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ORIGINAL RESEARCH

# Association of Chronic Kidney Disease With Atrial Fibrillation in the General Adult Population: A Nationwide Population-Based Study

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**BACKGROUND:** The incidences of atrial fibrillation (AF) and chronic kidney disease (CKD) are increasing, and AF is prevalent in patients with CKD. However, few studies have investigated the incidence or association of AF in a large CKD population from a longitudinal study.

**METHODS AND RESULTS:** From a nationwide cohort, a total of 4 827 987 Korean individuals without prior AF, who received biennial health checkups provided by the National Health Insurance Service between 2009 and 2012 in Korea, were analyzed. Incidence of AF was ascertained through the end of 2018. During a median follow-up of 8.1 years, the annual incidence rate of AF was 1.17 per 1000 person-years among subjects without CKD, 1.55 for stage 1 CKD, 1.86 for stage 2 CKD, 2.1 for stage 3 CKD, and 4.33 for stage 4 CKD. In Fine-Gray regression models, CKD was associated with an increased risk of AF; the adjusted hazard ratios and 95% CIs of AF occurrence were 1.77 (1.69–1.85), 1.85 (1.80–1.91), 1.99 (1.95–2.04), and 4.04 (3.07–5.33) in individuals with CKD stages 1, 2, 3, and 4, respectively, compared with non-CKD. The association between CKD and incident AF remained statistically significant after adjustment for multiple confounding factors and was consistent across subgroups stratified by sex and age.

**CONCLUSIONS:** CKD is associated with an increased incidence of AF. Even mild CKD is associated with incident AF, and there was a stepwise increase in the risk of incident AF with a decrease in renal function.

**Key Words:** atrial fibrillation ■ chronic kidney disease ■ incidence ■ nationwide cohort



Atrial fibrillation (AF) is one of the most common forms of cardiac arrhythmia[1] and is associated with cerebrovascular and cardiovascular complications resulting in significant morbidity and mortality.[2–5] Furthermore, increased prevalence and incidence of AF represent a significant global health care economic burden.[6]

Chronic kidney disease (CKD) is defined as abnormality of kidney structure or renal function lasting for >3 months with implications on health.[7] CKD is a rapidly growing public health problem, and a meta-analysis reported an estimated global CKD prevalence of 13.4%.[8,9] Patients with CKD exhibit an elevated cardiovascular risk manifesting as not only heart failure,

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## CLINICAL PERSPECTIVE

### What Is New?

- The association between renal dysfunction and risk of atrial fibrillation (AF) has been explored in several prior studies, but most research has been based on a small number of subjects or Western populations, resulting in insufficient power to prove elevated risk of AF development in chronic kidney disease.
- Based on a Korean nationwide population study with ≈5 million subjects, with a median follow-up of 8.5 years, chronic kidney disease was found to be significantly associated with an elevated risk of incident AF.
- There was a stepwise increase in the risk of incident AF with a decrease in renal function.

### What Are the Clinical Implications?

- Regardless of severity, chronic kidney disease is associated with an increased risk of incident AF.
- Patients with chronic kidney disease need more intensive monitoring for AF to prevent subsequent AF complications.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **ARIC** | Atherosclerosis Risk in Communities Study Description |
| **NHID** | National Health Insurance Database |
| **NHIS** | National Health Insurance Service |

coronary heart disease, and mortality, but also AF.[10–12] AF and CKD are closely connected conditions that share common risk factors such as hypertension, diabetes, and coronary artery disease.[13,14] CKD activates the renin–angiotensin–aldosterone system and sympathetic nervous system, which induce oxidative stress, systemic inflammation, and volume overload.[15] Angiotensin II can increase atrial pressure, accelerate atrial fibrosis, and cause ion channel dysfunction; all of which are related to structural and electrical remodeling of the atria, thus resulting in AF.[16,17] Moreover, poor blood pressure control is both a cause and effect of CKD and affects the vast majority of patients with CKD.[18] Left ventricular hypertrophy is secondary to both pressure and volume overload in patients with CKD, which contributes to diastolic dysfunction and is another independent risk factor for incident AF.[19,20] These factors are highly correlated with atrial electrical and structural remodeling, contributing to the development of AF. The growing prevalence of both AF and CKD suggests that more patients will suffer from concurrent conditions. Therefore, we have to understand the importance of the implications of coexisting AF and CKD.

As mentioned, CKD has been demonstrated to be an independent risk factor contributing to the higher incidence and prevalence of AF, but there were important limitations to the preceding studies involving patients with AF in CKD. The small number of recruited subjects resulted in insufficient power to discriminate differences of AF incidence in CKD compared with non-CKD.[21–24] Moreover, to date, many of studies have been targeted to Western populations.[2,11,22,23,25,26] Therefore, the aim of the current study is to evaluate the development of AF across CKD stages, compared with subjects without CKD, in a nationwide Asin population representative study with longitudinal follow-up. To do so, we analyzed data from participants enrolled in the National Health Insurance Database (NHID).

## METHODS

### Data Sharing Statement

Because of ethical issues and data protection regulations, data that support the findings of the present study cannot be made publicly available.

### Ethical Considerations

The institutional review board of Seoul National University Hospital (institutional review board number E-2001-095-1096) approved the study. The attending government organization approved the use of the National Health Insurance Service (NHIS; number NHIS-2020-1-474). The requirement to obtain informed consent from the patients was waived by the board. This study was conducted in accordance with the Declaration of Helsinki.

