proteinuria, and eGFR on clinical outcomes at discharge. Further studies will be required to elucidate the association of these parameters on the long-term outcome after ischemic stroke.

AUTHOR CONTRIBUTIONS

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DISCLOSURE

REFERENCES

1. Chadban SJ, Briganti EM, Kerr PG, et al. Prevalence of kidney damage in Australian adults: The AusDiab Kidney Study. J Am Soc Nephrol 2003;14:S131–138.
2. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 2003;41:1–12.
3. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–1305.
4. Nickolas TL, Khatri M, Boden-Albala B, et al. The association between kidney disease and cardiovascular risk in a multiethnic cohort: findings from the Northern Manhattan Study (NOMAS). Stroke 2008;39:2876–2879.
5. Ninomiya T, Kiyohara Y, Tokuda Y, et al. Impact of kidney disease and blood pressure on the development of cardiovascular disease: an overview from the Japan Arteriosclerosis Longitudinal Study. Circulation 2008;118:2694–2701.
6. Ovbiagele B. Impairment in glomerular filtration rate or glomerular filtration barrier and occurrence of stroke. Arch Neurol 2008;65:934–938.
7. McCullough PA, Soman SS, Shah SS, et al. Risks associated with renal dysfunction in patients in the coronary care unit. J Am Coll Cardiol 2000;36:679–684.
8. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2004;351:1285–1295.
9. Brosius FC 3rd, Hostetter TH, Kelepouris E, et al. Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease: a science advisory from the American Heart Association Kidney And Cardiovascular Disease Council; the Councils on High Blood Pressure Research, Cardiovascular Disease in the Young, and Epidemiology and Prevention; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: developed in collaboration with the National Kidney Foundation. Circulation 2006;114:1083–1087.
10. MacWalter RS, Wong SY, Wong KY, et al. Does renal dysfunction predict mortality after acute stroke? A 7-year follow-up study. Stroke 2002;33:1630–1635.
11. Tsagalis G, Akrivos T, Alevizaki M, et al. Renal dysfunction in acute stroke: an independent predictor of long-term all combined vascular events and overall mortality. Nephrol Dial Transplant 2009;24:194–200.

12. Yahalom G, Schwartz R, Schwammenthal Y, et al. Chronic kidney disease and clinical outcome in patients with acute stroke. Stroke 2009;40:1296–1303.

13. Agrawal V, Rai B, Fellows J, McCullough PA. In-hospital outcomes with thrombolytic therapy in patients with renal dysfunction presenting with acute ischaemic stroke. Nephrol Dial Transplant 2010;25:1150–1157.

14. Naganuma M, Koga M, Shiokawa Y, et al. Reduced estimated glomerular filtration rate is associated with stroke outcome after intravenous rt-PA: the Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) rt-PA registry. Cerebrovasc Dis 2011;31:123–129.

15. Kamouchi M, Matsuki T, Hata J, et al. Prestroke glycemic control is associated with the functional outcome in acute ischemic stroke: the Fukuoka Stroke Registry. Stroke 2011;42:2788–2794.

16. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications: part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539–553.

17. Hemmelgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria, and adverse outcomes. JAMA 2010;303:423–429.

18. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982–992.

19. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1–266.

20. Go AS, Fang MC, Udaltsova N, et al. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Circulation 2009;119:1363–1369.

21. Toyoda K, Fujimoto S, Kamouchi M, Iida M, Okada Y. Acute blood pressure levels and neurological deterioration in different subtypes of ischemic stroke. Stroke 2009;40:2585–2588.

22. Brzosko S, Szkolka T, Mysliwiec M. Kidney disease is a negative predictor of 30-day survival after acute ischaemic stroke. Nephron Clin Pract 2009;112:c79–85.

23. Ovbiagele B, Sanossian N, Liebeskind DS, et al. Indices of kidney dysfunction and discharge outcomes in hospitalized stroke patients without known renal disease. Cerebrovasc Dis 2009;28:582–588.

24. Irie F, Iso H, Sairenchi T, et al. The relationships of proteinuria, serum creatinine, glomerular filtration rate with cardiovascular disease mortality in Japanese general population. Kidney Int 2006;69:1264–1271.

25. Madison JR, Spies C, Schatz IJ, et al. Proteinuria and risk for stroke and coronary heart disease during 27 years of follow-up: the Honolulu Heart Program. Arch Intern Med 2006;166:884–889.

26. Agrawal V, Marinescu V, Agarwal M, McCullough PA. Cardiovascular implications of proteinuria: an indicator of chronic kidney disease. Nat Rev Cardiol 2009;6:301–311.

27. Rodriguez-Yanez M, Castellanos M, Blanco M, et al. Micro- and macroalbuminuria predict hemorrhagic transformation in acute ischemic stroke. Neurology 2006;67:1172–1177.

28. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA 2007;298:2038–2047.

29. Toyoda K, Fujii K, Fujimi S, et al. Stroke in patients on maintenance hemodialysis: a 22-year single-center study. Am J Kidney Dis 2005;45:1058–1066.