

Reduced Glomerular Filtration Rate and Risk of Stroke: A Nationwide Cohort Study in South Korea

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Aims: Although chronic kidney disease is recognized as an independent risk factor for cerebrovascular disease, its association with hemorrhagic and ischemic stroke remains controversial.

Methods: We conducted a retrospective cohort study using the National Health Insurance Service-National Sample Cohort, which is representative of the Korean population. A total of 195,772 Koreans who were not diagnosed with stroke before 2009 were included in this study from 2009 to 2013. The eGFR was divided into six categories (≥ 90 , 75–89, 60–74, 45–59, 30–44, <30 mL/min/1.73 m²). The Kaplan–Meier plot was illustrated to compare the incidence of stroke. Cox proportional hazard model was used to estimate the hazard ratio (HR) of eGFR for risk of ischemic and hemorrhagic stroke by sex.

Results: During an average of 4.36 years of follow-up period, 2,236 and 668 people were diagnosed with newly ischemic and hemorrhagic stroke, respectively. Age-adjusted incidence rate for ischemic stroke among people with eGFR <45 mL/min/1.73 m² was higher than those with eGFR ≥ 90 mL/min/1.73 m², whereas that for hemorrhagic stroke among people with eGFR ≥ 90 mL/min/1.73 m² was higher than those with eGFR <45 mL/min/1.73 m². After adjusting for multiple covariates, the adjusted HR for ischemic stroke increased with decreasing eGFR in men (p for trend <0.001), but not in women (p for trend = 0.48). On the other hand, there was no significant relationship between eGFR and risk of hemorrhagic stroke in both men and women.

Conclusions: Reduced glomerular filtration rate less than 45 mL/min/1.73 m² was associated with an increased risk of ischemic stroke, especially in men.

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Key words: Chronic renal insufficiency, Glomerular filtration rate, Stroke, Cerebral hemorrhage, Cerebral infarction

Introduction

Chronic kidney disease (CKD) is one of the most important non-communicable diseases worldwide. It is defined as kidney damage or decreased kidney

function for more than 3 months¹⁻²). According to the Global Burden of Disease Study 2017, the incidence of and mortality due to CKD have increased with the aging population, and the associated metabolic risk factors also show increasing trends²). The prevalence

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of CKD has also been rising in several developed countries, such as the United States and Norway³⁻⁴). In South Korea, the prevalence of CKD has gradually increased from 2009 to 2013, according to the Korean National Health and Nutrition Examination Survey data⁵).

The risk of cardiovascular disease in patients with CKD is higher than in the general population, regardless of conventional metabolic risk factors or comorbidities⁶⁻¹⁵). However, further studies are still required to determine whether CKD is associated with cerebrovascular disease, especially regarding the subtype of stroke, ischemic or hemorrhagic¹⁶⁻²¹). In particular, a uremia-induced disorder of platelet adhesion and aggregation or altered circadian blood pressure may increase the risk of bleeding²²⁻²⁴). However, there are few studies examining the association between CKD and risk of hemorrhagic stroke.

Therefore, our study aimed to investigate the association between reduced estimated glomerular filtration rate and risk of ischemic and hemorrhagic stroke using a nationwide retrospective cohort database of about 200,000 Korean adults.

Methods

Data Sources and Setting

In this study, we used retrospective cohort data from the National Health Insurance Service-National Sample Cohort (NHIS-NSC) database, which was provided by the National Health Insurance Corporation for research purposes. All populations living in South Korea and all medical institutions are compulsorily enrolled into the National Health Insurance under the National Health Insurance Act. Therefore, the database of national health insurance system represents the medical service usage of the entire Korean population²⁵). The NHIS-NSC is a retrospective cohort consisting of about 1 million people, which represented 2.2% of the total Korean population in year 2002²⁵). It includes not only medical information about the disease code, treatment, and medical institution but also basic administrative information, such as age, sex, residence area, and insurance premiums. In addition, all workers and self-employed persons and their family members in South Korea aged ≥ 40 years are required by law to have a health checkup once every year or every 2 years. Information on these health checks is also included in the NHIS-NSC database.

We set the start of the study as year 2009 because serum creatinine was not measured before 2009 in the

national health checkup examination. In this study, we followed up the people who had undergone the national health checkup examination, except those diagnosed with stroke before 2009 until the time of newly developed stroke or death or December 31, 2013 (end of the follow-up period).

The study protocol and research plan of this study were reviewed by the Institutional Review Board (IRB) of Kyung Hee Hospital (KHUH 2018-12-020). Informed consent requirement was exempted by IRB because researchers only retrospectively accessed a de-identified database for analytical purposes.

Study Participants

A total of 223,551 participants who received a medical health checkup in 2009 were included in the National Health Information Database. Of these, we initially excluded 3,058 individuals who previously had a stroke between 2002 and the date before the medical health examination in 2009. Among the 220,493 participants, 12,317 were excluded based on the following exclusion criteria that might have influenced cerebral infarction or CKD, 850 people did not have data about eGFR, and 11,509 previously had a diagnosis of cancer (ICD C00-C97) in 2009 from 2002 to the date before medical health examination. Some hospitals, including 12,171 subjects, were excluded, because they had abnormal serum creatinine levels. In addition, people with glomerular hyperfiltration (eGFR ≥ 135 mL/min/1.73 m²) were excluded in this study ($n=233$)²⁶).

Since some participants had more than one exclusion criteria, 195,772 were included in the final analysis and were observed for the development of cerebral infarction. The total follow-up period was 854,240.1 person-years, and the average follow-up period was 4.36 ± 0.50 years.

Health Survey Examinations and Laboratory Measurements

The general health checkup of the NHIC was conducted in two stages: The first stage examination was a massive screening test to determine the presence or absence of disease among the general population without symptoms, and the second stage examination was a consultation for screening tests and a more detailed examination to confirm the presence of disease. These health examinations also included a questionnaire for lifestyle or past medical histories. Study data included the level of physical activity based on information provided by a questionnaire, anthropometric measurements, and laboratory measurements. Smoking amount was defined as pack-years as calculated from the smoking-related

questionnaire. Alcohol intake was defined as consumption at least three times per week. Physical activity was defined as performing moderate-intensity physical activity at least 30 min per day for more than 4 days each week or vigorous-intensity physical activity at least 20 min per day for more than 4 days each week²⁷). Body mass index (BMI) was calculated as weight (kg) divided by the square of height (meters). Systolic blood pressure (BP) and diastolic BP were measured by trained examiners. The following laboratory data were measured while these participants underwent health examinations: fasting blood glucose, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and serum creatinine (SCr). Kidney function was measured with estimated glomerular filtration rate (eGFR), which was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation:

$$\text{eGFR} = 141 \times \min(\text{SCr}/K, 1)^a \times \max(\text{SCr}/K, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.018 \text{ [if female]},$$

where SCr is serum creatinine, K is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, \min indicates the minimum of SCr/K or 1, and \max indicates the maximum of SCr/K or 1²⁸). The eGFR was divided into six categories (≥ 90 , 75–89, 60–74, 45–59, 30–44, < 30 mL/min/1.73 m²)⁹.