### Data Source

This is a nationwide population-based cohort study using the NHID, which was provided by the NHIS of the Republic of Korea.[27] Korea provides health insurance for all citizens living in the country through social health insurance and public assistance. The general health checkup program is run by the NHIS and provides a health checkup for office workers/nonworkplace subscribers every 2 years and for nonoffice workers every year. The proportion of people receiving this charge-free health checkup was >70% in the year 2011 among a target population of ≈15 million people.[28] The diagnostic information was coded according to *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnostic codes with the diagnosis date. We obtained information including demographic variables

and laboratory results at the time of the health checkup from the NHID. In addition, claims data for medical procedures and prescription records were also obtained from the NHID.[29] Because the general health checkup measures serum creatinine and urine dipstick albuminuria every time, CKD stages were identifiable by reviewing the information.

## Study Population

We screened adult (≥40 years of age) health examinees who received 2 or more checkups from 2009 to 2012, and extracted 70% of subjects by random sampling due to the limit of data capacity set by the NHIS. According to *Kidney Disease Improving Global Outcomes* guidelines, CKD is classified according to the extent of estimated glomerular filtration rate (eGFR) and albuminuria.[30] The presence of incident CKD was defined by the presence of dipstick albuminuria ≥ +1 or eGFR <60 mL/min per 1.73 $m^2$, calculated from the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[31] CKD stages were defined using the recommendations of the National Kidney Foundation.[32] CKD stage 1 (eGFR ≥90 mL/min per 1.73 $m^2$) and stage 2 (eGFR ≥60 and <90 mL/min per 1.73 $m^2$) included subjects who had dipstick albuminuria ≥+1 but had normal or mildly reduced eGFR at baseline. Subjects with CKD stage 3 (eGFR ≥30 and <60 mL/min per 1.73 $m^2$) and stage 4 (eGFR ≥15 and <30 mL/min per 1.73 $m^2$) were also identified.

Subjects who met the CKD criteria at least once among several health checkups were classified as CKD. The initial health checkup date that met the definition of CKD was considered as the baseline date. We also defined non-CKD subjects as those who did not meet CKD criteria in every health checkup, and their first checkup date was designated as the baseline date. We inserted the washout period of 1 year from baseline date to exclude the subjects who had any outcome events within the 1-year period after the baseline date. We defined the index date as the date of starting follow-up, which means 1 year after the baseline date.

Subjects were excluded if baseline values of eGFR or dipstick albuminuria were missing or eGFR at baseline date was an outlying value (defined as <15 mL/min per 1.73 $m^2$ or >99.9th percentile) to minimize laboratory error. To exclude patients with valvular AF, those who were diagnosed with mitral stenosis or had preexisting mechanical heart valves before the baseline date were also excluded. Because we intended to confirm de novo AF in patients with CKD, those who were already diagnosed with AF before the baseline date were excluded. We inserted the washout period of 1 year after baseline date to analyze the association of CKD more accurately to AF occurrence by excluding those who were diagnosed with AF, end-stage kidney disease, or died of any cause during the washout period. The comorbid diseases were identified by *ICD-10* diagnostic codes, special certification codes for each disease, and NHIS claims data (Data S1). Therefore, the final study population comprised 4 827 987 participants (Figure S1).

## Study Outcomes

The main study outcome was de novo AF, and the subjects were followed until the development of de novo AF, death, or December 31, 2018, whichever came first. Subjects without AF during the follow-up period were censored at the end of follow-up. Deaths without AF were treated as competing events. De novo AF was defined using *ICD-10* diagnostic codes (I480–I484 and I489). To ensure diagnostic accuracy and exclude patients with transient AF, we defined patients with AF only when it was a discharge diagnosis or confirmed more than twice in an outpatient clinic.[22,33–35] The AF diagnosis has previously been validated with a positive predictive value of 94.1%.[36] De novo AF is referred to as AF throughout the remainder of this article.

## Data Collection and Measurements

Demographic and clinical characteristics on the bassline date were collected as baseline variables. Baseline information, including age, sex, body mass index, systolic/diastolic blood pressure, history of smoking and drinking, comorbidities, and laboratory findings, were collected. We stratified alcohol consumption into these 6 subgroups based on a self-reported questionnaire: unknown, nondrinker, occasional moderate (<6 drinks per week and <5 drinks on occasion), regular moderate (≥6 drinks per week and <5 drinks on occasion), occasional binge (<6 drinks per week and ≥5 drinks on occasion), and regular binge (≥6 drinks per week and ≥5 drinks on occasion).[37] The underlying comorbidities of hypertension, diabetes, and dyslipidemia were defined as follows. Hypertension was defined as the combination of a previous diagnosis of hypertension, corresponding *ICD-10* diagnostic codes (I10–I15) within 1 year before the index date, self-reported previous diagnosis of hypertension, or measured blood pressure ≥140/90 mm Hg at the health checkup. Diabetes was defined as the combination of a previous diagnosis of diabetes, corresponding *ICD-10* diagnostic codes (E10–E14) within 1 year before the index date, self-reported diagnosis of diabetes, history of prescribing diabetes medication or insulin within 1 year before the index date, or fasting glucose ≥126 mg/dL at the health checkup. Dyslipidemia was defined as the combination of a previous diagnosis of dyslipidemia with corresponding *ICD-10* diagnostic code (E78), self-reported diagnosis of dyslipidemia, or serum total cholesterol ≥240 mg/dL. The definitions of these comorbidities

were validated by previous studies based on an NHIS National Sample Cohort.[38,39]

## Statistical Analysis

To compare the differences among the CKD groups, continuous variables were summarized with means and SDs and analyzed using the ANOVA test. Categorical variables were presented as frequencies and percentages, and the $\chi^2$ test or Fisher exact test was used to compare the values. Incidence rates of AF were expressed as events per 1000 person-years. We account for the competing risk of death. The cumulative incidence function with the Gray test and Fine-Gray regression models was performed to examine the association between development of atrial fibrillation during follow-up. The results are provided as subhazard ratios with 95% CI. Model 1 included adjustment for age, sex, body mass index, smoking, and drinking. Model 2 included further adjustment for systolic blood pressure, diastolic blood pressure, and comorbidities.

