Decreased Estimated Glomerular Filtration Rate and Proteinuria and Long-Term Outcomes After Ischemic Stroke: A Longitudinal Observational Cohort Study

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Decreased eGFR and proteinuria and long-term outcomes after ischemic stroke: a longitudinal observational cohort study

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1 Abstract

2	Background: It remains unclear how chronic kidney disease (CKD) and its underlying
3	pathological conditions, kidney dysfunction and kidney damage, are associated with
4	cardiovascular outcomes. This study aimed to determine whether kidney dysfunction (i.e.,
5	decreased estimated glomerular filtration rate [eGFR]), kidney damage (i.e., proteinuria), or
6	both are associated with the long-term outcomes after ischemic stroke.
7	Methods: A total of 12,576 patients (mean age: 73.0±12.6 years; 41.3% women) with
8	ischemic stroke who were registered in a hospital-based multicenter registry, Fukuoka Stroke
9	Registry, between June 2007 and September 2019, were prospectively followed up after
10	stroke onset. Kidney function was assessed by eGFR and categorized into G1: ≥60
11	mL/min/1.73 m ² , G2: 45–59 mL/min/1.73 m ² , and G3: <45 mL/min/1.73 m ² . Kidney damage
12	was evaluated by proteinuria using a urine dipstick test and classified into P1: –, P2: $\pm/1+$,
13	and P3: \geq 2+. Hazard ratios (HR) and 95% confidence intervals (CI) for events of interest
14	were estimated by a Cox proportional hazards model. Long-term outcomes included
15	recurrence of stroke and all-cause death.
16	Results: During the median follow-up of 4.3 years (interquartile range: 2.1–7.3 years), 2481
17	patients had recurrent stroke (48.0/1,000 patient-years) and 4032 patients died (67.3/1,000
18	patient-years). CKD was independently associated with increased risks of stroke recurrence
19	and all-cause death even after adjustment for multiple confounding factors, including
20	traditional cardiovascular risk factors. Both eGFR and proteinuria were independently
21	associated with increased risks of stroke recurrence (multivariable-adjusted HR [95% CI]: G3
22	1.22 [1.09–1.37] vs. G1, P3 1.25 [1.07–1.46] vs. P1) and death (G3 1.45 [1.33–1.57] vs. G1,
23	P3 1.62 [1.45–1.81] vs. P1). In subgroup analyses, effect modifications were found in the
24	association of proteinuria with death by age and stroke subtype.
25	Conclusion: Kidney dysfunction and kidney damage were independently, but differently,

- 1 associated with increased risks of recurrent stroke and all-cause death.
- 2
- 3 Keywords: CKD, decreased eGFR, ischemic stroke, long-term outcomes, proteinuria
- 4
- 5 Non-standard Abbreviations and Acronyms: CKD: chronic kidney disease, eGFR:
- 6 estimated glomerular filtration rate.

1 Introduction

2 Stroke is a major cause of disability worldwide. Because stroke recurrence has further serious 3 consequences, such as severe functional impairment and death, recurrent stroke should be 4 prevented as much as possible through appropriate management of risk factors. Nevertheless, 5 recurrent stroke can still occur when cardiovascular risk factors are effectively controlled. Various risk factors for stroke have been identified to date, such as aging, lifestyle-related 6 7 diseases (hypertension, diabetes mellitus, dyslipidemia, obesity, smoking, drinking), and atrial fibrillation. Other than these traditional risk factors, CKD has been highlighted as a 8 novel potential risk factor for cardiovascular diseases, including ischemic stroke and death.¹⁻³ 9 10 However, because CKD shares similar risk factors to stroke, the causal relationship between CKD and cardiovascular diseases remains uncertain.⁴⁻⁶ 11 12 It is possible that non-traditional risk factors related to CKD may cause cardiovascular disorders that lead to ischemic stroke or death.⁷ Several clinical studies have attempted to 13 14 clarify the associations between CKD and risks of stroke and death, but produced inconsistent results in the general population⁸⁻¹¹ and patients with stroke. ^{12,13}Therefore, it 15 remains controversial whether CKD can act as a biomarker for underlying cardiovascular risk 16 17 factors. Moreover, although CKD has two underlying pathological conditions (i.e., kidney dysfunction and kidney damage), few studies have assessed the combined effect of both 18 conditions.^{12,13} Thus, whether either or both are associated with the risks of cardiovascular 19 20 events and death remains unclear. 21 The present study was conducted to address two questions: (1) whether CKD is a risk factor 22 for stroke recurrence or death independently of traditional cardiovascular risk factors and (2) 23 whether impaired kidney function and/or kidney damage are associated with the risk of stroke 24 recurrence or death in patients with ischemic stroke. Briefly, we simultaneously evaluated 25 estimated glomerular filtration rate (eGFR) and protein leakage into the urine in patients with

acute ischemic stroke, and followed them for occurrence of recurrent stroke and death after
 stroke onset to a maximum of 10 years in a large-scale multicenter prospective longitudinal
 observational cohort study.

4

5 Methods

6 Study design and setting

7 We constructed the Fukuoka Stroke Registry, a multicenter hospital-based registry that

8 enrolls consecutive patients with acute stroke admitted to seven participating stroke centers in

9 Fukuoka, Japan within 7 days of stroke onset (UMIN-Clinical Trial Registry 00000800).

10 The institutional review board of each hospital approved the study protocol. Written informed

11 consent was obtained from all participants or their family members. This study was

12 performed in accordance with the Strengthening Reporting of Observational Studies in

13 Epidemiology (STROBE) reporting guidelines.¹⁴

14

15 Study participants

16 A total of 15,569 patients with acute ischemic stroke were prospectively registered in the 17 Fukuoka Stroke Registry from June 2007 to September 2019. In the main analysis, we 18 excluded 15 patients who had missing data on variables required for the multivariable model 19 (body mass index, n=14; eGFR, n=1), and 475 patients who received renal replacement 20 therapy because a urine analysis could not be performed due to anuria. We further excluded 21 2,503 patients who had missing data for urine analysis. Finally, 12,576 patients were included 22 in the main analysis. In the sensitivity analyses, the patients who received renal replacement 23 therapy were included, and assumed to have had very low eGFR and high-grade proteinuria. 24 The patients with missing data for urine analysis were additionally included, and the missing 25 data were handled by multiple imputation. The patient selection process is shown in Figure

2

3 **Baseline characteristics**

The baseline characteristics, including age, sex, body mass index, cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking, drinking), coronary artery disease, history of previous stroke, stroke subtype, modified Rankin Scale score before stroke onset, stroke severity scored by National Institutes of Health Stroke Scale on admission, and stroke subtype, were investigated on admission or during hospitalization for index stroke. Definitions of the clinical variables are provided in the Supplemental Methods.

12 Assessment of eGFR and proteinuria

13 We measured serum creatinine levels on admission for index stroke and calculated the eGFR using the equation proposed by the Japanese Society of Nephrology.¹⁵ We categorized eGFR 14 15 into three groups based on the classification of the National Kidney Foundation as G1: eGFR >60 mL/min/1.73 m², G2: eGFR 45-59 mL/min/1.73 m², and G3: eGFR<45 mL/min/1.73 16 m^2 . Details for the eGFR assessment and categorization are provided in the Supplemental 17 18 Methods. 19 The urinary protein concentration was evaluated by a quasi-quantitative method using urine 20 dipstick readings and classified into negative (-), trace (\pm), mild (1+), and severe (\geq 2+) as previously described.¹⁰ The levels of proteinuria were then grouped into P1: -, P2: $\pm/1+$, and 21 P3: \geq 2+ according to the Kidney Disease Improving Global Outcomes (KDIGO) guideline 22

23 with minor modifications.^{2,10,16-18}

24

25 Definition of CKD and CKD risk categories

1	CKD was defined as low eGFR (<60 mL/min/1.73 m ²) and/or proteinuria (urine dipstick
2	\geq 1+) according to the CKD guideline. The risk categories for CKD were graded as low,
3	moderate, high, and very high according to combinations of eGFR and proteinuria based on
4	the KDIGO guideline.

5

6 Clinical outcomes

The clinical outcomes included recurrent stroke and death during the follow-up period from
onset to a maximum of 10 years after index stroke. Recurrent stroke was defined as a
recurrent event of ischemic or hemorrhagic stroke. Death was defined as death from any
cause.

11

12 Statistical methods

13 Detailed methods for comparing baseline characteristics according to various factors are 14 described in the Supplemental Methods. Cumulative event rates were calculated by the 15 Kaplan–Meier method, and inter-group differences in the curves were evaluated by the log-16 rank test. A Cox proportional hazards model was used to estimate the hazard ratio (HRs) and 17 95% confidence intervals (CIs) for the long-term outcomes in each categorized group. The 18 multivariable model included age, sex, risk factors (hypertension, diabetes mellitus, 19 dyslipidemia, atrial fibrillation, smoking, drinking), coronary artery disease, body mass 20 index, previous stroke, stroke subtype, prestroke modified Rankin Scale score, and National 21 Institutes of Health Stroke Scale score on admission. 22 Subgroup analyses were performed according to age, sex, risk factors, and stroke subtype. P-23 values for heterogeneity were calculated by adding the interaction term of eGFR or 24 proteinuria × subgroup variables in the model.

25 For sensitivity analyses, we repeated the analyses after including patients who received renal

1	replacement therapy in the G3 and P3 groups or very high risk group. We also performed	
2	multiple imputation to handle missing data for urine analysis. The missing data were	
3	imputed, and 20 imputed datasets were generated. The results for these datasets were	
4	combined into a single imputation result.	
5	All statistical analyses were performed using Stata15 (Stata Corp LP, College Station, TX,	
6	USA). Two-sided values of P<0.05 were considered statistically significant.	
7		
8	Results	
9	Baseline characteristics	
10	The mean (standard deviation) age of the 12,576 patients was 73.0 (12.6) years, and 41.3%	
11	were women. Most variables, except for dyslipidemia, differed significantly according to	
12	presence of CKD (Table S1). Table 1 shows the trends in baseline characteristics according	
13	to eGFR and proteinuria levels. Baseline characteristics significantly differed according to	
14	eGFR levels. Similar trends in baseline characteristics were observed for proteinuria levels,	
15	except for body mass index.	
16		
17	Associations of CKD, eGFR, and proteinuria with long-term risks of stroke recurrence and	
18	death	
19	The median (interquartile range) follow-up duration was 4.3 (2.1–7.3) years, and the	
20	maximum was 10 years. The total follow-up time was 59,893 patient-years. During follow-	
21	up, 2,481 patients (19.7%) had recurrent stroke and 4,032 patients (32.1%) died. The event	
22	rates of recurrent stroke and all-cause death were 48.0 and 67.3 events per 1,000 patient-	
23	years, respectively.	
24	The cumulative rate of recurrent stroke increased according to presence of CKD (Figure 1A),	
25	decreasing eGFR levels (Figure 1B), and increasing proteinuria levels (Figure 1C). In the	

1	Cox model, the HR for stroke recurrence increased significantly for presence of CKD even
2	after adjustment for potential confounding factors, including traditional cardiovascular risk
3	factors (Table 2). The multivariable-adjusted HR of recurrent stroke increased linearly with
4	decreasing eGFR levels after additional adjustment for proteinuria, whereas it slightly
5	increased for high-grade proteinuria only after additional adjustment for eGFR. When we
6	evaluated the associations after regarding death other than stroke as a competing risk,
7	decreasing eGFR levels were still significantly associated with an increased risk of stroke
8	recurrence, whereas the association of proteinuria levels with risk of stroke recurrence was
9	weakened (Table S2).
10	The cumulative rate of death increased significantly according to presence of CKD (Figure
11	2A), decreasing eGFR levels (Figure 2B), and increasing proteinuria levels (Figure 2C). Even
12	after adjustment for multiple confounding factors, the HR for death increased significantly
13	according to presence of CKD, decreasing eGFR levels, and increasing proteinuria levels
14	(Table 3).
15	

16 Associations of combinations of eGFR and proteinuria with long-term outcomes

We stratified the patients according to combinations of eGFR and proteinuria (Figure 3). The 17 18 multivariable-adjusted HR for recurrent stroke increased with decreasing eGFR levels in each 19 proteinuria group and with increasing proteinuria levels in each eGFR group. The risk of 20 death also increased linearly with decreasing eGFR levels and increasing proteinuria levels. 21 In the predictive model for recurrent stroke, model fit was improved when eGFR or 22 proteinuria was simultaneously included in the multivariable model in addition to proteinuria 23 and eGFR, respectively (Table S3). Similarly, the model fit in predicting death was 24 significantly improved by adding each factor to the other. Regarding discrimination, the 25 addition of each factor to the other tended to improve the prediction of death but not that of

1	recurrent stroke (Table S3). No interaction was found in the associations with stroke
2	recurrence and death by adding the interaction term of $eGFR \times proteinuria$ to the relevant
3	models (Table S4).
4	
5	CKD risk categories and long-term risks of stroke recurrence and death
6	We investigated whether the CKD risk categories proposed in the KDIGO guideline were
7	predictive of long-term outcomes after stroke. The cumulative rates of recurrent stroke and
8	death increased as the severity of the CKD risk category increased (Figure S2). The
9	multivariable-adjusted HRs for stroke recurrence and all-cause death increased in proportion
10	to the severity of the CKD risk category (Table S5).
11	
12	Subgroup analyses
13	We performed subgroup analyses for demographic characteristics (age [<75 years or \ge 75
14	years] and sex), risk factors (hypertension and diabetes mellitus), and stroke subtype
15	(cardioembolic or non-cardioembolic). No heterogeneity was found in the associations of
16	eGFR with risks of recurrent stroke (Figure S3) and death (Figure S4). Although there was no
17	heterogeneity in the association of proteinuria with risk of recurrent stroke (Figure S5),
18	heterogeneity existed in the association between proteinuria and risk of death: the association
19	was also stronger in patients aged <75 years compared with patients aged \ge 75 years, and the
20	association was also stronger in patients with non-cardioembolic stroke compared with
21	patients with cardioembolic stroke (Figure S6).
22	
23	Sensitivity analyses
24	Finally, to exclude any selection bias arising from the exclusion of patients who received

25 renal replacement therapy (Table S6), we performed sensitivity analyses after including the

1	patients who received renal replacement therapy in the G3 and P3 groups. In these
2	subanalyses, the associations of CKD, eGFR, and proteinuria with risks of recurrent stroke
3	and all-cause death were essentially unchanged (Table S7). The CKD risk categories also had
4	significant associations with the risks of stroke recurrence and all-cause death (Table S8).
5	Moreover, we performed multiple imputation to handle missing data for urine analysis after
6	additionally including patients with missing urinary protein concentration data (Table S9).
7	Similar results were found for the associations of CKD, eGFR, proteinuria (Table S10), and
8	CKD risk categories (Table S11) with risks of recurrent stroke and death.

