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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Abstract

Background: It remains unclear how chronic kidney disease (CKD) and its underlying pathological conditions, kidney dysfunction and kidney damage, are associated with cardiovascular outcomes. This study aimed to determine whether kidney dysfunction (i.e., decreased estimated glomerular filtration rate [eGFR]), kidney damage (i.e., proteinuria), or both are associated with the long-term outcomes after ischemic stroke.

Methods: A total of 12,576 patients (mean age: 73.0±12.6 years; 41.3% women) with ischemic stroke who were registered in a hospital-based multicenter registry, Fukuoka Stroke Registry, between June 2007 and September 2019, were prospectively followed up after stroke onset. Kidney function was assessed by eGFR and categorized into G1: ≥60 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 was evaluated by proteinuria using a urine dipstick test and classified into P1: −, P2: ±/1+, and P3: ≥2+. Hazard ratios (HR) and 95% confidence intervals (CI) for events of interest were estimated by a Cox proportional hazards model. Long-term outcomes included recurrence of stroke and all-cause death.

Results: During the median follow-up of 4.3 years (interquartile range: 2.1–7.3 years), 2481 patients had recurrent stroke (48.0/1,000 patient-years) and 4032 patients died (67.3/1,000 patient-years). CKD was independently associated with increased risks of stroke recurrence and all-cause death even after adjustment for multiple confounding factors, including traditional cardiovascular risk factors. Both eGFR and proteinuria were independently associated with increased risks of stroke recurrence (multivariable-adjusted HR [95% CI]: G3 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, P3 1.62 [1.45–1.81] vs. P1). In subgroup analyses, effect modifications were found in the association of proteinuria with death by age and stroke subtype.

Conclusion: Kidney dysfunction and kidney damage were independently, but differently,

associated with increased risks of recurrent stroke and all-cause death.

Keywords: CKD, decreased eGFR, ischemic stroke, long-term outcomes, proteinuria

Non-standard Abbreviations and Acronyms: CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate.

Introduction

Stroke is a major cause of disability worldwide. Because stroke recurrence has further serious consequences, such as severe functional impairment and death, recurrent stroke should be prevented as much as possible through appropriate management of risk factors. Nevertheless, 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 diseases (hypertension, diabetes mellitus, dyslipidemia, obesity, smoking, drinking), and atrial fibrillation. Other than these traditional risk factors, CKD has been highlighted as a novel potential risk factor for cardiovascular diseases, including ischemic stroke and death.[1-3] However, because CKD shares similar risk factors to stroke, the causal relationship between CKD and cardiovascular diseases remains uncertain.[4-6]

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 clarify the associations between CKD and risks of stroke and death, but produced inconsistent results in the general population[8-11] and patients with stroke. [12,13]Therefore, it remains controversial whether CKD can act as a biomarker for underlying cardiovascular risk 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 conditions.[12,13] Thus, whether either or both are associated with the risks of cardiovascular events and death remains unclear.

The present study was conducted to address two questions: (1) whether CKD is a risk factor for stroke recurrence or death independently of traditional cardiovascular risk factors and (2) whether impaired kidney function and/or kidney damage are associated with the risk of stroke recurrence or death in patients with ischemic stroke. Briefly, we simultaneously evaluated 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.

Methods

Study design and setting

We constructed the Fukuoka Stroke Registry, a multicenter hospital-based registry that enrolls consecutive patients with acute stroke admitted to seven participating stroke centers in Fukuoka, Japan within 7 days of stroke onset (UMIN-Clinical Trial Registry 000000800). The institutional review board of each hospital approved the study protocol. Written informed consent was obtained from all participants or their family members. This study was performed in accordance with the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[14]

Study participants

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

S1.

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.

Assessment of eGFR and proteinuria

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 into three groups based on the classification of the National Kidney Foundation as G1: eGFR ≥60 mL/min/1.73 m^2, G2: eGFR 45–59 mL/min/1.73 m^2, and G3: eGFR<45 mL/min/1.73 m^2. Details for the eGFR assessment and categorization are provided in the Supplemental Methods.

The urinary protein concentration was evaluated by a quasi-quantitative method using urine dipstick readings and classified into negative (−), trace (±), mild (1+), and severe (≥2+) as previously described.[10] The levels of proteinuria were then grouped into P1: −, P2: ±/1+, and P3: ≥2+ according to the Kidney Disease Improving Global Outcomes (KDIGO) guideline with minor modifications.[2,10,16-18]

Definition of CKD and CKD risk categories

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

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.

Statistical methods

Detailed methods for comparing baseline characteristics according to various factors are described in the Supplemental Methods. Cumulative event rates were calculated by the Kaplan–Meier method, and inter-group differences in the curves were evaluated by the log-rank test. A Cox proportional hazards model was used to estimate the hazard ratio (HRs) and 95% confidence intervals (CIs) for the long-term outcomes in each categorized 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.

Subgroup analyses were performed according to age, sex, risk factors, and stroke subtype. P-values for heterogeneity were calculated by adding the interaction term of eGFR or proteinuria × subgroup variables in the model.

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

replacement therapy in the G3 and P3 groups or very high risk group. We also performed multiple imputation to handle missing data for urine analysis. The missing data were imputed, and 20 imputed datasets were generated. The results for these datasets were combined into a single imputation result.

All statistical analyses were performed using Stata15 (Stata Corp LP, College Station, TX, USA). Two-sided values of $P<0.05$ were considered statistically significant.

Results

Baseline characteristics

The mean (standard deviation) age of the 12,576 patients was 73.0 (12.6) years, and 41.3% were women. Most variables, except for dyslipidemia, differed significantly according to presence of CKD (Table S1). Table 1 shows the trends in baseline characteristics according to eGFR and proteinuria levels. Baseline characteristics significantly differed according to eGFR levels. Similar trends in baseline characteristics were observed for proteinuria levels, except for body mass index.

Associations of CKD, eGFR, and proteinuria with long-term risks of stroke recurrence and death

The median (interquartile range) follow-up duration was 4.3 (2.1–7.3) years, and the maximum was 10 years. The total follow-up time was 59,893 patient-years. During follow-up, 2,481 patients (19.7%) had recurrent stroke and 4,032 patients (32.1%) died. The event rates of recurrent stroke and all-cause death were 48.0 and 67.3 events per 1,000 patient-years, respectively.

The cumulative rate of recurrent stroke increased according to presence of CKD (Figure 1A), decreasing eGFR levels (Figure 1B), and increasing proteinuria levels (Figure 1C). In the

Cox model, the HR for stroke recurrence increased significantly for presence of CKD even after adjustment for potential confounding factors, including traditional cardiovascular risk factors (Table 2). The multivariable-adjusted HR of recurrent stroke increased linearly with decreasing eGFR levels after additional adjustment for proteinuria, whereas it slightly increased for high-grade proteinuria only after additional adjustment for eGFR. When we evaluated the associations after regarding death other than stroke as a competing risk, decreasing eGFR levels were still significantly associated with an increased risk of stroke recurrence, whereas the association of proteinuria levels with risk of stroke recurrence was weakened (Table S2).

The cumulative rate of death increased significantly according to presence of CKD (Figure 2A), decreasing eGFR levels (Figure 2B), and increasing proteinuria levels (Figure 2C). Even after adjustment for multiple confounding factors, the HR for death increased significantly according to presence of CKD, decreasing eGFR levels, and increasing proteinuria levels (Table 3).

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 multivariable-adjusted HR for recurrent stroke increased with decreasing eGFR levels in each proteinuria group and with increasing proteinuria levels in each eGFR group. The risk of death also increased linearly with decreasing eGFR levels and increasing proteinuria levels. In the predictive model for recurrent stroke, model fit was improved when eGFR or proteinuria was simultaneously included in the multivariable model in addition to proteinuria and eGFR, respectively (Table S3). Similarly, the model fit in predicting death was significantly improved by adding each factor to the other. Regarding discrimination, the addition of each factor to the other tended to improve the prediction of death but not that of

recurrent stroke (Table S3). No interaction was found in the associations with stroke recurrence and death by adding the interaction term of eGFR × proteinuria to the relevant models (Table S4).

CKD risk categories and long-term risks of stroke recurrence and death

We investigated whether the CKD risk categories proposed in the KDIGO guideline were predictive of long-term outcomes after stroke. The cumulative rates of recurrent stroke and death increased as the severity of the CKD risk category increased (Figure S2). The multivariable-adjusted HRs for stroke recurrence and all-cause death increased in proportion to the severity of the CKD risk category (Table S5).

Subgroup analyses

We performed subgroup analyses for demographic characteristics (age [<75 years or ≥75 years] and sex), risk factors (hypertension and diabetes mellitus), and stroke subtype (cardioembolic or non-cardioembolic). No heterogeneity was found in the associations of eGFR with risks of recurrent stroke (Figure S3) and death (Figure S4). Although there was no heterogeneity in the association of proteinuria with risk of recurrent stroke (Figure S5), heterogeneity existed in the association between proteinuria and risk of death: the association was also stronger in patients aged <75 years compared with patients aged ≥75 years, and the association was also stronger in patients with non-cardioembolic stroke compared with patients with cardioembolic stroke (Figure S6).

