

The Risk for Incident Ischemic Heart Disease According to Estimated Glomerular Filtration Rate in A Korean Population

Sung Keun Park¹, Min-Ho Kim², Eunhee Ha³, Ju Young Jung¹, Chang-Mo Oh⁴, Joong-Myung Choi⁴, Hee Yong Kang⁵, Yong-Sung Choi⁶, Min Gi Kim⁷, Jung-Wook Kim⁸ and Jae-Hong Ryoo⁹

Sung Keun Park and Min-Ho Kim contributed equally to this work.

¹Total healthcare center, Kangbuk Samsung Hospital, Sungkyunkwan University, School of medicine, Seoul, Korea

²Ewha Institute of Convergence Medicine, Ewha Womans University Mokdong Hospital, Seoul, Korea

³Department of Occupational and Environment Medicine, College of Medicine, Ewha Womans University, Seoul, Korea.

⁴Department of Preventive Medicine, School of Medicine, Kyung Hee University, Seoul, Korea

⁵Department of Anesthesiology and Pain Medicine, Kyung Hee University Hospital, Seoul, Korea.

⁶Department of Pediatrics, School of Medicine, Kyung Hee University, Seoul, Korea

⁷Department of Occupational and Environmental Medicine, Dankook University College of Medicine, Cheonan, Korea

⁸Division of Gastroenterology and Hepatology, Department of Internal Medicine, Kyung Hee University School of Medicine, Seoul, Korea

⁹Department of Occupational and Environmental Medicine, School of Medicine, Kyung Hee University, Seoul, Republic of Korea

Aim: Chronic kidney disease, evaluated by the estimated glomerular filtration rate (eGFR), is an established risk factor for cardiovascular disease. However, the association between renal function stratified by the eGFR and the risk of incident ischemic heart disease (IHD) in a community-based Asian population is still inconclusive.

Study design: Retrospective longitudinal observational study.

Method: In data from 206,919 Korean patients registered in the National Health Insurance Corporation (NHIC), we analyzed the risk of incident IHD according to the quartiles (Q) of eGFR (ml/min/1.73 m²) (Q1 < 71.07, Q2: 71.07–83.16, Q3: 83.17–95.49, Q4 > 95.50). The identification of IHD was based on the International Classification of Diseases (ICD) for IHD (ICD code: I20–I25) registered in the NHIC. The Cox proportional hazards model was used to calculate the adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for IHD according to quartile groups of eGFR levels.

Results: Q1 had the more unfavorable baseline metabolic conditions than the other quartile groups. Considering Q4 as the reference, the unadjusted HRs (95% CIs) for IHD increased significantly in the order of Q3 (1.42 [1.29–1.56]), Q2 (1.51 [1.38–1.67]), and Q1 (2.11 [1.93–2.30]), and fully adjusted HRs (95% CIs) increased significantly from Q2 (1.15 [1.04–1.27]) to Q1 (1.31 [1.18–1.44]).

Conclusion: The risk of IHD increased significantly from individuals with an eGFR ≤ 83.16. Mildly decreased renal function is a potential risk factor for IHD.

Key words: Estimated glomerular filtration rate, Renal function, Ischemic heart disease

Abbreviations; CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, CVD: cardiovascular disease, IHD: ischemic heart disease, CAD: coronary artery disease, NHIC: National Health Insurance Corporation, BP: blood pressure, LDL: low-density lipoprotein, HDL: high-density lipoprotein, BMI: body mass index, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: γ -glutamyltransferase, SCr: serum creatinine, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration, HR: hazard ratio, CI: 95% confidence intervals, AMI: acute myocardial infarction

Introduction

With the high prevalence of non-communicable

diseases including diabetes mellitus, hypertension, and obesity, the increasing prevalence of chronic kidney disease (CKD) is a major public health problem

worldwide. The Korean National Health and Nutrition Examination Survey from 2011 to 2013 indicated that the total prevalence of CKD for adults aged ≥ 20 years in Korea was 8.2%¹⁾. CKD is associated with the age-related decline in renal function, in which the estimated glomerular filtration rate (eGFR: ml/min/1.73 m²) declines by approximately 10 ml/min/1.73 m² per decade in life²⁾. Clinical practice guidelines define an eGFR < 60 for three months or more as CKD³⁾. Thus, individuals with an eGFR 60–89 are regarded to be free from CKD as long as they have no evidence of kidney damage, such as proteinuria. Previous studies have indicated that reduced renal function with an eGFR < 60 was significantly associated with an increased cardiovascular risk and mortality in an Asian population⁴⁻⁷⁾. However, it is unclear whether a mildly decreased renal function (an eGFR of 60–89) is independently associated with an increased risk of cardiovascular disease (CVD).

