Metabolic Syndrome and the Risk of New-Onset Atrial Fibrillation in Middle-Aged East Asian Men

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Background: Although the prevalence of both atrial fibrillation (AF) and metabolic syndrome (MetS) has been increasing in East Asia, the association between them is uncertain.

Methods and Results: A total of 24,741 middle-aged Korean men without baseline AF were enrolled in a health screening program from January 2003 to December 2008. Among them, 21,981 subjects were evaluated to determine the risk of AF based on baseline MetS status through December 2016. At every visit, the subjects were evaluated for AF using ECG. MetS was defined using the criteria of the International Diabetes Federation and was present in 2,529 subjects (11.5%). Mean (±standard deviation) age was 45.9±5.3 years. During a mean follow-up of 8.7 years, 168 subjects (0.8%) were diagnosed with AF. The age-adjusted and multivariate-adjusted hazard ratios (HR) for MetS with AF were 1.62 (P=0.02) and 1.57 (P=0.03), respectively. Among the components of MetS, central obesity (age-adjusted HR 1.62, P<0.01) and raised blood pressure (age-adjusted HR 1.43, P=0.02) were associated with an increased risk of AF.

Conclusions: MetS is associated with an increased risk of AF in middle-aged East Asian men. Of the components of MetS, central obesity is the most potent risk factor for the development of AF in this population.

Key Words: Atrial fibrillation; Central obesity; Metabolic syndrome; Risk factors

Atrial fibrillation (AF) is the most common arrhythmia requiring treatment in clinical practice, and is associated with increased mortality rates. Although the prevalence of AF is known to be higher in the West than in Asia, the prevalence in Asia has been increasing with aging populations and a westernized lifestyle. In South Korea, prevalence rates of AF progressively increased 2.69-fold between 2004 and 2013. Metabolic syndrome (MetS) is a cluster of characteristics including central obesity (defined as waist circumference [WC] with ethnicity specific values), hypertension (HTN), diabetes mellitus (DM), and dyslipidemia, which are recognized as risk factors for cardiovascular disease; its prevalence has increased globally. In addition, previous studies suggest that MetS is associated with an increased risk of AF. However, previous studies were aimed at Western populations, or the definition of MetS was not exact (body mass index [BMI] used in place of WC, for example). BMI has a limitation for replacement of central obesity because Asians have a lower BMI in general at a given central obesity compared with Europeans.

In this study, we aimed to determine the association of MetS with the risk of new-onset AF in middle-aged East Asian men.

Methods

Study Population
We conducted a retrospective cohort study using data from 21,981 individuals who participated in an annual or biennial comprehensive health screening program at Ulsan University Hospital, Ulsan, Republic of Korea, from January 2003 to December 2008 (Figure 1). The Korean Industrial Safety and Health Law requires working individuals to participate in an annual or biennial health examination. In addition to mandatory health examination,
the health screening program of Ulsan University Hospital included a 12-lead ECG. Most of the individuals who participated in the health examination at our center were employees of heavy industries and most of them were men (n=24,800, 97%); Women (n=862) were excluded. In addition, we excluded subjects if they did not have an initial ECG, if they had AF or atrial flutter (AFL) on the initial ECG, if they did not have a follow-up ECG; or if data from questionnaires and the others including anthropometric measurements, blood pressure (BP), and blood tests were unavailable. AF and AFL were diagnosed from the 12-lead ECG recorded at a follow-up visit (annual or biennial). AFL was included as an endpoint because it is closely related to AF, often coexists with AF, and is associated with a similar risk of stroke.11-13 The study protocol was approved by the Institutional Review Board at Ulsan University Hospital (IRB No. 2017-02-023). Subjects’ information was anonymized and de-identified prior to analysis. The requirement for informed consent was waived because of the anonymity of the subjects and the nonintrusive nature of the study.