Outcome Definitions

In this study, the incidence of ischemic and hemorrhagic stroke was defined as the major diagnosis code [ischemic stroke, International Classification of Disease version 10 (ICD-10) code: I63; hemorrhagic stroke, ICD-10 code: I60-I62] at the hospital from 2009 to 2013²⁹). In addition, subgroup analysis was performed by dividing hemorrhagic stroke into subtypes (I60, subarachnoid hemorrhage; I61, intracerebral hemorrhage; I62, other non-traumatic intracranial hemorrhage).

Statistical Analysis

All statistical analysis was performed stratified by sex. Baseline characteristics of study participants were compared according to the categories of eGFR. Categorical variables were expressed as number (percentage), and continuous variables were presented as mean \pm standard deviation. The linear trend of continuous variables with increasing eGFR was analyzed using simple regression analysis, and the ordinal relationship between eGFR categories and categorical variables was tested by Mantel–Haenszel chi-square test. To estimate age-adjusted incidence rates of ischemic and hemorrhagic stroke, we

calculated the age-specific incidence rates for each age group from 40–44 years to ≥ 80 years old. Expected cases of each age and sex group were then obtained by multiplying the age- and sex-specific incidence rate by the proportion of the population in the corresponding age groups of Korean mid-year population in 2000. Finally, the age- and sex-standardized incidence rate was calculated per 100,000 person-years, and 95% confidence intervals were calculated using Poisson methods. To evaluate the associations of baseline CKD and incident cerebral infarction, a Kaplan–Meier plot was created and log-rank test was used to compare the cumulative incidence rates of ischemic and hemorrhagic stroke by eGFR categories. The Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for the risk of ischemic and hemorrhagic stroke after adjusting for age, BMI, systolic BP, fasting blood glucose, total cholesterol, smoking amount (pack-years), alcohol intake, regular exercise, and medication for hypertension, diabetes mellitus, and hyperlipidemia. To test the validity of the Cox proportional hazard models, we checked the proportional hazard assumption. The proportional hazard assumption was assessed by log-minus-log survival function and found to be graphically sound. P values < 0.05 were considered to be statistically significant. All statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA) and R software (version 3.1.1, Vienna, Austria).

Results

During an average of 4.33 years of follow-up, 1,385 (1.3%) men and 851 (1.0%) women were newly diagnosed with ischemic stroke between 2009 and 2013 (Tables 1 and 2). On the other hand, 359 (0.3%) men and 309 (0.4%) women were newly diagnosed with hemorrhagic stroke. During the study period, 2.9% of men and 2.1% of women with eGFR < 60 mL/min/1.73 m² had newly developed ischemic stroke, whereas 0.9% of men and 0.6% of women with eGFR ≥ 90 mL/min/1.73 m² had newly been diagnosed with ischemic stroke. As eGFR decreased, the frequency of ischemic and hemorrhagic stroke increased in both men and women.

At the baseline of the study, patients with lower eGFR were older and more obese and had higher blood pressure and higher fasting blood glucose than those with eGFR ≥ 90 mL/min/1.73 m². As eGFR decreased, there was a lower proportion of alcohol intake. However, as eGFR decreased, the proportion of current smoker has increased in women, but not in men.

Table 1. Baseline characteristics of study participants according to categories of estimated glomerular filtration rate (eGFR) in Korean men

Variables	Overall	eGFR (mL/min per 1.73 m ²)						<i>p</i> -value*
		≥ 90	75–89	60–74	45–59	30–44	< 30	
Number	109,372	34,041	41,244	26,285	5,749	680	1,373	
Person-year (total)	473484.9	147664.1	178928.3	113733.1	24501.5	2726.1	5931.9	
Person-year (average)	4.33±0.52	4.34±0.48	4.34±0.49	4.33±0.54	4.26±0.73	4.01±1.06	4.32±0.66	<0.001
Age (years)	57.2±8.4	55.3±6.5	56.1±8.4	59.4±8.8	64.4±10.0	69.0±9.7	55.9±8.6	<0.001
BMI (kg/m ²)	24.0±2.8	23.8±2.8	24.0±2.8	24.3±2.8	24.4±2.8	24.2±2.9	23.9±2.7	<0.001
Systolic BP (mmHg)	126.4±14.7	126.1±14.7	126.0±14.6	126.8±14.8	128.4±15.1	130.6±16.8	126.7±14.4	<0.001
Diastolic BP (mmHg)	78.9±9.8	79.0±9.9	78.9±9.8	78.9±9.8	78.7±9.9	78.3±10.6	79.0±9.6	0.052
Total cholesterol (mmol/L)	5.08±0.95	5.03±0.94	5.10±0.93	5.12±0.94	5.11±1.01	4.98±1.13	5.01±1.04	<0.001
Triglyceride (mmol/L)	1.74±1.17	1.72±1.22	1.73±1.17	1.75±1.13	1.78±1.11	1.89±1.21	1.78±1.21	<0.001
HDL-cholesterol (mmol/L)	1.37±0.74	1.40±0.81	1.36±0.64	1.35±0.64	1.32±0.53	1.36±1.10	1.70±2.24	0.04
LDL-cholesterol (mmol/L)	2.96±1.01	2.89±1.01	2.98±0.99	3.01±1.02	2.98±0.96	2.89±1.20	2.96±1.11	<0.001
Fasting blood glucose (mmol/L)	5.71±1.52	5.73±1.57	5.67±1.45	5.72±1.49	5.89±1.69	6.12±1.86	5.86±1.58	<0.001
eGFR (mL/min per 1.73 m ²)	81.9±16.9	99.8±6.0	82.7±4.5	68.5±4.1	54.9±3.8	39.4±4.0	7.3±5.9	<0.001
Smoking status								<0.001
Never smoker	37,588 (35.5)	11,116 (33.9)	13,841 (34.7)	9,595 (37.7)	2,333 (41.8)	285 (42.7)	418 (32.1)	
Past smoker	33,789 (31.9)	9,847 (30.0)	12,769 (32.0)	8,570 (33.6)	1,895 (33.9)	242 (36.3)	466 (35.8)	
Current smoker	34,412 (32.5)	11,879 (36.2)	13,310 (33.3)	7,307 (28.7)	1,358 (24.3)	140 (21.0)	418 (32.1)	
Smoking amount (pack-year)	13.8±16.1	14.3±16.0	13.6±15.7	13.7±16.4	13.7±17.9	13.8±17.0	13.2±14.6	<0.001
Alcohol intake (%)	26,197 (24.2)	9,182 (27.3)	9,825 (24.1)	5,719 (22.0)	1,106 (19.5)	118 (17.5)	247 (18.1)	<0.001
Regular exercise (%)	19,300 (18.0)	5,698 (17.1)	7,063 (17.5)	4,997 (19.4)	1,177 (20.8)	124 (18.6)	241 (18.0)	0.001
Development of ischemic stroke (%)	1,385 (1.3)	302 (0.9)	447 (1.1)	408 (1.6)	163 (2.8)	43 (6.3)	22 (1.6)	<0.001
Development of hemorrhagic stroke (%)	359 (0.3)	116 (0.3)	113 (0.3)	77 (0.3)	45 (0.8)	4 (0.6)	4 (0.3)	<0.001
Subarachnoid	73 (0.07)	31 (0.09)	25 (0.06)	10 (0.04)	5 (0.09)	1 (0.15)	1 (0.07)	
Intracerebral	206 (0.19)	64 (0.19)	71 (0.17)	44 (0.17)	25 (0.43)	2 (0.29)	0 (0.00)	
Other non-traumatic	80 (0.07)	21 (0.06)	17 (0.04)	23 (0.09)	15 (0.26)	1 (0.15)	3 (0.22)	

Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as number (percentage).

*Simple linear regression model was used to test linear trends of continuous variables with the eGFR, and Mantel–Haenszel chi-square test was used to examine ordinal relationship between eGFR and categorical variables.

The crude rates and age-standardized incidence rates for ischemic and hemorrhagic stroke are presented according to the eGFR in **Tables 3 and 4**, respectively. After adjusting for age, age-standardized incidence rates for ischemic stroke showed increasing trend with decreasing eGFR in men, but not in women (although it was not statistically significant, women with eGFR <45 mL/min/1.73 m² had a higher age-adjusted incidence rates for ischemic stroke than women with eGFR ≥ 90 mL/min/1.73 m²). In contrast, the age-standardized incidence rates of hemorrhagic strokes among people with eGFR <45 mL/min/1.73 m² were lower than those with normal kidney function with eGFR ≥ 90 mL/min/1.73 m² in both men and women.

A Kaplan–Meier plot was calculated to compare the cumulative risk of ischemic and hemorrhagic stroke with eGFR levels (**Supplementary Figs. 1 and 2**). Although there were significant differences in the

log-rank test for cumulative incidence risk of both ischemic and hemorrhagic stroke by eGFR levels, the difference in cumulative incidence of ischemic stroke between the eGFR groups was much larger than those with hemorrhagic stroke at 5-year follow-up period in both men and women.

After adjusting for multiple covariates, the Cox proportional regression model was calculated to identify the risk of ischemic stroke according to the eGFR categories in both men and women (**Table 5**). The group of patients with normal kidney function with eGFR ≥ 90 mL/min/1.73 m² was set as the reference group. After adjusting for age, BMI, systolic blood pressure, fasting blood glucose, total cholesterol level, smoking amount, regular exercise, alcohol intake, medication for hypertension, diabetes mellitus, and hyperlipidemia, as the eGFR decreased, the risk of ischemic stroke increased in men (*p* for trend < 0.001), but not in women (*p* for trend=0.48).

Table 2. Baseline characteristics of study participants according to categories of estimated glomerular filtration rate (eGFR) in Korean women

Variables	Overall	eGFR (mL/min per 1.73 m ²)						p-value*
		≥ 90	75–89	60–74	45–59	30–44	< 30	
Number	86,400	29,952	27,134	21,542	6,129	831	812	
Person-year (total)	380755.2	132336.8	119717.3	94797.8	26850.5	3516.3	3536.5	
Person-year (average)	4.41 ± 0.46	4.42 ± 0.40	4.41 ± 0.43	4.40 ± 0.49	4.38 ± 0.61	4.23 ± 0.88	4.36 ± 0.62	< 0.001
Age (years)	58.8 ± 8.9	56.0 ± 6.6	58.1 ± 9.0	60.9 ± 9.1	65.8 ± 9.8	71.6 ± 8.8	59.5 ± 9.4	< 0.001
BMI (kg/m ²)	24.0 ± 3.0	23.9 ± 3.0	23.9 ± 3.0	24.1 ± 3.1	24.3 ± 3.2	24.7 ± 3.6	24.0 ± 3.1	< 0.001
Systolic BP (mmHg)	123.8 ± 15.6	122.7 ± 15.2	123.4 ± 15.6	124.6 ± 15.8	127.1 ± 16.3	129.4 ± 17.2	123.9 ± 16.8	< 0.001
Diastolic BP (mmHg)	76.2 ± 9.9	75.8 ± 9.9	76.1 ± 9.9	76.5 ± 9.9	77.4 ± 10.0	77.4 ± 10.3	75.8 ± 10.4	< 0.001
Total cholesterol (mmol/L)	5.33 ± 0.98	5.28 ± 0.96	5.33 ± 0.98	5.40 ± 0.99	5.38 ± 1.03	5.35 ± 1.20	5.26 ± 1.00	< 0.001
Triglyceride (mmol/L)	1.44 ± 0.88	1.39 ± 0.86	1.41 ± 0.84	1.49 ± 0.91	1.62 ± 0.90	1.81 ± 0.97	1.72 ± 1.49	< 0.001
HDL-cholesterol (mmol/L)	1.50 ± 0.84	1.52 ± 0.91	1.48 ± 0.65	1.48 ± 0.67	1.46 ± 0.79	1.40 ± 0.71	2.32 ± 3.42	< 0.001
LDL-cholesterol (mmol/L)	3.22 ± 1.01	3.19 ± 1.05	3.22 ± 0.99	3.26 ± 0.98	3.21 ± 1.00	3.15 ± 1.08	3.15 ± 0.91	< 0.001
Fasting blood glucose (mmol/L)	5.42 ± 1.22	5.36 ± 1.18	5.38 ± 1.15	5.47 ± 1.22	5.68 ± 1.49	6.02 ± 2.09	5.52 ± 1.52	< 0.001
eGFR (mL/min per 1.73 m ²)	82.3 ± 17.4	100.2 ± 5.8	82.9 ± 4.1	68.8 ± 4.4	54.4 ± 4.0	40.4 ± 3.7	7.9 ± 6.7	< 0.001
Smoking status								< 0.001
Never smoker	83,353 (97.7)	28,954 (97.9)	26,216 (97.8)	20,742 (97.6)	5,873 (97.0)	791 (95.6)	777 (97.8)	
Past smoker	560 (0.6)	178 (0.6)	158 (0.6)	160 (0.7)	47 (0.8)	8 (1.0)	9 (1.1)	
Current smoker	1,417 (1.7)	457 (1.5)	435 (1.6)	357 (1.7)	131 (2.2)	28 (3.4)	9 (1.1)	
Smoking amount (pack-year)	0.24 ± 2.30	0.19 ± 1.88	0.23 ± 2.23	0.26 ± 2.5	0.41 ± 3.40	0.48 ± 3.07	0.17 ± 1.55	< 0.001
Alcohol intake (%)	2,049 (2.4)	797 (2.7)	648 (2.4)	486 (2.3)	99 (1.6)	8 (1.0)	11 (1.4)	< 0.001
Regular exercise (%)	12,855 (15.2)	4,605 (15.7)	3,987 (15.0)	3,260 (15.4)	815 (13.5)	76 (9.3)	112 (14.6)	0.001
Development of ischemic stroke (%)	851 (1.0)	167 (0.6)	250 (0.9)	274 (1.3)	113 (1.8)	36 (4.3)	11 (1.4)	< 0.001
Development of hemorrhagic stroke (%)	309 (0.4)	96 (0.3)	83 (0.3)	96 (0.5)	28 (0.5)	7 (0.8)	2 (0.3)	0.004
Subarachnoid	132 (0.15)	41 (0.14)	41 (0.15)	38 (0.18)	10 (0.16)	1 (0.12)	1 (0.12)	
Intracerebral	145 (0.17)	44 (0.15)	33 (0.12)	48 (0.22)	15 (0.24)	5 (0.60)	0 (0.00)	
Other non-traumatic	32 (0.04)	8 (0.03)	9 (0.03)	10 (0.05)	3 (0.25)	1 (0.15)	1 (0.12)	

Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as number (percentage).

*Simple linear regression model was used to test linear trends of continuous variables with the eGFR, and Mantel–Haenszel chi-square test was used to examine ordinal relationship between eGFR and categorical variables.

However, there was no significant dose–response relationship between eGFR categories and the risk of hemorrhagic stroke in both men (p for trend=0.69) and women (p for trend=0.58) (Table 6).

In the subgroup analysis of hemorrhagic stroke, there was no significant dose–response relationship between eGFR group and subtypes of hemorrhagic stroke (Supplementary Tables 1–3). Although there was no statistically significant relationship, the risk of subarachnoid hemorrhagic stroke was positively increased among people with eGFR < 45 mL/min/1.73 m² than those with eGFR ≥ 90 mL/min/1.73 m² in both men and women.

Discussion

In this large cohort study, our results showed an inverse dose–response relationship between eGFR and risk of ischemic stroke, especially in men. However,

there was no clear dose–response relationship between eGFR and risk of hemorrhagic stroke in both men and women. According to the level of eGFR, the risk of ischemic stroke has significantly increased among men with < 45 mL/min/1.73 m².

In a recent meta-analysis of 83 cohort studies and randomized clinical trials of 2,085,225 patients in 2015, eGFR clearly showed an inverse dose–response relationship with the risk of stroke²⁰. In this large meta-analysis study, the risk of all-cause stroke was significantly higher (1.39-fold) in patients with an eGFR < 90 mL/min/1.73 m² than in those with an eGFR ≥ 90 mL/min/1.73 m²²⁰. However, based on the relative risk of unspecified type of stroke, the relative risk of eGFR for ischemic stroke was 1.00, while that of eGFR for hemorrhagic stroke was 0.9 in the meta-regression, although it was not statistically significant²⁰. In four community-based cohorts of 29,595 participants in the United States and the

Table 3. Age-adjusted incidence rates for ischemic stroke and 95% confidence intervals (CI) according to estimated glomerular filtration rate (eGFR)

Categories of eGFR	Incidence cases	Person-years	Crude rates per 100,000 person-years	Age-adjusted rates per 100,000 person-years
Men				
≥ 90 mL/min/1.73 m ²	302	147664.1	204.5 (182.7–228.9)	329.9 (258.0–401.8)
75–89	447	178928.3	249.8 (227.7–274.1)	286.5 (257.7–315.2)
60–74	408	113733.1	358.7 (325.6–395.3)	307.1 (275.0–339.3)
45–59	163	24501.5	665.3 (570.6–775.7)	413.1 (330.0–496.2)
30–44	43	2726.1	1577.4 (1169.8–2126.8)	638.2 (369.0–907.5)
< 30	22	5931.9	370.9 (244.2–563.3)	519.8 (281.2–758.4)
Women				
≥ 90 mL/min/1.73 m ²	167	132336.8	126.2 (108.4–146.9)	255.1 (179.0–331.2)
75–89	250	119717.3	208.8 (184.5–236.4)	294.2 (252.2–336.2)
60–74	274	94797.8	289.0 (256.8–325.4)	292.3 (247.3–337.3)
45–59	113	26850.5	420.8 (350.0–506.1)	279.4 (221.6–337.3)
30–44	36	3516.3	1023.8 (738.5–1419.3)	415.7 (224.0–597.4)
< 30	11	3536.5	311.0 (172.3–561.7)	379.3 (136.6–622.1)

The age-adjusted rates are presented as number of stroke cases per 100,000 people using Korean mid-year population in 2000 as standard population, and Poisson method was used to estimate 95% confidence intervals.