9

10 **Discussion**

11 The major findings of the present study were as follows. First, presence of CKD, defined as 12 reduced eGFR and/or proteinuria, was significantly associated with increased risks of stroke 13 recurrence and death independently of traditional cardiovascular risk factors in patients with 14 ischemic stroke. Second, even when evaluating the combined effect of eGFR and proteinuria, 15 eGFR and proteinuria were independently associated with the long-term risks of recurrent 16 stroke and death in different ways. Specifically, decreased eGFR levels were associated with 17 the increased risks of stroke recurrence and all-cause death. Higher grades of proteinuria were also significantly associated with an increased risk of all-cause death. The risk of stroke 18 19 recurrence increased only for a high level of proteinuria, although the association was 20 weakened when regarding death as a competing risk. Third, CKD risk categories stratified by 21 the KDIGO guideline were predictive of the risks of stroke recurrence and death. Fourth, 22 heterogeneity in the associations was found for proteinuria, but not for eGFR: the association 23 between proteinuria and risk of death was stronger in patients aged <75 years compared with 24 patients aged \geq 75 years and the association was also stronger in patients with non-25 cardioembolic stroke compared with patients with cardioembolic stroke. These findings

1	suggest that both kidney dysfunction and kidney damage are independent risk factors for
2	recurrent stroke and death in patients with ischemic stroke, but increase the risks of
3	cardiovascular outcomes in different ways.

4

5 **CKD** and long-term outcomes

The present study clearly indicates that CKD is a risk factor for recurrent stroke and all-cause 6 7 death in patients with ischemic stroke, independently from traditional cardiovascular risk factors. Some hypotheses can be proposed for the mechanisms underlying the increased 8 cardiovascular risk with CKD.¹⁹ For example, various changes are observed in patients with 9 10 CKD, such as uremic toxin production, renin-angiotensin activation, chronic inflammation, 11 oxidative stress, anemia, and vascular calcification, that may lead to endothelial dysfunction and eventually promote arteriosclerosis.⁷ These pathological changes may also be involved in 12 13 the increased risks of unfavorable cardiovascular outcomes in patients with CKD, 14 independently of traditional cardiovascular risk factors. 15

16 Kidney dysfunction, kidney damage, and long-term outcomes

It remains controversial whether impaired kidney function, kidney damage, or both are 17 involved in cardiovascular outcomes.^{12,13} Previous studies produced various findings on the 18 associations of these two pathological conditions with cardiovascular outcomes in the general 19 population.^{1,9,10,20} Meanwhile, the results in studies with small cohorts of stroke patients 20 were inconsistent.^{12,13} These discrepancies may arise from differences in the sample sizes, 21 22 demographic characteristics, baseline comorbidities, and follow-up periods among the 23 studies. 24 In the present cohort of Japanese patients with ischemic stroke, decreased eGFR was

25 significantly associated with an increased risk of stroke recurrence. Proteinuria was also

1	associated with risk of stroke recurrence, although the association tended to be less
2	significant after considering death as a competing risk. Meanwhile, the risk of all-cause death
3	increased in proportion to the severity of both pathological conditions. The joint effects of
4	eGFR and proteinuria indicate that kidney dysfunction and kidney damage are mutually
5	independent risk factors of recurrent stroke and death in the long term after ischemic stroke.
6	The urinary protein concentration can reflect disorders of the glomerular capillaries and
7	possibly systemic microvessels, including cerebral small vessels. ^{8,21} We previously
8	demonstrated that proteinuria was significantly associated with 3-month functional outcomes
9	after ischemic stroke. ²² Assuming that proteinuria is an indicator of impairments in the
10	systemic microvasculature, such as capillary rarefaction, ²³ proteinuria would predict not only
11	short-term functional outcomes via impaired cerebral microcirculation but also future risks of
12	death and possibly stroke recurrence via end-organ damage. One possible explanation is that
13	reversible functional rarefaction may precede structural rarefaction in the microvasculature,
14	because proteinuria can be improved to some extent by appropriate treatments, such as
15	inhibition of the renin-angiotensin-aldosterone system. ^{24,25}
16	Unlike proteinuria, eGFR is considered a comprehensive indicator of small vessel disease and
17	arteriosclerosis. Furthermore, low eGFR possibly reflects increased levels of non-traditional
18	risk factors, such as total homocysteine, inflammation, nitric oxide production, oxidative
19	stress, and thrombogenic factors. ²⁶ For example, indoxyl sulfate, a well-known uremic toxin,
20	increases in inverse proportion to eGFR levels from CKD stage 3. ²⁷ On the one hand, uremic
21	toxins not only induce glomerular sclerosis but also cause damage to cardiomyocytes and
22	vasculatures. ²⁸ On the other hand, renal arteriosclerosis and glomerular sclerosis reduce
23	eGFR, which could further accelerate systemic atherosclerosis and eventually result in
24	unfavorable cardiovascular outcomes. Moreover, cardiac disorders due to increased afterload
25	following reduced eGFR may enhance the risks of vascular events and death. ^{5,29} In addition

1	to these biological changes, altered treatment strategies, such as limitations of
2	pharmacotherapy, endovascular treatment, and surgical treatment, would be disadvantageous
3	to the long-term risks of stroke recurrence and death in stroke patients with CKD. ^{6,30}
4	Our study revealed that effect modifications on the associations with long-term outcomes
5	existed for proteinuria, but not for eGFR. The association between proteinuria and increased
6	risk of death was strong in patients aged <75 years and patients with non-cardioembolic
7	stroke. In these patients, high urinary protein concentrations may be a warning sign for
8	serious impairment in the systemic microvasculature, and proteinuria may predict
9	unfavorable consequences in the future. By contrast, reduced eGFR may generally worsen
10	the long-term cardiovascular outcomes in patients irrespective of the baseline characteristics.
11	

12 *CKD risk stratification and long-term outcomes*

To our knowledge, we are the first to investigate whether CKD risk categories according to the KDIGO guideline are indicative of future risks of recurrent stroke and death. In the CKD classification, progression of CKD was stratified using not only eGFR levels but also albuminuria levels.² In the present study, the long-term risks of stroke recurrence and death increased linearly in proportion to the severity of the CKD risk category. Thus, the KDIGO CKD risk stratification can be a good indicator of future cardiovascular risks after ischemic stroke, implying that proteinuria should be considered in addition to eGFR for risk prediction.

20

21 Study strengths and limitations

The present study has several strengths: the sample size was large; the study patients were consecutively enrolled; the baseline confounders were assessed without missing data; and the follow-up period was long with a high follow-up rate. The study also has several limitations that require consideration. First, patients with missing data for urine analysis were excluded,

1 leading to a selection bias. However, similar results were obtained after multiple imputation. 2 Second, patients who received renal replacement therapy were excluded because data for 3 urine analysis were unavailable. However, the results were unchanged when the patients who 4 received renal replacement therapy were categorized into the G3 and P3 groups. Third, the 5 urinary protein levels were quasi-quantitatively evaluated by a dipstick test, rather than being 6 measured directly. However, the results were unchanged when the classification levels for proteinuria were shifted. Fourth, we did not control for long-term treatments or medications 7 8 during the follow-up period. Finally, the study patients were enrolled in a restricted local area 9 of Japan, and therefore generalization of the findings requires validation in other cohorts of 10 patients from different races and ethnicities.

11

12 Clinical perspectives

13 The present study demonstrated that two components of CKD, kidney dysfunction and 14 kidney damage, are independently and differently associated with an increased risk of 15 unfavorable post-stroke outcomes, aside from traditional risk factors. Cardiovascular risk 16 factors may additively increase the risk of cardiovascular events via the progression of CKD 17 in addition to the direct effects on the cardiovascular system. Although controlling 18 cardiovascular risk factors is the top priority in daily clinical practice, eGFR and proteinuria 19 require additional attention to reduce the residual risk of negative cardiovascular outcomes. 20 Treatments for CKD, such as inhibition of the renin-angiotensin-aldosterone system or 21 sodium-glucose transporter 2, have been shown to slow kidney dysfunction and kidney damage.^{25,31} Further studies are needed to determine whether interventions targeting CKD 22 23 can offer additional benefits to post-stroke outcomes following ischemic stroke.

24

25 **Conclusions**

1	Gradual loss of kidney function and progression of kidney damage are mutually independent
2	risk factors for stroke recurrence and death in the long term after ischemic stroke. However,
3	there was no interaction in the associations between eGFR and proteinuria. Because
4	heterogeneity in the associations was only found for proteinuria in subgroup analyses, the
5	pathophysiological mechanisms responsible for cardiovascular risks may differ between these
6	two pathological conditions. In addition to traditional cardiovascular risk factors, decreased
7	eGFR and proteinuria require close attention in daily clinical practice. Further studies are
8	warranted to validate the impacts of kidney dysfunction and kidney damage on
9	cardiovascular risks and to determine whether interventions for these pathological conditions
10	are effective in improving the cardiovascular outcomes in patients with ischemic stroke.
11	
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22	
23	Disclosures

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1 Supplemental Material

- 2 Supplemental Methods
- 3 Tables S1–S11
- 4 Figures S1–S6
- 5 Appendix
- 6

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	eGl	FR, mL/min/1.7	$^{\prime}3 \text{ m}^2$			Proteinuria		
	≥60	45–59	<45	•	_	\pm or 1+	≥2+	
	n=7976	n=2692	n=1908	P _{trend}	n=8806	n=2847	n=923	P _{trend}
Age, y, mean (SD)	69.9 (12.7)	77.6 (10.2)*	79.6 (10.6)*	< 0.001	72.2 (12.4)	75.2 (12.7) †	73.1 (13.1)	< 0.001
Female sex, n (%)	3129 (39.2)	1156 (42.9)*	903 (47.3)*	< 0.001	3696 (42.0)	1156 (40.6)	336 (36.4) †	0.002
Risk factor, n (%)								
Hypertension	6136 (76.9)	2285 (84.9)*	1722 (90.3)*	< 0.001	6880 (78.1)	2421 (85.0) †	842 (91.2) †	< 0.001
Diabetes mellitus	2472 (31.0)	768 (28.5)	692 (36.3)*	0.002	2379 (27.0)	1044 (36.7) [†]	509 (55.2) †	< 0.001
Dyslipidemia	4452 (55.8)	1488 (55.3)	1011 (53.0)	0.04	4837 (54.9)	1538 (54.0)	576 (62.4) †	0.005
Atrial fibrillation	1637 (20.5)	838 (31.1)*	683 (35.8)*	< 0.001	1939 (22.0)	939 (33.0) †	280 (30.3) [†]	< 0.001
Smoking	4426 (55.5)	1314 (48.8)*	918 (48.1)*	< 0.001	4611 (52.4)	1493 (52.4)	554 (60.0) †	0.001
Drinking	3064 (38.4)	811 (30.1)*	407 (21.3)*	< 0.001	3134 (35.6)	878 (30.8) †	270 (29.3) †	< 0.001
Coronary artery disease, n (%)	878 (11.0)	463 (17.2)*	461 (24.2)*	< 0.001	1132 (12.9)	502 (17.6) †	168 (18.2) †	< 0.001
BMI, kg/m ² , mean (SD)	23.1 (3.9)	22.9 (3.8)*	22.5 (3.9)*	< 0.001	23.0 (3.7)	22.8 (4.0)	23.3 (4.4) [†]	0.31
Previous stroke, n (%)	1371 (17.2)	643 (23.9)*	552 (28.9)*	< 0.001	1697 (19.3)	640 (22.5) †	229 (24.8) †	< 0.001
Cardioembolic stroke, n (%)	1476 (18.5)	752 (27.9)*	583 (30.6)*	< 0.001	1711 (19.4)	834 (29.3) †	266 (28.8) †	< 0.001
Prestroke mRS score, median (IQR)	0 (0-0)	0 (0–2)*	0 (0–3)*	< 0.001	0 (0–1)	0 (0–2) †	0 (0–2) †	< 0.001
NIHSS score, median (IQR)	3 (1-6)	3 (1-8)*	4 (2–10)*	< 0.001	3 (1-6)	4 (2–12) †	4 (2–12) †	< 0.001
Proteinuria, n (%)	983 (12.3)	505 (18.8)*	734 (38.5)*	< 0.001				
eGFR <60 mL/min/1.73 m ² , n (%)					2683 (30.5)	1323 (46.5) †	594 (64.4) †	< 0.001

1 Table 1. Background characteristics of patients according to eGFR or proteinuria

2 $^{*}P < 0.05$ vs. eGFR ≥ 60 mL/min/1.73 m². $^{\dagger}P < 0.05$ vs. negative proteinuria.

