Original Article

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# Association of proteinuria and hypertension with incident atrial fibrillation in an elderly population: nationwide data from a community-based elderly cohort

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**Objective:** The excess risk of atrial fibrillation in relation to the presence of proteinuria associated with hypertension has not been well elucidated. We aimed to determine the effect of hypertension and/or proteinuria on the incidence of atrial fibrillation. Second, we evaluated whether the associations with temporal changes in proteinuria status on the incidence of atrial fibrillation.

**Methods and results:** A total of 85 434 participants with hypertension and 125 912 participants without hypertension with age at least 60 years from the Korea National Health Insurance Service-Senior cohort were included. Amongst controls (participants without proteinuria and hypertension), hypertension only, proteinuria only, and hypertension with proteinuria groups, the adjusted incidences of atrial fibrillation were 0.51, 0.69. 0.78 and 0.99 per 100 person-years, respectively after inverse probability of treatment weighting. Compared with controls, the weighted risks of atrial fibrillation in the hypertension only, proteinuria only and hypertension with proteinuria groups were increased by 37% (hazard ratio 1.37, 95% confidence interval, CI 1.30–1.44, $P = 0.001$), 55% (hazard ratio 1.55, 95% CI 1.28–1.88, $P < 0.001$), and 98% (hazard ratio 1.98, 95% CI 1.62–2.43, $P < 0.001$), respectively. Populations who had proteinuria in the first examination had an increased risk of atrial fibrillation even in the group whereby the proteinuria was resolved on the second examination (hazard ratio 1.36, 95% CI 1.12–2.31, $P < 0.001$). The presence of proteinuria in first and second analysis had the highest risk of incident atrial fibrillation (hazard ratio 1.61, 95% CI 1.12–2.31).

**Conclusion:** In conclusion, hypertension and/or proteinuria were associated with increased risk of atrial fibrillation, with the greatest risks when both are present. Proteinuria could be a useful factor for predicting atrial fibrillation development.

**Keywords:** atrial fibrillation, change of proteinuria, hypertension, proteinuria, risk

**Abbreviations:** BP, blood pressure; CI, confidence interval; CVD, cardiovascular death; ICD-10, International Classification of Disease-10th Revision code; IPTW, inverse probability of treatment weighting; IQR, interquartile range; NHIS, the nationwide population-based National Health Insurance Service; pACR, predicted albumin–creatinine ratio; SD, standard deviation

## INTRODUCTION

Atrial fibrillation is the most common cardiac arrhythmia and is associated with an increased risk of ischemic stroke and heart failure, resulting in an increased morbidity and greater all-cause mortality [1–3]. Hypertension is highly prevalent in populations with atrial fibrillation and provides the highest attributable risk for the development of atrial fibrillation [4]. Patients with poorly controlled blood pressure (BP) have an associated increased risk of incident atrial fibrillation [5,6] and the development of adverse cardiovascular outcomes [7]. However, hypertension rarely occurs as an isolated disorder and is often accompanied by a number of comorbidities that are indicative of signs of target organ damage because of elevated BP [8]. For example, proteinuria is the earliest indicator of kidney damage caused by the progression of various diseases including hypertension. Several studies

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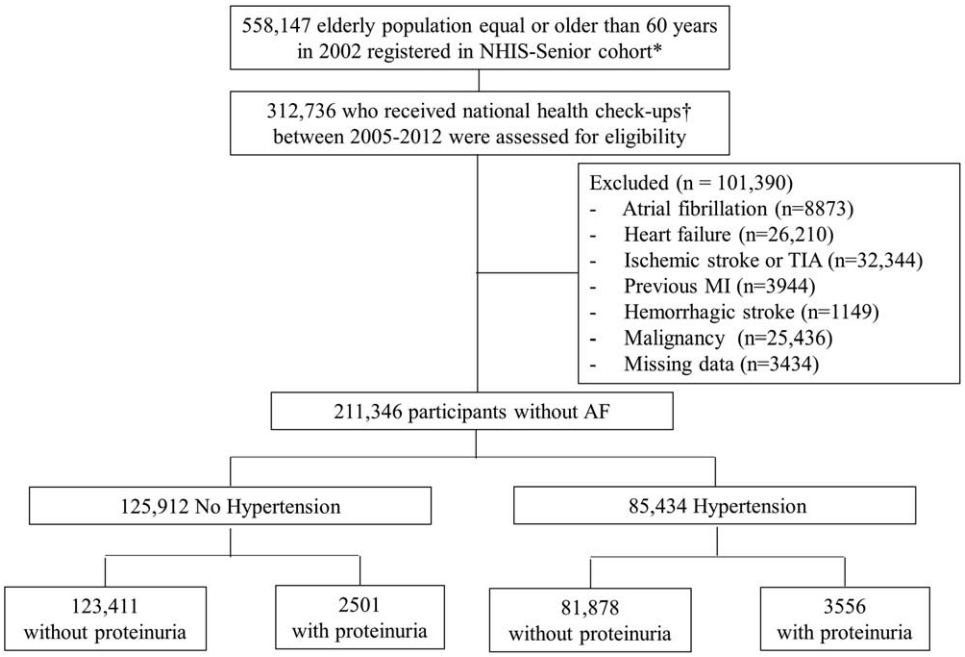