Table 4. Age-adjusted incidence rates for hemorrhagic stroke and 95% confidence intervals (CI) according to estimated glomerular filtration rate (eGFR)

Categories of eGFR	Incidence cases	Person-years	Crude rates per 100,000 person-years	Age-adjusted rates per 100,000 person-years
Men				
≥ 90 mL/min/1.73 m ²	116	147664.1	78.6 (65.5–94.2)	107.1 (64.8–149.3)
75–89	113	178928.3	63.2 (52.5–75.9)	70.8 (56.7–84.9)
60–74	77	113733.1	67.7 (54.2–84.6)	62.5 (47.5–77.5)
45–59	45	24501.5	183.7 (137.1–246.0)	150.2 (90.5–209.9)
30–44	4	2726.1	146.7 (55.1–391.0)	46.6 (0.0–101.6)
< 30	4	5931.9	67.4 (25.3–179.7)	75.7 (0.0–153.2)
Women				
≥ 90 mL/min/1.73 m ²	93	132336.8	70.3 (57.4–86.1)	107.7 (51.9–163.5)
75–89	83	119717.3	69.3 (55.9–86.0)	79.1 (59.7–98.5)
60–74	96	94797.8	101.3 (82.9–123.7)	102.7 (74.0–131.5)
45–59	28	26850.5	104.3 (72.0–151.0)	76.6 (44.6–108.7)
30–44	7	3516.3	199.1 (94.9–417.6)	60.6 (15.3–106.0)
< 30	2	3536.5	56.6 (14.1–226.1)	54.7 (0.0–132.8)

The age-adjusted rates are presented as number of stroke cases per 100,000 people using Korean mid-year population in 2000 as standard population, and Poisson method was used to estimate 95% confidence intervals.

Netherlands, patients with an eGFR of 45 mL/min/1.73 m² had a 30% higher risk of ischemic stroke than those with an eGFR of 95 mL/min/1.73 m², but there was no significant difference in the risk of hemorrhagic stroke between the two groups³⁰. In a Taiwanese cohort study of 17,026 people, lower eGFR was significantly associated with higher mortality risk from ischemic stroke, while eGFR was not

significantly associated with mortality risk of hemorrhagic stroke³¹. These previous findings are consistent with our study findings.

The association between renal function and subtype of stroke has not been conclusively determined. In a Japanese cohort study of 12,222 adults, the relationship between chronic kidney disease and subtype of stroke varied according to sex³². In

Table 5. Hazard ratios (HRs) and 95% confidence intervals (CI) for the incidence of ischemic stroke according to estimated glomerular filtration rate (eGFR)

Categories of eGFR	Unadjusted model	Age-adjusted model	Multivariable model 1	Multivariable model 2
Men				
≥ 90 mL/min/1.73 m ²	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
75–89	1.22 (1.06–1.41)	1.00 (0.86–1.16)	0.99 (0.85–1.15)	0.95 (0.78–1.15)
60–74	1.75 (1.51–2.03)	1.09 (0.94–1.27)	1.05 (0.90–1.23)	1.08 (0.89–1.32)
45–59	3.24 (2.68–3.93)	1.30 (1.06–1.59)	1.21 (0.99–1.49)	1.16 (0.90–1.48)
30–44	7.76 (5.64–10.68)	2.26 (1.62–3.14)	2.04 (1.46–2.85)	2.20 (1.54–3.15)
< 30	1.81 (1.17–2.79)	1.53 (0.99–2.35)	1.47 (0.94–2.29)	1.94 (1.19–3.16)
<i>p</i> for trend	< 0.001	< 0.001	< 0.001	< 0.001
Women				
≥ 90 mL/min/1.73 m ²	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
75–89	1.66 (1.36–2.01)	1.00 (0.81–1.22)	0.97 (0.79–1.19)	1.04 (0.82–1.32)
60–74	2.29 (1.89–2.77)	1.03 (0.84–1.27)	1.01 (0.82–1.23)	0.97 (0.76–1.23)
45–59	3.32 (2.61–4.21)	0.89 (0.69–1.16)	0.85 (0.66–1.11)	0.81 (0.61–1.09)
30–44	8.07 (5.63–11.57)	1.34 (0.92–1.96)	1.18 (0.81–1.74)	1.14 (0.76–1.73)
< 30	2.47 (1.34–4.54)	1.27 (0.69–2.35)	1.07 (0.54–2.10)	1.20 (0.58–2.46)
<i>p</i> for trend	< 0.001	0.62	0.95	0.48

The Cox proportional hazard models were performed after adjusting for multiple covariates.

Multivariable model 1 was adjusted for age, body mass index, systolic blood pressure, fasting blood glucose, and total cholesterol.

Multivariable model 2 was adjusted for Multivariable model 1 and smoking amount (pack-year), alcohol intake, regular exercise, medication for hypertension, diabetes mellitus, and hyperlipidemia.

Table 6. Hazard ratios (HRs) and 95% confidence intervals (CI) for the incidence of hemorrhagic stroke according to estimated glomerular filtration rate (eGFR) and proteinuria

Categories of eGFR	Unadjusted model	Age-adjusted model	Multivariable model 1	Multivariable model 2
Men				
≥ 90 mL/min/1.73 m ²	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
75–89	0.80 (0.62–1.04)	0.73 (0.56–0.95)	0.77 (0.59–1.01)	0.88 (0.61–1.27)
60–74	0.86 (0.65–1.15)	0.65 (0.48–0.87)	0.70 (0.51–0.95)	0.73 (0.48–1.09)
45–59	2.33 (1.65–3.29)	1.30 (0.90–1.88)	1.41 (0.97–2.05)	1.53 (0.96–2.43)
30–44	1.87 (0.69–5.08)	0.83 (0.30–2.29)	0.88 (0.32–2.44)	0.82 (0.25–2.67)
< 30	0.86 (0.32–2.32)	0.80 (0.29–2.16)	0.85 (0.31–2.29)	0.81 (0.20–3.31)
<i>p</i> for trend	0.02	0.61	0.84	0.69
Women				
≥ 90 mL/min/1.73 m ²	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
75–89	0.99 (0.73–1.33)	0.82 (0.60–1.10)	0.79 (0.58–1.07)	0.94 (0.62–1.41)
60–74	1.44 (1.08–1.92)	1.02 (0.75–1.37)	1.05 (0.77–1.42)	1.01 (0.67–1.52)
45–59	1.48 (0.97–2.26)	0.79 (0.51–1.24)	0.78 (0.49–1.23)	1.06 (0.63–1.80)
30–44	2.83 (1.31–6.10)	1.13 (0.51–2.49)	1.23 (0.55–2.72)	1.36 (0.56–3.29)
< 30	0.81 (0.20–3.27)	0.62 (0.15–2.53)	0.69 (0.17–2.81)	1.14 (0.28–4.71)
<i>p</i> for trend	0.003	0.70	0.81	0.58

The Cox proportional hazard models were performed after adjusting for multiple covariates.

Multivariable model 1 was adjusted for age, body mass index, systolic blood pressure, fasting blood glucose, and total cholesterol.

Multivariable model 2 was adjusted for Multivariable model 1 and smoking amount (pack-year), alcohol intake, regular exercise, medication for hypertension, diabetes mellitus, and hyperlipidemia.