3 eGFR: estimated glomerular filtration rate; P_{trend}: P for trend; SD: standard deviation; BMI: Body mass index; mRS: modified Rankin Scale;

4 IQR: interquartile range, NIHSS: National Institutes of Health Stroke Scale.

			Age- and sex-adjusted		Multivariable-ad		justed	
	Events, n (%)	Event rate	HR	(95% CI)	Р	HR	(95% CI)	Р
CKD								
No CKD, n=6993	1270 (18.2)	39.0	1.00	(reference)		1.00	(reference)	
CKD, n=5583	1211 (21.7)	63.5	1.29	(1.19–1.40)	< 0.001	1.19	(1.09–1.30)	< 0.001
eGFR								
G1 (eGFR ≥60 mL/min/1.73 m ²), n=7976	1448 (18.2)	40.2	1.00	(reference)		1.00	(reference)	
G2 (eGFR 45–59 mL/min/1.73 m ²), n=2692	585 (21.7)	58.7	1.18	(1.07–1.31)	0.001	1.13	(1.02–1.25)	0.02
G3 (eGFR <45 mL/min/1.73 m ²), n=1908	448 (23.5)	78.8	1.35	(1.21–1.52)	< 0.001	1.22	(1.09–1.37)	0.001
P _{trend}					< 0.001			< 0.001
Proteinuria								
P1 (-), n=8806	1718 (19.5)	43.5	1.00	(reference)		1.00	(reference)	
P2 (±/1+), n=2847	556 (19.5)	59.8	1.11	(1.01–1.23)	0.03	1.09	(0.98–1.20)	0.10
P3 (≥2+), n=923	207 (22.4)	72.6	1.30	(1.12–1.51)	0.001	1.25	(1.07 - 1.46)	0.004
P _{trend}					< 0.001			0.003

2 The event rates are shown as events/1,000 person-years. The multivariable model included age, sex, risk factors (hypertension, diabetes mellitus,

3 dyslipidemia, atrial fibrillation, smoking, drinking), coronary artery disease, body mass index, previous stroke, stroke subtype, prestroke

4 modified Rankin Scale score, and National Institutes of Health Stroke Scale score on admission. To estimate the HR of stroke recurrence for

5 eGFR or proteinuria, eGFR and proteinuria were simultaneously included in the multivariable model. CKD: chronic kidney disease; eGFR:

6 estimated glomerular filtration rate; P_{trend}: P for trend; HR: hazard ratio; CI: confidence interval.

			Ag	Age- and sex-adjusted			Multivariable-adjusted		
	Events, n (%)	Event rate	HR	(95% CI)	Р	HR	(95% CI)	Р	
СКД									
No CKD, n=6993	1603 (22.9)	43.0	1.00	(reference)		1.00	(reference)		
CKD, n=5583	2429 (43.5)	107.5	1.46	(1.37–1.56)	< 0.001	1.40	(1.31–1.50)	< 0.001	
eGFR									
G1 (eGFR ≥60 mL/min/1.73 m ²), n=7976	1966 (24.6)	47.7	1.00	(reference)		1.00	(reference)		
G2 (eGFR 45–59 mL/min/1.73 m ²), n=2692	1042 (38.7)	88.3	1.05	(0.97–1.13)	0.22	1.15	(1.07 - 1.25)	< 0.001	
G3 (eGFR <45 mL/min/1.73 m ²), n=1908	1024 (53.7)	149.4	1.34	(1.23–1.45)	< 0.001	1.45	(1.33–1.57)	< 0.001	
P _{trend}					< 0.001			< 0.001	
Proteinuria									
P1 (-), n=8806	2433 (27.6)	53.3	1.00	(reference)		1.00	(reference)		
P2 (±/1+), n=2847	1185 (41.6)	110.0	1.62	(1.51–1.74)	< 0.001	1.34	(1.25–1.44)	< 0.001	
P3 (≥2+), n=923	414 (44.9)	120.6	2.05	(1.84–2.29)	< 0.001	1.62	(1.45–1.81)	< 0.001	
P _{trend}					< 0.001			< 0.001	

1 Table 3. Associations of CKD, eGFR, and proteinuria with risk of death

2 The event rates are shown as events/1,000 person-years. The multivariable model included age, sex, risk factors (hypertension, diabetes mellitus,

3 dyslipidemia, atrial fibrillation, smoking, drinking), coronary artery disease, body mass index, previous stroke, stroke subtype, prestroke

4 modified Rankin Scale score, and National Institutes of Health Stroke Scale score on admission. To estimate the HR of death for eGFR or

5 proteinuria, eGFR and proteinuria were simultaneously included in the multivariable model. CKD: chronic kidney disease; eGFR: estimated

6 glomerular filtration rate; P_{trend}: P for trend; HR: hazard ratio; CI: confidence interval.

1 Figure legends

2 Figure 1. Cumulative rates of stroke recurrence according to CKD, eGFR, and

3 proteinuria

4 (A-C) Cumulative rates of stroke recurrence according to CKD (A), eGFR levels (B), and

5 proteinuria levels (C) are shown. The cumulative rates in the follow-up period were estimated

6 by the Kaplan–Meier method. The P-values were evaluated by the log-rank test. The numbers

7 at risk are shown beneath the cumulative incidence curves. CKD: chronic kidney disease;

8 eGFR: estimated glomerular filtration rate; UP: urine protein.

9

10 Figure 2. Cumulative rates of death according to CKD, eGFR, and proteinuria

11 (A–C) Cumulative rates of death according to CKD (A), eGFR levels (B), and proteinuria

12 levels (C) are shown. The cumulative rates in the follow-up period were estimated by the

13 Kaplan–Meier method. The P-values were evaluated by the log-rank test. The numbers at risk

14 are shown beneath the cumulative incidence curves. CKD: chronic kidney disease; eGFR:

15 estimated glomerular filtration rate; UP: urine protein.

16

17 Figure 3. Associations of combinations of eGFR and proteinuria with risks of stroke

18 recurrence and death

19 (A, B) The multivariable-adjusted HRs for stroke recurrence (A) or death (B) are shown for

20 combinations of eGFR and proteinuria. Patients were categorized according to their eGFR

21 levels (G1: $\geq 60 \text{ mL/min}/1.73 \text{ m}^2$; G2: 45–59 mL/min/1.73 m²; G3: <45 mL/min/1.73 m²) and

- 22 proteinuria levels (P1: -; P2: $\pm/1+$; P3: $\geq 2+$). The HRs were estimated by using patients with
- 23 G1 and P1 as the reference. The multivariable model included age, sex, risk factors
- 24 (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking, drinking),
- 25 coronary artery disease, body mass index, previous stroke, stroke subtype, prestroke modified

- 1 Rankin Scale score, and National Institutes of Health Stroke Scale score on admission. The
- 2 levels of eGFR and proteinuria were simultaneously included in the multivariable model. HR:
- 3 hazard ratio, eGFR: estimated glomerular filtration rate.

1	SUPPLEMENTAL MATERIAL
23	Decreased eGFR and proteinuria and long-term outcomes after ischemic stroke:
4	a longitudinal observational cohort study
5	
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36 Supplemental Appendix

1 Supplemental Methods

2 Clinical variables

- 3 Stroke was defined as sudden onset of a non-convulsive and neurological deficit that
- 4 persisted for \geq 24 hours. Ischemic stroke was confirmed by neuroimaging examinations,
- 5 including computed tomography and/or magnetic resonance imaging. Hypertension was
- 6 defined as systolic blood pressure \geq 140 mmHg or diastolic blood pressure \geq 90 mmHg in the
- 7 chronic stage, or as pre-stroke treatment with antihypertensive agents. Diabetes mellitus was
- 8 defined as fasting blood glucose concentration \geq 7.0 mmol/L, casual blood glucose
- 9 concentration \geq 11.1 mmol/L, positive 75-g oral glucose tolerance test result, or glycated
- 10 hemoglobin A1c concentration $\geq 6.5\%$ on 2 different days during hospitalization or in the
- 11 chronic stage, or as pre-stroke treatment with oral hypoglycemic agents or insulin.
- 12 Dyslipidemia was defined as low-density lipoprotein-cholesterol concentration \geq 3.62
- 13 mmol/L, high-density lipoprotein-cholesterol concentration <1.03 mmol/L, or triglyceride
- 14 concentration ≥ 1.69 mmol/L during hospitalization or in the chronic stage, or as pre-stroke
- 15 treatment with antihyperlipidemic agents. Atrial fibrillation was diagnosed based on previous
- 16 history or electrocardiography during hospitalization. Atrial fibrillation was defined as any
- 17 type of atrial fibrillation, including paroxysmal, persistent, or permanent. Smoking was
- 18 defined as current or former smoker. Drinking was defined as alcohol intake >20 g per day.
- 19 Coronary artery disease was defined as history of angina pectoris, myocardial infarction,
- percutaneous coronary intervention, or coronary artery bypass graft surgery. Body mass
 index was calculated on admission using height and weight. Previous stroke was defined as
- history of hemorrhagic and ischemic stroke before the index stroke. Stroke subtype was
- classified into cardioembolic or non-cardioembolic (large artery atherosclerosis, small-vessel
- occlusion, others) based on the Trial of Org 10172 in the Acute Stroke Treatment (TOAST)
- criteria. Prestroke functional status before onset was evaluated using the modified Rankin
- 26 Scale score. Stroke severity was assessed using National Institutes of Health Stroke Scale
- 27 score on admission.

28 Assessment of eGFR and proteinuria

- 29 The estimated glomerular filtration rate (eGFR) was determined using data for serum
- 30 creatinine levels measured on admission for index stroke. The eGFR was calculated using the
- 31 equation proposed by the Japanese Society of Nephrology as follows: eGFR (mL/min/1.73
- 32 m^2) = 194 × serum creatinine (mg/dL)^{-1.094} × age (years)^{-0.287} in males; eGFR
- 33 $(mL/min/1.73 \text{ m}^2) = 194 \times \text{serum creatinine } (mg/dL)^{-1.094} \times \text{age (years)}^{-0.287} \times 0.739 \text{ in}$ 34 formulas ¹⁵
- 34 females.¹⁵
- 35 In the Kidney Disease Improving Global Outcomes (KDIGO) guideline, eGFR was
- 36 categorized into six groups: normal or high ($\geq 90 \text{ mL/min}/1.73 \text{ m}^2$), mildly decreased (60–89
- 37 mL/min/1.73 m²), mildly to moderately decreased (45–59 mL/min/1.73 m²), moderately to
- 38 severely decreased (30–44 mL/min/1.73 m²), severely decreased (15–29 mL/min/1.73 m²),
- and kidney failure ($<15 \text{ mL/min}/1.73 \text{ m}^2$). In the present study, the normal or high and mildly
- 40 decreased groups were categorized as G1: eGFR ≥ 60 mL/min/1.73 m², the mildly to
- 41 moderately decreased group was categorized as G2: eGFR 45–59 mL/min/1.73 m², and the
- 42 moderately to severely decreased, severely decreased, and kidney failure groups were
- 43 categorized as G3: $eGFR < 45 mL/min/1.73 m^2$.
- 44 We performed urine analysis using a urine dipstick in the absence of potential urinary tract
- 45 infection during hospitalization for index stroke. The approximate amount of urinary protein
- 46 was estimated by the dipstick readings as follows: trace (\pm , 15 mg/dL), mild (1+, 30 mg/dL),
- 47 and severe $(\geq 2+, \geq 100 \text{ mg/dL})$.¹⁰ We then categorized dipstick results of negative (-) as P1,
- 48 trace (\pm) or mild (1+) as P2, and severe (\geq 2+) as P3, because previous studies demonstrated
- 49 that many patients with a trace (\pm) dipstick result had microalbuminuria based on the urinary
- 50 albumin-to-creatinine ratio.¹⁶

1 Follow-up study

- 2 Patients were enrolled from June 2007 to September 2019 and were prospectively followed
- 3 up until September 2021. After discharge, the patients were initially followed up at 3, 6, and
- 4 12 months after stroke onset, and then annually thereafter. The follow-up study was
- 5 facilitated by research nurses who were trained to interview the participants. The nurses were
- 6 blinded to the clinical data and conducted the interviews using a standardized interview form.
- 7 The following information was collected by face-to-face or telephone interviews with
- 8 patients, family members, or caregivers: vital status, functional status, and stroke recurrence.
- 9 The final date of follow-up was September 30, 2021. Duration of the follow-up period was
- 10 calculated by the time from the date of onset of index stroke to the date of the first relevant
- outcome, death, final follow-up when 10 years had not passed after the onset of index stroke, or 10 years when annual follow-up had been performed as long as 10 years after the onset of
- or 10 years when annual follow-up had been performed as long as 10 years after the onset of index stroke. Consequently, the follow-up period ranged from 2 days to 3653 days. Of 4,108
- patients whose follow-up period was 10 years, 3,342 (81.4%) patients could be followed up.
- 15 The Fukuoka Stroke Registry event adjudication committee reviewed the interview records.
- 16 If the committee suspected that an event of interest had occurred, additional information was
- 17 obtained from the hospitals or other healthcare providers as needed. Finally, the event
- 18 adjudication committee determined whether an event of interest had occurred without
- 19 knowledge of the CKD parameters.

20 Statistical analysis

- 21 The baseline characteristics were compared according to the presence of CKD, renal
- replacement therapy, and missing data for urine analysis using a t-test for parametric
- 23 variables, Mann-Whitney U test for non-parametric variables, and chi-square test for
- 24 categorical variables. Multiple comparisons were performed using Bonferroni's method.
- 25 Trends in baseline characteristics were evaluated using the Cochran-Armitage trend test
- 26 (categorical variables) or the Jonckheere-Terpstra trend test (continuous variables). To test
- 27 the trends of GFR levels and proteinuria levels, we conducted logistic regression analysis by
- 28 regarding their grades as ordinal variables.
- A Cox proportional hazards model was used to estimate hazard ratios and 95% confidence
- 30 intervals for outcomes of interest after adjusting for potential confounding factors. Data were
- 31 censored at the date of the first relevant outcome, death, or final follow-up. Competing risk
- 32 regression was also conducted using the Fine and Gray model. Subdistribution hazard ratios
- and 95% confidence intervals were estimated considering the competing risk of death of any
- 34 cause other than stroke recurrence.
- 35 Effect modification by eGFR or proteinuria was evaluated by adding a multiplicative
- 36 interaction term of eGFR level × proteinuria level to the relevant model. Model fit was
- 37 evaluated using the Akaike information criterion, and improvement in model fit was assessed
- 38 using likelihood ratios. Discrimination in predicting events of interest was evaluated by
- 39 Harrell's concordance index.
- 40 In the main analysis, we excluded patients who received renal replacement therapy, because
- 41 urination was not expected. In the sensitivity analyses, we included the patients who received
- 42 renal replacement therapy in the G3 and P3 groups, because their kidney dysfunction and
- 43 kidney damage were considered to be in the worst groups. In the main analysis, we also
- 44 excluded patients with missing data for urine analysis. However, the lack of data for urine
- analysis may not have occurred completely at random. For example, the opportunity to
- 46 collect urine may have been lost more frequently in certain populations, such as
- 47 normotensive patients, non-diabetic patients, and patients with minor stroke, than in other
- 48 populations. In these patients, urine analysis may have been regarded as an unnecessary test
- 49 during acute stroke care. Therefore, we performed multiple imputation to handle missing data
- 50 for urine analysis. In the multiple imputation, missing data for urine analysis were imputed

- 1 by data estimated by ordinal logistic regression. All variables potentially related to
- 2 missingness and outcomes were used to predict missing values, including age, sex, risk
- 3 factors (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking, drinking),
- 4 coronary artery disease, body mass index, previous stroke, stroke subtype, prestroke modified
- 5 Rankin Scale score, eGFR, National Institutes of Health Stroke Scale score on admission,
- 6 outcome events [stroke recurrence (0 or 1), time from admission to recurrence or last follow-
- 7 up, all-cause death (0 or 1), and time from admission to death or last follow-up]. Finally, 20
- 8 imputed datasets were generated and the analyses for each complete dataset were combined
- 9 into one set of results. Because data for other covariates used in the multivariable analysis
- 10 were complete, there was no listwise deletion for covariates other than proteinuria. All
- 11 statistical analyses were performed using Stata15 (Stata Corp LP, College Station, TX, USA).