Several predisposing factors for AF have been identified. There has been an accumulation of evidence on sex-specific and age-specific differences in incidence, prevalence, and outcomes of patients with AF.[40–43] With this rationale, we analyzed incident AF with subgroup analysis with sex (men versus women) and age (<65 versus ≥65 years of age) to determine whether CKD can affect incident AF even after considering the predisposing factors of AF. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

# RESULTS

## Patient Characteristics

The baseline characteristics are summarized in Table 1. The mean age of the study population was 51.9±7.8 years, and 50.6% were men. Among a total of 4 827 987 study subjects, 90.1% (n=4 348 104) were non-CKD, and 9.9% were defined as CKD (n=479 883). Subjects with CKD were classified into CKD stage 1 (n=80 551), stage 2 (n=104 481), stage 3 (n=292 892), and stage 4 (n=1959) (Figure S1). Subjects with more advanced CKD stages were older and more likely to have anemia and other comorbid diseases such as diabetes and hypertension.

## Association of CKD Stage With Risk of Incident AF

The Figure shows Fine-Gray cumulative incidence function curves of incident AF for up to 8 years according to the CKD stage. Higher stages of CKD were associated with a higher risk of AF development. The incidence rates of AF were 1.17 per 1000 person-years for subjects without CKD, 1.55 for CKD stage 1, 1.86 for stage 2, 2.10 for stage 3, and 4.33 for stage 4 (Table 2). CKD was associated with an increased risk of AF; adjusted hazard ratios (HRs) and 95% CIs for de novo AF were 1.77 (1.69–1.85), 1.85 (1.80–1.91), 1.99 (1.95–2.04), and 4.04 (3.07–5.33) in individuals with CKD stages 1, 2, 3, and 4, respectively, after adjustment in Model 2 (Table 2).

## Subgroup Analysis

There was no significant effect modification by sex or age when considering a more advanced stage of CKD had a trend with a higher risk of AF (*P* values for interaction: *P*=0.672 and *P*=0.646, respectively). After stratifying the subjects according to sex, we found the incidence rate was increased across CKD stage in both sexes (Table 3). More advanced stages of CKD had a trend with a higher risk of AF development in both sex groups. The risk of incident AF in subjects with stage 4 was approximately 4 times that of subjects without CKD in both sexes (HR, 4.24 [95% CI, 3.34–5.37]; *P*<0.001 for men; HR, 3.98 [95% CI, 2.14–7.40]; *P*<0.001 for women) after adjusting for multiple variables.

We stratified the subjects based on their age as of the index date (age <65 or ≥65 years of age). AF incidence rate increased across CKD stages in both age groups (Table 4). More advanced stages of CKD had a trend with a higher risk of AF development in both age groups. The risk of AF development in CKD stage 4 was approximately 3 times higher in subjects without CKD in the <65 years age group (HR, 3.27 [95% CI, 2.24–4.76]; *P*<0.001) and 2 times higher in the ≥65 years age group (HR, 3.86 [95% CI, 3.03–4.92]; *P*<0.001) after adjusting for multiple variables.

# DISCUSSION

From the current nationwide population-based study of ≈5 million Korean adults, CKD was associated with a greater risk of incident AF. The incidence of AF was highest in stage 4, and the association between CKD stage and AF persisted after multivariable adjustment and was consistent throughout subgroup analysis stratified by age and sex.

The prevalence and incidence of AF were high among patients with CKD and increased with higher CKD stages, which was supported by previous results.[2,21–25,44,45] Although further research is needed to investigate the biological mechanism explaining the relationship between CKD and AF, we found a strong association between CKD and incident AF in this study. The association between renal dysfunction and risk of AF had been explored in several prior studies, although not all studies found an association. In a recent study,