Ischemic heart disease (IHD) is a leading cause of death worldwide, occupying a substantial portion of cardiovascular mortality⁸⁾. There was a significant increase in mortality due to IHD over the past 30 years in Korea. Between 1983 and 2012, the crude mortality due to IHD increased from 3.0 per 100,000 to 30.6 per 100,000 men, and 1.6 per 100,000 to 27.3 per 100,000 women⁹⁾. CKD is an independent risk factor for the development of coronary artery disease (CAD), which is the leading cause of morbidity and mortality in patients with CKD¹⁰⁾. It was demonstrated that patients with an eGFR of 30–60 mL/min per 1.73 m² were at increased risk for obstructive CAD¹¹⁾. Moreover, CKD is associated with a poorer prognosis of CAD¹²⁾, which is partly attributable to the atypical clinical presentation of CAD in patients with CKD¹³⁾. These results have been derived from studies on individuals with an eGFR < 60 in Western countries. However, data on the association between the risk of CAD and mildly decreased eGFR in Asians are still limited. Additionally, there are few large-scale studies with subjects numbering more than hundreds or thousands.

Thus, we investigated the risk of incident IHD according to the eGFR levels in a Korean population. The aim of the study was to seek the eGFR level associated with the increased risk of IHD and to identify whether a mildly reduced renal function is an independent risk factor for IHD.

Participants and Methods

Data Sources

The national health insurance system covers the entire population living in South Korea over 97%, suggesting that the database of the national health insurance system can represent the medical service usage of the entire Korean population¹⁴⁾. In addition, almost all Koreans aged over 40 years are required to undergo a medical health checkup at least once every two years. Information on medical health checkups was collected and stored by the National Health Insurance Corporation (NHIC) in South Korea. In recent years, the national health insurance system in South Korea has provided the sample database for research purposes after deleting the personal identification information. The sampled database provided by the NHIC includes information on health checkups and is linked with the development of IHD in Statistics Korea. Ethical approval for the study protocol and data analysis was obtained from the institutional review board of Kyung Hee University Hospital. The informed consent requirement was exempted by the institutional review board because researchers only retrospectively accessed a de-identified database for analysis purposes.

Study Participants

A total of 223,551 participants who received medical health checkups in 2009 were included in the National Health Information Database. Of these, we initially excluded 5,082 individuals who had previously had IHD (International Classification of Diseases [ICD] I20–I25) from 2002 to the date before the medical health examination in 2009. Among the 218,469 participants, 11,550 participants were excluded based on the following exclusion criteria that might influence IHD or the baseline eGFR: 97 people did not have the information on the baseline eGFR in 2009 and 11,457 had previously had the information on the diagnosis of cancer (ICD C00–C97) from 2002 to the date before the medical health examination in 2009. As some participants had more than one exclusion criteria, 206,919 participants were included in the final analysis and were observed for the development of IHD. The total follow-up period was 899,333.2 person-years and the average follow-up period was 4.35 (standard deviation [SD], 0.55) years.

Health Survey Examinations And Laboratory Measurements

The general health checkup of the NHIC was conducted in two stages. The first stage of examination is a massive screening test to determine the presence or absence of disease among the general population without symptoms. The second stage of examination is consultation for the screening test and a more detailed examination to confirm the presence of disease. These health examinations also included a questionnaire on lifestyle and medical histories. Study data included physical activities, information provided by the questionnaire, anthropometric measurements, and laboratory measurements. Smoking amount was defined in pack-years, which was calculated from the smoking-related section of the questionnaire. Alcohol intake was defined as alcohol consumption more than three times per week. Physical activity was defined as performing moderate-intensity physical activity at least 30 minutes per day for more than 4 days each week or vigorous-intensity physical activity at least 20 minutes per day for more than 4 days each week. The 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 at the same time that these participants underwent health examinations: fasting blood glucose, total cholesterol, triglyceride, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, serum creatinine (SCr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ -glutamyl transferase (GGT). Kidney function was measured with the eGFR, which was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation: $eGFR = 141 \times \min(SCr/K, 1)^a \times \max(SCr/K, 1)^{-1.209} \times 0.993^{age} \times 1.018$ [if female] $\times 1.159$ [if Black], 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 1¹⁵. The urine protein level was determined from the results of a single urine dipstick analysis. The results of the urine test were based on a scale that quantified proteinuria as absent, 1+, and $\geq 2+$.