Sensitivity analyses

Finally, to exclude any selection bias arising from the exclusion of patients who received renal replacement therapy (Table S6), we performed sensitivity analyses after including the

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

Discussion

The major findings of the present study were as follows. First, presence of CKD, defined as reduced eGFR and/or proteinuria, was significantly associated with increased risks of stroke recurrence and death independently of traditional cardiovascular risk factors in patients with ischemic stroke. Second, even when evaluating the combined effect of eGFR and proteinuria, eGFR and proteinuria were independently associated with the long-term risks of recurrent stroke and death in different ways. Specifically, decreased eGFR levels were associated with 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 recurrence increased only for a high level of proteinuria, although the association was weakened when regarding death as a competing risk. Third, CKD risk categories stratified by the KDIGO guideline were predictive of the risks of stroke recurrence and death. Fourth, heterogeneity in the associations was found for proteinuria, but not for eGFR: the association between proteinuria and risk of death was stronger in patients aged <75 years compared with patients aged ≥75 years and the association was also stronger in patients with non-cardioembolic stroke compared with patients with cardioembolic stroke. These findings

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

CKD and long-term outcomes

The present study clearly indicates that CKD is a risk factor for recurrent stroke and all-cause death in patients with ischemic stroke, independently from traditional cardiovascular risk factors. Some hypotheses can be proposed for the mechanisms underlying the increased cardiovascular risk with CKD.[19] For example, various changes are observed in patients with CKD, such as uremic toxin production, renin-angiotensin activation, chronic inflammation, 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 the increased risks of unfavorable cardiovascular outcomes in patients with CKD, independently of traditional cardiovascular risk factors.

Kidney dysfunction, kidney damage, and long-term outcomes

It remains controversial whether impaired kidney function, kidney damage, or both are involved in cardiovascular outcomes.[12,13] Previous studies produced various findings on the associations of these two pathological conditions with cardiovascular outcomes in the general population.[1,9,10,20] Meanwhile, the results in studies with small cohorts of stroke patients were inconsistent.[12,13] These discrepancies may arise from differences in the sample sizes, demographic characteristics, baseline comorbidities, and follow-up periods among the studies.

In the present cohort of Japanese patients with ischemic stroke, decreased eGFR was significantly associated with an increased risk of stroke recurrence. Proteinuria was also

associated with risk of stroke recurrence, although the association tended to be less significant after considering death as a competing risk. Meanwhile, the risk of all-cause death increased in proportion to the severity of both pathological conditions. The joint effects of eGFR and proteinuria indicate that kidney dysfunction and kidney damage are mutually independent risk factors of recurrent stroke and death in the long term after ischemic stroke. The urinary protein concentration can reflect disorders of the glomerular capillaries and possibly systemic microvessels, including cerebral small vessels.[8,21] We previously demonstrated that proteinuria was significantly associated with 3-month functional outcomes after ischemic stroke.[22] Assuming that proteinuria is an indicator of impairments in the systemic microvasculature, such as capillary rarefaction,[23] proteinuria would predict not only short-term functional outcomes via impaired cerebral microcirculation but also future risks of death and possibly stroke recurrence via end-organ damage. One possible explanation is that reversible functional rarefaction may precede structural rarefaction in the microvasculature, because proteinuria can be improved to some extent by appropriate treatments, such as inhibition of the renin-angiotensin-aldosterone system.[24,25]

Unlike proteinuria, eGFR is considered a comprehensive indicator of small vessel disease and arteriosclerosis. Furthermore, low eGFR possibly reflects increased levels of non-traditional risk factors, such as total homocysteine, inflammation, nitric oxide production, oxidative stress, and thrombogenic factors.[26] For example, indoxyl sulfate, a well-known uremic toxin, increases in inverse proportion to eGFR levels from CKD stage 3.[27] On the one hand, uremic toxins not only induce glomerular sclerosis but also cause damage to cardiomyocytes and vasculatures.[28] On the other hand, renal arteriosclerosis and glomerular sclerosis reduce eGFR, which could further accelerate systemic atherosclerosis and eventually result in unfavorable cardiovascular outcomes. Moreover, cardiac disorders due to increased afterload following reduced eGFR may enhance the risks of vascular events and death.[5,29] In addition

to these biological changes, altered treatment strategies, such as limitations of pharmacotherapy, endovascular treatment, and surgical treatment, would be disadvantageous to the long-term risks of stroke recurrence and death in stroke patients with CKD.[6,30]

Our study revealed that effect modifications on the associations with long-term outcomes existed for proteinuria, but not for eGFR. The association between proteinuria and increased risk of death was strong in patients aged <75 years and patients with non-cardioembolic stroke. In these patients, high urinary protein concentrations may be a warning sign for serious impairment in the systemic microvasculature, and proteinuria may predict unfavorable consequences in the future. By contrast, reduced eGFR may generally worsen the long-term cardiovascular outcomes in patients irrespective of the baseline characteristics.

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.

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,

leading to a selection bias. However, similar results were obtained after multiple imputation. Second, patients who received renal replacement therapy were excluded because data for urine analysis were unavailable. However, the results were unchanged when the patients who received renal replacement therapy were categorized into the G3 and P3 groups. Third, the urinary protein levels were quasi-quantitatively evaluated by a dipstick test, rather than being 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 during the follow-up period. Finally, the study patients were enrolled in a restricted local area of Japan, and therefore generalization of the findings requires validation in other cohorts of patients from different races and ethnicities.

Clinical perspectives

The present study demonstrated that two components of CKD, kidney dysfunction and kidney damage, are independently and differently associated with an increased risk of unfavorable post-stroke outcomes, aside from traditional risk factors. Cardiovascular risk factors may additively increase the risk of cardiovascular events via the progression of CKD in addition to the direct effects on the cardiovascular system. Although controlling cardiovascular risk factors is the top priority in daily clinical practice, eGFR and proteinuria require additional attention to reduce the residual risk of negative cardiovascular outcomes. Treatments for CKD, such as inhibition of the renin-angiotensin-aldosterone system or 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 can offer additional benefits to post-stroke outcomes following ischemic stroke.

Conclusions

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

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Disclosures

None.

Supplemental Material

Supplemental Methods

Tables S1–S11

Figures S1–S6

Appendix

References

1. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Gansevoort RT. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073-2081.

2. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, Gansevoort RT, Kasiske BL, Eckardt KU. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011;80:17-28.

3. Matsushita K, Coresh J, Sang Y, Chalmers J, Fox C, Guallar E, Jafar T, Jassal SK, Landman GWD, Muntner P, et al. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. Lancet Diabetes Endocrinol. 2015;3:514-525.

4. Paisley KE, Beaman M, Tooke JE, Mohamed-Ali V, Lowe GD, Shore AC. Endothelial dysfunction and inflammation in asymptomatic proteinuria. Kidney Int. 2003;63:624-633.

5. Schrier RW. Role of diminished renal function in cardiovascular mortality: marker or pathogenetic factor? J Am Coll Cardiol. 2006;47:1-8.

6. Tonelli M, Pfeffer MA. Kidney disease and cardiovascular risk. Annu Rev Med.

2007;58:123-139.

7. Jankowski J, Floege J, Fliser D, Bohm M, Marx N. Cardiovascular disease in chronic kidney disease: pathophysiological insights and therapeutic options. Circulation. 2021;143:1157-1172.

8. Ninomiya T, Perkovic V, Verdon C, Barzi F, Cass A, Gallagher M, Jardine M, Anderson C, Chalmers J, Craig JC, et al. Proteinuria and stroke: a meta-analysis of cohort studies. Am J Kidney Dis. 2009;53:417-425.

9. Aguilar MI, O'Meara ES, Seliger S, Longstreth WT, Jr., Hart RG, Pergola PE, Shlipak MG, Katz R, Sarnak MJ, Rifkin DE. Albuminuria and the risk of incident stroke and stroke types in older adults. Neurology. 2010;75:1343-1350.

10. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, Wiebe N, Tonelli M, Alberta Kidney Disease Network. Relation between kidney function, proteinuria, and adverse outcomes. JAMA. 2010;303:423-429.

11. Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B. Low glomerular filtration rate and risk of stroke: meta-analysis. BMJ. 2010;341:c4249.

12. Lima HN, Cabral NL, Goncalves AR, Hauser A, Pecoits-Filho R. Association between albuminuria, glomerular filtration rate and mortality or recurrence in stroke patients. Nephron Clin Pract. 2011;117:c246-252.

13. Lee SJ, Lee DG. Relationship between kidney dysfunction and ischemic stroke outcomes: albuminuria, but not estimated glomerular filtration rate, is associated with the risk of further vascular events and mortality after stroke. PLoS One. 2016;11:e0155939.

14. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370:1453-1457.

15. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53:982-992.