**Table 1. Baseline Characteristics of Subjects According to CKD Stage**

| Variables | Total, n=4 827 987 | Non-CKD, n=4 348 104 | CKD stage | | | | *P* value |
|---|---|---|---|---|---|---|---|
| | | | Stage 1 | Stage 2 | Stage 3 | Stage 4 | |
| | | | n=80 551 | n=104 481 | n=292 892 | n=1959 | |
| Age, y | 51.9±7.8 | 51.5±7.7 | 51.6±7.6 | 53.7±7.7 | 58.3±7.7 | 57.1±7.9 | <0.001 |
| Age groups, n (%) | | | | | | | |
| 40–64 y | 4 448 894 (92.2%) | 4 060 268 (93.4%) | 76 084 (94.5%) | 92 754 (88.8%) | 218 226 (74.5%) | 1562 (79.7%) | |
| ≥65 y | 379 093 (7.9%) | 287 836 (6.6%) | 4467 (5.5%) | 11 727 (11.2%) | 74 666 (25.5%) | 397 (20.3%) | <0.001 |
| Men, n (%) | 2 444 323 (50.6%) | 2 189 637 (50.4%) | 39 049 (48.5%) | 45 201 (43.3%) | 169 408 (57.8%) | 1028 (52.5%) | <0.001 |
| Body mass index, kg/m$^2$ | 23.9±2.9 | 23.9±2.9 | 24.4±3.2 | 24.6±3.1 | 24.5±2.9 | 24.3±3.1 | <0.001 |
| Blood pressure, mm Hg | | | | | | | |
| Systolic | 122.9±14.6 | 122.6±14.5 | 126.2±16.0 | 126.7±15.9 | 125.6±15.0 | 128.5±16.7 | <0.001 |
| Diastolic | 76.8±9.9 | 76.7±9.8 | 78.9±10.6 | 79.2±10.5 | 77.8±9.8 | 78.7±10.6 | <0.001 |
| Dipstick urine protein, n (%)* | | | | | | | |
| – | 4 528 904 (93.8%) | 4 256 495 (97.9%) | … | … | 271 261(92.6%) | 1148 (58.6%) | <0.001 |
| ± | 99 773 (2.1%) | 91 609 (2.1%) | … | … | 8044 (2.7%) | 120 (6.1%) | |
| 1–2 | 187 390 (3.9%) | … | 76 189 (94.6%) | 98 578 (94.4%) | 12 084 (4.1%) | 539 (27.5%) | |
| 3–4 | 11 920 (0.3%) | … | 4362 (5.4%) | 5903 (5.6%) | 1503 (0.5%) | 152 (7.8%) | |
| Smoking, n (%) | | | | | | | |
| Nonsmoker | 3 056 720 (63.6%) | 2 741 280 (63.1%) | 47 964 (59.5%) | 60 472 (57.9%) | 205 677 (70.2%) | 1327 (67.7%) | <0.001 |
| Former | 748 777 (15.6%) | 671 631 (15.5%) | 12 339 (15.3%) | 19 553 (18.7%) | 44 919 (15.3%) | 335 (17.1%) | |
| Current | 1000,412 (20.8%) | 914 733 (21.0%) | 20 072 (24.9%) | 24 085 (23.1%) | 41 233 (14.1%) | 289 (14.8%) | |
| Unknown | 22 078 (0.5%) | 20 460 (0.5%) | 176 (0.2%) | 371 (0.4%) | 1063 (0.4%) | 8 (0.4%) | |
| Drinking, n (%) | | | | | | | |
| Nondrinker | 463 648 (9.6%) | 419 508 (9.6%) | 5711 (7.1%) | 8248 (7.9%) | 29 956 (10.2%) | 225 (11.5%) | <0.001 |
| Occasional moderate | 643 379 (13.3%) | 585 314 (13.5%) | 9905 (12.3%) | 13 067 (12.5%) | 34 891 (11.9%) | 202 (10.3%) | |
| Regular moderate | 282 145 (5.8%) | 254 569 (5.9%) | 4990 (6.2%) | 6558 (6.3%) | 15 931 (5.4%) | 97 (5.0%) | |
| Occasional binge | 126 554 (2.6%) | 116 865 (2.7%) | 1852 (2.3%) | 2654 (2.5%) | 5159 (1.8%) | 24 (1.2%) | |
| Regular binge | 1 138 182 (23.6%) | 1 041 535 (24.0%) | 23 418 (29.1%) | 28 624 (27.4%) | 44 319 (15.1%) | 286 (14.6%) | |
| Unknown | 2 174 079 (45.0%) | 1 930 313 (44.4%) | 34 675 (43.0%) | 45 330 (43.4%) | 162 636 (55.5%) | 1125 (57.4%) | |
| Comorbidities, n (%) | | | | | | | |
| Diabetes | 198 889 (4.1%) | 150 051 (3.5%) | 11 690 (14.5%) | 13 716 (13.1%) | 23 131 (7.9%) | 301 (15.4%) | <0.001 |
| Hypertension | 829 172 (17.2%) | 716 711 (16.5%) | 19 457 (24.2%) | 26 700 (25.6%) | 65 687 (22.4%) | 617 (31.5%) | <0.001 |
| Dyslipidemia | 715 409 (14.8%) | 618 067 (14.2%) | 14 769 (18.3%) | 21 203 (20.3%) | 61 012 (20.8%) | 358 (18.3%) | <0.001 |
| Laboratory findings | | | | | | | |
| Hemoglobin, g/dL | 13.8±1.6 | 13.8±1.6 | 14.0±1.7 | 14.2±1.7 | 13.6±1.5 | 12.2±1.9 | <0.001 |
| Total cholesterol, mg/dL | 200.9±40.6 | 200.3±40.3 | 202.8±42.6 | 205.9±43.6 | 206.5±43.0 | 196.2±47.5 | <0.001 |
| LDL cholesterol, mg/dL | 120.3±72.3 | 120.1±73.0 | 118.0±59.3 | 121.3±58.6 | 123.3±70.7 | 113.7±58.1 | <0.001 |
| HDL cholesterol, mg/dL | 55.8±26.5 | 55.8±26.8 | 55.4±20.9 | 54.6±18.6 | 54.9±24.4 | 50.6±22.5 | <0.001 |
| Triglycerides, mg/dL | 138.1±101.5 | 136.4±99.8 | 157.2±136.4 | 158.2±121.3 | 149.8±103.8 | 173.1±151.2 | <0.001 |
| Fasting blood sugar, mg/dL | 98.7±22.3 | 98.0±21.1 | 110.7±38.9 | 109.6±35.4 | 102.2±24.8 | 107.1±33.4 | <0.001 |
| Creatinine, mg/dL | 0.9±0.2 | 0.9±0.2 | 0.8±0.1 | 1.0±0.2 | 1.2±0.2 | 2.5±0.6 | <0.001 |
| eGFR, mL/min per 1.73 m$^2$ | 86.7±15.9 | 88.8±14.0 | 101.3±7.4 | 76.8±8.1 | 54.7±5.0 | 24.3±4.3 | <0.001 |

CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; and HDL, high-density lipoprotein.
*Results of the dipstick urinalysis were interpreted on the basis of a color scale that semi-quantified proteinuria as negative, trace, 1+, 2+, 3+, or 4+.