Japanese men, chronic kidney disease was associated with increased risk of hemorrhagic stroke but not of ischemic stroke, whereas in Japanese women, people

with chronic kidney disease had a significantly increased risk of ischemic stroke but not of hemorrhagic stroke³². In a Swedish cohort study of

539,287 people, eGFR using the Mayo formula showed an inverse dose–response relationship with risk of ischemic stroke in both sexes, whereas decreased eGFR was associated with increased risk of hemorrhagic stroke only in women but not in men³³).

As observed in the above examples, most studies have shown that reduced renal function was consistently associated with increased risk of ischemic stroke, but not hemorrhagic stroke. One possible reason for this heterogeneity is the inaccuracy in diagnosis of competing risks. People with chronic kidney disease, especially those with end-stage renal-disease patients, had a risk for hemorrhagic events and atherosclerosis. In end-stage renal disease, these risks are intertwined. In patients with chronic kidney disease, pathologic changes that increase the likelihood of bleeding, such as endothelial or platelet dysfunction, and changes that increase the risk of thromboembolic events, such as platelet adhesion and aggregation, occur simultaneously³⁴). According to the report of the Korean Stroke Registry, the most common type of stroke in South Korea was large artery atherosclerosis (LAA) (37.3%) and followed by small vessel occlusion (SVO, 30.8%)³⁵). Considering that most common type of ischemic stroke was due to atherosclerosis or vessel occlusion, atherosclerotic changes due to chronic kidney disease could significantly contribute to the increased risk of ischemic stroke³⁶). In addition, 15% were intracerebral hemorrhage and 9% were subarachnoid hemorrhage among hemorrhagic stroke (24%) in South Korea, according to the 2018 stroke factsheet³⁷). In our subgroup analysis presented in the supplementary tables, lower eGFR did not show a tendency to increase the risk of intracerebral hemorrhage.

Another possible explanation is that reduced eGFR might not be directly associated with an increased risk of bleeding. Bleeding in patients with chronic renal failure is the result of events such as endothelial dysfunction or platelet abnormality, which may be more closely related to albuminuria rather than to reduced eGFR itself³⁸). The finding that eGFR < 45 mL/min/1.73 m² was not significantly associated with increased hemorrhagic stroke could be the result of low statistical power given the small number of hemorrhagic stroke patients in this study.

In our study, there was a different association between low eGFR and risk of ischemic stroke between men and women. In several previous studies, the relationship between eGFR and risk of subtypes of stroke was varied by sex^{32, 33}). It was very well known that women have a lower risk of ischemic stroke than men³⁹).

Both biological and behavioral differences could

explain the difference risk of ischemic stroke between men and women. Estrogen and progesterone play a role in protecting against ischemic stroke through vasodilation, while testosterone increased the risk of ischemic stroke through vasoconstriction^{39, 40}). In addition, Korean women have lower rates of smoking and alcohol intake than Korean men, and the prevalence of hypertension is also lower in Korean women than Korean men⁴¹).

This study has several limitations. First, there may be a problem with the accuracy of the diagnostic classification. The category of unspecified strokes, such as ICD-10 codes I67-I69, affects the accuracy of the diagnostic classification, although there was only a small number of cases in that category. The second issue is that subtypes of ischemic stroke could not be classified by disease mechanism such as lacunar infarction or cardiogenic cerebral infarction. We used the secondary data source collected by the National Health Insurance Service. Therefore, diagnosis of diseases had to be classified according to the ICD-10 code system. The third important issue is that our study could not consider the type and frequency of dialysis and medication. In particular, the compliance of patients with dialysis is a very important issue in determining the general condition and prognosis of patients. Although the multivariable models were adjusted for medication for hypertension, diabetes mellitus, and hyperlipidemia, we could not adjust for anticoagulants medication. Anticoagulants medications may affect the risk of bleeding or thromboembolic events. Finally, the relatively short follow-up period and small number of hemorrhagic stroke patients may lower statistical power. Especially, the number of hemorrhagic stroke was very low among eGFR with 30–44 ($n=11$) and < 30 mL/min/1.73 m² ($n=6$). Therefore, it is difficult to conclude within this study on the association between low eGFR of < 45 mL/min/1.73 m² and risk of hemorrhagic stroke.

Despite these limitations, our study is a rare large-scaled cohort study to investigate the association between reduced renal function and the risk of ischemic and hemorrhagic stroke in a large representative Korean population. Since ischemic and hemorrhagic stroke have quite different treatment modalities, it is clinically very important to know which of these two diseases poses a greater risk for patients with chronic kidney disease.

Conclusions

In this representative cohort study, our findings showed a clear inverse dose–response relationship between eGFR and risk of ischemic stroke in Korean

men. However, there was no significant dose–response relationship between eGFR and risk of hemorrhagic stroke. However, in our study, the number of hemorrhagic stroke among low eGFR was very small. Therefore, further study with a large number of study participants would be necessary to examine the association between decreased eGFR and risk of subtypes of hemorrhagic stroke. Our findings may help clinicians predict and prevent the risk of cerebrovascular disease in patients with chronic kidney disease, according to the level of eGFR.

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Authors' Contributions

Jae-Hong Ryou made substantial contributions to the conception of the work, acquisition and interpretation of the data, and data analysis. Chang-Mo Oh wrote the manuscript and contributed to the study design and interpretation of data and data analysis. Sung Keun Park, Ju Young Jung, Joong-Myung Choi, Eun-Young Lee, Jung-Wook Kim, Hee Yong Kang, Hong-Jun Yang and Eunhee Ha made substantial contributions to the acquisition of the data and critical revision of the study protocol and manuscript.

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Conflict of Interest Statement

The authors declare they have no conflicts of interest relevant to this article.