Outcome Definitions

The NHIC database was linked to the diagnosis of disease data from Statistics Korea. In this study, the entry date was the first health checkup since 2009, and the last follow-up date for incident IHD was December 31, 2013. The identification of IHD was based on the ICD for IHD (ICD code: I20–I25) reg-

istered in the NHIC. The ICD code was registered in medical centers across Korea that actually provided patients with medical care for IHD. The detailed items within each ICD code (I20–I25) are as follows: I20: angina pectoris; I21: acute myocardial infarction; I22: subsequent ST elevation and non-ST elevation myocardial infarction; I23: certain current complications following ST elevation and non-ST elevation myocardial infarction (within the 28-day period); I24: other acute IHDs; and I25: chronic IHD. Incident IHD was defined in subjects with a newly identified ICD of I20–I25 during the follow-up. The primary clinical endpoint of interest for our study was the incident IHD as a composite endpoint.

Statistical Analysis

Data were expressed as the means \pm (SD) or medians (interquartile range) for continuous variables and the percentages of the number for categorical variables. The study subjects were divided into four groups according to the eGFR quartile levels (quartile 1: <71.07 ; quartile 2: 71.07 – 83.16 ; quartile 3: 83.17 – 95.49 ; quartile 4: ≥ 95.50).

The one-way analysis of variance (ANOVA) and the χ^2 -test were used to analyze the statistical differences among the characteristics of the study participants at the time of enrollment in relation to the quartile groups of baseline eGFR levels. The person-years were calculated as the sum of follow-up times from the baseline until the diagnosis of IHD development or until December 31, 2013. To evaluate the associations between the quartile groups of baseline eGFR levels and incident IHD, we used Cox proportional hazards models to estimate the adjusted hazard ratio (HR) and 95% confidence intervals (CI) for incident IHD (adjusted HR [95% CI]), comparing quartiles 1, 2, and 3 of baseline eGFR vs quartile 4 (reference group). This analysis was conducted for subjects grouped by the classic cut-off of CKD stage (group 1: $eGFR < 45$; group 2: $45 \leq eGFR < 60$; group 3: $60 \leq eGFR < 90$; group 4: $eGFR \geq 90$). Additionally, we evaluated the HR and 95% CI for IHD according to the levels of urine dipstick proteinuria (absence, 1+, and $\geq 2+$). The Cox proportional hazards models were adjusted for multiple confounding factors, including age, gender, BMI, systolic BP, fasting blood glucose, LDL-cholesterol, triglyceride, GGT, smoking amount (pack-years), alcohol intake, and physical activity. To test the validity of the Cox proportional hazards models, we checked the proportional hazards assumption. The proportional hazards assumption was assessed by the log-minus-log survival function and found to be graphically unviolated. Kaplan–Meier survival analysis was used to see the trend of the association with IHD

Table 1. Baseline characteristics of study participants according to quartile groups of eGFR levels ($N=206,919$)