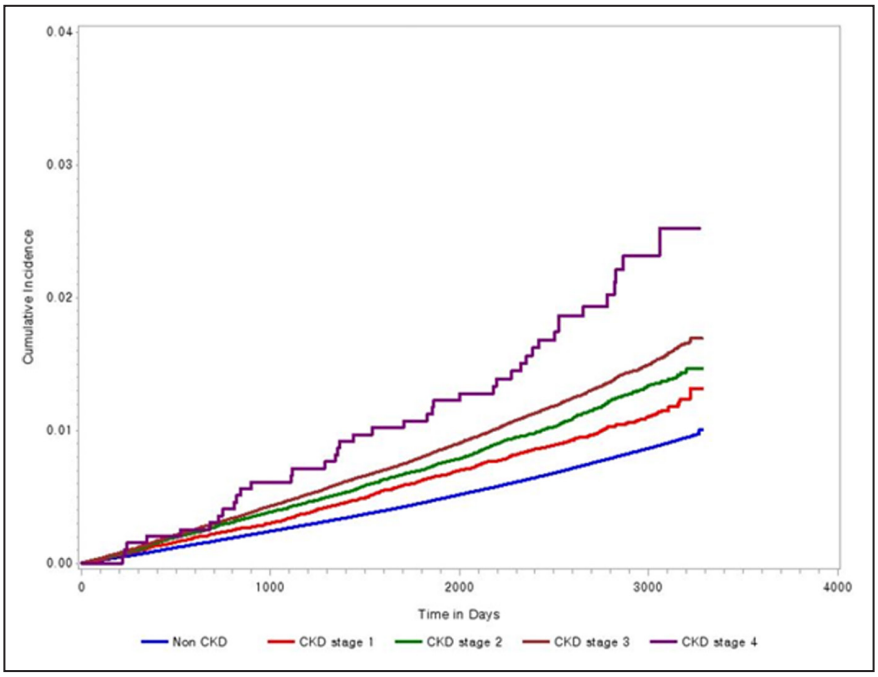


**Figure. Fine-Gray cumulative incidence function curves of incident AF according to the CKD stage (*P*<0.001).**
Higher stages of CKD were associated with a higher risk of AF during the follow-up period than lower stages of CKD. AF indicates atrial fibrillation; and CKD, chronic kidney disease.

AF showed a causal effect on kidney function, but the study found that kidney function was difficult to use to predict the occurrence of AF.[46] This may be due to the limited number of subjects who had severe renal dysfunction. Moreover, the causal effect analyzed by genetic instrument had limitations in the analytic method itself, so there still remained a possibility of effect of renal function on AF. In the PREVEND (Prevention of Renal and Vascular End-stage Disease) study, no association was shown between incidence of AF and markers of renal function such as creatinine, eGFR, and cystatin C.[47] The PREVEND study oversampled the subjects with albuminuria to investigate the cardiovascular and renal outcomes of albuminuria subjects, whereas the present study was based on the general population, showing the association of CKD and AF. In the CHS (Cardiovascular Health Study), no relation between incidence or prevalence of AF and eGFR was observed. However, there was a limitation to generalizing the results to all ages, because the study was only targeted

**Table 2. Association of CKD Stage With Risk of Incident Atrial Fibrillation: Death Before AF as a Competing Risk**

| | CKD stages | | | | |
|---|---|---|---|---|---|
| | Non-CKD | CKD stage 1 | CKD stage 2 | CKD stage 3 | CKD stage 4 |
| No. at risk | 4348104 | 80551 | 104481 | 292892 | 1959 |
| AF, n (%) | 40329 (0.93%) | 886 (1.10%) | 1391 (1.33%) | 4405 (1.50%) | 64 (3.27%) |
| Incidence rate of AF* | 1.17 | 1.55 | 1.86 | 2.10 | 4.33 |
| Death before AF, n (%) | 98040 (2.25%) | 2799 (3.47%) | 4102 (3.93%) | 11675 (3.99%) | 280 (14.29%) |
| Incidence rate of death* | 2.84 | 4.90 | 5.48 | 5.55 | 19.28 |
| Hazard ratio (95% CI) | | | | | |
| Crude | 1.0 (Reference) | 2.13 (2.05–2.22) | 2.20 (2.13–2.28) | 2.17 (2.13–2.22) | 5.15 (4.14–6.40) |
| Model 1 | 1.0 (Reference) | 2.09 (2.00–2.18) | 1.77(1.70–1.84) | 1.48(1.45–1.52) | 3.94 (3.21–4.84) |
| Model 2 | 1.0 (Reference) | 1.77 (1.69–1.85) | 1.85 (1.80–1.91) | 1.99 (1.95–2.04) | 4.04 (3.07–5.33) |

Model 1: Adjusted with age, sex, body mass index, smoking, and drinking.
Model 2: Model 1 plus systolic/diastolic blood pressure and comorbidities.
AF indicates atrial fibrillation; and CKD, chronic kidney disease.
*Incidence rate: 1000 person-years.