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Supplementary Table 1. Hazard ratios (HRs) and 95% confidence intervals (CI) for the incidence of subarachnoid hemorrhagic stroke according to estimated glomerular filtration rate (eGFR)

Categories of eGFR	Unadjusted model	Age adjusted model	Multivariable model1	Multivariable model2
Men				
≥ 90 mL/min/1.73 m ²	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
75-89	0.67 (0.39 – 1.13)	0.66 (0.39 – 1.11)	0.64 (0.37 – 1.09)	0.54 (0.23 – 1.28)
60-74	0.42 (0.21 – 0.86)	0.39 (0.19 – 0.81)	0.38 (0.19 – 0.80)	0.48 (0.18 – 1.28)
45-59	0.97 (0.38 – 2.51)	0.84 (0.31 – 2.24)	0.63 (0.21 – 1.87)	1.13 (0.35 – 3.69)
30-44	1.75 (0.24– 12.82)	1.40 (0.19 – 10.67)	1.31 (0.17 – 9.99)	1.99 (0.25 – 16.25)
<30	0.80 (0.11 – 5.89)	0.80 (0.11 – 5.85)	0.82 (0.11 – 6.01)	1.87 (0.24 – 14.32)
<i>p</i> for trend	0.19	0.12	0.10	0.94
Women				
≥ 90 mL/min/1.73 m ²	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
75-89	1.11 (0.72 – 1.70)	1.02 (0.66 – 1.59)	0.95 (0.61 – 1.50)	1.45 (0.76 – 2.75)
60-74	1.29 (0.83 – 2.01)	1.11 (0.70 – 1.75)	1.13 (0.71 – 1.79)	1.17 (0.58 – 2.34)
45-59	1.20 (0.60 – 2.40)	0.89 (0.43 – 1.84)	0.94 (0.45 – 1.94)	1.76 (0.76 – 4.06)
30-44	0.92 (0.13 – 6.70)	0.59 (0.08 – 4.37)	0.64 (0.09 – 4.74)	1.01 (0.13 – 7.90)
< 30	0.91 (0.13 – 6.64)	0.82 (0.11 – 5.96)	0.91 (0.12 – 6.59)	1.99 (0.26 – 15.06)
<i>p</i> for trend	0.41	0.87	0.96	0.36

The Cox-proportional hazard models were performed after adjusting for multiple covariates.

Multivariable model 1 was adjusted for age, body mass index, systolic blood pressure, fasting blood glucose, total cholesterol.

Multivariable model 2 was adjusted for Multivariable model 1 and smoking amount (pack-year), alcohol intake, regular exercise, medication for hypertension, diabetes mellitus, hyperlipidemia.

Supplementary Table 2. Hazard ratios (HRs) and 95% confidence intervals (CI) for the incidence of intracerebral hemorrhagic stroke according to estimated glomerular filtration rate (eGFR)

Categories of eGFR	Unadjusted model	Age adjusted model	Multivariable model1	Multivariable model2
Men				
≥ 90 mL/min/1.73 m ²	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
75-89	0.92 (0.65 – 1.28)	0.83 (0.59 – 1.17)	0.91 (0.64– 1.29)	1.18 (0.74 – 1.89)
60-74	0.89 (0.61 – 1.31)	0.68 (0.46 – 1.01)	0.78 (0.52 – 1.17)	0.76 (0.44 – 1.33)
45-59	2.34 (1.48 – 3.72)	1.35 (0.83 – 2.21)	1.63 (0.99 – 2.70)	1.61 (0.85 – 3.05)
30-44	1.70 (0.42 – 6.94)	0.79 (0.19 – 3.29)	0.92 (0.22 – 3.83)	0.59 (0.08 – 4.40)
< 30	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)
<i>p</i> for trend	0.29	0.35	0.67	0.73
Women				
≥ 90 mL/min/1.73 m ²	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
75-89	0.83 (0.53 – 1.30)	0.66 (0.42 – 1.05)	0.67 (0.42 – 1.07)	0.61 (0.34 – 1.10)
60-74	1.52 (1.01 – 2.29)	1.01 (0.66 – 1.55)	1.05 (0.68 – 1.62)	0.87 (0.50 – 1.52)
45-59	1.68 (0.94 – 3.02)	0.81 (0.43 – 1.51)	0.86 (0.46 – 1.61)	0.94 (0.46 – 1.91)
30-44	4.26 (1.69 – 10.75)	1.48 (0.56 – 3.89)	1.61 (0.61 – 4.27)	1.49 (0.49 – 4.51)
< 30	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)
<i>p</i> for trend	0.008	0.91	0.99	0.92

The Cox-proportional hazard models were performed after adjusting for multiple covariates.

Multivariable model 1 was adjusted for age, body mass index, systolic blood pressure, fasting blood glucose, total cholesterol.

Multivariable model 2 was adjusted for Multivariable model 1 and smoking amount (pack-year), alcohol intake, regular exercise, medication for hypertension, diabetes mellitus, hyperlipidemia.

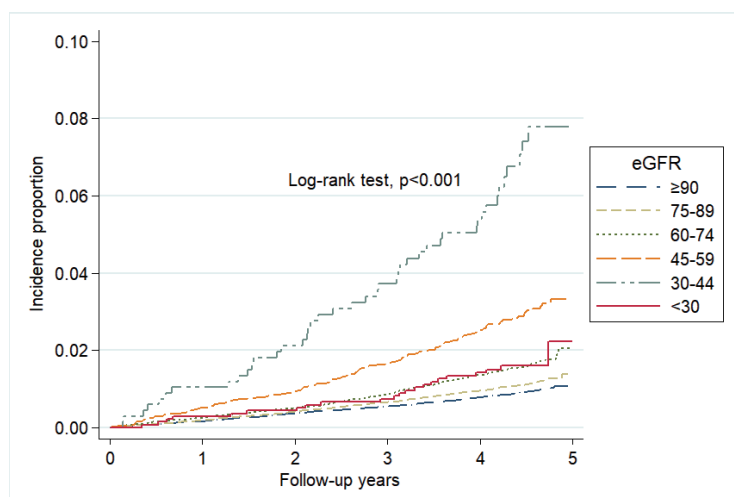
Supplementary Table 3. Hazard ratios (HRs) and 95% confidence intervals (CI) for the incidence of non-traumatic hemorrhagic stroke according to estimated glomerular filtration rate (eGFR)

Categories of eGFR	Unadjusted model	Age adjusted model	Multivariable model1	Multivariable model2
Men				
≥ 90 mL/min/1.73 m ²	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
75-89	0.67 (0.35 – 1.27)	0.52 (0.27 – 1.00)	0.55 (0.28– 1.09)	0.53 (0.22 – 1.26)
60-74	1.42 (0.79 – 2.57)	0.82 (0.44 – 1.52)	0.84 (0.44 – 1.60)	0.80 (0.36 – 1.80)
45-59	4.31 (2.22 – 8.36)	1.51 (0.73 – 3.12)	1.54 (0.73 – 3.25)	1.47 (0.60 – 3.56)
30-44	2.59 (0.35 – 19.24)	0.64 (0.08 – 4.88)	0.57 (0.07 – 4.43)	0.58 (0.07 – 4.71)
< 30	3.55 (1.06 – 11.89)	2.83 (0.84 – 9.56)	2.86 (0.84 – 9.77)	1.30 (0.16 – 10.33)
<i>p</i> for trend	<0.001	0.08	0.13	0.31
Women				
≥ 90 mL/min/1.73 m ²	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
75-89	1.24 (0.48 – 3.22)	0.60 (0.22 – 1.64)	0.55 (0.20 – 1.53)	1.10 (0.27 – 4.48)
60-74	1.74 (0.69 – 4.41)	0.61 (0.22 – 1.64)	0.63 (0.23 – 1.71)	1.02 (0.25 – 4.12)
45-59	1.83 (0.49 – 6.90)	0.34 (0.08 – 1.41)	0.12 (0.01 – 1.00)	0.22 (0.02 – 2.33)
30-44	4.63 (0.58 – 36.98)	0.49 (0.06 – 4.28)	0.52 (0.06 – 4.56)	0.93 (0.09 – 9.87)
< 30	4.69 (0.59 – 37.45)	1.81 (0.22 – 15.01)	1.93 (0.23 – 16.11)	3.25 (0.31 – 33.75)
<i>p</i> for trend	0.054	0.86	0.38	0.66

The Cox-proportional hazard models were performed after adjusting for multiple covariates.