16. Konta T, Hao Z, Takasaki S, Abiko H, Ishikawa M, Takahashi T, Ikeda A, Ichikawa K, Kato T, Kawata S, et al. Clinical utility of trace proteinuria for microalbuminuria screening in the general population. Clin Exp Nephrol. 2007;11:51-55.

17. Gansevoort RT, Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, Coresh J, Chronic Kidney Disease Prognosis Consortium. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. Kidney Int. 2011;80:93-104.

18. Nagai K, Yamagata K. Quantitative evaluation of proteinuria for health checkups is more efficient than the dipstick method. Clin Exp Nephrol. 2015;19:152-153.

19. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: effects on the cardiovascular system. Circulation. 2007;116:85-97.

20. Nagata M, Ninomiya T, Kiyohara Y, Murakami Y, Irie F, Sairenchi T, Miura K, Okamura T, Ueshima H, Epoch-Japan Research Group. Prediction of cardiovascular disease mortality by proteinuria and reduced kidney function: pooled analysis of 39,000 individuals from 7 cohort studies in Japan. Am J Epidemiol. 2013;178:1-11.

21. Ito S, Nagasawa T, Abe M, Mori T. Strain vessel hypothesis: a viewpoint for linkage of albuminuria and cerebro-cardiovascular risk. Hypertens Res. 2009;32:115-121.

22. Kumai Y, Kamouchi M, Hata J, Ago T, Kitayama J, Nakane H, Sugimori H, Kitazono T, FSR Investigators. Proteinuria and clinical outcomes after ischemic stroke. Neurology. 2012;78:1909-1915.

23. Martens RJ, Henry RM, Houben AJ, van der Kallen CJ, Kroon AA, Schalkwijk CG, Schram MT, Sep SJ, Schaper NC, Dagnelie PC, et al. Capillary rarefaction associates with

albuminuria: the Maastricht Study. J Am Soc Nephrol. 2016;27:3748-3757.

24. Levy BI, Ambrosio G, Pries AR, Struijker-Boudier HA. Microcirculation in hypertension: a new target for treatment? Circulation. 2001;104:735-740.

25. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. Ann Intern Med. 2008;148:30-48.

26. Madore F. Uremia-related metabolic cardiac risk factors in chronic kidney disease. Semin Dial. 2003;16:148-156.

27. Barreto FC, Barreto DV, Liabeuf S, Meert N, Glorieux G, Temmar M, Choukroun G, Vanholder R, Massy ZA, European Uremic Toxin Work Group. Serum indoxyl sulfate is associated with vascular disease and mortality in chronic kidney disease patients. Clin J Am Soc Nephrol. 2009;4:1551-1558.

28. Lim YJ, Sidor NA, Tonial NC, Che A, Urquhart BL. Uremic Toxins in the Progression of chronic kidney disease and cardiovascular disease: mechanisms and therapeutic targets. Toxins (Basel). 2021;13:142.

29. Shlipak MG, Fried LF, Cushman M, Manolio TA, Peterson D, Stehman-Breen C, Bleyer A, Newman A, Siscovick D, Psaty B. Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. JAMA. 2005;293:1737-1745.

30. Toyoda K, Ninomiya T. Stroke and cerebrovascular diseases in patients with chronic kidney disease. Lancet Neurol. 2014;13:823-833.

31. Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383:1436-1446.

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

	eGFR, mL/min/1.73 m^2				Proteinuria			
	≥60	45–59	<45		−	± 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

*P <0.05 vs. eGFR ≥60 mL/min/1.73 m^2. †P <0.05 vs. negative proteinuria.

eGFR: estimated glomerular filtration rate; P_{trend}: P for trend; SD: standard deviation; BMI: Body mass index; mRS: modified Rankin Scale; IQR: interquartile range, NIHSS: National Institutes of Health Stroke Scale.

Table 2. Associations of CKD, eGFR, and proteinuria with risk of stroke recurrence

			Age- and sex-adjusted			Multivariable-adjusted		
	Events, n (%)	Event rate	HR	(95% CI)	P	HR	(95% CI)	P
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

The event rates are shown as events/1,000 person-years. 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. To estimate the HR of stroke recurrence for eGFR or proteinuria, eGFR and proteinuria were simultaneously included in the multivariable model. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; P_{trend}: P for trend; HR: hazard ratio; CI: confidence interval.

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

			Age- and sex-adjusted			Multivariable-adjusted		
	Events, n (%)	Event rate	HR	(95% CI)	P	HR	(95% CI)	P
CKD								
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

The event rates are shown as events/1,000 person-years. 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. To estimate the HR of death for eGFR or proteinuria, eGFR and proteinuria were simultaneously included in the multivariable model. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; P_{trend}: P for trend; HR: hazard ratio; CI: confidence interval.

Figure legends

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

(A–C) Cumulative rates of stroke recurrence according to CKD (A), eGFR levels (B), and proteinuria levels (C) are shown. The cumulative rates in 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 cumulative incidence curves. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; UP: urine protein.

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

(A–C) Cumulative rates of death according to CKD (A), eGFR levels (B), and proteinuria levels (C) are shown. The cumulative rates in 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 cumulative incidence curves. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; UP: urine protein.

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

(A, B) The multivariable-adjusted HRs for stroke recurrence (A) or death (B) are shown for combinations of eGFR and proteinuria. Patients were categorized according to their eGFR levels (G1: ≥60 mL/min/1.73 m^2; G2: 45–59 mL/min/1.73 m^2; G3: <45 mL/min/1.73 m^2) and proteinuria levels (P1: −; P2: ±/1+; P3: ≥2+). The HRs were estimated by using patients with G1 and P1 as the reference. 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. The levels of eGFR and proteinuria were simultaneously included in the multivariable model. HR: hazard ratio, eGFR: estimated glomerular filtration rate.

SUPPLEMENTAL MATERIAL

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

Supplemental Methods

Clinical variables

Stroke was defined as sudden onset of a non-convulsive and neurological deficit that persisted for ≥24 hours. Ischemic stroke was confirmed by neuroimaging examinations, including computed tomography and/or magnetic resonance imaging. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg in the chronic stage, or as pre-stroke treatment with antihypertensive agents. Diabetes mellitus was defined as fasting blood glucose concentration ≥7.0 mmol/L, casual blood glucose concentration ≥11.1 mmol/L, positive 75-g oral glucose tolerance test result, or glycated hemoglobin A1c concentration ≥6.5% on 2 different days during hospitalization or in the chronic stage, or as pre-stroke treatment with oral hypoglycemic agents or insulin. Dyslipidemia was defined as low-density lipoprotein-cholesterol concentration ≥3.62 mmol/L, high-density lipoprotein-cholesterol concentration <1.03 mmol/L, or triglyceride concentration ≥1.69 mmol/L during hospitalization or in the chronic stage, or as pre-stroke treatment with antihyperlipidemic agents. Atrial fibrillation was diagnosed based on previous history or electrocardiography during hospitalization. Atrial fibrillation was defined as any type of atrial fibrillation, including paroxysmal, persistent, or permanent. Smoking was defined as current or former smoker. Drinking was defined as alcohol intake >20 g per day. 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 Scale score. Stroke severity was assessed using National Institutes of Health Stroke Scale score on admission.

Assessment of eGFR and proteinuria

The estimated glomerular filtration rate (eGFR) was determined using data for serum creatinine levels measured on admission for index stroke. The eGFR was calculated using the equation proposed by the Japanese Society of Nephrology as follows: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine (mg/dL) $^{-1.094}$ × age (years) $^{-0.287}$ in males; eGFR (mL/min/1.73 m^2) = 194 × serum creatinine (mg/dL) $^{-1.094}$ × age (years) $^{-0.287}$ × 0.739 in females.[15]

In the Kidney Disease Improving Global Outcomes (KDIGO) guideline, eGFR was categorized into six groups: normal or high (≥90 mL/min/1.73 m^2), mildly decreased (60–89 mL/min/1.73 m^2), mildly to moderately decreased (45–59 mL/min/1.73 m^2), moderately to severely decreased (30–44 mL/min/1.73 m^2), severely decreased (15–29 mL/min/1.73 m^2), and kidney failure (<15 mL/min/1.73 m^2). In the present study, the normal or high and mildly decreased groups were categorized as G1: eGFR ≥60 mL/min/1.73 m^2, the mildly to moderately decreased group was categorized as G2: eGFR 45–59 mL/min/1.73 m^2, and the moderately to severely decreased, severely decreased, and kidney failure groups were categorized as G3: eGFR <45 mL/min/1.73 m^2.