Characteristic	Overall	Quartile 1 (<71.07) ($n=51,345$)	Quartile 2 ($71.07-83.16$), ($n=52,498$)	Quartile 3 ($83.17-95.49$), ($n=51,707$)	Quartile 4 (≥ 95.50) ($n=51,369$)	<i>P</i> for trend
Person-year (total)	899,333.2	222,000.0	228,152.0	225,387.0	223,794.2	
Person-year (average)	$4.35 \pm (0.55)$	$4.32 \pm (0.64)$	$4.34 \pm (0.54)$	$4.36 \pm (0.54)$	$4.36 \pm (0.46)$	<0.001
Age (years)	$57.8 \pm (8.6)$	$61.3 \pm (9.6)$	$58.1 \pm (8.3)$	$58.1 \pm (8.8)$	$53.5 \pm (5.4)$	<0.001
Gender						<0.001
Male (%)	116,690 (56.4)	29,240 (56.9)	30,683 (58.5)	29,260 (56.6)	27,507 (53.5)	
Female (%)	90,229 (43.6)	22,105 (43.1)	21,815 (41.5)	22,447 (43.4)	23,862 (46.5)	
BMI (kg/m^2)	$24.0 \pm (2.9)$	$24.2 \pm (2.9)$	$24.1 \pm (2.9)$	$23.9 \pm (2.9)$	$23.8 \pm (2.9)$	<0.001
Systolic BP (mmHg)	$125.3 \pm (15.2)$	$126.8 \pm (15.3)$	$125.3 \pm (15.1)$	$125.3 \pm (15.3)$	$123.7 \pm (14.8)$	<0.001
Diastolic BP (mmHg)	$77.7 \pm (9.9)$	$78.1 \pm (9.9)$	$77.8 \pm (9.9)$	$77.7 \pm (9.9)$	$77.3 \pm (10.1)$	<0.001
Total cholesterol (mg/dL)	$200.8 \pm (37.2)$	$202.8 \pm (38.2)$	$201.9 \pm (36.9)$	$199.8 \pm (36.9)$	$198.6 \pm (36.8)$	<0.001
Triglyceride (mg/dL)	118 (83-171)	125 (89-179)	119 (84-172)	116 (81-167)	113 (79-166)	<0.001
HDL-cholesterol (mg/dL)	$55.4 \pm (32.2)$	$55.5 \pm (38.8)$	$54.4 \pm (24.8)$	$54.9 \pm (26.1)$	$56.9 \pm (36.5)$	<0.001
LDL-cholesterol (mg/dL)	$118.9 \pm (38.9)$	$120.5 \pm (38.1)$	$120.1 \pm (39.2)$	$118.3 \pm (38.7)$	$116.7 \pm (39.6)$	<0.001
Fasting blood glucose (mg/dL)	$100.7 \pm (25.2)$	$102.5 \pm (26.7)$	$100.5 \pm (24.3)$	$99.9 \pm (24.4)$	$99.7 \pm (25.4)$	<0.001
SCr (mg/dL)	$1.15 \pm (1.45)$	$2.01 \pm (2.70)$	$0.97 \pm (0.13)$	$0.85 \pm (0.12)$	$0.72 \pm (0.14)$	<0.001
eGFR (mL/min per 1.73 m^2)	$80.9 \pm (20.2)$	$55.7 \pm (19.2)$	$76.9 \pm (3.5)$	$88.5 \pm (3.5)$	$102.5 \pm (8.2)$	<0.001
Proteinuria (%)						<0.001
absent	97.2	95.6	97.4	97.7	97.9	
1+	1.8	2.6	1.8	1.6	1.5	
$\geq 2+$	1.0	1.8	0.8	0.7	0.6	
AST (U/L)	24 (20-29)	24 (20-29)	24 (20-29)	24 (20-29)	23 (29-29)	0.044
ALT (U/L)	21 (16-29)	21 (16-29)	21 (16-29)	21 (16-29)	21 (16-30)	<0.001
GGT (U/L)	25 (17-41)	25 (17-41)	25 (17-42)	24 (17-40)	25 (16-43)	<0.001
Smoking amount (pack-year)	$7.8 \pm (13.8)$	$7.7 \pm (14.0)$	$8.0 \pm (13.9)$	$8.0 \pm (14.0)$	$7.5 \pm (13.2)$	0.065
Alcohol intake (%)	14.7	12.7	14.6	15.5	16.0	<0.001
Physical activity (%)	16.8	17.6	17.1	16.5	15.9	<0.001
Incident IHD (%)	4,259 (2.06)	1,468 (2.86)	1,084 (2.06)	1,005 (1.94)	702 (1.37)	<0.001

Data are means (standard deviation), medians (interquartile range), or percentages.

**P*-value by ANOVA-test for continuous variables and Chi square test for categorical variables.

BMI: body mass index, BP: blood pressure, HDL: high density lipoprotein, LDL: low density lipoprotein, SCr: serum creatinine, AST: aspartate transaminase, ALT: alanine transaminase, GGT: gamma glutamyl transferase, IHD: ischemic heart disease

among the quartile groups.

P values <0.05 were considered statistically significant. All statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC, USA).

Results

During 899,333.2 person-years of follow-up, 4,259 (2.06 %) incident cases of IHD developed between 2009 and 2013. The baseline characteristics of the study participants in relation to the quartile groups of baseline eGFR levels are presented in [Table 1](#). At baseline, the mean (SD) age and BMI of the study participants were 57.8 (8.6) years and 24.0 (2.9) kg/m^2 , respectively. There were significant differences between all the listed variables and quartile groups of baseline eGFR levels except for smoking amount.

In contrast to participants without incident IHD, those with incident IHD were older (61.8 vs 57.7 years) and more likely to have less favorable metabolic profiles at baseline. As expected, all clinical variables showed statistically significant differences between two groups, except for LDL-cholesterol, SCr, AST, alcohol intake, and physical activity ([Table 2](#)).