**FIGURE 1** Flow diagram.

have shown that proteinuria was independently associated with all-cause mortality [9] and cardiovascular mortality [10]. Proteinuria is also an independent risk factor of atrial fibrillation development [11,12]. However, the excess risk of atrial fibrillation associated with proteinuria in patient with hypertension and the impact of temporal changes in proteinuria status is unclear.

The aim of this study was to determine the effect of hypertension and/or proteinuria on the incidence of atrial fibrillation. Second, we evaluated whether the associations with temporal changes in proteinuria status. We investigated these associations in an elderly population with and without hypertension, using the database of the nationwide population-based National Health Insurance Service (NHIS)-senior cohort (NHIS-Senior).

## METHODS

Data were collected from the NHIS-Senior cohort, which included about 558 147 individuals, accounting for approximately 10% of the total elderly population over 60 years old in South Korea (approximately 5.1 million) in 2002 [13]. The NHIS-Senior database included the following parameters: sociodemographic and socioeconomic information, insurance status, health checkup examinations and records of patients' medical and dental history. These parameters have been anonymized in the cohort study to protect the privacy of individuals. This study was approved by the Institutional Review Board of Yonsei University Health System (4-2021-0032). Informed consent was waived. The NHIS-Senior database used in this study (NHIS-2016-2-171) was made by the NHIS of Korea. The authors declare no conflicts of interest with the NHIS.

### Study population

From the Korean NHIS-Senior, a total of 312 736 participants who had a health checkup between 2005 and 2012 were enrolled, and follow-up data were reviewed until December 2014. The exclusion criteria were as follows: participants who had atrial fibrillation before enrollment ($n = 8873$), those who had heart failure before enrollment ($n = 26\,210$), those who had ischemic stroke or transient ischemic attack before enrollment ($n = 32\,344$), those who had myocardial infarction before enrollment ($n = 3944$), those who had hemorrhagic stroke before enrollment ($n = 1149$), those who had malignancy before enrollment ($n = 25\,436$) and those who had missing data ($n = 3434$). Finally, we included 211 346 participants without atrial fibrillation (Fig. 1).

Participants were divided into four groups according to the presence of hypertension and proteinuria: 123 411 participants were included in the control group including participants without hypertension and proteinuria; 81 878 participants in the group with hypertension *only*, 2501 participants in the group with proteinuria *only* and 3556 participants in the group with both hypertension *and* proteinuria.

Atrial fibrillation was diagnosed using the International Classification of Disease-10th Revision code (ICD-10), code I48. To ensure diagnostic accuracy, the patients were defined as having atrial fibrillation only when it was a discharge diagnosis or had been confirmed at least twice in the outpatient department. This atrial fibrillation diagnosis definition has been previously validated in the NHIS database with a positive-predictive value of 94.1% [14,15]. Hypertension was defined as the combination of previous hypertension diagnosis (ICD-10 codes) and use of one or more antihypertensive drugs. The hypertension onset date for duration calculations was determined using information on the first date of hypertension diagnosis.

### Proteinuria

Proteinuria was measured with dipstick test and defined as at least 1+ of urine dipstick test. The predicted albumin–creatinine ratio (pACR) was calculated by the equation to

convert urine dipstick protein to ACR [16]. The pACR was divided into three groups. The A1 group was defined as pACR greater than 30 mg/g and the A2 group was defined as pACR between 30 and 300 mg/g. The A3 group was defined as pACR greater than 300 mg/g.

## Covariates

We obtained information on selected comorbidities in inpatient and outpatient hospital diagnoses. Baseline comorbidities were defined using the medical claims and information about prescription medication prior to the index date. To ensure the accuracy of diagnosis, the patients were considered to have comorbid condition when the condition was a discharge diagnosis or confirmed at least twice in an outpatient setting according to previous studies using the NHIS (see Supplementary Table S1, http://links.lww.com/HJH/B758) [2,14]. For the status of standard income, the total amount of national health insurance premiums paid by the insured in the year was evaluated in proportion to personal income.

## Statistical analysis

Continuous variables were expressed as means ± standard deviation (SD). Categorical variables were expressed as proportions. The baseline characteristics of participants were compared using Student's *t*-test and Pearson's chi-square test. The incidence rates of events were calculated by dividing the number of events by person-times at risk, with the 95% confidence intervals (CI) estimated by exact Poisson distributions.