We performed urine analysis using a urine dipstick in the absence of potential urinary tract infection during hospitalization for index stroke. The approximate amount of urinary protein was estimated by the dipstick readings as follows: trace (±, 15 mg/dL), mild (1+, 30 mg/dL), and severe (≥2+, ≥100 mg/dL).[10] We then categorized dipstick results of negative (–) as P1, trace (±) or mild (1+) as P2, and severe (≥2+) as P3, because previous studies demonstrated that many patients with a trace (±) dipstick result had microalbuminuria based on the urinary albumin-to-creatinine ratio.[16]

Follow-up study

Patients were enrolled from June 2007 to September 2019 and were prospectively followed up until September 2021. After discharge, the patients were initially followed up at 3, 6, and 12 months after stroke onset, and then annually thereafter. The follow-up study was facilitated by research nurses who were trained to interview the participants. The nurses were blinded to the clinical data and conducted the interviews using a standardized interview form. The following information was collected by face-to-face or telephone interviews with patients, family members, or caregivers: vital status, functional status, and stroke recurrence. The final date of follow-up was September 30, 2021. Duration of the follow-up period was 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 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. The Fukuoka Stroke Registry event adjudication committee reviewed the interview records. If the committee suspected that an event of interest had occurred, additional information was obtained from the hospitals or other healthcare providers as needed. Finally, the event adjudication committee determined whether an event of interest had occurred without knowledge of the CKD parameters.

Statistical analysis

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 variables, Mann-Whitney U test for non-parametric variables, and chi-square test for categorical variables. Multiple comparisons were performed using Bonferroni's method. Trends in baseline characteristics were evaluated using the Cochran-Armitage trend test (categorical variables) or the Jonckheere-Terpstra trend test (continuous variables). To test the trends of GFR levels and proteinuria levels, we conducted logistic regression analysis by regarding their grades as ordinal variables.

A Cox proportional hazards model was used to estimate hazard ratios and 95% confidence intervals for outcomes of interest after adjusting for potential confounding factors. Data were censored at the date of the first relevant outcome, death, or final follow-up. Competing risk 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 cause other than stroke recurrence.

Effect modification by eGFR or proteinuria was evaluated by adding a multiplicative interaction term of eGFR level × proteinuria level to the relevant model. Model fit was evaluated using the Akaike information criterion, and improvement in model fit was assessed using likelihood ratios. Discrimination in predicting events of interest was evaluated by Harrell's concordance index.

In the main analysis, we excluded patients who received renal replacement therapy, because urination was not expected. In the sensitivity analyses, we included the patients who received renal replacement therapy in the G3 and P3 groups, because their kidney dysfunction and kidney damage were considered to be in the worst groups. In the main analysis, we also 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 collect urine may have been lost more frequently in certain populations, such as normotensive patients, non-diabetic patients, and patients with minor stroke, than in other populations. In these patients, urine analysis may have been regarded as an unnecessary test during acute stroke care. Therefore, we performed multiple imputation to handle missing data for urine analysis. In the multiple imputation, missing data for urine analysis were imputed

by data estimated by ordinal logistic regression. All variables potentially related to missingness and outcomes were used to predict missing values, including 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, eGFR, National Institutes of Health Stroke Scale score on admission, outcome events [stroke recurrence (0 or 1), time from admission to recurrence or last follow-up, all-cause death (0 or 1), and time from admission to death or last follow-up]. Finally, 20 imputed datasets were generated and the analyses for each complete dataset were combined into one set of results. Because data for other covariates used in the multivariable analysis were complete, there was no listwise deletion for covariates other than proteinuria. All statistical analyses were performed using Stata15 (Stata Corp LP, College Station, TX, USA).

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

	No CKD n=6993	CKD n=5583	P
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: interquartile range; NIHSS: National Institutes of Health Stroke Scale; eGFR: estimated glomerular filtration rate.

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

	Age- and sex-adjusted			Multivariable-adjusted		
	SHR	(95% CI)	P	SHR	(95% CI)	P
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
P_{trend}			<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
P_{trend}			0.21			0.12

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. To estimate the SHR of stroke recurrence for eGFR or proteinuria, eGFR and proteinuria were simultaneously included in the multivariable model. CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; SHR: subdistribution hazard ratio; CI: confidence interval; P_{trend}: P for trend.

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

	AIC	P	C-statistic	P
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

Model 1 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, National Institutes of Health Stroke Scale score on admission, and proteinuria. In model 2, eGFR was added to model 1. Model 3 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, National Institutes of Health Stroke Scale score on admission, and eGFR. In model 4, proteinuria was added to model 3. eGFR: estimated glomerular filtration rate; AIC: Akaike information criterion; CI: confidence interval.

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

	Multivariable-adjusted		
	HR	(95% CI)	P
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

Model 1 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, National Institutes of Health Stroke Scale score on admission, eGFR, and proteinuria. In model 2, the interaction term of eGFR × proteinuria was added to model 1. eGFR (≥60, 45–59, <45 mL/min/1.73 m^2) and proteinuria (−, ±/1+, ≥2+) were converted into ordinal variables according to their grades. eGFR: estimated glomerular filtration rate; HR: hazard ratio; CI: confidence interval.

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

			Age- and sex-adjusted			Multivariable-adjusted		
	Events, n (%)	Event rate	HR	(95% CI)	P	HR	(95% CI)	P
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
P_{trend}					<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
P_{trend}					<0.001			<0.001

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 Global Outcomes guidelines. 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; HR: hazard ratio; CI: confidence interval; P_{trend}: P for trend.

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

	No RRT n=12576	RRT n=475	P
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: interquartile range; NIHSS: National Institutes of Health Stroke Scale; eGFR: estimated glomerular filtration rate.

Table S7. Associations of CKD, eGFR, and proteinuria with risks of stroke recurrence and death after inclusion of patients who received renal replacement therapy

			Age- and sex-adjusted			Multivariable-adjusted		
	Events, n (%)	Event rate	HR	(95% CI)	P	HR	(95% CI)	P
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 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	1.19	(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
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	(1.01–1.22)	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
P_{trend}					<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 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	1.06	(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
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	1.35	(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
P_{trend}					<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 G3 and P3 groups. 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. 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; P_{trend}: P for trend.

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

			Age- and sex-adjusted			Multivariable-adjusted		
	Events, n (%)	Event rate	HR	(95% CI)	P	HR	(95% CI)	P
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
P_{trend}					<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
P_{trend}					<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; P_{trend}: P for trend.

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

	No urine analysis n=2503	Urine analysis n=12576	P
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

SD: standard deviation; mRS: modified Rankin Scale; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale; eGFR: estimated glomerular filtration rate.

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

	Age- and sex-adjusted			Multivariable-adjusted		
	HR	(95% CI)	P	HR	(95% CI)	P
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 m^2)	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
P_{trend}			<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
P_{trend}			<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 m^2)	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
P_{trend}			<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
P_{trend}			<0.001			<0.001

The patients who received renal replacement therapy were categorized into the G3 and P3 groups. Multiple imputation was conducted to handle missing data for urine analysis. 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. 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; P_{trend}: P for trend.

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

	Age- and sex-adjusted			Multivariable-adjusted		
	HR	(95% CI)	P	HR	(95% CI)	P
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
P_{trend}			<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
P_{trend}			<0.001			<0.001

The risk categories were based on the criteria proposed in the Kidney Disease Improving Global Outcomes guideline. The patients who received renal replacement therapy were categorized into the very high risk group. Multiple imputation was conducted to handle missing data for urine analysis. 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. 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; P_{trend}: P for trend.