[Table 3](#) shows the HR and 95% CI for IHD according to the baseline eGFR. In the unadjusted model, when quartile 4 was set as the reference, the HR and 95% CI for incident IHD significantly increased in inverse proportion to the baseline quartile of eGFR (quartile 1: 2.11 [1.93–2.30]; quartile 2: 1.51 [1.38–1.67]; and quartile 3: 1.42 [1.29–1.56]) (*P* for trend <0.001). These associations attenuated, but remained statistically significant, even after further adjustments for covariates in models 1 and 2. In

Table 2. Comparison of baseline characteristics between participants with and without incident ischemic heart disease

Characteristic	Without incident ischemic heart disease (N=202,660)	With incident ischemic heart disease (N=4,259)	P-value*
Person-year (average)	4.39 ± (0.42)	2.23 ± (1.29)	< 0.001
Age (years)	57.7 ± (8.6)	61.8 ± (9.0)	< 0.001
Gender			< 0.001
Male (%)	113,886 (56.2)	2,804 (65.8)	
Female (%)	88,774 (43.8)	1,455 (34.2)	
BMI (kg/m ²)	24.0 ± (2.9)	24.6 ± (2.9)	< 0.001
Systolic BP (mmHg)	125.2 ± (15.2)	128.4 ± (15.3)	< 0.001
Diastolic BP (mmHg)	77.7 ± (9.9)	78.8 ± (9.9)	< 0.001
Total cholesterol (mg/dL)	200.7 ± (37.2)	203.1 ± (40.3)	< 0.001
Triglyceride (mg/dL)	141.7 ± (94.1)	161.7 ± (101.8)	< 0.001
HDL-cholesterol (mg/dL)	55.5 ± (32.2)	52.6 ± (30.7)	< 0.001
LDL-cholesterol (mg/dL)	118.9 ± (38.9)	119.9 ± (40.5)	0.108
Fasting blood glucose (mg/dL)	100.5 ± (25.0)	107.1 ± (33.3)	< 0.001
SCr (mg/dL)	1.15 ± (1.45)	1.19 ± (1.43)	0.090
eGFR (mL/min per 1.73 m ²)	81.0 ± (20.1)	76.7 ± (20.6)	< 0.001
AST (U/L)	26.5 ± (16.5)	26.9 ± (13.2)	0.064
ALT (U/L)	25.3 ± (19.3)	26.4 ± (18.4)	< 0.001
GGT (U/L)	39.1 ± (54.0)	42.4 ± (52.4)	< 0.001
Smoking amount (pack-year)	7.7 ± (13.7)	11.2 ± (17.0)	< 0.001
Alcohol intake (%)	14.7	15.1	0.452
Physical activity (%)	16.8	16.1	0.251

BMI: body mass index, BP: blood pressure, HDL: high density lipoprotein, LDL: low density lipoprotein, SCr: serum creatinine, eGFR: estimated glomerular filtration rate, AST: aspartate transaminase, ALT: alanine transaminase, GGT: gamma glutamyl transferase

Data are expressed as means (standard deviation) or percentages.

* P-value by t-test for continuous variables and Chi square test for categorical variables

Table 3. Hazard ratios (HRs) and 95% confidence intervals (CI) for the incidence of ischemic heart disease according to the quartile groups of baseline eGFR levels

	Person-year	Incidence cases	Incidence density	HR (95% CI)*		
				Unadjusted	Model 1	Model 2
eGFR						
Quartile 1	222,000.0	1,468	66.1	2.11 (1.93-2.30)	1.30 (1.18-1.44)	1.31 (1.18-1.44)
Quartile 2	228,152.0	1,084	47.5	1.51 (1.38-1.67)	1.13 (1.02-1.25)	1.15 (1.04-1.27)
Quartile 3	225,387.0	1,005	44.6	1.42 (1.29-1.56)	1.08 (0.97-1.19)	1.09 (0.98-1.21)
Quartile 4	223,794.2	702	31.4	1.00 (reference)	1.00 (reference)	1.00 (reference)
P for trend				< 0.001	< 0.001	< 0.001
Age					1.05 (1.04-1.05)	1.05 (1.04-1.05)
Gender					0.60 (0.56-0.64)	0.66 (0.61-0.71)
BMI					1.06 (1.05-1.07)	1.06 (1.05-1.07)
Systolic BP					1.004 (1.002-1.006)	1.004 (1.002-1.006)
Fasting blood glucose					1.005 (1.004-1.006)	1.005 (1.004-1.006)
LDL-cholesterol					1.001 (1.001-1.002)	1.001 (1.001-1.002)
Triglyceride					1.001 (1.001-1.001)	1.001 (1.001-1.001)
GGT					1.000 (1.000-1.001)	1.000 (1.000-1.001)
Smoking amount						1.010 (1.008-1.012)
Alcohol intake						0.830 (0.757-0.911)
Physical activity						0.906 (0.833-0.985)