Table S1. Background characteristics of patients according to presence of 1 2 CKD

	No CKD	CKD	
	n=6993	n=5583	Р
Age, y, mean (SD)	69.6 (12.6)	77.2 (11.3)	<0.001
Female sex, n (%)	2754 (39.4)	2434 (43.6)	<0.001
Risk factor, n (%)			
Hypertension	5308 (75.9)	4835 (86.6)	<0.001
Diabetes mellitus	2034 (29.1)	1898 (34.0)	<0.001
Dyslipidemia	3874 (55.4)	3077 (55.1)	0.75
Atrial fibrillation	1318 (18.9)	1840 (33.0)	<0.001
Smoking	3876 (55.4)	2782 (49.8)	<0.001
Drinking	2725 (39.0)	1557 (27.9)	<0.001
Coronary artery disease, n (%)	735 (10.5)	1067 (19.1)	<0.001
Body mass index, kg/m ² , mean (SD)	23.1 (3.8)	22.8 (3.9)	<0.001
Previous stroke, n (%)	1170 (16.7)	1396 (25.0)	<0.001
Cardioembolic stroke, n (%)	1184 (16.9)	1627 (29.1)	<0.001
Prestroke mRS score, median (IQR)	0 (0–0)	0 (0–2)	<0.001
NIHSS score, median (IQR)	3 (1–5)	4 (1–9)	<0.001
Negative proteinuria, n (%)	6993 (100.0)	3361 (60.2)	<0.001
eGFR, mL/min/1.73 m ² , mean (SD)	80.9 (17.1)	50.7 (18.7)	<0.001

CKD: chronic kidney disease; SD: standard deviation; mRS: modified Rankin Scale; IQR: 3

interquartile range; NIHSS: National Institutes of Health Stroke Scale; eGFR: estimated glomerular filtration rate. 4

5

- 1 Table S2. Associations of CKD, eGFR, and proteinuria with risk of stroke recurrence after regarding death as a competing
- 2 **risk**

	Ag	e- and sex-adj	usted	Multivariable-adju		usted
	SHR	(95% CI)	Р	SHR	(95% CI)	Р
CKD						
No CKD, n=6993	1.00	(reference)		1.00	(reference)	
CKD, n=5583	1.20	(1.10–1.31)	<0.001	1.13	(1.03–1.23)	0.007
eGFR						
G1 (eGFR ≥60 mL/min/1.73 m2), n=7976	1.00	(reference)		1.00	(reference)	
G2 (eGFR 45–59 mL/min/1.73 m2), n=2692	1.18	(1.06–1.30)	0.001	1.11	(1.00–1.23)	0.04
G3 (eGFR <45 mL/min/1.73 m2), n=1908	1.26	(1.13–1.42)	<0.001	1.14	(1.02–1.29)	0.03
Ptrend			<0.001			0.01
Proteinuria						
P1 (−), n=8806	1.00	(reference)		1.00	(reference)	
P2 (±/1+), n=2847	1.01	(0.91 - 1.11)	0.91	1.02	(0.93 - 1.13)	0.66
P3 (≥2+), n=923	1.14	(0.98–1.33)	0.09	1.16	(0.99–1.35)	0.06
Ptrend			0.21			0.12

3 The multivariable model included age, sex, risk factors (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking, drinking), coronary

4 artery disease, body mass index, previous stroke, stroke subtype, prestroke modified Rankin Scale score, and National Institutes of Health Stroke

5 Scale score on admission. To estimate the SHR of stroke recurrence for eGFR or proteinuria, eGFR and proteinuria were simultaneously included in

6 the multivariable model. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; SHR: subdistribution hazard ratio; CI: confidence

7 interval; Ptrend: P for trend.

1 Table S3. Improvement in model performance by the addition of eGFR or

2 proteinuria

	AIC	Р	C-statistic	Р
Stroke recurrence				
Model 1 (proteinuria)	44431		0.622	
Model 2 (proteinuria + eGFR)	44422	0.002	0.624	0.22
Model 3 (eGFR)	44427		0.623	
Model 4 (eGFR +proteinuria)	44422	0.01	0.624	0.35
Death				
Model 1 (proteinuria)	66371		0.837	
Model 2 (proteinuria + eGFR)	66298	<0.001	0.838	0.06
Model 3 (eGFR)	66398		0.837	
Model 4 (eGFR +proteinuria)	66298	<0.001	0.838	0.002

3 Model 1 included age, sex, risk factors (hypertension, diabetes mellitus, dyslipidemia, atrial

4 fibrillation, smoking, drinking), coronary artery disease, body mass index, previous stroke, stroke

5 subtype, prestroke modified Rankin Scale score, National Institutes of Health Stroke Scale score

6 on admission, and proteinuria. In model 2, eGFR was added to model 1. Model 3 included age,

7 sex, risk factors (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking,

8 drinking), coronary artery disease, body mass index, previous stroke, stroke subtype, prestroke

9 modified Rankin Scale score, National Institutes of Health Stroke Scale score on admission, and

10 eGFR. In model 4, proteinuria was added to model 3. eGFR: estimated glomerular filtration rate;

11 AIC: Akaike information criterion; CI: confidence interval.

	Multivariable-adjusted					
	HR	(95% CI)	Р			
Stroke recurrence						
Model 1						
eGFR	1.11	(1.05–1.17)	<0.001			
Proteinuria	1.11	(1.03–1.18)	0.003			
Model 2						
eGFR	1.13	(0.99–1.28)	0.06			
Proteinuria	1.13	(0.97–1.32)	0.12			
eGFR x proteinuria	0.99	(0.92–1.07)	0.77			
Death						
Model 1						
eGFR	1.20	(1.15–1.25)	<0.001			
Proteinuria	1.29	(1.23–1.36)	<0.001			
Model 2						
eGFR	1.20	(1.09–1.32)	<0.001			
Proteinuria	1.30	(1.16–1.46)	<0.001			
eGFR x proteinuria	1.00	(0.95–1.05)	0.96			

1 Table S4. Interaction in associations by the addition of eGFR and proteinuria

2 Model 1 included age, sex, risk factors (hypertension, diabetes mellitus, dyslipidemia, atrial

3 fibrillation, smoking, drinking), coronary artery disease, body mass index, previous stroke, stroke

4 subtype, prestroke modified Rankin Scale score, National Institutes of Health Stroke Scale score

5 on admission, eGFR, and proteinuria. In model 2, the interaction term of eGFR \times proteinuria was

6 added to model 1. eGFR (\geq 60, 45–59, <45 mL/min/1.73 m²) and proteinuria (– , ±/1+, \geq 2+) were

7 converted into ordinal variables according to their grades. eGFR: estimated glomerular filtration

8 rate; HR: hazard ratio; CI: confidence interval.

			Ag	e- and sex-ad	usted	М	Multivariable-adjusted		
	Events, n (%)	Event rate	HR	(95% CI)	Р	HR	(95% CI)	Р	
Stroke									
Low risk, n=6123	1108 (18.1)	37.7	1.00	(reference)		1.00	(reference)		
Moderate risk, n=3330	676 (20.3)	52.9	1.19	(1.08–1.32)	<0.001	1.14	(1.03–1.26)	0.008	
High risk, n=1696	371 (21.9)	66.8	1.35	(1.20–1.53)	<0.001	1.24	(1.09–1.40)	0.001	
Very high risk, n=1427	326 (22.8)	82.3	1.54	(1.36–1.75)	<0.001	1.37	(1.20–1.56)	<0.001	
Ptrend					<0.001			<0.001	
Death									
Low risk, n=6123	1346 (22.0)	40.1	1.00	(reference)		1.00	(reference)		
Moderate risk, n=3330	1132 (34.0)	75.8	1.30	(1.20–1.41)	<0.001	1.26	(1.16–1.36)	<0.001	
High risk, n=1696	763 (45.0)	115.8	1.60	(1.46–1.75)	<0.001	1.46	(1.33–1.60)	<0.001	
Very high risk, n=1427	791 (55.4)	165.8	2.23	(2.03–2.44)	<0.001	2.00	(1.82–2.20)	<0.001	
Ptrend				-	<0.001		_	<0.001	

Table S5. Associations between CKD risk categories and risks of stroke recurrence and death

1

2 The event rates are shown as events/1,000 person-years. The risk categories were based on the criteria proposed in the Kidney Disease Improving

3 Global Outcomes guidelines. The multivariable model included age, sex, risk factors (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation,

4 smoking, drinking), coronary artery disease, body mass index, previous stroke, stroke subtype, prestroke modified Rankin Scale score, and National

5 Institutes of Health Stroke Scale score on admission. CKD: chronic kidney disease; HR: hazard ratio; CI: confidence interval; Ptrend: P for trend.

Table S6. Background characteristics of patients according to renal 1 2 replacement therapy

	No RRT	RRT	
	n=12576	n=475	Р
Age, y, mean (SD)	73.0 (12.6)	71.1 (11.1)	0.001
Female sex, n (%)	5188 (41.3)	156 (32.8)	<0.001
Risk factor, n (%)			
Hypertension	10143 (80.7)	433 (91.2)	<0.001
Diabetes mellitus	3932 (31.3)	265 (55.8)	<0.001
Dyslipidemia	6951 (55.3)	181 (38.1)	<0.001
Atrial fibrillation	3158 (25.1)	131 (27.6)	0.22
Smoking	6658 (52.9)	272 (57.3)	0.06
Drinking	4282 (34.1)	79 (16.6)	<0.001
Coronary artery disease, n (%)	1802 (14.3)	150 (31.6)	<0.001
Body mass index, kg/m ² , mean (SD)	22.9 (3.9)	21.2 (3.4)	<0.001
Previous stroke, n (%)	2566 (20.4)	148 (31.2)	<0.001
Cardioembolic stroke, n (%)	2811 (22.4)	117 (24.6)	0.24
Prestroke mRS score, median (IQR)	0 (0–1)	0 (0–2)	<0.001
NIHSS score, median (IQR)	3 (1–7)	3 (2–6)	0.61
eGFR, mL/min/1.73 m ² , mean (SD)	67.5 (23.3)	8.0 (4.7)	<0.001

RRT: renal replacement therapy; SD: standard deviation; mRS: modified Rankin Scale; IQR: 3

4 interquartile range; NIHSS: National Institutes of Health Stroke Scale; eGFR: estimated

5 glomerular filtration rate. 1 Table S7. Associations of CKD, eGFR, and proteinuria with risks of stroke recurrence and death after inclusion of patients 2 who received renal replacement therapy

			Ag	e- and sex-ad	usted	Multivariable-adjusted		
	Events, n (%)	Event rate	HR	(95% CI)	Р	HR	(95% CI)	Р
Stroke								
CKD								
No CKD, n=6993	1270 (18.2)	39.0	1.00	(reference)		1.00	(reference)	
CKD, n=6058	1336 (22.1)	66.0	1.35	(1.25–1.46)	<0.001	1.23	(1.13–1.34)	<0.001
eGFR								
G1 (eGFR ≥60 mL/min/1.73 m²), n=7976	1448 (18.2)	40.2	1.00	(reference)		1.00	(reference)	
G2 (eGFR 45–59 mL/min/1.73 m ²), n=2692	585 (21.7)	58.7	1.19	(1.08–1.31)	0.001	1.14	(1.03–1.26)	0.01
G3 (eGFR <45 mL/min/1.73 m ²), n=2383	573 (24.0)	83.5	1.38	(1.24–1.55)	<0.001	1.24	(1.11–1.39)	<0.001
Ptrend					<0.001			<0.001
Proteinuria								
P1 (−), n=8806	1718 (19.5)	43.5	1.00	(reference)		1.00	(reference)	
P2 (±/1+), n=2847	556 (19.5)	59.8	1.11	(1.01–1.22)	0.03	1.08	(0.98–1.20)	0.11
P3 (≥2+), n=1398	332 (23.7)	82.4	1.36	(1.19–1.55)	<0.001	1.28	(1.12–1.47)	<0.001
Ptrend	()			,	<0.001		, , , , , , , , , , , , , , , , , , ,	<0.001
Death								
CKD								
No CKD, n=6993	1603 (22.9)	43.0	1.00	(reference)		1.00	(reference)	
CKD, n=6058	2690 (44.4)	111.4	1.59	(1.49–1.69)	<0.001	1.50	(1.40–1.60)	<0.001
eGFR								
G1 (eGFR ≥60 mL/min/1.73 m²), n=7976	1966 (24.6)	47.7	1.00	(reference)		1.00	(reference)	
G2 (eGFR 45–59 mL/min/1.73 m ²), n=2692	1042 (38.7)	88.3	1.06	(0.98–1.15)	0.12	1.16	(1.08–1.26)	<0.001
G3 (eGFR <45 mL/min/1.73 m ²), n=2383	1285 (53.9)	153.2	1.41	(1.31–1.53)	<0.001	1.50	(1.38–1.62)	<0.001
Ptrend	. ,				<0.001			<0.001
Proteinuria								
P1 (−), n=8806	2433 (27.6)	53.3	1.00	(reference)		1.00	(reference)	
P2 (±/1+), n=2847	1185 (41.6)	110.0	1.62	(1.51–1.74)	<0.001	1.35	(1.25–1.45)	<0.001
P3 (≥2+), n=1398	675 (48.3)	135.9	2.27	(2.07–2.49)	<0.001	1.73	(1.57–1.90)	<0.001
Ptrend	. ,			- /	<0.001		- /	<0.001