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

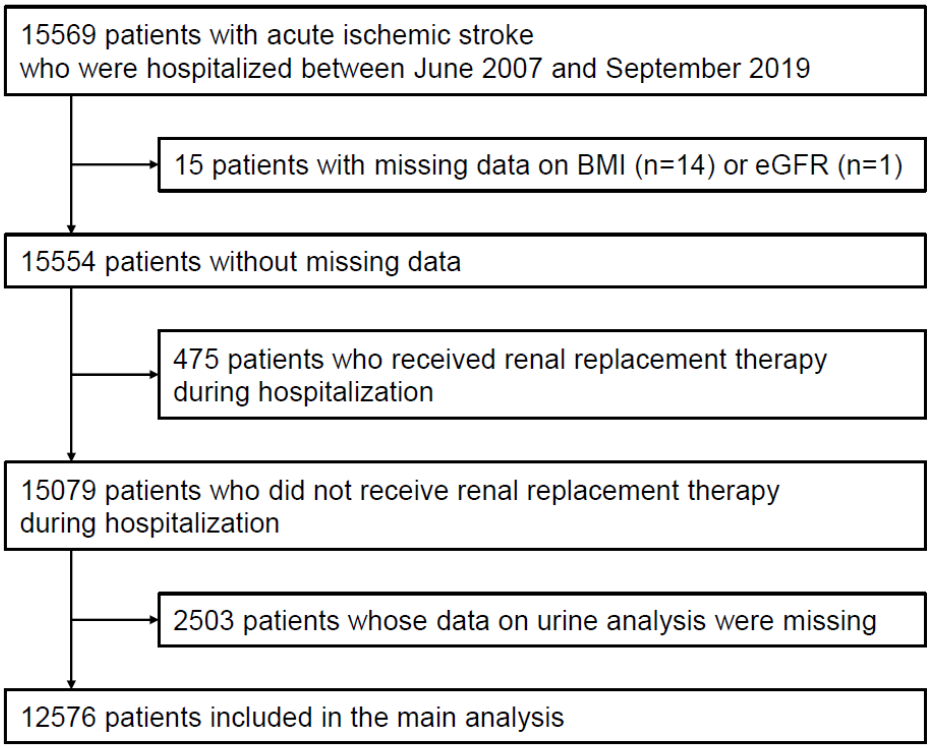
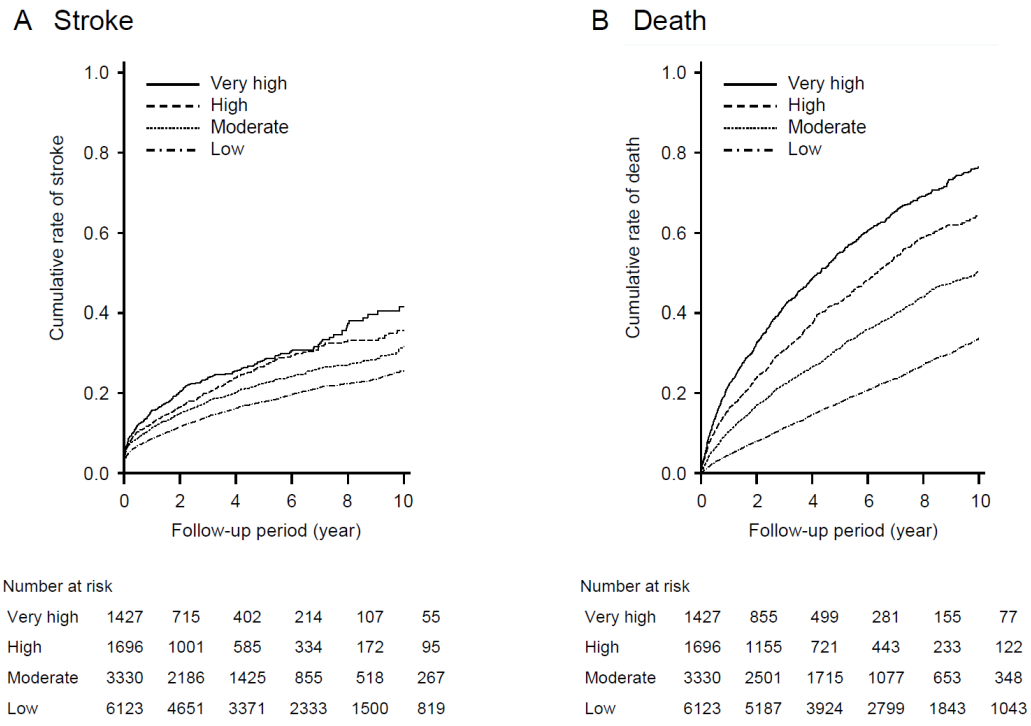


Figure S2. Cumulative rates of stroke recurrence and death according to CKD risk categories



Number at risk

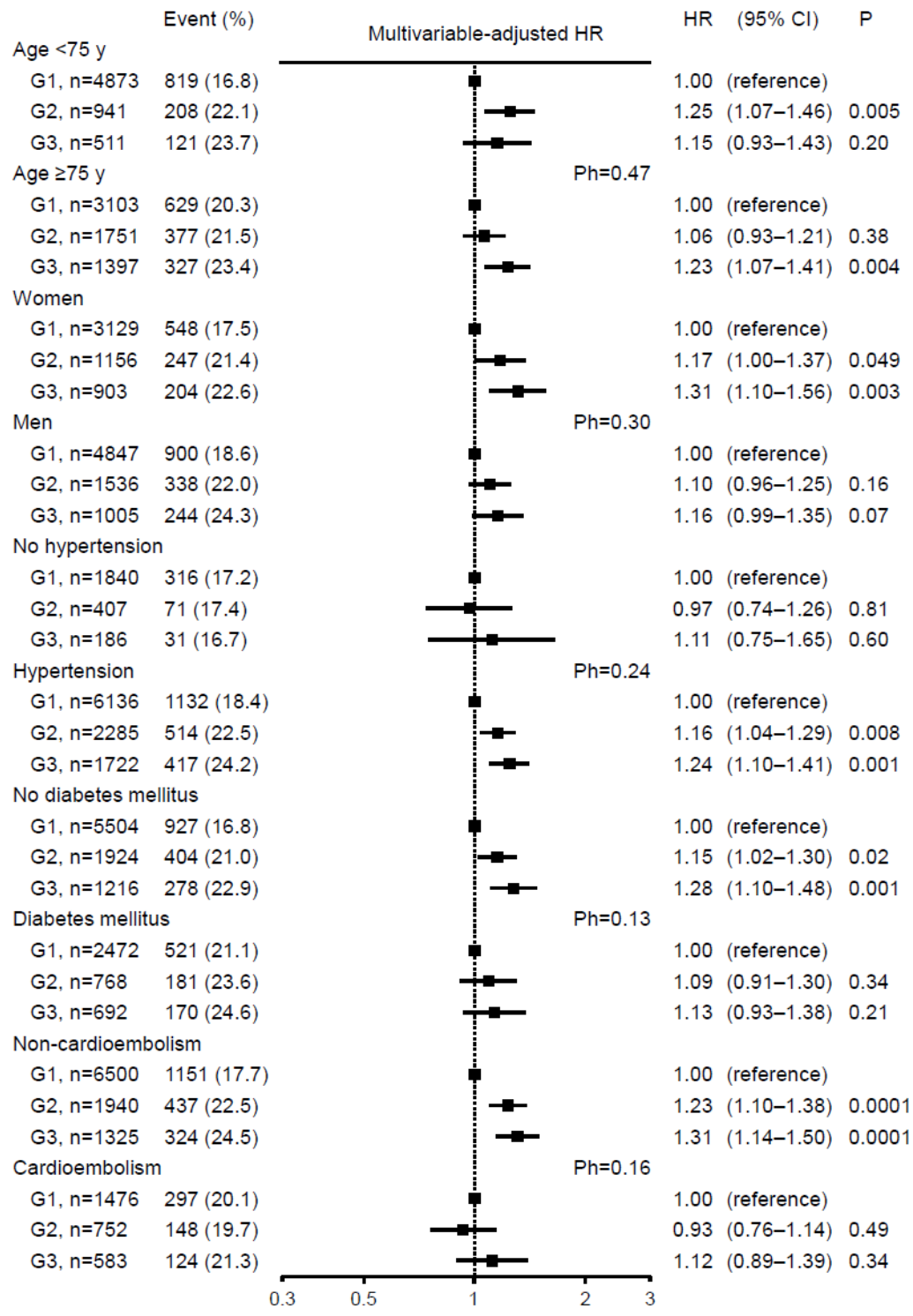
Very high	1427	715	402	214	107	55
High	1696	1001	585	334	172	95
Moderate	3330	2186	1425	855	518	267
Low	6123	4651	3371	2333	1500	819

Number at risk

Very high	1427	855	499	281	155	77
High	1696	1155	721	443	233	122
Moderate	3330	2501	1715	1077	653	348
Low	6123	5187	3924	2799	1843	1043