**Table 3. Sex-Specific Risk of AF by CKD Stage: Death Before AF as a Competing Risk**

| | CKD stages | | | | |
|---|---|---|---|---|---|
| | Non-CKD | CKD stage 1 | CKD stage 2 | CKD stage 3 | CKD stage 4 |
| No. at risk | | | | | |
| Men | 2 189 637 | 39 049 | 45 201 | 169 408 | 1028 |
| Women | 2 158 467 | 41 502 | 59 280 | 123 484 | 931 |
| AF, n (%) | | | | | |
| Men | 24 957 (1.14%) | 598 (1.53%) | 984 (2.18%) | 2396 (1.41%) | 39 (3.49%) |
| Women | 15 372 (0.71%) | 288 (0.69%) | 407 (0.69%) | 2009 (1.63%) | 25 (2.69%) |
| Incidence rate of AF* | | | | | |
| Men | 1.45 | 2.04 | 2.33 | 2.72 | 5.57 |
| Women | 0.89 | 1.04 | 1.25 | 1.65 | 3.22 |
| Death before AF, n (%) | | | | | |
| Men | 70 804 (3.23%) | 2208 (5.65%) | 3186 (7.05%) | 7249 (4.08%) | 176 (17.12%) |
| Women | 27 236 (1.26%) | 591 (1.42%) | 916 (1.55%) | 4426 (3.58%) | 104 (11.17%) |
| Incidence rate of death* | | | | | |
| Men | 4.14 | 7.55 | 7.54 | 8.22 | 25.71 |
| Women | 1.57 | 2.12 | 2.81 | 3.63 | 13.55 |
| Hazard ratio (95% CI) | | | | | |
| Crude | | | | | |
| Men | 1.0 (Reference) | 2.25 (2.15–2.35) | 2.08 (2.00–2.17) | 2.21 (2.15–2.27) | 5.04 (3.91–6.49) |
| Women | 1.0 (Reference) | 1.71 (1.57–1.86) | 2.11 (1.97–2.27) | 2.55 (2.46–2.64) | 5.69 (3.78–8.57) |
| Model 1 | | | | | |
| Men | 1.0 (Reference) | 2.21 (2.10–2.32) | 1.74 (1.67–1.82) | 1.44 (1.40–1.48) | 3.74 (2.96–4.73) |
| Women | 1.0 (Reference) | 1.73 (1.58–1.88) | 1.88 (1.75–2.02) | 1.57 (1.52–1.63) | 3.84 (2.47–5.95) |
| Model 2 | | | | | |
| Men | 1.0 (Reference) | 1.85 (1.76–1.95) | 1.77 (1.70–1.84) | 2.04 (1.98–2.10) | 4.24 (3.34–5.37) |
| Women | 1.0 (Reference) | 1.54 (1.42–1.67) | 1.85 (1.71–2.00) | 2.31 (2.22–2.40) | 3.98 (2.14–7.40) |

Model 1: Adjusted with age, body mass index, smoking, and drinking.
Model 2: Model 1 plus systolic/diastolic blood pressure and comorbidities.
AF indicates atrial fibrillation; and CKD, chronic kidney disease.
*Incidence rate: 1000 person-years.

at the elderly, with an average age of ≈75 years. Our analysis differs from the previous studies. This is one of the largest-scale studies, based on 480 000 patients with CKD and a non-CKD study population of almost 5 million to determine the association of CKD with incident AF. Considering that the NHID represents the entire Korean population, this study can be regarded as one of the largest population-based nationwide studies of incident AF among patients with CKD. Second, we excluded subjects previously diagnosed with AF and followed the study subjects for up to 8 years to investigate the development of de novo AF. To date, many of the studies have been cross-sectional studies taking a snapshot of a temporal relationship, from which it is hard to establish an association between AF and CKD.[2,25,44,45,48] With long-term follow-up duration, we found that there was an incremental increase of incidence and risk of AF according to CKD stages, which was difficult to find in a short-term follow-up period.[26]

Most of the epidemiological reports on AF from CKD have been derived from Western populations.[2,11,22,23,25,26] Therefore, the risk of AF among groups of different ethnicities should be evaluated with caution, because studies on the clinical epidemiology of AF in non-Western groups are limited. Previous studies presenting global and regional differences in the prevalence of AF reported a lower prevalence of AF among the Asian population compared with the Western population.[6,49–51] The different incidences of AF between Asian and Western patients with CKD might be attributed to different genetic backgrounds, diet, and lifestyles between Asian and Western countries. According to the ARIC (Atherosclerosis Risk in Communities) cohort study, which targets the US population, the incidence rates of AF were 10.2 per 1000 person-years in CKD stage 3 and 15.2 per 1000 person-years in CKD stage 4.[22] The incidence of AF from the ARIC study was higher than that shown by the

**Table 4. Age-Specific Risk of Atrial Fibrillation by CKD Stage: Death Before AF as a Competing Risk**

| | CKD stages | | | | |
|---|---|---|---|---|---|
| | Non-CKD | CKD stage 1 | CKD stage 2 | CKD stage 3 | CKD stage 4 |
| No. at risk | | | | | |
| Age <65 y | 4 060 268 | 76 084 | 92 754 | 218 226 | 1562 |
| Age ≥65 y | 287 836 | 4467 | 11 727 | 74 666 | 397 |
| AF, n (%) | | | | | |
| Age <65 y | 33 422 (0.82%) | 762 (1.00%) | 1028 (1.11%) | 2610 (1.20%) | 47 (3.01%) |
| Age ≥65 y | 6907 (2.40%) | 124 (2.78%) | 363 (3.10%) | 1795 (2.40%) | 17 (4.28%) |
| Incidence rate of AF* | | | | | |
| Age <65, y | 1.04 | 1.41 | 1.55 | 1.67 | 3.97 |
| Age ≥65, y | 3.02 | 3.97 | 4.39 | 3.36 | 5.78 |
| Death before AF, n (%) | | | | | |
| Age <65 y | 75 129 (3.43%) | 2354 (6.03%) | 2715 (6.01%) | 6032 (3.56%) | 172 (16.73%) |
| Age ≥65 y | 22 911 (7.96%) | 445 (9.96%) | 1387 (11.83%) | 5643 (7.56%) | 108 (27.20%) |
| Incidence rate of death* | | | | | |
| Age <65 y | 2.33 | 4.36 | 4.08 | 3.85 | 14.72 |
| Age ≥65 y | 10.07 | 14.23 | 16.79 | 10.54 | 38.09 |
| Hazard ratio (95% CI) | | | | | |
| Crude | | | | | |
| Age <65 y | 1.0 (Reference) | 2.29 (2.19–2.39) | 1.99 (1.91–2.07) | 1.86 (1.81–1.91) | 4.33 (3.28–5.72) |
| Age ≥65 y | 1.0 (Reference) | 1.77 (1.60–1.96) | 2.08 (1.96–2.21) | 1.32 (1.28–1.36) | 4.13 (3.19–5.34) |
| Model 1 | | | | | |
| Age <65 y | 1.0 (Reference) | 2.22 (2.12–2.33) | 1.93 (1.85–2.01) | 2.03 (1.97–2.09) | 4.47 (3.16–6.32) |
| Age ≥65 y | 1.0 (Reference) | 1.82 (1.64–2.03) | 1.95 (1.84–2.08) | 1.55 (1.50–1.59) | 4.49 (3.63–5.54) |
| Model 2 | | | | | |
| Age <65 y | 1.0 (Reference) | 1.90 (1.81–1.99) | 1.69 (1.62–1.76) | 1.75 (1.70–1.80) | 3.27 (2.24–4.76) |
| Age ≥65 y | 1.0 (Reference) | 1.65 (1.48–1.83) | 1.90 (1.79–2.02) | 1.30 (1.26–1.34) | 3.86 (3.03–4.92) |