Incidence density: a case per 10,000 person-year

Gender: female vs male

Smoking amount: pack year

BMI: body mass index, BP: blood pressure, GGT: gamma glutamyl transferase

Model 1 was adjusted for age, gender, BMI, systolic BP, fasting blood glucose, LDL-cholesterol, triglyceride and GGT

Model 2 was adjusted for model 1 plus smoking amount (pack-year), alcohol intake and physical activity

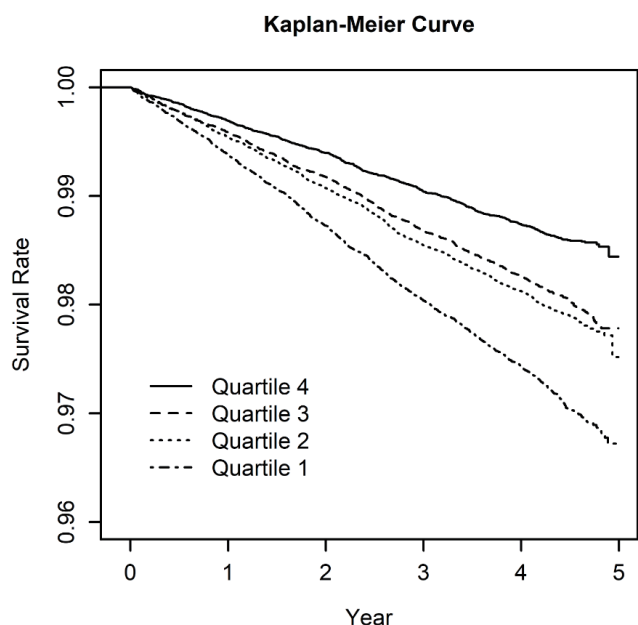


Fig. 1. Kaplan-Meier analysis of ischemic heart disease according to the quartile levels of eGFR

model 2, the adjusted HR and 95% CI for incident IHD were 1.31 (1.18–1.44) in quartile 1, 1.15 (1.04–1.27) in quartile 2, and 1.09 (0.98–1.21) in quartile 3, respectively (P for trend < 0.001). These findings were similarly observed in study groups divided by the classic cut-offs of CKD stage (**Supplementary Table 1**). The adjusted HRs for IHD significantly increased with the inverse proportion to the eGFR levels (group 4: reference; group 3: 1.09 [1.01–1.18]; group 2: 1.39 [1.24–1.57]; and group 1: 1.40 [1.20–1.63]). **Supplementary Table 2** shows the adjusted HR and 95% CI for IHD according to baseline urine dipstick proteinuria. Compared to absent proteinuria, the risk for IHD significantly increased in 1+ proteinuria (1.32 [1.10–1.59]) and 2+ proteinuria (1.89 [1.55–2.31]). Kaplan–Meier survival analysis indicated that lower quartile groups tend to have a higher risk of IHD than higher quartile groups (**Fig. 1**).

Discussion

In the present study, we found that the risk of incident IHD significantly increased under the third quartile of eGFR in Koreans, even after adjusting for covariates including classic cardiovascular risk factors. This finding indicates that reduced renal function is a potential risk factor for IHD. In terms of the association between decreased renal function and cardiovascular risk, our results are line with previous reports that reduced renal function is associated with cardiovascular risk and mortality in Asian populations.