3 The event rates are shown as events/1,000 person-years. The patients who received renal replacement therapy were categorized into the G3 and P3

4 groups. The multivariable model included age, sex, risk factors (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking, drinking),

5 coronary artery disease, body mass index, previous stroke, stroke subtype, prestroke modified Rankin Scale score, and National Institutes of Health

6 Stroke Scale score on admission. To estimate the HR of stroke recurrence or death for eGFR or proteinuria, eGFR and proteinuria were

simultaneously included in the multivariable model. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HR: hazard ratio; CI: confidence interval; Ptrend: P for trend. 1

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1 Table S8. Associations between CKD risk categories and risks of stroke recurrence and death after inclusion of patients 2 who received renal replacement therapy

	Age- and sex-adjusted			Mu	Multivariable-adjusted			
	Events, n (%)	Event rate	HR	(95% CI)	Р	HR	(95% CI)	Р
Stroke								
Low risk, n=6123	1108 (18.1)	37.7	1.00	(reference)		1.00	(reference)	
Moderate risk, n=3330	676 (20.3)	52.9	1.20	(1.09 - 1.32)	<0.001	1.15	(1.04–1.27)	0.006
High risk, n=1696	371 (21.9)	66.8	1.36	(1.21 - 1.54)	<0.001	1.25	(1.10 - 1.41)	<0.001
Very high risk, n=1902	451 (23.7)	87.8	1.68	(1.50 - 1.87)	<0.001	1.45	(1.29–1.63)	<0.001
Ptrend					<0.001			<0.001
Death								
Low risk, n=6123	1346 (22.0)	40.1	1.00	(reference)		1.00	(reference)	
Moderate risk, n=3330	1132 (34.0)	75.8	1.32	(1.22 - 1.43)	<0.001	1.27	(1.17–1.38)	<0.001
High risk, n=1696	763 (45.0)	115.8	1.64	(1.50 - 1.80)	<0.001	1.49	(1.36 - 1.63)	<0.001
Very high risk, n=1902	1052 (55.3)	166.8	2.56	(2.36 - 2.79)	<0.001	2.20	(2.02 - 2.40)	<0.001
Ptrend				,	<0.001		. ,	<0.001

The event rates are shown as events/1,000 person-years. The patients who received renal replacement therapy were categorized into the very high

risk group. The multivariable model included age, sex, risk factors (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking, drinking),

coronary artery disease, body mass index, previous stroke, stroke subtype, prestroke modified Rankin Scale score, and National Institutes of Health

Stroke Scale score on admission. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HR: hazard ratio; CI: confidence interval;

7 Ptrend: P for trend.

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1 Table S9. Background characteristics of patients according to missing data for 2 urine analysis

	No urine analysis	Urine analysis	
	n=2503	n=12576	Р
Age, y, mean (SD)	72.5 (13.0)	73.0 (12.6)	0.11
Female sex, n (%)	1018 (40.7)	5188 (41.3)	0.59
Risk factor, n (%)			
Hypertension	1953 (78.0)	10143 (80.7)	0.003
Diabetes mellitus	576 (23.0)	3932 (31.3)	<0.001
Dyslipidemia	1366 (54.6)	6951 (55.3)	0.52
Atrial fibrillation	581 (23.2)	3158 (25.1)	0.04
Smoking	1339 (53.5)	6658 (52.9)	0.61
Drinking	897 (35.8)	4282 (34.1)	0.09
Coronary artery disease, n (%)	340 (13.6)	1802 (14.3)	0.33
Body mass index, kg/m ² , mean (SD)	22.9 (3.6)	22.9 (3.9)	0.46
Previous stroke, n (%)	535 (21.4)	2566 (20.4)	0.27
Cardioembolic stroke, n (%)	497 (19.9)	2881 (22.4)	0.006
Prestroke mRS score, median (IQR)	0 (0–1)	0 (0–1)	0.06
NIHSS score, median (IQR)	2 (1–5)	3 (1–7)	<0.001
eGFR, mL/min/1.73 m ² , mean (SD)	70.0 (21.7)	67.5 (23.3)	<0.001

3 SD: standard deviation; mRS: modified Rankin Scale; IQR: interquartile range; NIHSS: National

4 Institutes of Health Stroke Scale; eGFR: estimated glomerular filtration rate.

	Ag	e- and sex-adj	usted	Μι	Multivariable-adjusted			
	HR	(95% CI)	Р	HR	(95% CI)	Р		
Stroke								
CKD								
No CKD	1.00	(reference)		1.00	(reference)			
CKD	1.32	(1.23–1.43)	<0.001	1.21	(1.12–1.30)	<0.001		
eGFR		, , , , , , , , , , , , , , , , , , ,			· · · · ·			
G1 (eGFR ≥60 mL/min/1.73 m²)	1.00	(reference)		1.00	(reference)			
G2 (eGFR 45–59 mL/min/1.73 m ²)	1.17	(1.07–1.29)	0.001	1.12	(1.02–1.23)	0.02		
G3 (eGFR <45 mL/min/1.73 m ²)	1.36	(1.23–1.51)	<0.001	1.22	(1.10–1.35)	<0.001		
Ptrend		(, , , , , , , , , , , , , , , , , , ,	<0.001		(, , , , , , , , , , , , , , , , , , ,	<0.001		
Proteinuria								
P1 (-)	1.00	(reference)		1.00	(reference)			
P2 (±/1+)	1.11	(1.00–1.22)	0.04	1.07	(0.97–1.19)	0.16		
P3 (≥2+)	1.36	(1.19–1.55)	<0.001	1.28	(1.12–1.46)	<0.001		
Ptrend		,	<0.001		· · · · ·	0.001		
Death								
CKD								
No CKD	1.00	(reference)		1.00	(reference)			
CKD	1.56	(1.47–1.66)	<0.001	1.44	(1.36–1.54)	<0.001		
eGFR		,			· · · · ·			
G1 (eGFR ≥60 mL/min/1.73 m²)	1.00	(reference)		1.00	(reference)			
G2 (eGFR 45–59 mL/min/1.73 m ²)	1.04	(0.97–1.11)	0.32	1.12	(1.04–1.20)	0.003		
G3 (eGFR <45 mL/min/1.73 m ²)	1.41	(1.31–1.51)	<0.001	1.46	(1.36–1.57)	<0.001		
Ptrend		, , , , , , , , , , , , , , , , , , ,	<0.001		· · · · ·	<0.001		
Proteinuria								
P1 (-)	1.00	(reference)		1.00	(reference)			
P2 (±/1+)	1.62	(1.51–1.74)	<0.001	1.34	(1.25–1.44)	<0.001		
P3 (≥2+)	2.28	(2.08–2.49)	<0.001	1.72	(1.56–1.89)	<0.001		
Ptrend		. ,	<0.001		. ,	<0.001		

1

Table S10. Associations of CKD, eGFR, and proteinuria with risks of stroke recurrence and death after multiple imputation

2 The patients who received renal replacement therapy were categorized into the G3 and P3 groups. Multiple imputation was conducted to handle

3 missing data for urine analysis. The multivariable model included age, sex, risk factors (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation,

4 smoking, drinking), coronary artery disease, body mass index, previous stroke, stroke subtype, prestroke modified Rankin Scale score, and National

5 Institutes of Health Stroke Scale score. To estimate the HR of stroke recurrence or death for eGFR or proteinuria, eGFR and proteinuria were

simultaneously included in the multivariable model. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HR: hazard ratio; CI: confidence interval; Ptrend: P for trend. 1

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	Ag	e- and sex-ad	usted	Mu	Multivariable-adjusted			
	HR	(95% CI)	Р	HR	(95% CI)	Р		
Stroke								
Low risk	1.00	(reference)		1.00	(reference)			
Moderate risk	1.19	(1.08 - 1.31)	<0.001	1.13	(1.03–1.25)	0.01		
High risk	1.34	(1.19–1.51)	<0.001	1.22	(1.09 - 1.37)	0.001		
Very high risk	1.64	(1.47 - 1.82)	<0.001	1.41	(1.26–1.58)	<0.001		
Ptrend		. ,	<0.001		. ,	<0.001		
Death								
Low risk	1.00	(reference)		1.00	(reference)			
Moderate risk	1.30	(1.20 - 1.40)	<0.001	1.24	(1.15–1.34)	<0.001		
High risk	1.63	(1.49 - 1.78)	<0.001	1.45	(1.32 - 1.59)	<0.001		
Very high risk	2.52	(2.33–2.74)	<0.001	2.11	(1.94–2.30)	<0.001		
Ptrend		. ,	<0.001		. ,	<0.001		

1 Table S11. Associations between CKD risk categories and risks of stroke 2 recurrence and death after multiple imputation

3 The risk categories were based on the criteria proposed in the Kidney Disease Improving Global 4 Outcomes guideline. The patients who received renal replacement therapy were categorized into 5 the very high risk group. Multiple imputation was conducted to handle missing data for urine

6 analysis. The multivariable model included age, sex, risk factors (hypertension, diabetes mellitus,

7 dyslipidemia, atrial fibrillation, smoking, drinking), coronary artery disease, body mass index,

8 previous stroke, stroke subtype, prestroke modified Rankin Scale score, and National Institutes

9 of Health Stroke Scale score on admission. To estimate the HR of stroke recurrence or death for

10 eGFR or proteinuria, eGFR and proteinuria were simultaneously included in the multivariable

11 model. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HR: hazard

12 ratio; CI: confidence interval; Ptrend: P for trend.



Figure S1. Flow chart of patient selection for the main analysis 1



1 Figure S2. Cumulative rates of stroke recurrence and death according to CKD 2 risk categories

(A, B) The cumulative rates of stroke recurrence (A) or death (B) are shown according to the
 CKD risk categories. The cumulative rates during the follow-up period were estimated by the
 Kaplan-Meier method. The P-values were evaluated by the log-rank test. The numbers at risk
 are shown beneath the sumulative insidence survey. CKD: abronic kidney disease.

29 are shown beneath the cumulative incidence curves. CKD: chronic kidney disease.

1 Figure S3. Subgroup analysis for the association between eGFR and risk of 2 stroke recurrence

3		Event (%)	Multi-serielate editor to d. UD	HR	(95% CI)	P
4	Age <75 y		Multivariable-adjusted HR			
5	G1, n=4873	819 (16.8)	÷.	1.00	(reference)	
6	G2, n=941	208 (22.1)		1.25	(1.07–1.46)	0.005
7	G3, n=511	121 (23.7)		1.15	(0.93-1.43)	0.20
8	Age ≥75 y		Ph=0.47			
9	G1, n=3103	629 (20.3)	÷	1.00	(reference)	
10	G2, n=1751	377 (21.5)	- 	1.06	(0.93-1.21)	0.38
11	G3, n=1397	327 (23.4)	- -	1.23	(1.07–1.41)	0.004
12	Women					
13	G1, n=3129	548 (17.5)	•	1.00	(reference)	
14	G2, n=1156	247 (21.4)		1.17	(1.00–1.37)	0.049
15	G3, n=903	204 (22.6)		1.31	(1.10–1.56)	0.003
16	Men		Ph=0.30			
17	G1, n=4847	900 (18.6)	÷	1.00	(reference)	
18	G2, n=1536	338 (22.0)	₩ ₽₽	1.10	(0.96–1.25)	0.16
19	G3, n=1005	244 (24.3)		1.16	(0.99–1.35)	0.07
20	No hypertensio	n				
21	G1, n=1840	316 (17.2)	•	1.00	(reference)	
21	G2, n=407	71 (17.4)		0.97	(0.74–1.26)	0.81
22	G3, n=186	31 (16.7)		1.11	(0.75–1.65)	0.60
23	Hypertension		Ph=0.24			
2 1 25	G1, n=6136	1132 (18.4)	•	1.00	(reference)	
25	G2, n=2285	514 (22.5)		1.16	(1.04–1.29)	0.008
20	G3, n=1722	417 (24.2)		1.24	(1.10–1.41)	0.001
27	No diabetes me	ellitus				
28	G1, n=5504	927 (16.8)	•	1.00	(reference)	
29	G2, n=1924	404 (21.0)		1.15	(1.02–1.30)	0.02
30	G3, n=1216	278 (22.9)		1.28	(1.10–1.48)	0.001
31	Diabetes mellit	us	Ph=0.13			
32	G1, n=2472	521 (21.1)		1.00	(reference)	
33	G2, n=768	181 (23.6)	┼ ┳──	1.09	(0.91–1.30)	0.34
34	G3, n=692	170 (24.6)	÷=	1.13	(0.93–1.38)	0.21
35	Non-cardioemb	olism				
36	G1, n=6500	1151 (17.7)	•	1.00	(reference)	
37	G2, n=1940	437 (22.5)	_ ₩_	1.23	(1.10–1.38)	0.0001
38	G3, n=1325	324 (24.5)	- - -	1.31	(1.14–1.50)	0.0001
39	Cardioembolisr	n	Ph=0.16			
40	G1, n=1476	297 (20.1)	÷	1.00	(reference)	
41	G2, n=752	148 (19.7)		0.93	(0.76–1.14)	0.49
42	G3, n=583	124 (21.3)		1.12	(0.89–1.39)	0.34
43		0.3	0.5 1 2 3			
-						

The multivariable-adjusted HRs for stroke recurrence are shown for eGFR groups according to 44 age (<75 years or ≥75 years), sex, hypertension, diabetes mellitus, and stroke subtype (non-45 cardioembolic or cardioembolic). The multivariable model included age, sex, risk factors 46 47 (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking, drinking), coronary 48 artery disease, body mass index, previous stroke, stroke subtype, prestroke modified Rankin 49 Scale score. National Institutes of Health Stroke Scale score on admission, and proteinuria. The 50 P-values for heterogeneity were evaluated by adding the interaction term of eGFR × subgroup. 51 HR: hazard ratio; CI: confidence interval; Ph: P for heterogeneity.