Model 1: Adjusted with sex, body mass index, smoking, and drinking.
Model 2: Model 1 plus systolic/diastolic blood pressure and comorbidities.
AF indicates atrial fibrillation; and CKD, chronic kidney disease.
*Incidence rate: 1000 person-years.

present study from Korean subjects with CKD. Based on a Japanese population study, the incidence rate of AF, confirmed by ECG, was 2.2 per 1000 person-years at CKD stages 1 and 2, 5.1 at CKD stage 3, and 6.6 at CKD stages 4 and 5.[24] Possible explanations for the discrepancy between the Japanese study and ours include the older age of the subjects in the Japanese study (average age of 63 years versus 52 years in our study) and the method used to define AF. However, we could confirm that the AF incidence of CKD in Asian subjects was lower than that in the Western population. Our findings extend previous observations about the prevalence of AF in different stages of CKD in a large population of Korean adults.

In addition to evaluating the overall incidence of AF in CKD, we analyzed incident AF with subgroup analysis. The association between the severity of CKD and incident AF showed a robust relationship across several subgroup analyses and after multivariable adjustments. The incidence of AF in the general population has been estimated to be 1.5- to 2.0-fold higher in men than in women.[52] Therefore, we analyzed the difference in incidence of AF across the stages of CKD after stratification by sex. We showed that the incidence rate of AF increased across CKD stages in both sexes. We also analyzed incident AF after stratification by age. Aging is the most important risk factor of AF.[53] We stratified the study subjects into younger (<65 years of age) and older (≥65 years of age) groups, because there is a marked increase in AF between 60 and 65 years of age.[54] Due to the characteristics of the national health checkup population, our study subjects were predominantly <65 years of age (n=4 452 329, 92.1%). We showed that the incidence rate of AF was increased across CKD stages in both age groups. The association between CKD stage and AF was consistent across both sex and age subgroups.

Our study had several limitations. First, this study was an observational study, and there were inherent limitations such as hidden confounding factors. Second,

this study was a nationwide, population-based retrospective observational study, which was susceptible to several biases including selection bias. The NHIS provides biennial health checkups to all health insurance subscribers, and the study subjects most likely included those who maintain healthier lifestyles or those who are more concerned about their health. In other words, patients with advanced CKD tend to have regular hospital visits rather than regular health checkups; thus, such patients might be excluded from this study, also resulting in selection bias. Third, the incidence of AF was based entirely on claims data, and there could have been undetected or unreported episodes of AF. Population studies using claims data inherently do not directly screen the ECG, so there is a possibility of underestimation of silent AF. Conversely, misclassification of AF diagnostic codes could lead to overestimation of AF. However, the method of identifying AF using *ICD-10* diagnostic codes in systemic studies has been statistically verified, and others have previously shown that the validity of AF ascertainment using hospitalizations is acceptable.[55] Fourth, measurement of the baseline serum creatinine and urine dipstick protein may not be representative of kidney function. We defined the subjects who met the CKD criteria at least a single time from a regular health checkup. A few subjects with temporarily reduced renal function or albuminuria might have been classified to CKD. It could be hard to reflect on the chronicity of CKD. This may lead to random measurement error and regression dilution bias, which tends to underestimate the real association between CKD and AF development. However, it is an exceptional situation that acutely ill patients with acute kidney injury receive regular health checkups. Changes in the level of renal function or albuminuria during the follow-up may also dilute the impact of CKD on the risk of AF development, which tends to underestimate the real association between CKD and AF development. We could say the incidence or hazard ratio of AF to CKD would be more intense in the real world. Fifth, according to our study design, there would be some concern about occurrence of immortal time bias to CKD, because the first measurement of eGFR or albuminuria defined the CKD. However, as the length of follow-up and the total population size increases, the proportion of the group, which was misclassified to CKD, becomes a smaller and smaller portion of the total person-time denominator, and the magnitude of immortal time bias diminishes. Despite these several limitations, this study is meaningful in that this is the first big data study on a nationwide scale to follow subjects for 10 years and observe the incidence of de novo AF in patients with CKD.

In conclusion, CKD was associated with an increased incidence of AF in this large population-based study. This association was present among patients with CKD stages from 1 to 4, remained consistent across several subgroups, and persisted after adjustment for multiple potential confounders. Given the large number of Korean adults with CKD and their high risk of cardiovascular or cerebrovascular disease, these findings have important clinical implications. Patients with CKD need more intensive monitoring for AF to prevent subsequent AF complications.