In a cross-sectional study, 2,308 Chinese subjects with an eGFR of 60–89 and 30–59 tended to have more cardiovascular risk factors and a higher prevalence of CVD than individuals with an eGFR > 90 ⁴. An analysis of 2,813 patients with acute stroke indicated the significant association between reduced renal function and hospital death, in which adjusted odds ratios and 95% CIs for in-hospital death were 1.54 (1.04–2.27) when the eGFR < 45 , 1.07 (0.72–1.58) when the eGFR was 45–59, and 1.04 (0.67–1.59) when the eGFR ≥ 90 ⁵. In a 4.6-year longitudinal observation of 70 asymptomatic Japanese participants without CKD, median values of coronary artery calcium score and abdominal aortic calcification index increased from 40.2 to 113.3 and from 13.2% to 21.7%, respectively⁶. A longitudinal observation of 333 Chinese subjects free from CVD with an eGFR > 60 found a significant reverse association between the eGFR and the Framingham risk score, with Pearson correlation coefficients of -0.669 in 2008 and -0.698 in 2011⁷. However, these studies have some limitations. The cross-sectional study design limits the ability to identify the causative relationship between factors^{4, 5, 7}, and the small number of study subjects has the weakness in generalizing the findings⁶. In contrast, we monitored the incident IHD for an average follow-up period of 4.35 ± 0.55 years based on the ICD code of IHD registered in hospitals where patients were actually treated. Additionally, the total number of study subjects was 206,919, and each group had more than 50,000 subjects. The features of our study may assure the statistical power of results, being more representative.

Previous studies have suggested the significant results in the association between CKD and IHD. In a follow-up analysis of 2,364 Japanese without CVD, the age-adjusted incidence of coronary heart disease was significantly higher in subjects with CKD than in those without it (6.2 vs 2.9 per 1000 person-years) ($P < 0.05$) in men¹⁶. Compared with individuals with an eGFR > 60 , HRs for acute myocardial infarction were 1.8 (1.1–3.0) in individuals with an eGFR of 30–60 and 3.0 in individuals with an eGFR < 30 ¹⁷. However, most studies have been designed to compare the cardiovascular outcomes of patients with an eGFR < 60 to that of patients with an eGFR ≥ 60 , and it is unclear whether the risk of incident IHD increases in mildly decreased eGFR from 60 to 90. Moreover, evidence has suggested that the incidence and the risk of CVD may differ among ethnic populations^{18, 19}. The Chronic Kidney Disease Japan Cohort Study reported that the Japanese had lower incidences of cardiovascular events and all-cause death at all CKD stages than Caucasians¹⁸. Our results provide additional informa-

tion on the previously identified association between the eGFR level and incident IHD. In our study, the risk of IHD significantly increased from an eGFR \leq 83 in the quartile 2 group. Given the mean eGFR (76.9 ± 3.5) and rate of subjects without proteinuria (97.4%) in quartile 2, most subjects in quartile 2 might be free from CKD. Thus, it is inferred that a mildly decreased eGFR between 71.07 and 83.16 is significantly associated with an increased risk of IHD even in Asians without CKD. These results suggest that a subtle decrease of renal function may be an independent risk factor for IHD in Asians. Nonetheless, it should be acknowledged that the adjusted HR in the quartile 2 group was modest in the degree of association. The degree to which mildly decreased renal function contributes to incident IHD may not be so great. Presumably, the statistical significance of this association in a Korean population may be insignificant in other ethnic groups. This potential discrepancy may be attributable to the greater vulnerability of Asians to cardiovascular risk under given metabolic conditions^{20, 21}). Thus, it is necessary to conduct further large-scale studies in other ethnic groups.

Several potential mechanisms have accounted for the increased risk of IHD in impaired renal function. The presence of CKD was a marker for subclinical atherosclerosis as an independent risk factor of ventricular and vascular remodeling^{22, 23}). Atherosclerosis is linked with elevated asymmetric dimethyl arginine, reduced nitric oxide bioavailability, and endothelial dysfunction^{24, 25}), which can mediate the association between impaired renal function and the risk of incident CAD. Understandably, it is postulated that unfavorable metabolic conditions accompanying renal impairment contributes to incident IHD. It is established that CKD often coexists with traditional risk factors for CAD, including older age, smoking, hypertension, and dyslipidemia¹⁰). Indeed, compared to quartile group 1, other quartile groups tended to have higher levels of baseline BMI, BP, TG, LDL, and fasting glucose. The degree of association between the eGFR and IHD was markedly attenuated by adjustment for these metabolic covariates, which indicates the potential role of metabolic conditions on incident IHD.

The merit of the study is tracking the risk of incident IHD diagnosed at hospitals in community-based large populations. Adjustments for baseline metabolic covariates enable us to evaluate the independent influence of the eGFR on incident IHD.

Nonetheless, the limitations of this study should be recognized.

First, evaluation of renal function depended only on the eGFR calculated by the CKD-EPI equation.

The eGFR calculated by the CKD-EPI equation is a widely available and reasonable tool in evaluating renal function but is not an absolute standard. The CKD-EPI equation was based on serum creatinine that can be influenced by creatinine generation as a result of muscle mass and its turnover²⁶). Chronic illness results in muscle wasting related to lower creatinine generation, leading to an overestimation of the eGFR²⁷). The individuals with muscle wasting may have an increased risk of IHD, despite an increased eGFR induced by lower creatinine generation. Thus, there is the possibility that the observed HR in our study is underestimated.