1 Figure S4. Subgroup analysis for the association between eGFR and risk of 2 death

3		Event (%)		HR	(95% CI)	Р
4	Age <75 y		Multivariable-adjusted HR			
5	G1, n=4873	614 (12.6)		1.00	(reference)	
6	G2, n=941	162 (17.2)		1.20	(1.01–1.44)	0.04
7	G3, n=511	145 (28.4)	_ _	1.47	(1.20-1.82)	0.0001
8	Age ≥75 y		Ph=0.37			
9	G1, n=3103	1352 (43.6)	÷	1.00	(reference)	
10	G2, n=1751	880 (50.3)	-#-	1.29	(1.18–1.40)	0.0001
11	G3, n=1397	879 (62.9)		1.67	(1.53–1.82)	0.0001
12	Women		_			
13	G1, n=3129	792 (25.3)	•	1.00	(reference)	
14	G2, n=1156	470 (40.7)	-=-	1.16	(1.03–1.31)	0.01
15	G3, n=903	532 (58.9)		1.58	(1.41–1.78)	0.0001
16	Men		Ph=0.49			
17	G1, n=4847	1174 (24.2)	÷	1.00	(reference)	
18	G2, n=1536	572 (37.2)		1.15	(1.04–1.28)	0.007
19	G3, n=1005	492 (49.0)		1.35	(1.20–1.52)	0.0001
20	No hypertensio	'n				
21	G1, n=1840	470 (25.5)	•	1.00	(reference)	
21	G2, n=407	166 (40.8)	÷=	1.12	(0.93–1.35)	0.22
22	G3, n=186	123 (66.1)		1.40	(1.13–1.74)	0.002
23	Hypertension		Ph=0.89			
2 4 25	G1, n=6136	1496 (24.4)	•	1.00	(reference)	
25	G2, n=2285	876 (38.3)		1.16	(1.06–1.26)	0.001
20	G3, n=1722	901 (52.3)	i -=-	1.45	(1.32–1.58)	0.0001
27	No diabetes me	ellitus				
28	G1, n=5504	1334 (24.2)	•	1.00	(reference)	
29	G2, n=1924	753 (39.1)	-=-	1.13	(1.03–1.24)	0.009
30	G3, n=1216	671 (55.2)		1.43	(1.30–1.58)	0.0001
31	Diabetes mellit	us	Ph=0.72			
32	G1, n=2472	632 (25.6)		1.00	(reference)	
33	G2, n=768	289 (37.6)		1.19	(1.03–1.38)	0.02
34	G3, n=692	353 (51.0)		1.46	(1.27–1.69)	0.0001
35	Non-cardioemb	olism				
36	G1, n=6500	1338 (20.6)	•	1.00	(reference)	
37	G2, n=1940	656 (33.8)		1.20	(1.09–1.33)	0.0001
38	G3, n=1325	646 (48.8)		1.45	(1.31–1.61)	0.0001
39	Cardioembolisr	n	Ph=0.43			
40	G1, n=1476	628 (42.5)	Ŧ	1.00	(reference)	
41	G2, n=752	386 (51.3)	+ - -	1.10	(0.96–1.25)	0.17
42	G3, n=583	378 (64.8)		1.45	(1.27–1.66)	0.0001
43		0.3	0.5 1 2 3			

44 The multivariable-adjusted HRs for all-cause death are shown for eGFR groups according to age (<75 years or ≥75 years), sex, hypertension, diabetes mellitus, and stroke subtype (non-45 cardioembolic or cardioembolic). The multivariable model included age, sex, risk factors 46 47 (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking, drinking), coronary 48 artery disease, body mass index, previous stroke, stroke subtype, prestroke modified Rankin 49 Scale score. National Institutes of Health Stroke Scale score on admission, and proteinuria. The 50 P-values for heterogeneity were evaluated by adding the interaction term of eGFR × subgroup. 51 HR: hazard ratio; CI: confidence interval; Ph: P for heterogeneity.

1 Figure S5. Subgroup analysis for the association between proteinuria and risk 2 of stroke recurrence

3		Event (%)	Multiveriable editated UD	HR	(95% CI)	P
4	Age <75 y		Multivariable-adjusted HR			
5	P1, n=4670	823 (17.6)		1.00	(reference)	
6	P2, n=1201	210 (17.5)	- ---	1.05	(0.89-1.22)	0.57
7	P3, n=454	115 (25.3)		1.41	(1.13–1.75)	0.002
8	Age ≥75 y		Ph=0.18			
9	P1, n=4136	895 (21.6)	÷	1.00	(reference)	
10	P2, n=1646	346 (21.0)	+ - -	1.10	(0.97-1.25)	0.14
11	P3, n=469	92 (19.6)	_ +=	1.10	(0.88–1.37)	0.40
12	Women					
13	P1, n=3696	714 (19.3)	÷	1.00	(reference)	
14	P2, n=1156	219 (18.9)	_ 	1.07	(0.91-1.25)	0.41
15	P3, n=336	66 (19.6)		1.18	(0.90-1.53)	0.23
16	Men		Ph=0.77			
17	P1, n=5110	1004 (19.6)	÷.	1.00	(reference)	
18	P2, n=1691	337 (19.9)	÷∎-	1.10	(0.96-1.24)	0.16
19	P3, n=587	141 (24.0)		1.30	(1.07-1.57)	0.007
20	No hypertensio	n				
20 21	P1, n=1926	328 (17.0)	÷.	1.00	(reference)	
21 22	P2, n=426	75 (17.6)	÷	1.26	(0.97-1.64)	0.08
22	P3, n=81	15 (18.5)		1.33	(0.78-2.27)	0.30
23 24	Hypertension		Ph=0.61			
24 25	P1, n=6880	1390 (20.2)	•	1.00	(reference)	
25	P2, n=2421	481 (19.9)		1.06	(0.95–1.18)	0.29
26	P3, n=842	192 (22.8)		1.24	(1.05-1.45)	0.009
27	No diabetes me	ellitus				
28	P1, n=6427	1199 (18.7)	•	1.00	(reference)	
29	P2, n=1803	329 (18.2)	- -	1.05	(0.92-1.19)	0.49
30	P3, n=414	81 (19.6)	÷	1.19	(0.94–1.50)	0.14
31	Diabetes mellit	us	Ph=0.59			
32	P1, n=2379	519 (21.8)	÷	1.00	(reference)	
33	P2, n=1044	227 (21.7)	÷=	1.14	(0.97–1.34)	0.11
34	P3, n=509	126 (24.8)	-	1.32	(1.07–1.63)	0.01
35	Non-cardioemb	oolism				
36	P1, n=7095	1352 (19.1)	÷	1.00	(reference)	
37	P2, n=2013	399 (19.8)	÷∎−	1.09	(0.97-1.22)	0.17
38	P3, n=657	161 (24.5)	- -	1.26	(1.05–1.50)	0.01
39	Cardioembolis	m	Ph=0.11			
40	P1, n=1711	366 (21.4)	÷	1.00	(reference)	
41	P2, n=834	157 (18.8)	—	1.06	(0.87-1.28)	0.58
42	P3, n=266	46 (17.3)		1.15	(0.84–1.59)	0.38
43		0.3	0.5 1 2 3			
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44 The multivariable-adjusted HRs for stroke recurrence are shown for proteinuria groups according to age (<75 years or ≥75 years), sex, hypertension, diabetes mellitus, and stroke subtype (non-45 cardioembolic or cardioembolic). The multivariable model included age, sex, risk factors 46 47 (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking, drinking), coronary 48 artery disease, body mass index, previous stroke, stroke subtype, prestroke modified Rankin 49 Scale score, National Institutes of Health Stroke Scale score on admission, and eGFR. The P-50 values for heterogeneity were evaluated by adding the interaction term of proteinuria × subgroup. 51 HR: hazard ratio, CI: confidence interval, Ph: P for heterogeneity.

Figure S6. Subgroup analysis for the association between proteinuria and risk of death