To adjust for differences among different exposure groups, inverse probability of treatment weighting (IPTW) based on multinomial propensity scores was used. In time-to-event analyses, IPTW minimizes bias relative to the other methods of applying propensity scores [17]. Also, the IPTW approach is suitable when comparing multiple groups [18]. The propensity scores were estimated by using generalized boosted models based on 10 000 regression trees. We adjusted for age, sex and clinical variables, including diabetes mellitus, dyslipidemia, chronic kidney disease, liver disease, anemia, BMI, alcohol, blood pressure and smoking habits.

Cox proportional hazard regressions using IPTW were used to compare the incidence of atrial fibrillation, stroke, heart failure, cardiovascular death (CVD) associated with hypertension and proteinuria. The risk of incident atrial fibrillation associated with hypertension and proteinuria was compared using Kaplan–Meier analysis. The proportional hazard assumption was tested based on the Schoenfeld residuals. Two-sided *P* values less than 0.05 were considered statistically significant. Statistical analyses were conducted using SPSS (version 25; IBM Corp., Armonk, New York, USA) and R version 4.0.1 (The R Foundation, www.R-project.org).

# RESULTS

Baseline characteristics of the study cohort by categories of hypertension and/or proteinuria are showed in Table 1. The mean age of study population was 70.5 ± 5.4 years and

**TABLE 1. Baseline Characteristics before IPTW**

| | Prot−[a] | | Prot+[b] | | ASD | |
|---|---|---|---|---|---|---|
| | HTN−[c] (*n* = 123 411) | HTN+[d] (*n* = 81 878) | HTN− (*n* = 2501) | HTN+ (*n* = 3556) | Before IPTW | After IPTW |
| Age (years) | 70.1 ± 5.3 | 71.1 ± 5.5 | 70.7 ± 5.6 | 71.7 ± 5.7 | 0.154 | 0.006 |
| Male [*n* (%)] | 58 466 (47.4) | 30 851 (37.7) | 1220 (48.8) | 1621 (45.6) | 0.119 | 0.010 |
| BMI (kg/m$^2$) | 23.2 ± 3.04 | 24.6 ± 3.16 | 23.4 ± 3.31 | 24.78 ± 3.29 | 0.317 | 0.014 |
| SBP (mmHg) | 129.7 ± 17.7 | 136.3 ± 17.4 | 133.6 ± 20.4 | 140.6 ± 19.2 | 0.314 | 0.007 |
| DBP (mmHg) | 78.6 ± 10.7 | 81.6 ± 10.7 | 80.4 ± 11.8 | 82.3 ± 11.8 | 0.177 | 0.010 |
| Smoking | | | | | 0.147 | 0.020 |
| No | 89 502 (76.6) | 65 007 (83.1) | 1771 (74.3) | 2678 (79.0) | | |
| Former | 8503 (7.3) | 5596 (7.2) | 204 (8.6) | 311 (9.2) | | |
| Current | 18 864 (16.1) | 7629 (9.8) | 410 (17.2) | 400 (11.8) | | |
| Alcohol | | | | | 0.066 | 0.018 |
| Low | 87 407 (72.4) | 61 443 (76.6) | 1777 (72.5) | 2633 (75.3) | | |
| Moderate | 18 851 (15.6) | 11 530 (14.4) | 394 (16.1) | 507 (14.5) | | |
| Heavy[e] | 14 406 (11.9) | 7272 (9.1) | 281 (11.5) | 356 (10.2) | | |
| Dyslipidemia | 21 972 (17.8) | 37 158 (45.4) | 525 (21.0) | 1860 (52.3) | 0.473 | 0.030 |
| CKD or ESRD | 631 (0.5) | 1187 (1.4) | 20 (0.8) | 176 (4.9) | 0.153 | 0.008 |
| COPD | 6581 (5.3) | 6130 (7.5) | 141 (5.6) | 302 (8.5) | 0.075 | 0.063 |
| History of liver disease | 21 107 (17.1) | 19 512 (23.8) | 452 (18.1) | 900 (25.3) | 0.125 | 0.014 |
| Coronary artery disease | 386 (0.3) | 1394 (1.7) | 7 (0.3) | 56 (1.6) | 0.094 | 0.070 |
| Sleep apnea | 40 (0.0) | 48 (0.1) | 1 (0.0) | 2 (0.1) | 0.007 | 0.010 |
| Venous thromboembolism | 355 (0.3) | 771 (0.9) | 9 (0.4) | 35 (1.0) | 0.056 | 0.039 |
| Hypothyroidism | 2043 (1.7) | 2786 (3.4) | 36 (1.4) | 114.0 (3.2) | 0.081 | 0.041 |
| Hyperthyroidism | 1845 (1.5) | 2605 (3.2) | 39 (1.6) | 133.0 (3.7) | 0.089 | 0.047 |
| Osteoporosis | 30 587 (24.8) | 27 947 (34.1) | 556 (22.2) | 1008 (28.3) | 0.147 | 0.059 |

Values are presented as *n* (%) or mean ± SD. ASD, absolute standardized difference; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; HTN, hypertension; IPTW, inverse probability of treatment weighting; Prot, proteinuria; SD, standard deviation.
[a]Prot− means the group of populations without proteinuria.
[b]Prot+ means the group of populations with proteinuria.
[c]HTN− means the group of populations without treated hypertension.
[d]HTN+ means the group of populations with treated hypertension.
[e]Male: greater than 112 g/week or more than 42 g/day, female: more than 56 g/week or more than 28 g/day (14 g per a glass).

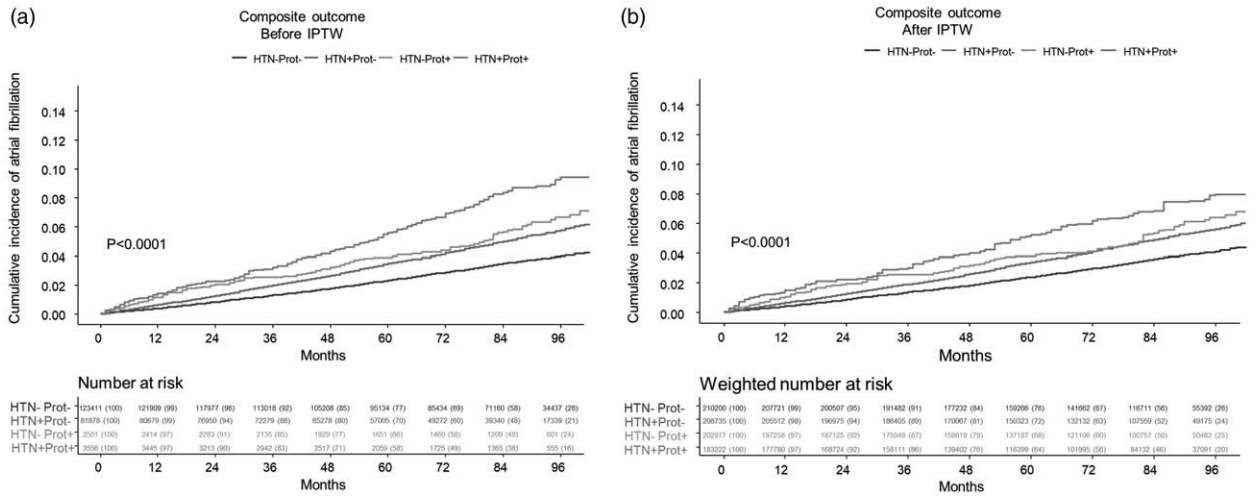


**FIGURE 2** The cumulative incidence of atrial fibrillation according to hypertension and proteinuria (a) before after inverse probability of treatment weighting and (b) after inverse probability of treatment weighting. HTN, hypertension; IPTW, inverse probability of treatment weighting; Prot, proteinuria.

43.6% were men. Patients with hypertension and/or proteinuria showed higher mean SBP and mean DBP and more comorbidities compared with participants without hypertension and proteinuria. After IPTW, all baseline characteristics had standardized differences less than 0.1. Baseline characteristics of the study cohort after IPTW was summarized in Supplementary Table S2, http://links.lww.com/HJH/B758.

## Risk of incident atrial fibrillation

During the median follow-up of 7.2 years [interquartile range (IQR) 5.1–8.1], 4.4% of individuals with hypertension and 3.2% of individuals without hypertension were diagnosed with atrial fibrillation. Amongst controls (participants without proteinuria and hypertension), hypertension only, proteinuria only and hypertension with proteinuria groups, the adjusted incidences of atrial fibrillation were 0.51, 0.69. 0.78 and 0.99 per 100 person-years, respectively. Individuals with hypertension and proteinuria had a higher cumulative incidence of atrial fibrillation compared with the unweighted (log-rank $P < 0.001$) and weighted group without hypertension and proteinuria (log-rank $P < 0.001$, Fig. 2).

After multivariable adjustment for potentially confounding clinical covariates, compared with controls, the weighted risks of atrial fibrillation in the hypertension only, proteinuria only and hypertension with proteinuria groups, were increased by 37% (hazard ratio 1.37, 95% CI: 1.30–1.44, $P = 0.001$), 55% (hazard ratio 1.55, 95% CI 1.28–1.88, $P < 0.001$), and 98% (hazard ratio 1.98, 95% CI 1.62–2.43, $P < 0.001$), respectively (Table 2). Compared with the group with hypertension only, risk of incident atrial fibrillation was increased in the group with hypertension and proteinuria (hazard ratio 1.68, 95% CI 1.38–2.05, $P < 0.001$).

In subgroup analysis, the population with hypertension and proteinuria had the highest risk of incident atrial fibrillation than controls in all subgroups, although nonsignificant in participants with low estimated glomerular filtration rate (hazard ratio 1.97, 95% CI 0.83–4.67, $P = 0.3$) (Supplementary Figure 1, http://links.lww.com/HJH/B758).

## Risks of stroke, heart failure and cardiovascular disease

Event rates and risk of other clinical outcomes according to hypertension and proteinuria were shown in Table 2. The adjusted incidences of stroke in the control, hypertension only, proteinuria only and hypertension with proteinuria groups were 0.78, 0.93, 1.0 and 1.12 per 100 person-years, respectively. After multivariable adjustment for potentially confounding clinical covariates, the risks of stroke were increased by 20% in hypertension only (hazard ratio 1.20, 95% CI 1.15–1.26, $P < 0.001$), 30% in the proteinuria only (hazard ratio 1.30, 95% CI 1.10–1.53, $P < 0.001$) and 47% in the hypertension with proteinuria groups (hazard ratio 1.47, 95% CI 1.22–1.77, $P < 0.001$).

After multivariable adjustment for potentially confounding clinical covariates, the risks of heart failure in hypertension only, proteinuria only, and hypertension with proteinuria groups were increased by 43% (hazard ratio 1.43, 95% CI 1.33–1.55, $P < 0.001$), 90% (hazard ratio 1.90, 95% CI 1.47–2.45, $P < 0.001$), and 163% (hazard ratio 2.63, 95% CI 2.05–3.38, $P < 0.001$), respectively. The risks of cardiovascular death were increased in hypertension only, proteinuria only, and hypertension with proteinuria groups by 42% (hazard ratio 1.42, 95% CI 1.33–1.51, $P < 0.001$), 43% (hazard ratio 1.43, 95% CI 1.12–1.82, $P < 0.001$), and 116% (hazard ratio 2.16, 95% CI 1.71–2.73, $P < 0.001$), respectively (Table 2). In subgroup analysis, the risk of stroke, heart failure and cardiovascular death in hypertension with proteinuria group were higher than the control group in participants with normal estimated glomerular filtration rate (Supplementary Figure 2, http://links.lww.com/HJH/B758). In populations with eGFR 60 ml/min per 1.73 $m^2$ or less, compared with control, the subgroup with hypertension and proteinuria showed the tendency of increased risk of stroke, heart failure and cardiovascular death.

**TABLE 2. Incidences of outcomes**

| Group | Event (*n*) | Incidence per 100 person-years | | Absolute rate difference per 100 person-years (95% CI) | Weighted hazard ratio (95% CI) | *P* for trend |
|---|---|---|---|---|---|---|
| | | Crude | Weighted | | | |
| Atrial fibrillation | | | | | | <0.001 |
| HTN−[a]Prot−[b] (*n* = 123 411) | 3936 | 0.49 | 0.51 | 1 (Reference) | 1 (Reference) | |
| HTN+[c]Prot− (*n* = 81 878) | 3528 | 0.71 | 0.69 | 0.18 (0.17–0.20) | 1.37 (1.30–1.44) | |
| HTN−Prot+[d] (*n* = 2501) | 122 | 0.82 | 0.78 | 0.28 (0.26–0.30) | 1.55 (1.28–1.88) | |
| HTN+Prot+ (*n* = 3556) | 222 | 1.14 | 0.99 | 0.49 (0.46–0.51) | 1.98 (1.62–2.43) | |
| Stroke | | | | | | <0.001 |
| HTN−Prot− (*n* = 123 411) | 5787 | 0.72 | 0.78 | 1 (reference) | 1 (reference) | |
| HTN+Prot− (*n* = 81 878) | 4812 | 0.98 | 0.93 | 0.15 (0.13–0.18) | 1.20 (1.15–1.26) | |
| HTN−Prot+ (*n* = 2501) | 175 | 1.19 | 1.00 | 0.22 (0.20–0.24) | 1.30 (1.10–1.53) | |
| HTN+Prot+ (*n* = 3556) | 291 | 1.51 | 1.12 | 0.35 (0.32–0.37) | 1.47 (1.22–1.77) | |
| Heart failure | | | | | | <0.001 |
| HTN−Prot− (*n* = 123 411) | 1714 | 0.21 | 0.24 | 1 (reference) | 1 (reference) | |
| HTN+Prot− (*n* = 81878) | 1787 | 0.36 | 0.33 | 0.09 (0.08–0.11) | 1.43 (1.33–1.55) | |
| HTN−Prot+ (*n* = 2501) | 71 | 0.47 | 0.43 | 0.20 (0.18–0.21) | 1.90 (1.47–2.45) | |
| HTN+Prot+ (*n* = 3556) | 153 | 0.78 | 0.58 | 0.34 (0.33–0.36) | 2.63 (2.05–3.38) | |
| Cardiovascular death | | | | | | <0.001 |
| HTN−Prot− (*n* = 123 411) | 2465 | 0.30 | 0.31 | 1 (reference) | 1 (reference) | |
| HTN+Prot− (*n* = 81 878) | 2176 | 0.43 | 0.43 | 0.12 (0.10–0.13) | 1.42 (1.33–1.51) | |
| HTN−Prot+ (*n* = 2501) | 83 | 0.55 | 0.43 | 0.12 (0.10–0.13) | 1.43 (1.12–1.82) | |
| HTN+Prot+ (*n* = 3556) | 168 | 0.83 | 0.62 | 0.31 (0.29–0.32) | 2.16 (1.71–2.73) | |

*P* value less than 0.0125 was considered statistically significant. Covariates adjusted for age, sex, diabetes mellitus and chronic kidney disease. CI, confidence interval; HTN, hypertension; Prot, proteinuria.
[a]HTN− means the group of populations without treated hypertension.
[b]Prot− means the group of populations without proteinuria.
[c]HTN+ means the group of populations with treated hypertension.
[d]Prot+ means the group of populations with proteinuria.

## The severity of proteinuria and risk of new-onset atrial fibrillation

The degree of proteinuria was divided into four groups according to the dipstick test results and three groups according to the pACR calculated from the dipstick test. As levels of dipstick proteinuria and pACR increased, the risk of incident atrial fibrillation increased in both participants with and without hypertension (Fig. 3). The distribution of pACR are shown in supplementary Table S3, http://links.lww.com/HJH/B758.

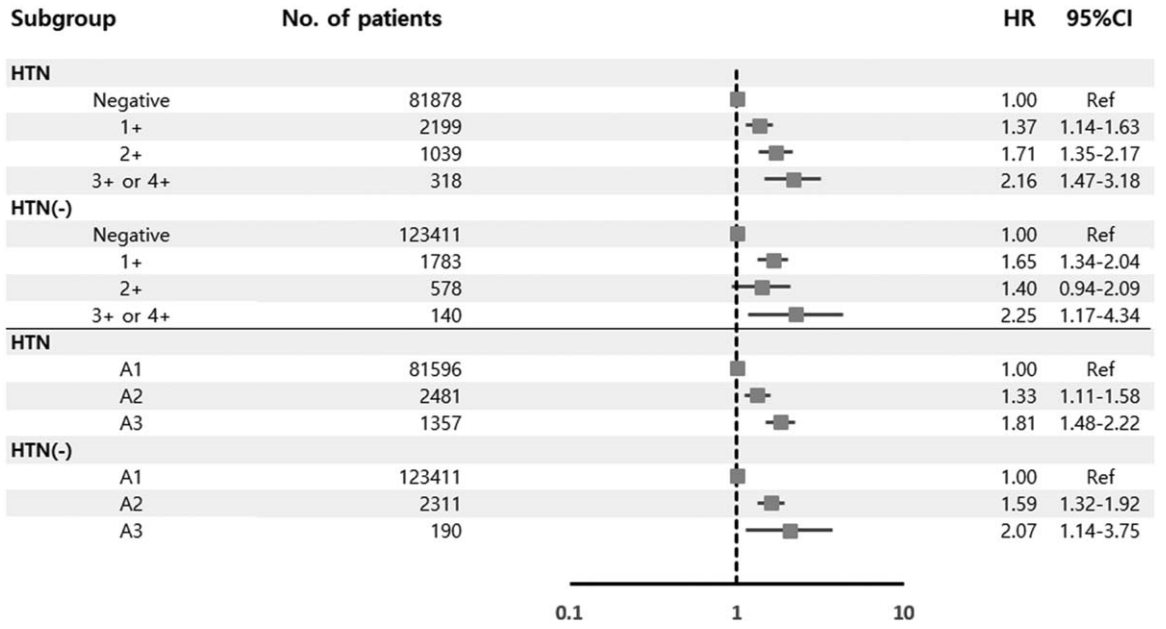


**FIGURE 3** Hazard ratio for incident atrial fibrillation according to the degree of proteinuria by dipstick test and predicted albumin–creatinine ratio. A1, predicted albumin-to-creatinine ratio, less than 30 mg/g; A2, predicted albumin-to-creatinine ratio, 30–300 mg/g; A3 predicted albumin-to-creatinine ratio, greater than 300 mg/g. HTN, hypertension; HR, hazard ratio; CI, confidence interval.

**TABLE 3. Incidence rate of atrial fibrillation according to proteinuria change**

| Change in proteinuria | Patients (*n*) | Events (*n*) | Incidence per 100 patient-years (95% CI) | Hazard ratio (95% CI) |
|---|---|---|---|---|
| Negative/trace → Negative/trace | 107 941 | 3155 | 0.62 (0.60–0.65) | 1 (reference) |
| Negative/trace → positive | 2606 | 106 | 0.97 (0.80–1.17) | 1.47 (1.21–1.78) |
| Positive → Negative/trace | 2173 | 82 | 0.87 (0.69–1.08) | 1.36 (1.09–1.67) |
| positive → positive | 663 | 30 | 1.15 (0.77–1.64) | 1.61 (1.12–2.31) |

Covariates adjusted for age, sex, diabetes mellitus and chronic kidney disease. CI, confidence interval.

### The risk of atrial fibrillation according to the change of proteinuria

Among the 113 383 population who underwent a second health check-up, the temporal change from first urine dipstick test to second urine dipstick test were used to compare the effect of change of proteinuria on incident atrial fibrillation. There was a median interval of 1.9 (IQR 1.6–2.2) years between the first and second health check-ups in patients who underwent two urine dipstick tests. Participants with persistent proteinuria had higher cumulative incidence of atrial fibrillation compared with the participants who had negative results consistently (Table 3 and Fig. 4). Populations who had proteinuria in the first examination had an increased risk of atrial fibrillation even in the group whereby the proteinuria was resolved on the second examination.

## DISCUSSION

In this large nationwide study investigating the impact of hypertension and/or proteinuria on incident atrial fibrillation, our principal findings are that proteinuria was associated with risk of incident atrial fibrillation and patients with hypertension and proteinuria had an even greater increased risk of incident atrial fibrillation compared with control groups. Second, the severity of proteinuria was associated with higher risk of incident atrial fibrillation. Third, groups in which the proteinuria was positive at the first examination had higher risk of atrial fibrillation than the group, which had persistently negative proteinuria.

### Association of hypertension and/or proteinuria with atrial fibrillation

Hypertension is the most common risk factor of incident atrial fibrillation [8,19], and increased blood pressure is associated with a greater burden of atrial fibrillation [5,6]. Atrial fibrillation is not only related with impaired quality of life because of more hospitalizations and cognitive impairment but also is associated with a substantial risk of mortality and morbidity resulting from stroke and congestive heart failure [1,3,13]. Proteinuria is frequent in patients with diabetes mellitus and hypertension, which are risk factors for atrial fibrillation [5,20]. Other studies have shown that proteinuria is an independent risk factor of atrial fibrillation development [11,12].

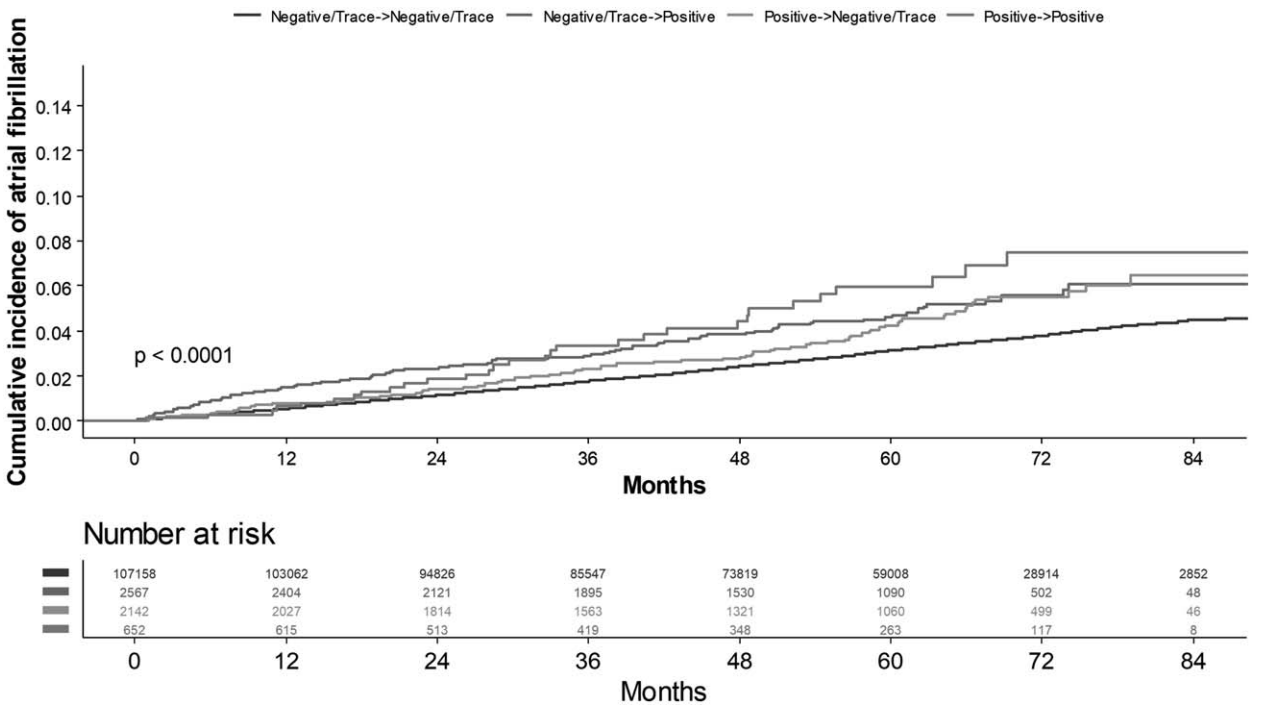


**FIGURE 4** The risk of incident atrial fibrillation according to the change of proteinuria.

Our study demonstrates that hypertension and/or proteinuria were related with atrial fibrillation development, especially if both are present. Indeed, patients with hypertension and proteinuria had increased risk of incident atrial fibrillation compared with patients with hypertension only or proteinuria only. Proteinuria in hypertension may represent hypertensive end-organ damage and be related with an increased risk of atrial fibrillation development. As hypertension alone is already a strong independent risk factor of incident atrial fibrillation, the addition of proteinuria may not significantly (and independently) add to the risk of incident atrial fibrillation. However, proteinuria was still associated with an increased risk of atrial fibrillation development and an increase in the level of proteinuria was also related with a linear increase in risk of incident atrial fibrillation. Therefore, proteinuria per se may still serve as a marker for atrial fibrillation development.

In our study, we also show that participants with positive proteinuria in the first examination did not reduce their risk of atrial fibrillation even though proteinuria was resolved in the second examination. Proteinuria may act as an indicator of hypertensive end-organ damage, endothelial dysfunction or cardiometabolic syndrome [21–23]. Proteinuria is a marker of target organ damage and making it negative with appropriated treatment may reduce risk of atrial fibrillation or cardiovascular disease. Several studies have reported that reducing proteinuria has been shown to reduce the risk of cardiovascular event [24,25]. However, there have been conflicting results on the effect of remitted proteinuria on cardiovascular events [26–28]. The progression of endothelial dysfunction and end-organ damage is a chronic process, so the risk of atrial fibrillation may be less affected by reducing proteinuria, especially in older patients like our report. In addition, longer periods of positive proteinuria may affect the risk of atrial fibrillation incidence even after proteinuria is resolved.

Although the urine ACR is the preferred measurement of proteinuria, the urine dipstick test also has a high sensitivity and specificity to screen proteinuria [29,30]. Our study also calculated predicted ACR and analyzed the risk of incident atrial fibrillation according to the group of predicted ACR. The patient groups with predicted ACR and dipstick test showed similar distribution. Predicted ACR also showed consistent results that incident atrial fibrillation was increased in the population with proteinuria compared with those without proteinuria compared with those using the dipstick test.

### Associations of hypertension and proteinuria with stroke, heart failure and cardiovascular disease

Hypertension and proteinuria are independently associated with risk for cardiovascular disease [10,23,31]. Proteinuria is an easily measured indicator of cardiovascular factors and existing endothelial dysfunction and is likely to reflect underlying macrovascular and microvascular diseases [10,32]. In our study, hypertension and proteinuria, whenever present together, were related to the highest increased risk of stroke, heart failure and CVD compared with controls.

### Limitations

Our study has several limitations. First, diagnosis of disease using coding from administrative databases can lead to errors because of coding inaccuracy. Hence, we applied the definitions that we had already validated in previous studies to minimize the problem [1,13,33]. Second, we could not differentiate between atrial fibrillation and atrial flutter because of unavailable data about differential diagnosis. Third, the baseline urine dipstick test was obtained by a single measurement. By evaluating the temporal relationship between change of proteinuria and incident atrial fibrillation, our study showed that the development of proteinuria was associated with an increased risk of incident atrial fibrillation compared with the group with constantly negative proteinuria.

Hypertension and/or proteinuria were associated with increased risk of atrial fibrillation, stroke, heart failure admissions and cardiovascular death, with the greatest risks whenever both are present. Proteinuria could be a useful factor for predicting atrial fibrillation development, and as a prognostic marker.

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### Conflicts of interest

G.Y.H.L. has been consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally. B.J. has served as a speaker for Bayer, BMS/Pfizer, Medtronic and Daiichi-Sankyo, and received research funds from Medtronic and Abbott. No fees have been received directly/personally. The remaining authors have nothing to declare.

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