Second, the follow-up period for incident IHD was relatively short. In the study, the average follow-up period was 4.35 years, with the longest follow-up period being less than 7 years. Considering that more IHD might develop after follow-up, a longer duration of follow-up might reinforce the association between a low eGFR and incident IHD.

Third, several pieces of information were missing in our raw data. In particular, we could not identify the important variables including HbA1c, medical complications, and mortality. The absent information for these variables limits our ability to identify their influence on our results.

In conclusion, our study indicates that the risk of IHD significantly increases even at the mildly decreased eGFR levels between 60 and 80. Our results may provide the individuals with a mild renal dysfunction with the clinical insights to prevent IHD.

Conflict of Interest

We have no conflict of interest.

Financial Support

The authors have nothing to disclose.

Authorship

All authors had access to the data used in this study and participated in writing the manuscript.

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We used the National Health Insurance Service–National Sample Cohort database and the dataset was obtained from the National Health Insurance Service. Our study findings were not related to the National Health Insurance Service.

Author Contribution

Jae-Hong Ryoo is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Sung Keun Park and Min-Ho Kim equally participated in writing the manuscript and contributing to the study design and interpreting the results. Therefore, Sung Keun Park and Min-Ho Kim should be considered as first authors. Eunhee Ha, Ju Young Jung, Chang-Mo Oh, Joong-Myung Choi, Hee Yong Kang, Yong-Sung Choi, Min Gi Kim, and Jung-Wook Kim made substantial contributions to the acquisition of data and the critical revision of the study protocol and manuscript.

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Supplementary Table 1. Hazard ratios (HRs) and 95% confidence intervals (CI) for the incidence of ischemic heart disease according to the four groups of baseline eGFR levels

	HR (95% CI)*		
	Unadjusted	Model 1	Model 2
eGFR			
Group 1	1.84 (1.59-2.13)	1.39 (1.20-1.61)	1.40 (1.20-1.63)
Group 2	2.37 (2.13-2.65)	1.40 (1.25-1.57)	1.39 (1.24-1.57)
Group 3	1.33 (1.24-1.43)	1.09 (1.01-1.17)	1.09 (1.01-1.18)
Group 4	1.00 (reference)	1.00 (reference)	1.00 (reference)
<i>P</i> for trend	< 0.001	< 0.001	< 0.001

Group 1: eGFR < 45, Group 2: 45

eGFR < 60, Group 3: 60

eGFR < 90, Group 4: eGFR ≥ 90

Model 1 was adjusted for age, gender, BMI, systolic BP, fasting blood glucose, total cholesterol and GGT.

Model 2 was adjusted for model 1 plus smoking amount (pack-year), alcohol intake and physical activity.

Supplementary Table 2. Hazard ratios (HRs) and 95% confidence intervals (CI) for the incidence of IHD according to the four groups of urine protein levels

	Person-year	Incidence cases	Incidence density (per 10,000 person-year)	HR (95% CI)*	
				Unadjusted	Multivariate adjusted model
Urine protein levels					
absence	871,800.20	4,017	46.1	1.00 (reference)	1.00 (reference)
1+	16,197.60	122	75.3	1.64 (1.37-1.96)	1.32 (1.10-1.59)
≥ 2+	8,563.00	106	123.8	2.69 (2.22-3.26)	1.89 (1.55-2.31)
<i>P</i> for trend				< 0.001	< 0.001
Age					1.05 (1.05-1.06)
Gender (female Vs male)					0.64 (0.60-0.70)
BMI					1.07 (1.05-1.08)
Systolic BP					1.003 (1.001-1.005)
Fasting blood glucose					1.005 (1.004-1.006)
Total cholesterol					1.002 (1.001-1.003)
GGT					1.000 (0.999-1.001)
Smoking amount					1.010 (1.008-1.012)
Alcohol intake					1.227 (1.118-1.346)
Physical activity					0.911 (0.838-0.991)

Incidence density: a case per 10,000 person-year

Gender: female vs male

Smoking amount: pack year

BMI: body mass index, BP: blood pressure, GGT: gamma glutamyl transferase

Multivariate adjusted model was adjusted for age, gender, BMI, systolic BP, fasting blood glucose, total cholesterol, GGT, smoking amount, alcohol intake and physical activity