4 Age <75 y Multivalable-adjusted HR 5 P1, n=4570 561 (12.0) 6 P2, n=1201 234 (19.5) 7 P3, n=454 126 (27.8) 9 P1, n=4136 1872 (45.3) 10 Pa, n=1646 951 (57.8) 11 P3, n=469 288 (61.4) 12 Women 1.35 (12.4-1.46) 0.0001 13 P1, n=3696 1085 (29.4) 1.00 (reference) 14 P2, n=1156 546 (47.2) 1.38 (12.4-1.53) 0.0001 15 P3, n=336 163 (48.5) 1.58 (1.34-1.88) 0.0001 16 Men 1.00 (reference) 1.32 (1.19-1.46) 0.0001 17 P1, n=587 251 (42.8) 1.00 (reference) 1.32 (1.19-1.46) 0.0001 19 P3, n=587 251 (42.8) 1.00 (reference) 1.33 (1.23-1.44) 0.0001 20 P2, n=2421 95 (41.1) - 1.33 (1.23-1.47) 0.0001 21 P1, n=5680 1906 (27.7) 1.00 (reference) - 1.65 (1.43-1.91) 0.0001 24 P1, n	3		Event (%)		HR	(95% CI)	Р
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	4	Age <75 y	_	Multivariable-adjusted HR			
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	5	P1, n=4670	561 (12.0)		1.00	(reference)	
7 P3, n=454 126 (27.8) 1.78 (1.42-2.22) 0.0001 8 Age ≥ 75 y Ph=0.001 Ph=0.001 9 P1, n=4136 1872 (45.3) 1.00 (reference) 10 P2, n=1646 951 (57.8) 1.00 (reference) 11 P3, n=366 1085 (29.4) 1.47 (1.29-1.67) 0.0001 12 Women 1.00 (reference) 1.38 (1.24-1.53) 0.0001 13 P1, n=3566 1085 (29.4) 1.58 (1.34-1.88) 0.0001 16 Men 1.00 (reference) 1.38 (1.24-1.53) 0.0001 17 P1, n=5110 1348 (26.4) 1.67 (1.44-1.92) 0.0001 18 P2, n=1691 639 (37.8) 1.67 (1.44-1.92) 0.0001 19 P3, n=81 42 (51.9) 1.33 (1.23-1.46) 0.0001 21 P2, n=2421 995 (41.1) 1.35 (0.97-1.87) 0.08 26 P2, n=2421 995 (41.1) 1.35 (1.24-1.48) 0.0001 27 P2, n=2421 995 (41.1) 1.35 (1.24-1.48) 0.0001 28 P1, n=6427 1770 (27.5) 1.00 (reference) 29 P2, n=1803 72 (42.8) 1.00 (reference) 32 <	6	P2, n=1201	234 (19.5)		1.51	(1.29–1.77)	0.0001
8 Age $275 y$ Ph=0.001 9 P1, n=4136 1872 (45.3) 1.00 (reference) 10 P2, n=1646 961 (67.8) 1.35 (1.24-1.46) 0.0001 11 P3, n=469 288 (61.4) 1.47 (1.29-1.67) 0.0001 12 Women 1.00 (reference) 1.47 (1.29-1.67) 0.0001 12 Women 1.00 (reference) 1.38 (1.24-1.53) 0.0001 15 P3, n=336 163 (48.5) 1.58 (1.34-1.38) 0.0001 16 Men P1, n=5110 1348 (26.4) 1.67 (1.44-1.92) 0.0001 19 P3, n=587 251 (42.8) 1.00 (reference) 1.35 (0.97-1.87) 0.8 21 P2, n=1426 190 (44.6) 1.39 (1.17-1.65) 0.0001 23 P1, n=6820 1906 (27.7) 1.35 (1.24-1.48) 0.0001 24 P1, n=6427 1772 (42.8) 1.00 (reference) 1.35 (1.24-1.48) 0.001 25 P2, n=1803 772 (42.8) 1.00 (reference) 1.35 (1.24-1.48) 0.001 25 P2, n=1603 772 (42.8) 1.00 (reference) 1.35 (1.24-1.48) <td>7</td> <td>P3, n=454</td> <td>126 (27.8)</td> <td></td> <td>1.78</td> <td>(1.42-2.22)</td> <td>0.0001</td>	7	P3, n=454	126 (27.8)		1.78	(1.42-2.22)	0.0001
9 P1, n=4136 1872 (45.3) 1.00 (reference) 10 P2, n=1646 951 (57.8) 1.35 (1.24-1.46) 0.0001 11 P3, n=469 288 (61.4) 1.47 (1.29-1.67) 0.0001 13 P1, n=3696 1085 (29.4) 1.00 (reference) 1.38 (1.24-1.53) 0.0001 15 P3, n=316 634 (87.2) 1.38 (1.24-1.53) 0.0001 16 Men P1, n=5110 1348 (26.4) 1.58 (1.34-1.88) 0.0001 17 P1, n=5110 1348 (26.4) 1.57 (1.44-1.92) 0.0001 19 P3, n=587 251 (42.8) 1.57 (1.44-1.92) 0.0001 20 No hypertension 1.39 (1.17-1.65) 0.0001 21 P1, n=5810 1906 (27.7) 1.39 (1.17-1.65) 0.0001 26 P2, n=2421 95 (41.1) 1.35 (1.23-1.44) 0.0001 26 P3, n=842 372 (44.2) 1.00 (reference) 1.35 (1.24-1.48) 0.0001 27 No diabetes meilitus 1.35 (1.24-1.48) 0.0001 1.56 (1.43-1.91) 0.0001 28 P1, n=6632 7170 (27.5) 1.00 (reference)	8	Age ≥75 y		Ph=0.001			
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	9	P1, n=4136	1872 (45.3)	÷	1.00	(reference)	
11 $P3, n=469$ $288 (61.4)$ 12 Women 13 $P1, n=3696$ $1085 (29.4)$ 14 $P2, n=1156$ $546 (47.2)$ 15 $P3, n=336$ $163 (48.5)$ 16 Men $1.58 (1.34-1.53) 0.0001$ 17 $P1, n=5110$ $1348 (26.4)$ 18 $P2, n=1691$ $639 (37.8)$ 19 $P3, n=572$ $251 (42.8)$ 00 No hypertension $1.67 (1.44-1.92) 0.0001$ 21 $P1, n=7926$ $527 (27.4)$ 22 $P2, n=426$ $190 (44.6)$ 23 $P3, n=81$ $42 (51.9)$ Hypertension $1.35 (0.97-1.87) 0.08$ 24 $P1, n=6427 1770 (27.5)$ $1.00 (reference)$ 25 $P2, n=1803 772 (42.8)$ $1.56 (1.43-1.91) 0.0001$ 26 $P1, n=2379 663 (27.9)$ $1.00 (reference)$ 31 Diabetes mellitus $P1, n=2379 663 (27.9)$ $1.00 (reference)$ 32 $P1, n=2379 663 (27.9)$ $1.00 (reference)$ 33 $P2, n=2013 722 (35.9)$ $1.00 (reference)$ 34 $P3, n=657 250 (38.1$	10	P2, n=1646	951 (57.8)		1.35	(1.24-1.46)	0.0001
12Women13P1, n=36961085 (29.4)14P2, n=1156546 (47.2)15P3, n=336163 (48.5)16Men17P1, n=51101348 (26.4)18P2, n=1691639 (37.8)19P3, n=587251 (42.8)20No hypertension21P1, n=1926527 (27.4)22P2, n=24223P3, n=8142 (51.9)1.00 (reference)24P1, n=688025P2, n=242195 (41.1)26P2, n=242195 (41.1)27No diabetes mellitus28P1, n=642729P2, n=180321Diabetes mellitus22P2, n=104423P1, n=237924P1, n=237925P2, n=104426(27.7)29P2, n=104421Diabetes mellitus22P1, n=237933P2, n=104434P1, n=709535Non-cardioembolism36P1, n=709537P2, n=201338P3, n=65739Cardioembolism30P3, n=26541P2, n=834463 (55.5)42P3, n=266430.001430.001	11	P3, n=469	288 (61.4)		1.47	(1.29-1.67)	0.0001
13P1, n=36961085 (29.4)1.00 (reference)14P2, n=1155546 (47.2)1.38 (1.24-1.53)0.000115P3, n=336163 (48.5)1.38 (1.24-1.53)0.000116MenP1, n=51101348 (26.4)1.00 (reference)17P1, n=1501639 (37.8)Ph=0.691.00 (reference)18P2, n=1691639 (37.8)1.00 (reference)19P3, n=567251 (42.8)1.00 (reference)20P2, n=426190 (44.6)1.33 (1.17-1.65)0.000121P1, n=1926527 (27.4)1.00 (reference)22P2, n=422190 (44.6)1.33 (1.23-1.44)0.00123P3, n=8142 (51.9)1.35 (0.97-1.87)0.0824P1, n=68201906 (27.7)1.00 (reference)25P2, n=2421995 (41.1)1.33 (1.23-1.44)0.000126P3, n=810772 (42.8)1.00 (reference)27No diabetes mellitus1.00 (reference)28P1, n=64271770 (27.5)1.00 (reference)29P2, n=1044413 (39.6)1.55 (1.43-1.91)0.000131Diabetes mellitus1.51 (1.24-1.48)0.000132P1, n=70951668 (23.5)1.00 (reference)33P2, n=1044413 (39.6)1.57 (1.33-1.87)0.000134P3, n=509198 (33.5)1.57 (1.33-1.87)0.000135Non-cardioembolism1.67 (1.46-1.33)0.000136P1, n=1711765 (44.7)	12	Women					
14 P2, n=1156 546 (47.2) 15 P3, n=336 163 (48.5) 16 Men 17 P1, n=5110 1348 (26.4) 18 P2, n=1691 639 (37.8) 19 P3, n=587 251 (42.8) 20 No hypertension 1.00 (reference) 21 P1, n=1926 527 (27.4) 22 P2, n=2426 190 (44.6) 23 P3, n=81 42 (51.9) 24 P1, n=6880 1906 (27.7) 25 P2, n=2421 995 (41.1) 26 P3, n=842 372 (44.2) 27 No diabetes mellitus 28 P1, n=6277 1.00 (reference) 29 P2, n=1044 413 (39.6) 31 Diabetes mellitus 1.57 (1.33-1.87) 0.0001 32 P1, n=7095 1668 (23.5) 37 P2, n=2013 722 (35.9) 38 P3, n=667 250 (38.1) 39 Cardioembolism 1.00 (reference) 40 P1, n=7117 765 (44.7) 41 P2, n=834 463 (55.5)	13	P1, n=3696	1085 (29.4)	÷.	1.00	(reference)	
15 P3, n=336 163 (48.5) 16 Men $P1$, n=5110 1348 (26.4) 17 P1, n=5110 1348 (26.4) $P1$, n=5110 1348 (26.4) 19 P2, n=1691 639 (37.8) $P3$, n=587 251 (42.8) 20 No hypertension $P1$, n=1926 527 (27.4) 1.00 (reference) 21 P1, n=1926 527 (27.4) 1.35 (0.97-1.87) 0.0001 23 P3, n=81 42 (51.9) 1.35 (0.97-1.87) 0.001 24 P1, n=6880 1906 (27.7) 1.56 (1.48-1.87) 0.0001 26 P3, n=842 372 (44.2) 1.56 (1.48-1.87) 0.0001 27 No diabetes mellitus $P1$, n=6427 1770 (27.5) 1.00 (reference) 29 P2, n=1803 772 (42.8) 1.55 (1.24-1.48) 0.0001 31 Diabetes mellitus 1.50 (1.43-1.91) 0.0001 32 P1, n=7095 1668 (23.5) 1.57 (1.33-1.87) 0.0001 34 P3, n=567 250 (38.1) 1.57 (1.46-1.93) 0.0001 35 Non-cardioembolism	14	P2, n=1156	546 (47.2)		1.38	(1.24-1.53)	0.0001
16MenPh=0.6917P1, n=51101348 (26.4)1.00 (reference)18P2, n=1691639 (37.8)1.32 (1.19-1.46)0.000119P3, n=587251 (42.8)1.67 (1.44-1.92)0.000120No hypertension1.67 (1.44-1.92)0.000121P1, n=1926527 (27.4)1.00 (reference)22P2, n=426190 (44.6)1.33 (1.17-1.65)0.000123P3, n=8142 (51.9)1.35 (0.97-1.87)0.0824P1, n=68801906 (27.7)1.00 (reference)25P2, n=2421995 (41.1)-1.33 (1.23-1.44)0.000126P3, n=842372 (44.2)1.00 (reference)27No diabetes mellitus1.66 (1.48-1.87)0.000128P1, n=64271770 (27.5)1.00 (reference)29P2, n=1803772 (42.8)1.00 (reference)30P3, n=414216 (52.2)1.00 (reference)31Diabetes mellitus91.32 (1.16-1.50)0.000132P1, n=70951668 (23.5)1.00 (reference)33P2, n=2013722 (35.9)1.00 (reference)34P3, n=567250 (38.1)1.67 (1.46-1.93)39Cardioembolism1.67 (1.46-1.35)0.003130P3, n=266164 (61.7)1.00 (reference)41P2, n=344463 (55.5)1.001.53 (1.28-1.82)430.30.5123	15	P3, n=336	163 (48.5)		1.58	(1.34–1.88)	0.0001
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	16	Men		Ph=0.69			
18 P2, n=1691 639 (37.8) 19 P3, n=587 251 (42.8) 20 No hypertension 1.67 21 P1, n=1926 527 (27.4) 22 P2, n=426 190 (44.6) 23 P3, n=81 42 (51.9) 24 P1, n=6880 1906 (27.7) 25 P2, n=2421 995 (41.1) 26 P3, n=842 372 (44.2) 27 No diabetes mellitus P1, n=6427 28 P1, n=6427 1770 (27.5) 29 P2, n=1803 772 (42.8) 30 P3, n=414 216 (52.2) 31 Diabetes mellitus 32 P1, n=2379 663 (27.9) 33 P2, n=1044 413 (39.6) 34 P3, n=509 198 (38.9) 35 Non-cardioembolism 36 P1, n=7095 1668 (23.5) 37 P2, n=2013 722 (35.9) 38 P3, n=657 250 (38.1) 39 Cardioembolism 1.00 30 Cardioembolism 310 Cardio	17	P1, n=5110	1348 (26.4)	•	1.00	(reference)	
19P3, n=587251 (42.8)20No hypertension21P1, n=1926 $527 (27.4)$ 22P2, n=426190 (44.6)23P3, n=8142 (51.9)24P1, n=68801906 (27.7)25P2, n=2421995 (41.1)26P3, n=842372 (44.2)27No diabetes mellitus28P1, n=642729P2, n=1803772 (42.8)29P2, n=1803772 (42.8)30P3, n=414216 (52.2)31Diabetes mellitus32P1, n=2379663 (27.9)1.00 (reference)33P2, n=10444193.667P2, n=201372(35.9)37P2, n=201372(36.1)39Cardioembolism30P3, n=65720(36.05.5)31P1, n=7111765 (44.7)41P2, n=834463 (55.5)420.3430.3430.3440.3450.3460.55.541P2, n=834463 (55.5)420.3430.3440.3450.3460.55.5471.20480.3490.540P1, n=7111411.55420.3430.34430.5450.3 </td <td>18</td> <td>P2, n=1691</td> <td>639 (37.8)</td> <td>---</td> <td>1.32</td> <td>(1.19–1.46)</td> <td>0.0001</td>	18	P2, n=1691	639 (37.8)	- - -	1.32	(1.19–1.46)	0.0001
NoNo hypertension20P1, n=1926 $527 (27.4)$ 21P2, n=426190 (44.6)22P3, n=8142 (51.9)23Hypertension1.39 (1.17-1.65) 0.000124P1, n=68801906 (27.7)25P2, n=2421995 (41.1)26P3, n=842372 (44.2)27No diabetes mellitus28P1, n=642729P2, n=180329P2, n=180320P3, n=414216 (52.2)29P2, n=104421Diabetes mellitus22P1, n=237923P2, n=104424P1, n=709533P2, n=10444193.634P3, n=657250 (38.1)39Cardioembolism36P1, n=709537P2, n=201338P3, n=65739Cardioembolism30P3, n=66731P2, n=834463 (55.5)32P1, n=171133P2, n=834463 (55.5)34P3, n=266350.0336P1, n=1711370.3380.5391.00 (reference)41P2, n=834463 (55.5)420.3430.3430.3440.3450.34610.4471.00480.3490.340<	19	P3, n=587	251 (42.8)		1.67	(1.44–1.92)	0.0001
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	20	No hypertensio	'n				
21P2, n=426190 (44.6)1.39 (1.17-1.65)0.0001 23 P3, n=8142 (51.9)1.35 (0.97-1.87)0.08 24 P1, n=68801906 (27.7)1.00 (reference) 25 P2, n=2421995 (41.1)-1.33 (1.23-1.44)0.0001 26 P3, n=842372 (44.2)-1.66 (1.48-1.87)0.0001 27 No diabetes mellitus-1.66 (1.48-1.87)0.0001 28 P1, n=64271770 (27.5)1.00 (reference) 29 P2, n=1803772 (42.8)-1.65 (1.43-1.91)0.0001 30 P3, n=414216 (52.2)1.65 (1.43-1.91)0.0001 31 Diabetes mellitus-1.65 (1.43-1.91)0.0001 32 P1, n=2379663 (27.9)1.65 (1.43-1.91)0.0001 34 P3, n=509198 (38.9)1.57 (1.33-1.87)0.0001 35 Non-cardioembolism-1.67 (1.46-1.50)0.0001 36 P1, n=70951668 (23.5)-1.67 (1.46-1.93)0.0001 37 P2, n=2013722 (35.9)-1.67 (1.46-1.93)0.0001 38 P3, n=657250 (38.1)-1.67 (1.46-1.33)0.0001 39 Cardioembolism-1.20 (1.06-1.35)0.003 41 P2, n=834463 (55.5)-1.20 (1.06-1.35)0.003 42 P3, n=266164 (61.7)-1.23	20	P1, n=1926	527 (27.4)	•	1.00	(reference)	
223P3, n=81 $42 (51.9)$ $1.35 (0.97-1.87) 0.08$ 234 Hypertension $1.35 (0.97-1.87) 0.08$ 244 P1, n=6880 $1906 (27.7)$ $1.00 (reference)$ 25 P2, n=2421 $995 (41.1)$ $1.33 (1.23-1.44) 0.0001$ 26 P3, n=842 $372 (44.2)$ $1.66 (1.48-1.87) 0.0001$ 27 No diabetes mellitus $1.00 (reference)$ 28 P1, n=6427 $1770 (27.5)$ $1.00 (reference)$ 29 P2, n=1803 $772 (42.8)$ $1.35 (1.24-1.48) 0.0001$ 30 P3, n=414 $216 (52.2)$ $1.65 (1.43-1.91) 0.0001$ 31 Diabetes mellitus $1.32 (1.16-1.50) 0.0001$ 32 P1, n=2379 $663 (27.9)$ $1.00 (reference)$ 33 P2, n=1044 $413 (39.6)$ $1.57 (1.33-1.87) 0.0001$ 34 P3, n=509 $198 (38.9)$ $1.57 (1.33-1.87) 0.0001$ 35 Non-cardioembolism $1.67 (1.46-1.93) 0.0001$ 36 P1, n=7705 1668 (23.5) $1.00 (reference)$ 37 P2, n=2013 722 (35.9) $1.67 (1.46-1.93) 0.0001$ 38 P3, n=657 250 (38.1) $1.00 (reference)$ 39 Cardioembolism $1.00 (reference)$ 40 P1, n=1711 765 (44.7) $1.00 (reference)$ 41 P2, n=834 463 (55.5) $1.20 (1.06-1.35) 0.003$ 42 $0.3 0.5$ $1 2 3$	$\frac{21}{22}$	P2, n=426	190 (44.6)		1.39	(1.17–1.65)	0.0001
23 24Hypertension $Ph=0.49$ 25 25 26, n=2421995 (41.1)-1.33 (1.23-1.44) 0.000126 27 28 29P3, n=842372 (44.2)-1.66 (1.48-1.87) 0.000128 29 29 29, n=1803772 (42.8)-1.65 (1.43-1.91) 0.000130 30 31 31 32 32 32 32 33 32 32 33 32 32 33 34 35, n=509 33 36 36 37 36 37 37 36 37 36 37 36 37 37 37 38 39 39 30, n=657 39 39 30 301.00 (reference)36 37 39 39 30, n=657 30 311.00 (reference)36 39 30 30 30 311.167 (1.46-1.50) 0.000136 37 39 30 30 301.00 (reference)37 39 40 40 40 41 41 41 41 43 463 (55.5)1.00 (reference)39 41 42 431.177 (155 (44.7) 41 42 431.00 (reference)41 43 43 430.3 0.51 42 343 430.3 0.51 42 3	22	P3, n=81	42 (51.9)	÷	1.35	(0.97–1.87)	0.08
24P1, n=68801906 (27.7)1.00 (reference) 25 P2, n=2421995 (41.1)-1.33 (1.23-1.44)0.0001 26 P3, n=842372 (44.2)-1.66 (1.48-1.87)0.0001 27 No diabetes mellitus-1.35 (1.24-1.48)0.0001 28 P1, n=64271770 (27.5)1.00 (reference) 29 P2, n=1803772 (42.8)-1.55 (1.43-1.91)0.0001 30 P3, n=414216 (52.2)1.65 (1.43-1.91)0.0001 31 Diabetes mellitus-1.32 (1.16-1.50)0.0001 32 P1, n=2379663 (27.9)1.00 (reference) 33 P2, n=1044413 (39.6)-1.32 (1.16-1.50)0.0001 34 P3, n=509198 (38.9)1.57 (1.33-1.87)0.0001 35 Non-cardioembolism-1.67 (1.46-1.93)0.0001 36 P1, n=70951668 (23.5)1.67 (1.46-1.93)0.0001 38 P3, n=657250 (38.1)-1.67 (1.46-1.93)0.0001 39 Cardioembolism-1.60 (reference)-1.20 (1.06-1.35)0.003 41 P2, n=834463 (55.5)-1.20 (1.06-1.35)0.0031.53 (1.28-1.82)0.0001 43 0.30.51231.53 (1.28-1.82)0.0001	23	Hypertension		Ph=0.49			
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	24 25	P1, n=6880	1906 (27.7)	÷	1.00	(reference)	
26P3, n=842 $372 (44.2)$ $1.66 (1.48-1.87) 0.0001$ 27 No diabetes mellitus $1.00 (reference)$ 28 P1, n=6427 $1770 (27.5)$ $1.00 (reference)$ 29 P2, n=1803 $772 (42.8)$ $1.35 (1.24-1.48) 0.0001$ 30 P3, n=414 $216 (52.2)$ $1.65 (1.43-1.91) 0.0001$ 31 Diabetes mellitus $Ph=0.53$ 32 P1, n=2379 $663 (27.9)$ $1.00 (reference)$ 33 P2, n=1044 $413 (39.6)$ $1.32 (1.16-1.50) 0.0001$ 34 P3, n=509 $198 (38.9)$ $1.57 (1.33-1.87) 0.0001$ 35 Non-cardioembolism $1.67 (1.46-1.93) 0.0001$ 36 P1, n=7095 $1668 (23.5)$ $1.00 (reference)$ 37 P2, n=2013 $722 (35.9)$ $1.67 (1.46-1.93) 0.0001$ 38 P3, n=657 250 (38.1) $1.67 (1.46-1.93) 0.0001$ 39 Cardioembolism $1.67 (1.46-1.93) 0.0001$ 41 P2, n=834 463 (55.5) $1.20 (1.06-1.35) 0.003$ 42 $0.3 0.5 1$ $2 3$	25	P2, n=2421	995 (41.1)	-	1.33	(1.23–1.44)	0.0001
27No diabetes mellitus 28 P1, n=64271770 (27.5) 29 P2, n=1803772 (42.8) 30 P3, n=414216 (52.2) 31 Diabetes mellitus 32 P1, n=2379663 (27.9) 33 P2, n=1044413 (39.6) 34 P3, n=509198 (38.9) 36 P1, n=70951668 (23.5) 37 P2, n=2013722 (35.9) 38 P3, n=657250 (38.1) 39 Cardioembolism 40 P1, n=1711 765 (44.7)1.67 (1.46-1.93) 41 P2, n=834 463 (55.5)1.00 (reference) 42 0.3 0.3 0.5 43 0.3 0.3 0.5 1 2 2 3	26	P3, n=842	372 (44.2)		1.66	(1.48–1.87)	0.0001
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	27	No diabetes me	ellitus				
29P2, n=1803 $772 (42.8)$ 30 P3, n=414 $216 (52.2)$ 31 Diabetes mellitus 32 P1, n=2379 $663 (27.9)$ 33 P2, n=1044 $413 (39.6)$ 34 P3, n=509 $198 (38.9)$ 35 Non-cardioembolism 36 P1, n=7095 $1668 (23.5)$ 37 P2, n=2013 $722 (35.9)$ 38 P3, n=657 $250 (38.1)$ 39 Cardioembolism 40 P1, n=1711 $765 (44.7)$ 41 P2, n=834 $463 (55.5)$ 42 P3, n=266 43 0.3 0.5 1 2 3	28	P1, n=6427	1770 (27.5)	•	1.00	(reference)	
30P3, n=414216 (52.2)1.65 (1.43-1.91)0.0001 31 Diabetes mellitusPh=0.53 32 P1, n=2379663 (27.9)1.00 (reference) 33 P2, n=1044413 (39.6)1.32 (1.16-1.50)0.0001 34 P3, n=509198 (38.9)1.57 (1.33-1.87)0.0001 35 Non-cardioembolism1.00 (reference) 36 P1, n=70951668 (23.5)1.00 (reference) 37 P2, n=2013722 (35.9)1.43 (1.31-1.57)0.0001 38 P3, n=657250 (38.1)Ph=0.049 40 P1, n=1711765 (44.7)Ph=0.049 41 P2, n=834463 (55.5)1.20 (1.06-1.35)0.003 42 P3, n=266164 (61.7)1.53 (1.28-1.82)0.0001 43 0.30.5123	29	P2, n=1803	772 (42.8)	i - ≡ -	1.35	(1.24–1.48)	0.0001
31Diabetes mellitus $Ph=0.53$ 32P1, n=2379663 (27.9)1.00 (reference)33P2, n=1044413 (39.6)1.32 (1.16-1.50)0.000134P3, n=509198 (38.9)1.57 (1.33-1.87)0.000135Non-cardioembolism1.00 (reference)36P1, n=70951668 (23.5)1.00 (reference)37P2, n=2013722 (35.9)1.43 (1.31-1.57)0.000138P3, n=657250 (38.1)1.67 (1.46-1.93)0.000139Cardioembolism1.67 (1.46-1.93)0.000140P1, n=1711765 (44.7)1.00 (reference)41P2, n=834463 (55.5)1.20 (1.06-1.35)0.00342P3, n=266164 (61.7)1.53 (1.28-1.82)0.0001430.30.5123	30	P3, n=414	216 (52.2)		1.65	(1.43–1.91)	0.0001
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	31	Diabetes mellit	us	Ph=0.53			
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	32	P1, n=2379	663 (27.9)	•	1.00	(reference)	
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	33	P2, n=1044	413 (39.6)		1.32	(1.16–1.50)	0.0001
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	34	P3, n=509	198 (38.9)	_ 	1.57	(1.33–1.87)	0.0001
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	35	Non-cardioemb	oolism				
37 P2, n=2013 722 (35.9) - 1.43 (1.31-1.57) 0.0001 38 P3, n=657 250 (38.1) 1.67 (1.46-1.93) 0.0001 39 Cardioembolism P1, n=1711 765 (44.7) Ph=0.049 40 P1, n=1711 765 (44.7) 1.00 (reference) 41 P2, n=834 463 (55.5) 1.20 (1.06-1.35) 0.003 42 P3, n=266 164 (61.7) 1.53 (1.28-1.82) 0.0001 43 0.3 0.5 1 2 3	36	P1, n=7095	1668 (23.5)	•	1.00	(reference)	
38 P3, n=657 250 (38.1) Image: formula in the image: for	37	P2, n=2013	722 (35.9)	-#-	1.43	(1.31–1.57)	0.0001
39 Cardioembolism Ph=0.049 40 P1, n=1711 765 (44.7) 1.00 (reference) 41 P2, n=834 463 (55.5) 1.20 (1.06-1.35) 0.003 42 P3, n=266 164 (61.7) 1.53 (1.28-1.82) 0.0001 43 0.3 0.5 1 2 3	38	P3, n=657	250 (38.1)	i − = −	1.67	(1.46–1.93)	0.0001
40 P1, n=1711 765 (44.7) 1.00 (reference) 41 P2, n=834 463 (55.5) 1.20 (1.06-1.35) 0.003 42 P3, n=266 164 (61.7) 1.53 (1.28-1.82) 0.0001 43 0.3 0.5 1 2 3	39	Cardioembolisr	n	Ph=0.049			
41 P2, n=834 463 (55.5) 1.20 (1.06-1.35) 0.003 42 P3, n=266 164 (61.7) 1.53 (1.28-1.82) 0.0001 43 0.3 0.5 1 2 3	40	P1, n=1711	765 (44.7)	÷.	1.00	(reference)	
42 P3, n=266 164 (61.7) 43 0.3 0.5 1 2 3	41	P2, n=834	463 (55.5)	 -	1.20	(1.06–1.35)	0.003
43 0.3 0.5 1 2 3	42	P3, n=266	164 (61.7)		1.53	(1.28–1.82)	0.0001
	43		0.3	3 0.5 1 2 3			