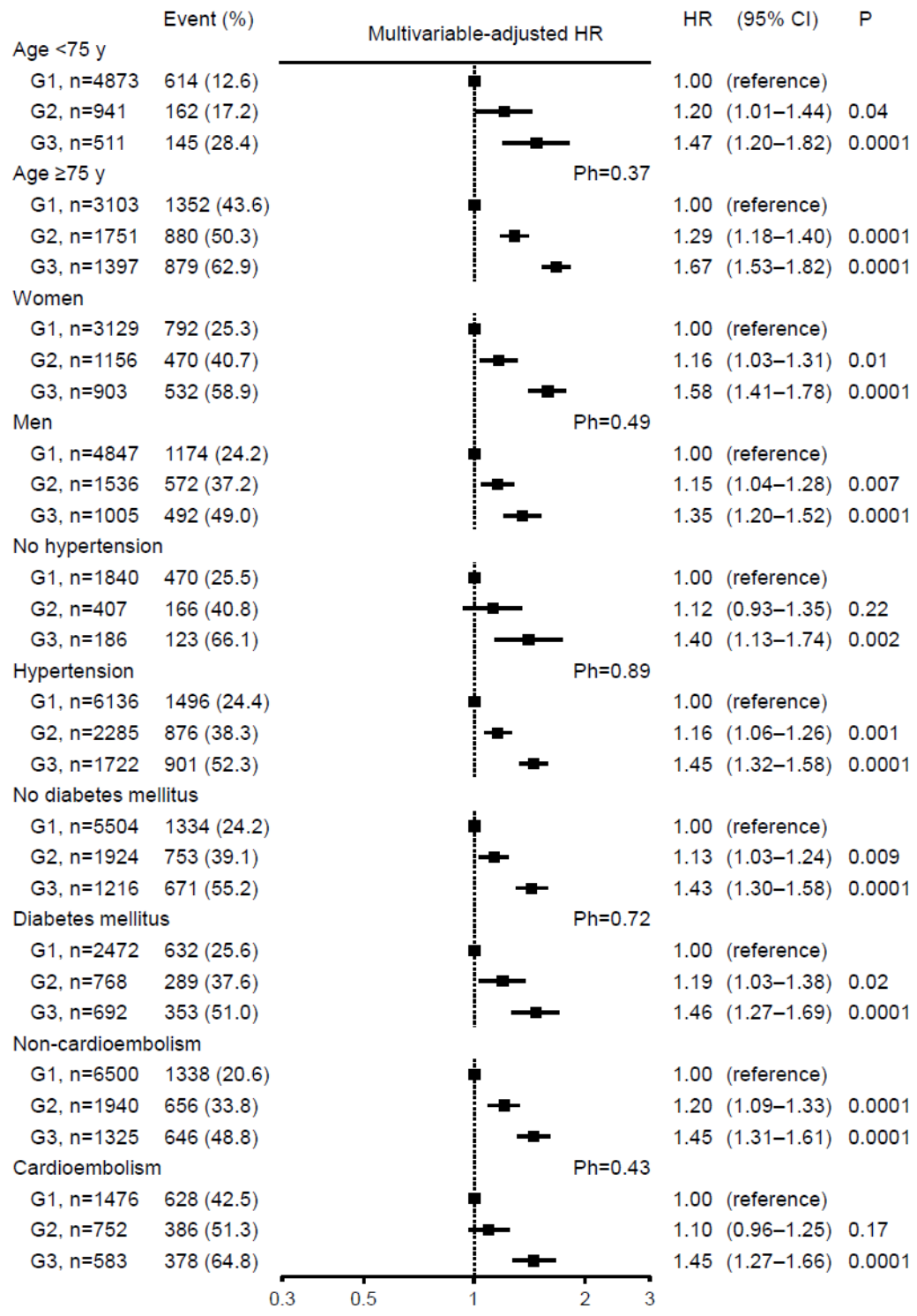
(A, B) The cumulative rates of stroke recurrence (A) or death (B) are shown according to the CKD risk categories. The cumulative rates during the follow-up period were estimated by the Kaplan-Meier method. The P-values were evaluated by the log-rank test. The numbers at risk are shown beneath the cumulative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

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



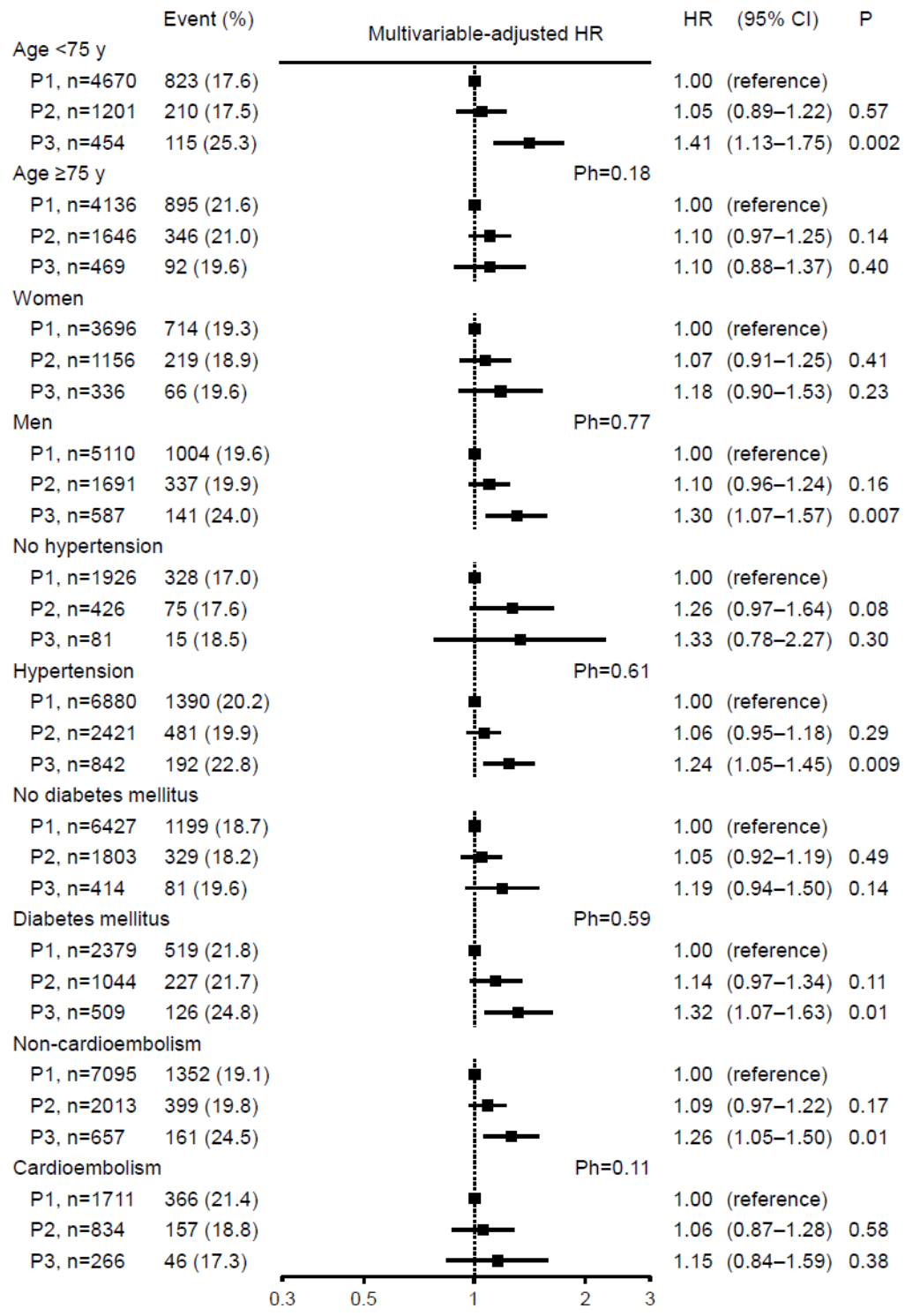
The multivariable-adjusted HRs for stroke recurrence are shown for eGFR groups according to age (<75 years or ≥75 years), sex, hypertension, diabetes mellitus, and stroke subtype (non-cardioembolic or cardioembolic). The multivariable model included age, sex, risk factors (hypertension, diabetes mellitus,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

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



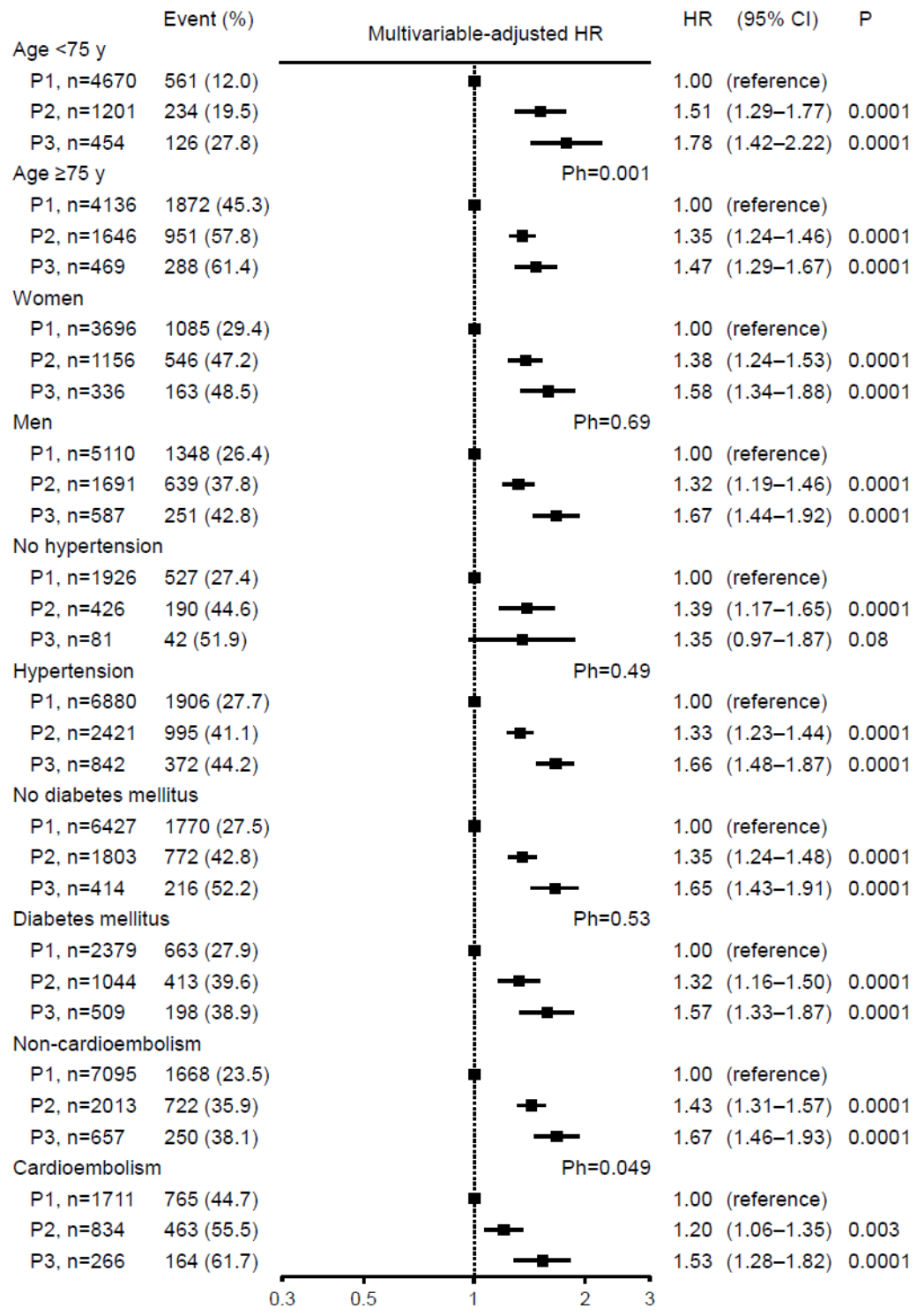
The multivariable-adjusted HRs for all-cause death are shown for eGFR groups according to age (<75 years or ≥75 years), sex, hypertension, diabetes mellitus, and stroke subtype (non-cardioembolic or cardioembolic). The multivariable model included age, sex, risk factors (hypertension, diabetes mellitus,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

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



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-cardioembolic or cardioembolic). 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, National Institutes of Health Stroke Scale score on admission, and eGFR. The P-values for heterogeneity were evaluated by adding the interaction term of proteinuria × subgroup. HR: hazard ratio, CI: confidence interval, Ph: P for heterogeneity.

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



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-cardioembolic or cardioembolic). 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, National Institutes of Health Stroke Scale score on admission, and eGFR. The P-values for heterogeneity were evaluated by adding the interaction term of proteinuria × subgroup. HR: hazard ratio; CI: confidence interval; Ph: P for heterogeneity.

Supplemental Appendix

Participating hospitals

Kyushu University Hospital (Fukuoka, Japan), National Hospital Organization Kyushu Medical Center (Fukuoka, Japan), National Hospital Organization Fukuoka-Higashi Medical Center (Koga, Japan), Fukuoka Red Cross Hospital (Fukuoka, Japan), St Mary's Hospital (Kurume, Japan), Steel Memorial Yawata Hospital (Kitakyushu, Japan), and Japan Labor Health and Welfare Organization Kyushu Rosai Hospital (Kitakyushu, Japan).

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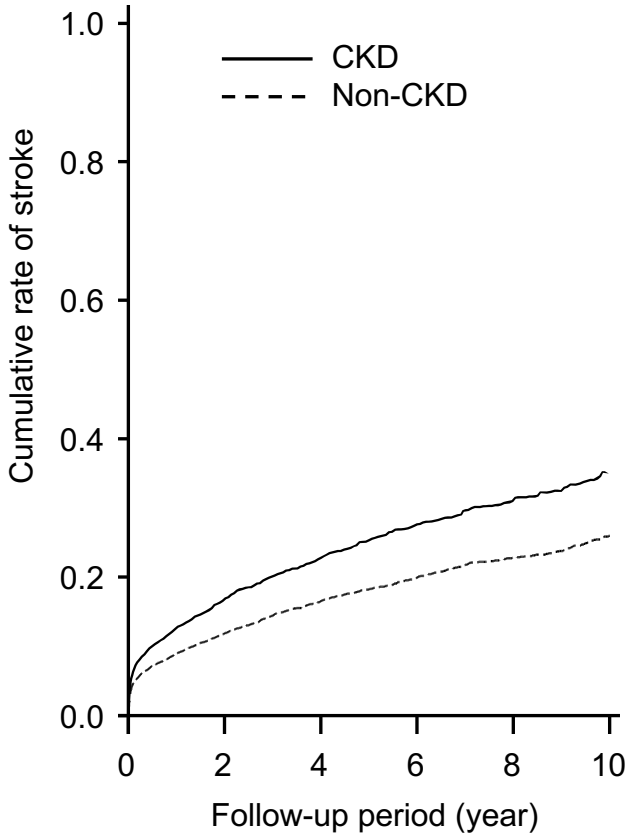
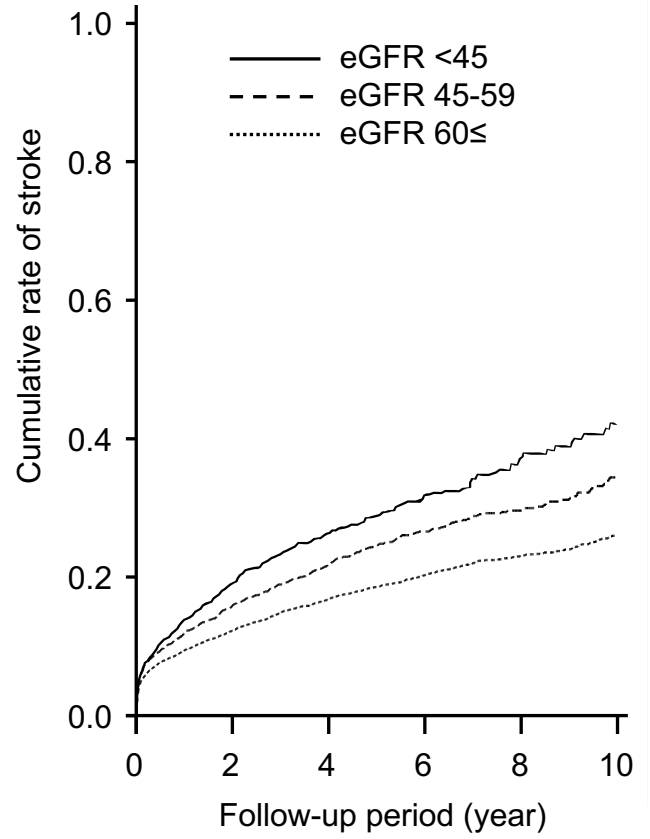
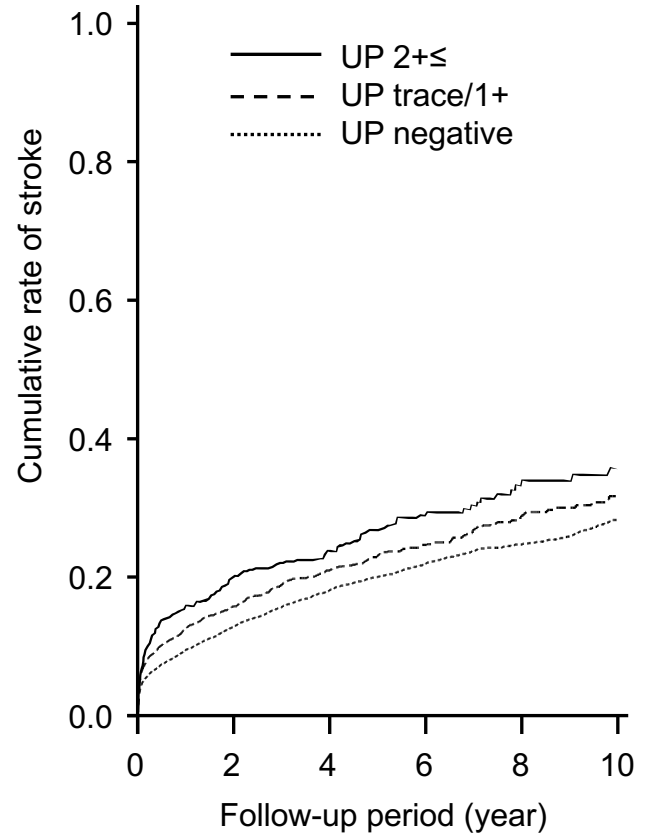






Number at risk

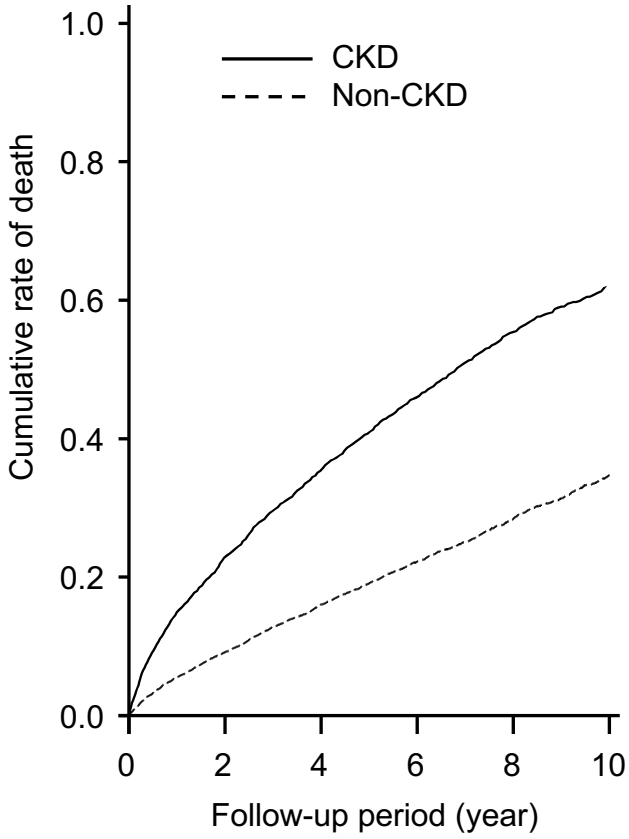
CKD	5583	3334	2055	1193	671	346
Non-CKD	6993	5219	3728	2543	1626	890