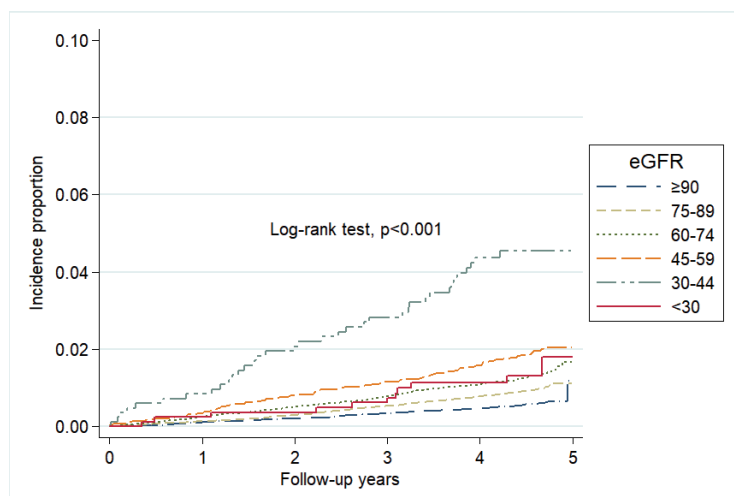
Multivariable model 1 was adjusted for age, body mass index, systolic blood pressure, fasting blood glucose, total cholesterol.

Multivariable model 2 was adjusted for Multivariable model 1 and smoking amount (pack-year), alcohol intake, regular exercise, medication for hypertension, diabetes mellitus, hyperlipidemia.



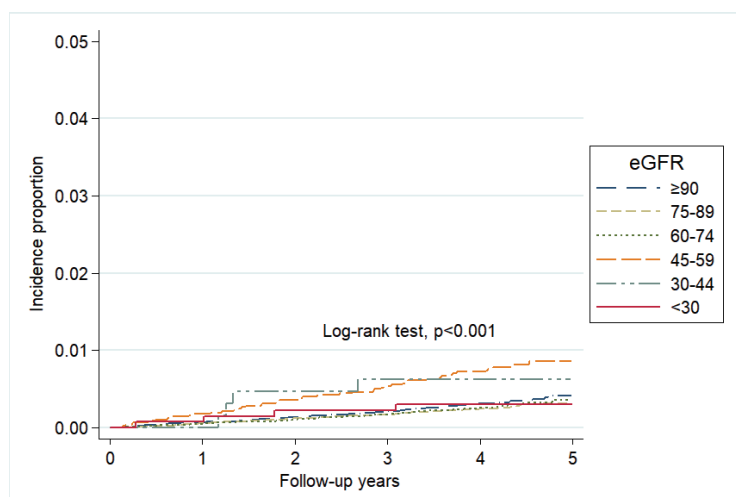
Supplementary Fig. 1A. Comparison of cumulative incidence rate of ischemic stroke according to the estimated glomerular filtration rates in men

Footnotes: The Kaplan–Meier plot was calculated to compare the cumulative incidence rate of ischemic stroke according to the estimated glomerular filtration rates categories. Log-rank test was used to test the difference of cumulative incidence rate of ischemic stroke by estimated glomerular filtration rates categories.



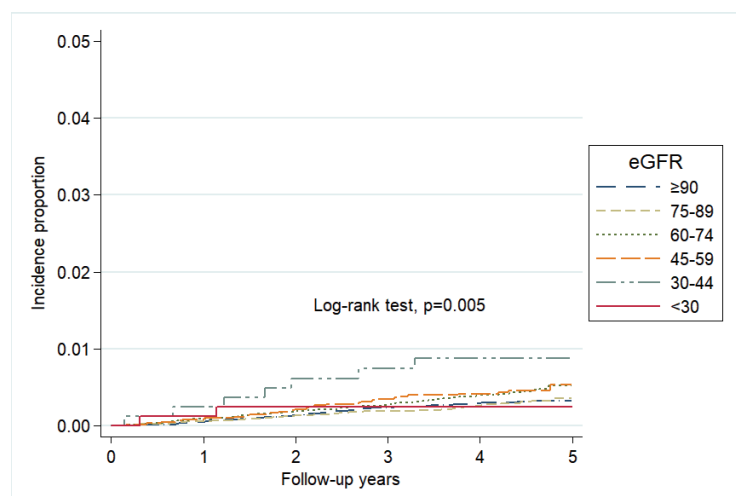
Supplementary Fig. 1B. Comparison of cumulative incidence rate of ischemic stroke according to the estimated glomerular filtration rates in women

Footnotes: The Kaplan–Meier plot was calculated to compare the cumulative incidence rate of ischemic stroke according to the estimated glomerular filtration rates categories. Log-rank test was used to test the difference of cumulative incidence rate of ischemic stroke by estimated glomerular filtration rates categories.



Supplementary Fig. 2A. Comparison of cumulative incidence rate of hemorrhagic stroke according to the estimated glomerular filtration rates in men

Footnotes: The Kaplan–Meier plot was calculated to compare the cumulative incidence rate of hemorrhagic stroke according to the estimated glomerular filtration rates categories. Log-rank test was used to test the difference of cumulative incidence rate of hemorrhagic stroke by estimated glomerular filtration rates categories.



Supplementary Fig. 2B. Comparison of cumulative incidence rate of hemorrhagic stroke according to the estimated glomerular filtration rates in women

Footnotes: The Kaplan–Meier plot was calculated to compare the cumulative incidence rate of hemorrhagic stroke according to the estimated glomerular filtration rates categories. Log-rank test was used to test the difference of cumulative incidence rate of hemorrhagic stroke by estimated glomerular filtration rates categories.