44 The multivariable-adjusted HRs for all-cause death are shown for proteinuria groups according to age (<75 years or ≥75 years), sex, hypertension, diabetes mellitus, and stroke subtype (non-45 cardioembolic or cardioembolic). The multivariable model included age, sex, risk factors 46 47 (hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, smoking, drinking), coronary 48 artery disease, body mass index, previous stroke, stroke subtype, prestroke modified Rankin 49 Scale score, National Institutes of Health Stroke Scale score on admission, and eGFR. The P-50 values for heterogeneity were evaluated by adding the interaction term of proteinuria × subgroup. 51 HR: hazard ratio; CI: confidence interval; Ph: P for heterogeneity.

1 Supplemental Appendix

2 **Participating hospitals**

- 3 Kyushu University Hospital (Fukuoka, Japan), National Hospital Organization Kyushu
- 4 Medical Center (Fukuoka, Japan), National Hospital Organization Fukuoka-Higashi Medical
- 5 Center (Koga, Japan), Fukuoka Red Cross Hospital (Fukuoka, Japan), St Mary's Hospital
- 6 (Kurume, Japan), Steel Memorial Yawata Hospital (Kitakyushu, Japan), and Japan Labor
- 7 Health and Welfare Organization Kyushu Rosai Hospital (Kitakyushu, Japan).
- 8 Steering Committee and Research Working Group Members
- 9 Takao Ishitsuka, MD, PhD (Fukuoka Mirai Hospital, Fukuoka, Japan), Setsuro Ibayashi, MD,
- 10 PhD (Chair, Seiai Rehabilitation Hospital, Onojo, Japan), Kenji Kusuda, MD, PhD (Seiai
- 11 Rehabilitation Hospital, Onojo, Japan), Kenichiro Fujii, MD, PhD (Japan Seafarers Relief
- 12 Association Moji Ekisaikai Hospital, Kitakyushu, Japan), Tetsuhiko Nagao, MD, PhD
- 13 (Safety Monitoring Committee, Seiai Rehabilitation Hospital, Onojo, Japan), Yasushi Okada,
- 14 MD, PhD (Vice-Chair, National Hospital Organization Kyushu Medical Center, Fukuoka,
- 15 Japan), Masahiro Yasaka, MD, PhD (National Hospital Organization Kyushu Medical
- 16 Center, Fukuoka, Japan), Hiroaki Ooboshi, MD, PhD (Fukuoka Dental College Medical and
- 17 Dental Hospital, Fukuoka, Japan), Takanari Kitazono, MD, PhD (Principal Investigator,
- 18 Kyushu University, Fukuoka, Japan), Katsumi Irie, MD, PhD (Hakujyuji Hospital, Fukuoka,
- 19 Japan), Tsuyoshi Omae, MD, PhD (Imazu Red Cross Hospital, Fukuoka, Japan), Kazunori
- 20 Toyoda, MD, PhD (National Cerebral and Cardiovascular Center, Suita, Japan), Hiroshi
- 21 Nakane, MD, PhD (National Hospital Organization Fukuoka-Higashi Medical Center, Koga,
- 22 Japan), Masahiro Kamouchi, MD, PhD (Kyushu University, Fukuoka, Japan), Hiroshi
- 23 Sugimori, MD, PhD (National Hospital Organization Kyushu Medical Center, Fukuoka,
- 24 Japan), Shuji Arakawa, MD, PhD (Steel Memorial Yawata Hospital, Kitakyushu, Japan),
- 25 Kenji Fukuda, MD, PhD (St Mary's Hospital, Kurume, Japan), Tetsuro Ago, MD, PhD
- 26 (Kyushu University Hospital, Fukuoka, Japan), Jiro Kitayama, MD, PhD (Fukuoka Red
- 27 Cross Hospital, Fukuoka, Japan), Shigeru Fujimoto, MD, PhD (Jichi Medical University,
- 28 Shimotsuke, Japan), Shoji Arihiro, MD (Japan Labor Health and Welfare Organization
- 29 Kyushu Rosai Hospital, Kitakyushu, Japan), Junya Kuroda, MD, PhD (National Hospital
- Organization Fukuoka-Higashi Medical Center, Koga, Japan), Yoshinobu Wakisaka, MD,
 PhD (Kyushu University Hospital, Fukuoka, Japan), Yoshihisa Fukushima, MD (St Mary's
- PhD (Kyushu University Hospital, Fukuoka, Japan), Yoshinisa Fukushima, MD (St Mary s
 Hospital, Kurume, Japan), Ryu Matsuo, MD, PhD (Secretariat, Kyushu University, Fukuoka,
- Japan), Kuriyuki Nakamura, MD, PhD (Kyushu University Hospital, Fukuoka, Japan), Kuniyuki Nakamura, MD, PhD (Kyushu University Hospital, Fukuoka, Japan), Fumi
- Japan, Kunyuki Nakamura, WD, Fild (Kyushu University Fukuoka, Japan),
 Irie, MD, PhD (Kyushu University, Fukuoka, Japan), and Takuya Kiyohara, MD, PhD
- 35 (Kyushu University Hospital, Fukuoka, Japan).
- 36 Event Adjudication Committee Members
- 37 Ryu Matsuo, MD, PhD (Kyushu University), Jun Hata, MD, PhD (Kyushu University), and
- 38 Yasuhiro Kumai, MD, PhD (Hakujyuji Hospital).







A Stroke

B Death