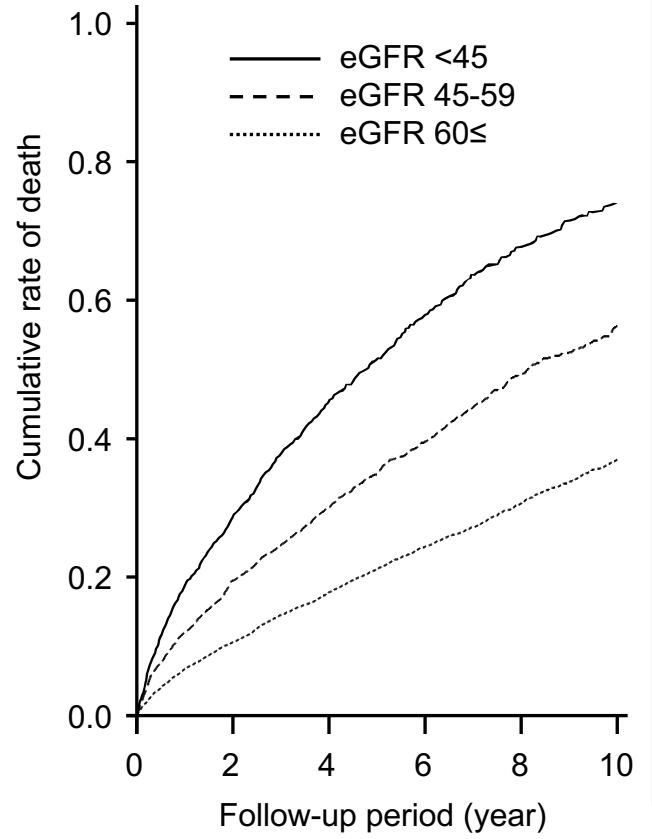
Number at risk

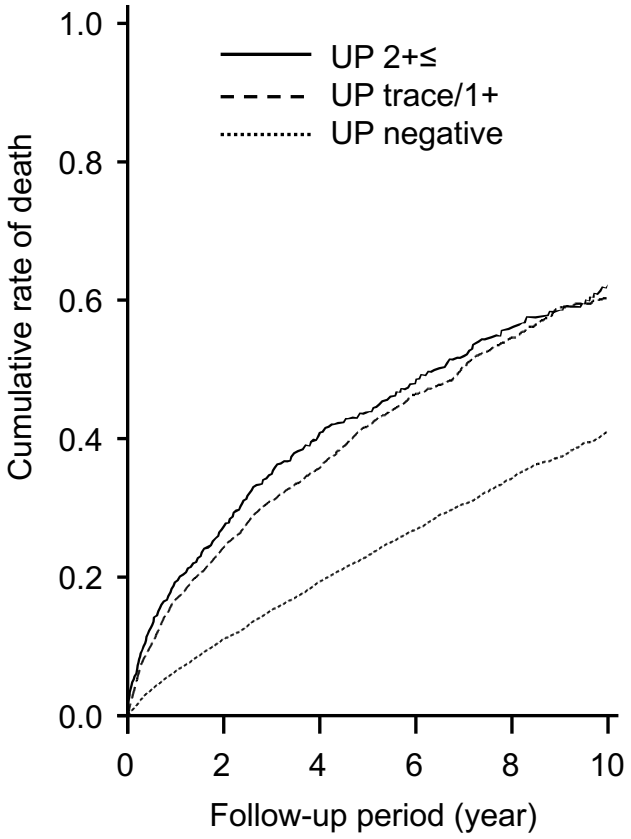
<45	1908	1021	586	317	161	76
45-59	2692	1715	1093	653	385	202
60≤	7976	5817	4104	2766	1751	958

Number at risk

2+≤	923	491	293	177	100	65
Trace/1+	2847	1687	999	564	297	155
Negative	8806	6375	4491	2995	1900	1016







Number at risk

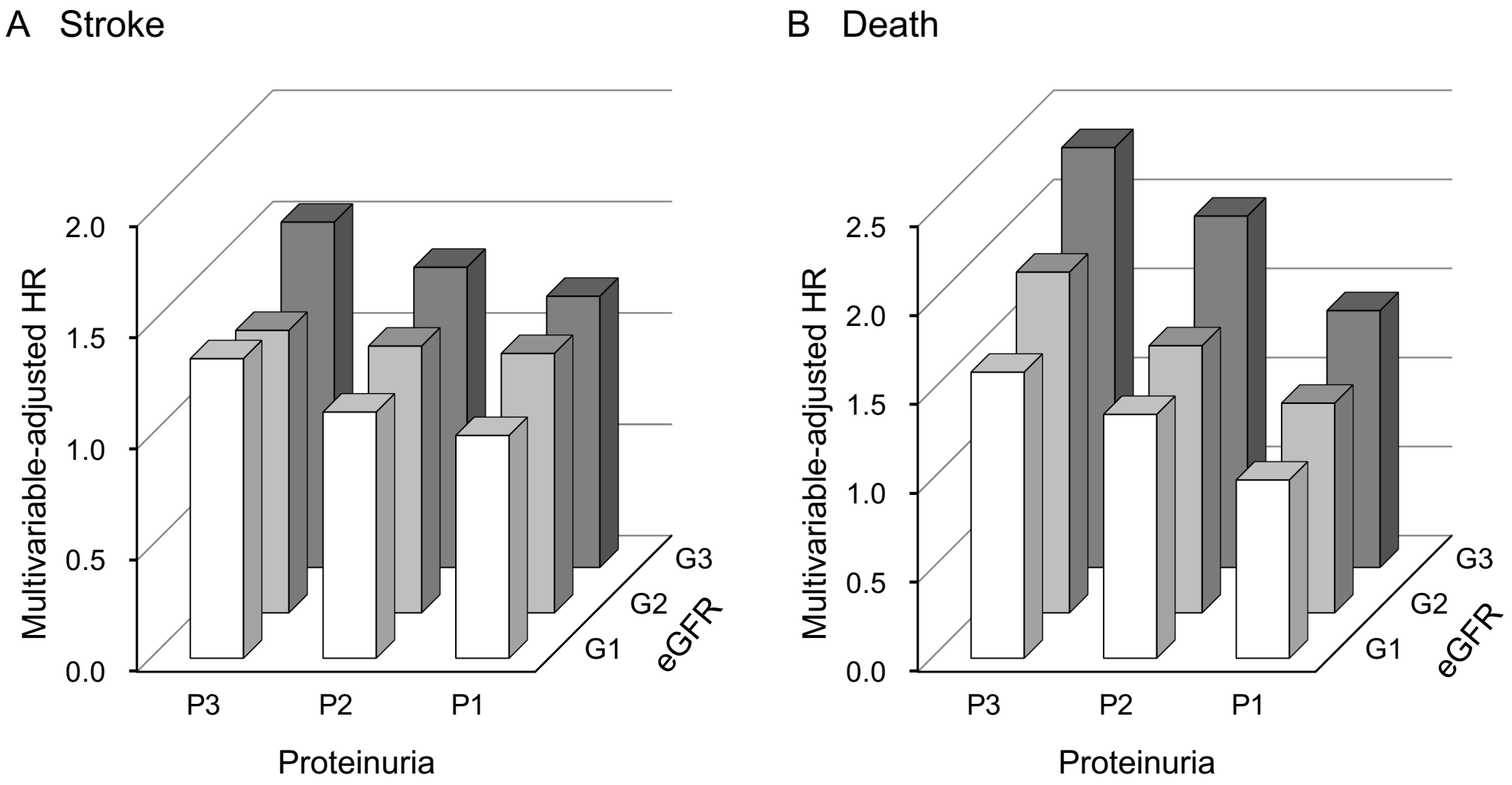
CKD	5583	3871	2518	1553	888	456
Non-CKD	6993	5827	4341	3047	1996	1134

Number at risk

<45	1908	1217	736	421	225	108
45-59	2692	1971	1337	854	503	267
60≤	7976	6510	4786	3325	2156	1215

Number at risk

2+≤	923	588	355	232	143	81
Trace/1+	2847	1919	1196	696	380	201
Negative	8806	7191	5308	3672	2361	1308


A Stroke
B Death
Multivariable-adjusted HR
2.0
1.5
1.0
0.5
0.0
2.5
P3
P2
P1
Proteinuria
G1
G2
G3
eGFR