## ARTICLE INFORMATION

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### Disclosures

None.

### Supplemental Material

Data S1
Figure S1
Reference[56]

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# Supplemental Material

## Supplemental Methods

### Data S1. Definition of excluded subjects.

We define cancer patients as those with International Classification of Diseases, Tenth Revision (ICD-10) diagnostic codes (C0, C1, C2, C3, C40, C41, C43, C45, C46, C47, C48, C49, C5, C6, C70, C71, C72, C74, C75, C76, C80, C81, C82, C83, C84, C85, C883, C887, C889, C900, C901, C91, C92, C93, C940, C941, C942, C943, C9451, C947, C95, or C96) and a special certification code of newly diagnosed malignancy (V193).

We define cardiovascular disease patients as those with ICD-10 diagnostic codes (I20, I21, I22, I23, I24, or I25) and National Health Insurance Service (NHIS) claim data for a coronary artery procedure (O1641, O1642, O1647, OA641, OA641, OA642, OA647, M6551, M6552, M6561, M6571, M6572, or M6634) [56].

We defined end-stage kidney disease patients as those who underwent kidney replacement therapy or kidney transplantation. Kidney replacement therapy was confirmed by NHIS claim data for a dialysis procedure (O7011-O7018, O7020, O7021, O7061, O7062, or O7071-7075) and a special certification code for maintenance hemodialysis or peritoneal dialysis patients (V001 or V003). Kidney transplantation was confirmed by NHIS claim data (R3280) and a special certification code (V005)

Mitral stenosis patients were defined with one of the following ICD-10 diagnostic codes: I5.0, I5.2, and I5.9.

Preexisting mechanical heart valves were defined with one of the following ICD-10 diagnostic codes: Z95.2–Z94.5.

Figure S1

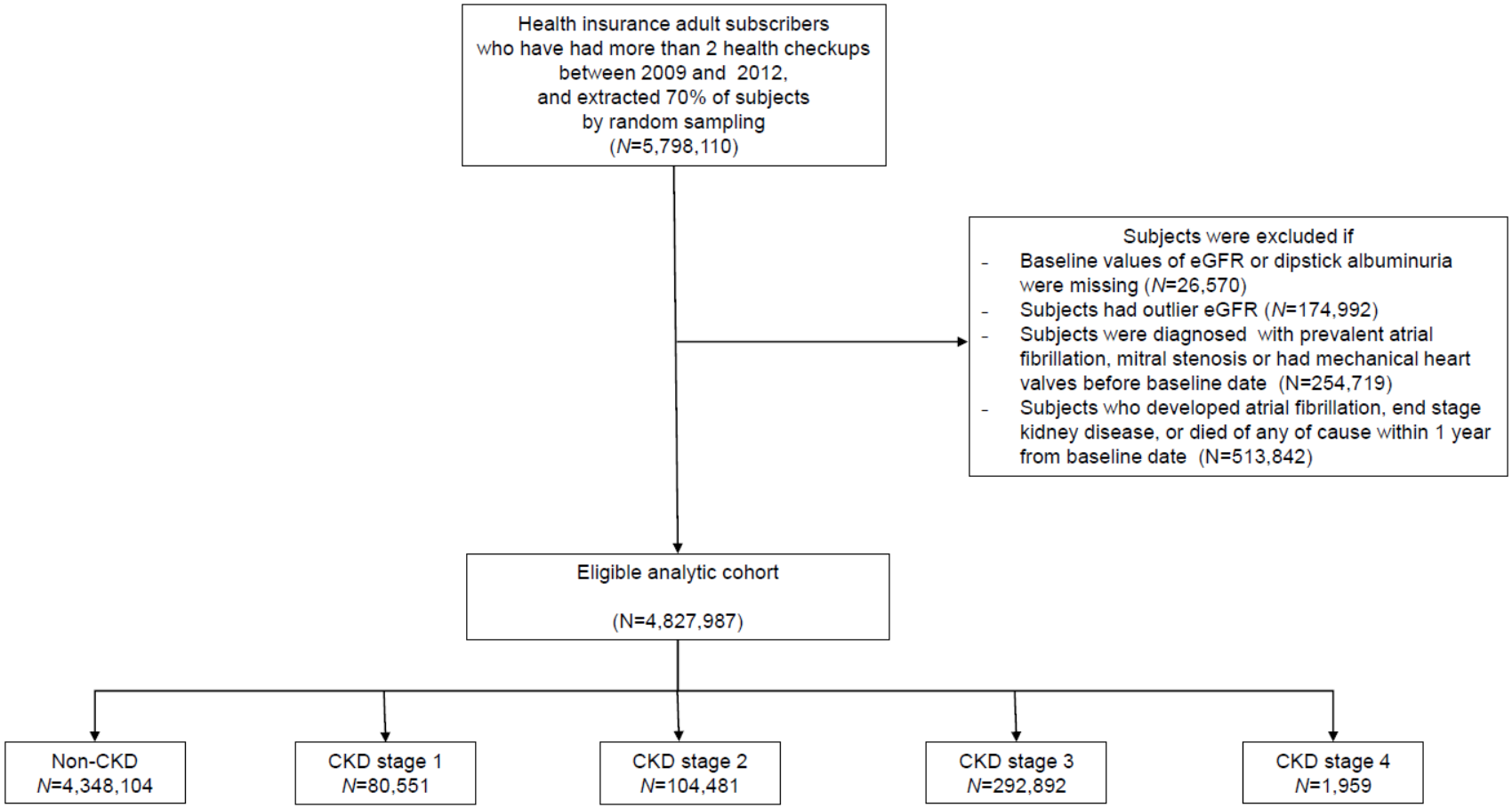


**Figure S1. Study design**
Abbreviation: eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease