Uric Acid and Risk of Atrial Fibrillation in the Korean General Population

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Background: Increased serum uric acid is associated with prevalence and incidence of atrial fibrillation (AF), but there is a lack of studies on the association between serum uric acid and risk of AF in the general population.

Methods and Results: We used the data from the Kangbuk Samsung Hospital health screening cohort recorded between 2002 and 2015. The primary outcome was incidence of AF diagnosed on 12-lead electrocardiography. We analyzed and compared the hazard ratios (HR) according to baseline serum uric acid quartiles. The present study involved 282,473 subjects without baseline AF. Mean follow-up was 5.4±3.6 years. During follow-up, AF was identified in 365 subjects (cumulative incidence, 0.13%). After multivariable adjustment, including that for C-reactive protein, the risk of AF was significantly higher in the upper 2 quartiles than in the lowest quartile in men (upper third quartile: adjusted HR, 1.53; 95% confidence interval [CI]: 1.11–2.89; highest quartile: HR, 1.60; 95% CI: 1.13–2.25). In women, even though AF incidence rate was very low (0.6 of 10,000 person-years), the risk of AF in the highest quartile was 6.93-fold that in the lowest quartile (95% CI: 1.53–31.29).

Conclusions: Serum uric acid is significantly and positively associated with incident AF in the Korean general population.

Key Words: Atrial fibrillation; General population; Korea; Serum uric acid
Health Law requires working individuals to participate in an annual or biennial health examination. Approximately 80% of the participants were employees of companies or local governmental organizations and their spouses, and the remaining participants registered individually for the program (Figure 1). Exclusion criteria were missing data on baseline variables (n=8,285), AF on 12-lead electrocardiography (ECG; n=225), and history of malignancy (n=3,553). Finally, a total of 282,473 subjects (57.1% men) were enrolled.

As part of the health screening program, individuals completed questionnaires related to their medical and social history, and medication use. Individuals were asked about frequency of exercise (none, less than once a week, or at least once a week [regular exercise]), smoking history (never, former, or current smoker), and alcohol consumption (frequency per week and amount [g/week]). Previous medical history including diabetes mellitus and hypertension was defined as the current usage of medication for a specific disease, or a positive response to the corresponding question. Chronic kidney disease was defined as the presence of kidney damage or decreased kidney function for ≥3 months, irrespective of the cause. This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, which exempted it from the requirement for informed consent because de-identified data were used for analysis.

**Laboratory Measurements**

All blood samples were drawn from antecubital veins after at least 10-h fasting, and were analyzed in the same core clinical laboratory, which has been accredited and participates annually in inspections and surveys by the Korean Association of Quality Assurance for Clinical Laboratories. Serum glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured using Bayer Reagent Packs (Bayer Diagnostics, Leverkusen, Germany) on an automated chemistry analyzer (Advia 1650 Autoanalyzer; Bayer Diagnostics). CRP was analyzed using particle-enhanced immunonephelometry on a BNIIITM System (Dade Behring, Marburg, Germany). Serum uric acid was measured on the Advia 1650 Autoanalyzer using the Fossati enzymatic reaction that used uricase with a Trinder-like endpoint. Serum creatinine was measured using the kinetic alkaline picrate (Jaffe) method.

**Outcome Definition and Measurement**

The primary outcome was the incidence of AF. AF was characterized by (1) irregular R-R interval (when atrioventricular conduction was present); (2) absence of distinct repeating P waves; and (3) irregular atrial activity on 12-lead ECG. Incident AF was diagnosed on 12-lead ECG during an annual or biennial follow-up visit.

**Statistical Analysis**

Statistical analysis was performed using STATA version 11.2 (StataCorp, College Station, TX, USA). Data are expressed as mean±SD for continuous variables and as frequency for categorical variables. Reported P-values were 2-tailed, and P<0.05 was considered statistically significant. The distribution of continuous variables was evaluated, and transformations were conducted for non-parametric variables. In comparisons of baseline variables between groups according to rhythm status at follow-up or uric acid quartiles, continuous variables were compared using Student’s t-test or 1-way analysis of variance, and categorical variables were compared using chi-squared or Fisher’s exact test.

Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals for the incidence of AF during follow-up by comparing uric acid quartiles with the lowest quartile (Q1) as the reference group. The models were initially adjusted for age. Further adjustments were made for age, sex, body mass index (BMI), smoking status, alcohol intake, regular exercise, and medical history (hypertension, diabetes mellitus, stroke, coronary artery disease (CAD), and chronic kidney disease; model 1). Model 2 was adjusted as model 1 and also for systolic blood pressure (SBP), statin medication, and concentration of LDL-C, HDL-C, triglycerides, creatinine, and glucose. Model 3 was adjusted as model 2 and also for...
Mean follow-up was 5.4±3.6 years. During the follow-up, 365 subjects had AF. Kaplan-Meier survival curves were given in Figure 2; cumulative event rates for incident AF according to uric acid quartiles are listed in Table 3. Even though the total AF incidence rate was low (2.4 events per 10,000 person-years), it progressively increased significantly according to uric acid quartile (from 0.7 in Q1 to 3.7 in Q4). The age-adjusted risk of incident AF differed significantly according to uric acid quartile in the total population (P<0.001). After multivariate adjustments, the risk of incident AF was significantly higher in Q3 and Q4 than in Q1 for all 3 models. The AF incidence rate was higher in men than in women (3.6 and 0.6 events per 10,000 patient-years, respectively). This difference prompted us to use a Cox proportional hazard model in men and women. Men in Q3 and Q4 had significantly higher HR than those in Q1 on multivariate analysis. In women, HR remained significantly higher in Q4 than in Q1 after multivariate adjustment. Adjustment for CRP, a representative marker of inflammation in model 3, did not change the result for either men or women. Cox proportional hazard modeling was performed in the subjects with normal kidney func-

CRP. Kaplan-Meier curves were used to display the incidence rates of AF according to uric acid quartiles in men and women. The incidence rates were compared using log-rank test.

**Results**

**Subject Characteristics**

Subject baseline characteristics are listed in Tables 1, 2. Development of AF was significantly associated with the following variables: higher uric acid; being older; higher proportion of being male; higher BMI; higher BP; higher current smoker; higher alcohol intake; higher regular exercise; higher prevalence of hypertension; higher LDL-C; lower HDL-C; higher triglycerides; higher creatinine; higher glucose; and higher CRP. The proportion of male subjects, BMI, and BP increased significantly from the lowest uric acid quartile (Q1) to the highest uric acid quartile (Q4). Prevalence of cardiovascular comorbidities and of worse cardiometabolic profiles was significantly higher in the higher uric acid quartiles.

| Primary Outcome |

Mean follow-up was 5.4±3.6 years. During the follow-up, 365 subjects had AF. Kaplan-Meier survival curves were given in Figure 2; cumulative event rates for incident AF according to uric acid quartiles are listed in Table 3. Even though the total AF incidence rate was low (2.4 events per 10,000 person-years), it progressively increased significantly according to uric acid quartile (from 0.7 in Q1 to 3.7 in Q4). The age-adjusted risk of incident AF differed significantly according to uric acid quartile in the total population (P<0.001). After multivariate adjustments, the risk of incident AF was significantly higher in Q3 and Q4 than in Q1 for all 3 models. The AF incidence rate was higher in men than in women (3.6 and 0.6 events per 10,000 patient-years, respectively). This difference prompted us to use a Cox proportional hazard model in men and women. Men in Q3 and Q4 had significantly higher HR than those in Q1 on multivariate analysis. In women, HR remained significantly higher in Q4 than in Q1 after multivariate adjustment. Adjustment for CRP, a representative marker of inflammation in model 3, did not change the result for either men or women. Cox proportional hazard modeling was performed in the subjects with normal kidney func-

**Table 1. Baseline Subject Characteristics vs. Incident AF**

|                   | All (n=282,473) | NSR (n=282,108) | AF (n=365) | P-value |
|-------------------|----------------|-----------------|------------|---------|
| Uric acid (mg/dL) | 5.3±1.5        | 5.3±1.5         | 6.2±1.4    | <0.001  |
| Age (years)       | 37.5±8.1       | 37.5±8.0        | 45.1±11.0  | <0.001  |
| Male              | 161,362 (57.1) | 161,033 (57.1)  | 329 (90.1) | <0.001  |
| BMI (kg/m²)       | 23.3±3.2       | 23.3±3.2        | 25.3±3.0   | <0.001  |
| SBP (mmHg)        | 112.1±13.8     | 112.1±13.8      | 120.5±15.4 | <0.001  |
| DBP (mmHg)        | 72.3±10.1      | 72.3±10.1       | 78.5±11.1  | <0.001  |
| Smoking status    |                |                 |            | <0.001  |
| Never smoker      | 153,080 (57.6) | 152,974 (57.7)  | 106 (30.3) | <0.001  |
| Former smoker     | 44,334 (16.7)  | 44,229 (16.7)   | 105 (30.0) | <0.001  |
| Current smoker    | 68,170 (25.7)  | 68,031 (25.6)   | 139 (39.7) | <0.001  |
| Alcohol intake    |                |                 |            | <0.001  |
| 0 g/day           | 80,137 (30.1)  | 80,068 (30.1)   | 69 (19.7)  | <0.001  |
| <20 g/day         | 142,046 (53.4) | 141,866 (53.4)  | 180 (51.4) | <0.001  |
| ≥20 g/day         | 44,006 (16.5)  | 43,905 (16.5)   | 101 (28.9) | <0.001  |
| Regular exercise† | 40,751 (14.6)  | 40,674 (14.6)   | 77 (21.6)  | <0.001  |
| Medical history   |                |                 |            |         |
| Hypertension      | 16,662 (5.9)   | 16,609 (5.9)    | 53 (14.5)  | <0.001  |
| Diabetes mellitus | 4,349 (1.5)    | 4,342 (1.5)     | 7 (1.9)    | 0.557   |
| Stroke            | 610 (0.2)      | 609 (0.2)       | 1 (0.3)    | 0.811   |
| CAD               | 6,728 (2.4)    | 6,718 (2.4)     | 10 (2.7)   | 0.654   |
| CKD               | 4,039 (1.7)    | 4,035 (1.7)     | 4 (1.4)    | 0.615   |
| Statin            | 2,291 (1.0)    | 2,289 (1.0)     | 2 (0.7)    | 0.592   |
| Laboratory data   |                |                 |            |         |
| LDL-C (mg/dL)     | 114.0±30.2     | 114.0±30.2      | 117.3±28.4 | 0.037   |
| HDL-C (mg/dL)     | 56.5±13.4      | 56.5±13.4       | 52.0±11.5  | <0.001  |
| Triglycerides (mg/dL) | 97 (68–144) | 97 (68–144) | 130 (91–190) | <0.001  |
| Creatinine (mg/dL) | 1.0 (0.8–1.1)  | 1.0 (0.8–1.1)  | 1.1 (1.0–1.2) | <0.001  |
| Glucose (mg/dL)   | 93.8±14.2      | 93.8±14.2       | 97.3±16.3  | <0.001  |
| CRP (mg/L)        | 0.4 (0.2–0.9)  | 0.4 (0.2–0.9)   | 0.6 (0.3–1.4) | <0.001  |

Data given as mean±SD, median (IQR), or n (%). †≥once per week. AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NSR, normal sinus rhythm; SBP, systolic blood pressure.
Uric Acid and Risk of AF

Table 2. Baseline Subject Characteristics vs. Serum Uric Acid Quartile

| Uric acid (mg/dL) | Quartile 1 (n=74,397) | Quartile 2 (n=67,304) | Quartile 3 (n=71,410) | Quartile 4 (n=69,362) | P<sub>rend</sub> |
|------------------|----------------------|----------------------|----------------------|----------------------|------------------|
| Overall (n=282,473) | 5.3±1.5 | 3.6±0.5 | 4.7±0.3 | 5.8±0.3 | 7.3±0.8 | <0.001 |
| Age (years) | 37.5±8.1 | 37.5±8.0 | 37.8±8.6 | 37.8±8.2 | 37.0±7.5 | <0.001 |
| Male | 161,362 (57.1) | 8,194 (11.0) | 25,214 (37.5) | 60,218 (84.3) | 67,736 (97.7) | <0.001 |
| BMI (kg/m²) | 23.3±3.2 | 21.6±2.8 | 22.6±3.0 | 23.9±2.9 | 25.2±3.0 | <0.001 |
| SBP (mmHg) | 112.2±13.8 | 106.8±13.0 | 109.8±13.7 | 114.7±12.8 | 117.7±12.8 | <0.001 |
| DBP (mmHg) | 72.3±10.1 | 68.1±9.2 | 70.5±9.8 | 74.2±9.5 | 76.6±9.6 | <0.001 |
| Smoking status | | | | | | <0.001 |
| Never smoker | 153,080 (57.6) | 59,805 (87.2) | 43,929 (69.9) | 27,948 (41.2) | 21,398 (32.3) | |
| Former smoker | 44,334 (16.7) | 3,921 (5.7) | 7,621 (12.1) | 15,166 (22.3) | 17,626 (26.6) | |
| Current smoker | 68,170 (25.7) | 4,887 (7.1) | 11,325 (18.0) | 24,798 (36.5) | 27,160 (41.0) | |
| Alcohol intake | | | | | <0.001 |
| 0g/day | 80,137 (30.1) | 33,988 (50.3) | 23,843 (38.1) | 13,326 (19.4) | 8,980 (13.3) | |
| <20g/day | 142,046 (53.4) | 29,937 (44.3) | 31,688 (50.6) | 40,280 (58.7) | 40,141 (59.6) | |
| ≥20g/day | 44,006 (16.5) | 3,599 (5.3) | 7,102 (11.3) | 15,037 (21.9) | 18,268 (27.1) | |
| Regular exercise† | 40,751 (14.6) | 9,689 (13.5) | 9,693 (14.6) | 10,594 (15.0) | 10,595 (15.5) | <0.001 |
| Medical history | | | | | | <0.001 |
| Hypertension | 16,662 (5.9) | 2,255 (3.0) | 3,304 (4.9) | 4,739 (6.6) | 6,364 (9.2) | <0.001 |
| Diabetes mellitus | 4,349 (1.5) | 1,042 (1.4) | 1,275 (1.9) | 1,164 (1.6) | 868 (1.3) | 0.002 |
| Stroke | 610 (0.22) | 120 (0.16) | 155 (0.23) | 166 (0.23) | 169 (0.24) | 0.001 |
| CAD | 6,728 (2.4) | 1,652 (2.2) | 1,646 (2.5) | 1,632 (2.3) | 1,798 (2.6) | <0.001 |
| CKD | 4,039 (1.7) | 1,139 (1.9) | 1,017 (1.8) | 927 (1.6) | 956 (1.7) | 0.001 |
| Statin | 2,291 (0.8) | 405 (0.66) | 571 (1.04) | 598 (1.01) | 717 (1.25) | <0.001 |
| Laboratory data | | | | | | <0.001 |
| LDL-C (mg/dL) | 114.0±30.2 | 103.5±27.3 | 110.3±29.1 | 117.8±29.6 | 124.8±30.7 | <0.001 |
| HDL-C (mg/dL) | 56.5±13.4 | 62.0±13.7 | 58.9±13.7 | 54.0±12.3 | 51.0±11.0 | <0.001 |
| Triglycerides (mg/dL) | 97 (68–144) | 74 (56–101) | 85 (63–122) | 109 (78–156) | 136 (95–195) | <0.001 |
| Creatinine (mg/dL) | 1.0 (0.8–1.1) | 0.8 (0.7–0.9) | 0.9 (0.8–1.0) | 1.0 (0.9–1.1) | 1.1 (1.0–1.2) | <0.001 |
| Glucose (mg/dL) | 93.8±14.3 | 91.9±15.4 | 93.3±15.5 | 94.6±13.7 | 95.5±11.9 | <0.001 |
| CRP (mg/L) | 0.4 (0.2–0.9) | 0.3 (0.1–0.6) | 0.4 (0.2–0.8) | 0.5 (0.2–1.0) | 0.6 (0.3–1.3) | <0.001 |

Data given as mean±SD, median (interquartile range) or n (%). †≥once per week. Abbreviations as in Table 1.

Discussion

The present study has demonstrated that increased serum uric acid is significantly associated with an increased risk of incident AF in the Korean general population. This association remained unchanged even after adjustment for other cardiovascular risk factors including CRP.

The Atherosclerosis Risk in Communities Study, which involved 15,382 AF-free black adults and white adults, reported that elevated serum uric acid was associated with a greater risk of AF, particularly in black people and in women. An European cohort study, which involved 6,308 men and women, showed that high baseline serum uric acid was associated with an increased risk of future AF in both sexes. An Asian cohort study (n=122,524) also found that hyperuricemia is a significant risk factor for new-onset AF. Meta-analyses that included these studies supported the notion that serum uric acid is a predictive biomarker for future AF.

In the present study, increased serum uric acid was associated with a greater risk of incident AF in women. This is consistent with previous studies. Interestingly, hyperuricemia is more strongly associated with cardiovascular events and with death in women than in men. Although the mechanism for the gender difference has not been elucidated yet, it may be linked to differences in the sex hormones. Menopause is associated with increased serum uric acid because estrogen is known to be uricosuric.
Figure 2. Kaplan-Meier survival curves for the incidence of atrial fibrillation (AF) according to serum uric acid quartiles in (A) the total population, (B) men, and (C) women.
Uric Acid and Risk of AF

Table 3. Risk of AF vs. Baseline Serum Uric Acid Quartile

| Uric acid quartile (mg/dL) | Follow-up (person-years) | No. events | AF incidence rate (per 10,000 person-years) | Age-adjusted HR (95% CI) | Multivariate HR (95% CI) |
|---------------------------|--------------------------|------------|---------------------------------------------|--------------------------|-------------------------|
|                           |                          |            |                                             | Model 1                  | Model 2                 | Model 3                 |
| Total                     | 1,529,459                | 365        | 2.4                                         | 1.0 (Ref.)               | 1.0 (Ref.)              | 1.0 (Ref.)              |
| Q1 (<4.3)                 | 387,833                  | 28         | 0.7                                         | 2.03 (1.29–3.19)         | 1.27 (0.78–2.07)        | 1.27 (0.78–2.07)        |
| Q2 (4.3–5.2)              | 354,446                  | 56         | 1.6                                         | 4.62 (3.07–6.94)         | 1.81 (1.12–2.92)        | 1.79 (1.11–2.89)        |
| Q3 (5.3–6.3)              | 397,396                  | 136        | 3.4                                         | 5.58 (3.72–8.36)         | 1.94 (1.19–3.14)        | 1.87 (1.14–3.07)        |
| Q4 (≥6.4)                 | 389,786                  | 145        | 3.7                                         | 1.0 (Ref.)               | 1.0 (Ref.)              | 1.0 (Ref.)              |
| P<0.001                   | <0.001                   | 0.002      | 0.005                                       | 0.005                    | 0.005                   | 0.005                   |
| Men                       | 910,884                  | 329        | 3.6                                         |                          |                         |                         |
| Q1 (<5.5)                 | 237,259                  | 76         | 3.2                                         | 1.0 (Ref.)               | 1.0 (Ref.)              | 1.0 (Ref.)              |
| Q2 (5.5–6.1)              | 224,787                  | 80         | 3.6                                         | 1.33 (0.97–1.82)         | 1.39 (1.00–1.94)        | 1.39 (1.00–1.94)        |
| Q3 (6.2–6.9)              | 235,338                  | 87         | 3.7                                         | 1.49 (1.09–2.03)         | 1.54 (1.11–2.13)        | 1.53 (1.10–2.13)        |
| Q4 (≥7.0)                 | 213,460                  | 86         | 4.0                                         | 1.65 (1.21–2.25)         | 1.62 (1.16–2.26)        | 1.60 (1.13–2.26)        |
| P<0.001                   | <0.001                   | 0.003      | 0.006                                       | 0.006                    | 0.006                   | 0.006                   |
| Women                     | 618,615                  | 36         | 0.6                                         |                          |                         |                         |
| Q1 (<3.7)                 | 161,523                  | 2          | 0.1                                         | 1.0 (Ref.)               | 1.0 (Ref.)              | 1.0 (Ref.)              |
| Q2 (3.7–4.2)              | 181,102                  | 10         | 0.6                                         | 4.49 (0.98–20.50)        | 4.34 (0.95–19.80)       | 4.33 (0.94–19.81)       |
| Q3 (4.3–4.7)              | 133,199                  | 6          | 0.5                                         | 3.55 (0.72–17.59)        | 3.44 (0.69–17.07)       | 3.52 (0.70–17.57)       |
| Q4 (≥4.8)                 | 142,791                  | 18         | 1.3                                         | 7.54 (1.74–32.70)        | 6.61 (1.50–29.05)       | 6.78 (1.50–30.58)       |
| P<0.001                   | <0.001                   | 0.011      | 0.013                                       | 0.013                    | 0.013                   | 0.013                   |

Cox proportional hazard models were used to estimate HR and 95% CI. Model 1: adjustment for age, sex, BMI, smoking status, alcohol intake, regular exercise, and medical history (hypertension, diabetes mellitus, stroke, CAD, and CKD); model 2: model 1 plus adjustment for SBP, statin medication, and concentration of LDL-C, HDL-C, triglycerides, creatinine, and glucose; model 3: model 2 plus adjustment for CRP. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

Uric acid and AF is not well characterized. Conceptually, the elevated serum uric acid may contribute to the pathophysiology of AF via both inflammatory signaling-induced changes and inflammation-independent mechanisms.30 Gicquel et al showed that monosodium urate-stimulated human macrophages secrete IL-1β following activation of purinergic receptors and of the NACHT, LRR, and PYD domains-containing protein 3 (NLRP3)-inflammasome pathway.31 Secreted IL-1β promotes the proliferation and differentiation of fibroblasts to myofibroblasts, which secrete larger amounts of cytokines, chemokines and growth factors including tumor growth factor (TGF)-β1.32 The NLRP3-inflammasome activity is upregulated in atrial tissue of AF patients; cardiomyocyte-restricted activation of NLRP3 inflammasome promotes the development of premature atrial contractions and predisposes mice to pacing-induced AF.32 In fibroblasts, the internalization of uric acid via uric acid transporter (UAT) can increase the production of reactive oxidative species, which can activate Ca2+-permeable transient receptor potential melastatin-related type 7 channels (TRPM7).33 TRPM7 are upregulated in atrial fibroblasts of AF patients and contribute to TGF-β1-induced fibroblast differentiation.34 Ultimately, these events increase collagen deposition and related fibrosis, which are expected to facilitate the development of AF by maintaining re-entrant circuits and slowing heterogeneous conduction.35 The suggested inflammation-independent effects of hyperuricemia include intracellular accumulation of uric acid via activation of UAT, which is posited to cause cell injury through several signaling pathways.34 In addition, in a recent study, intracellular uric acid uptake by UAT enhanced Kv1.5 protein expression, which may be attributable to shortening of the action potential duration, resulting in the initiation or maintenance of AF.36

Although the current lines of evidence, including the present study, show an independent relationship between increased serum uric acid and risk of AF, whether uric acid-lowering therapy may be beneficial in lowering AF risk remains unknown. In a recent study on mice fed a Western diet, the increase in serum uric acid after 16 weeks was accompanied by an increase in cardiac xanthine oxidase activity, which induced cardiomyocyte hypertrophy, myocardial oxidative stress, interstitial fibrosis, and impaired diastolic relaxation through activation of the S6 kinase-1 growth pathway, the profibrotic transforming growth factor-β1/Smad2/3 signaling pathway, and pro-inflammatory macrophage polarization.36 These conditions improved with allopurinol treatment, which lowered cardiac xanthine oxidase and serum uric acid.36 Xanthine oxidase catalyzes the final 2 reactions in the biochemical chain that leads to uric acid formation: the conversion of hypoxanthine to xanthine and of xanthine to uric acid.37 This enzyme uses molecular oxygen as the electron acceptor and leads to formation of the free radical superoxide anion.37

Circulation Journal Vol.82, November 2018
Hence, xanthine oxidase is a critical source of reactive oxygen species. Also, superoxide reacts with nitric oxide to form cytotoxic oxidant peroxynitrite. These reactive oxygen species contribute to the decrease of nitric oxide, leading to endothelial dysfunction and contributing to atherosclerosis and cardiovascular disease. The role of xanthine oxidase in the pathogenesis of AF has been investigated. In a porcine model of atrial pacing-induced AF, AF increased superoxide production in both the left atrium (LA) and LA appendage. Increased NADPH oxidase and xanthine oxidase activities contributed to the observed increase in LA appendage superoxide production. This increase in superoxide and its reactive metabolites may contribute to the pathological consequences of AF such as thrombosis, inflammation, and tissue remodeling. Xanthine oxidase has been shown to play a pivotal role in the generation of superoxide free radicals in the human atrium. Uric acid-lowering therapy is beneficial in patients with CAD and heart failure. In a canine model of atrial tachypacing left ventricular dysfunction, a xanthine oxidase inhibitor, allopurinol, suppressed AF promotion by preventing both electrical and structural remodeling. Therefore, future prospective clinical trials are needed to establish the causative role of uric acid in AF development and to evaluate the potential therapeutic value of xanthine oxidase inhibitor in the prevention and treatment of AF.

Clinical Implications
After several adjustments, including that for CRP, the risk of incident AF was significantly higher in both men and women in the highest uric acid quartile than in those in the lowest quartile. Because intracellular uric acid uptake by urate transporters is strongly associated with the initiation or sustainment of AF because it enhances K<sub>v</sub>1.5 protein expression, which shortens the atrial action potential duration, the present findings support the recently proposed hypothesis that the association between serum uric acid and AF is not mediated by inflammation. Thus, lowering of serum uric acid through lifestyle interventions, pharmacologic urate-lowering therapy, or both might prevent incident AF or AF recurrence in people with high serum uric acid. Randomized controlled trials are required to assess whether an intervention to reduce serum uric acid would be effective for the prevention of incident AF in the hyperuricemic population.

Study Limitations
First, because this was a retrospective analysis of subjects from a single center in Korea, the positive association between uric acid level and incident AF might not be found in other Asian populations. Consequently, the present findings may not necessarily be applicable to other ethnicities. Second, the diagnosis of AF was based only on 12-lead ECG during an annual or biennial visit, but not on any clinical visits or hospitalizations with clinically indicated documentation of AF. Thus, we might have underestimated the incident AF. Third, we could not include baseline medical treatment, especially several drugs influencing serum uric acid level. Fourth, we could not exclude valvular heart disease or hyperthyroidism in advance because we did not have past history information on valvular heart disease or hyperthyroidism, and did not have echocardiographic data. Finally, the present study did not take into account echocardiographic risk factors for AF development, including LA enlargement, decreased ventricular ejection fraction, and increased left ventricular wall thickness. Despite these limitations, the present results may have clinical significance because this analysis included a large, relatively healthy, young–middle-aged population with a very low risk of incident AF.

Conclusions
Increased serum uric acid level is significantly associated with higher risk of incident AF in the Korean general population. This association was observed regardless of CRP. Further studies are required to elucidate the detailed mechanisms underlying the association between serum uric acid level and incident AF.

Acknowledgment
We acknowledge the efforts of the health screening group at Kangbuk Samsung Hospital, Seoul, Korea.

Funding
None.

Disclosures
The authors declare no conflicts of interest.

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Supplementary Files

Table S1. Risk of AF vs. baseline serum uric acid quartile in people with normal kidney function

Please find supplementary file(s):

http://dx.doi.org/10.1253/circj.CJ-18-0748