Data Collection
Data were collected by a clinical data warehouse platform in conjunction with electronic medical records in Ulsan University Hospital. Anthropometric measurements were made by well-trained examiners while individuals were wearing light clothing and without shoes. Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. BMI values were calculated by dividing weight (kg) by height squared (m²). WC was measured in the standing position, midway between the lowest rib and the iliac crest with a measuring tape. Seated BP was measured by well-trained nurses using a mercury sphygmomanometer after subjects rested for ≥10 min. Following an overnight fast (≥8 h), blood samples were collected and 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. Blood tests included fasting glucose, hemoglobin A1c (HbA1c), fasting plasma lipid profile including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, and triglycerides (TG), serum creatinine, and blood urea nitrogen. The estimated glomerular filtration rate (eGFR) was calculated with the Modification of Diet in Renal Disease equation (eGFR=175×(serum creatinine)−1.154×age−0.203). Data on smoking status (never, former, or current),
Table 1. Baseline Characteristics by Baseline MetS Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>No MetS (n=19,452)</th>
<th>MetS (n=2,529)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.9±5.2</td>
<td>46.0±5.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>66.6±7.9</td>
<td>79.8±8.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.2±2.3</td>
<td>27.0±2.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>82.2±6.1</td>
<td>94.1±4.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>119.5±13.9</td>
<td>128.7±14.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>77.0±8.6</td>
<td>83.3±10.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>42.6±6.1</td>
<td>45.4±8.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HTN (%)</td>
<td>3,554 (18.3)</td>
<td>1,096 (43.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>DM (%)</td>
<td>1,648 (8.5)</td>
<td>422 (16.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>65 (0.3)</td>
<td>5 (0.2)</td>
<td>0.35</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td></td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Never smoker</td>
<td>6,300 (32.7)</td>
<td>752 (30)</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>4,898 (25.4)</td>
<td>644 (25.7)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>8,083 (41.9)</td>
<td>1,113 (44.4)</td>
<td></td>
</tr>
<tr>
<td>Regular exercise (%)</td>
<td>12,972 (67.0)</td>
<td>1,755 (69.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Alcohol drinking status (%)</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&lt;40 g/day</td>
<td>18,732 (96.5)</td>
<td>2,387 (94.5)</td>
<td></td>
</tr>
<tr>
<td>≥40 g/day</td>
<td>670 (3.5)</td>
<td>138 (5.5)</td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>100.1±15.6</td>
<td>108.5±20.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.29±0.62</td>
<td>5.56±0.76</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>194.6±32.5</td>
<td>204.8±34.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>124.1±73.2</td>
<td>197.0±104.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>121.7±29.9</td>
<td>124.2±33.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>48.0±11.1</td>
<td>41.3±8.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>15.7±3.9</td>
<td>15.5±3.6</td>
<td>0.05</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.09±0.16</td>
<td>1.12±0.14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GFR (mL/min/1.73 m²)</td>
<td>74.1±9.9</td>
<td>72.0±10.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CKD</td>
<td>975 (5.0)</td>
<td>233 (9.2)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are reported as mean±SD or as number (%). a≥Once/week. BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CKD, chronic kidney disease; DM, diabetes mellitus; GFR, glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; TG, triglycerides; WC, waist circumference.

Definition of MetS
MetS was defined according to the criteria of the International Diabetes Federation. Central obesity (WC ≥90 cm) had to be present and any 2 of the following 4 components were required: (1) raised BP (SBP ≥130 mmHg or DBP ≥85 mmHg or treatment of previously diagnosed HTN); (2) raised FPG (≥100 mg/dL or diagnosed type 2 DM); (3) raised TG (≥150 mg/dL or drug treatment for high TG); and (4) reduced HDL-C (<40 mg/dL or drug treatment for lowering HDL-C).

Statistical Analysis
All baseline patient characteristics were summarized as mean±standard deviation (SD) or frequency (percentage) for continuous or categorical variables. The baseline characteristics by baseline MetS status were compared by chi-square test and Student’s t test for categorical and continuous variables, respectively. Follow-up years were computed from the baseline examination until a first AF or AFL diagnosis, loss to follow-up, or the end date of December 2016. We estimated the cumulative incidence of AF based on the Kaplan-Meier method and we compared the cumulative incidence rates curves by log-rank test.
Overall and age-adjusted incidence rates for AF by the baseline MetS status were also calculated. Age-adjusted and multivariate-adjusted hazard ratios (HRs) of MetS were estimated by Cox proportional hazard regression model. Multivariate-adjustments were made for age, smoking status, regular exercise, alcohol drinking status, and CKD. HRs for individual components of MetS after additional adjustment for the other components were also evaluated by Cox model. Results of the Cox proportional hazard model are presented as the HR and 95% confidence interval (95% CI). Analyses were performed with R software, version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). All reported P-values are 2-sided, and P<0.05 was considered to indicate statistical significance.
Results

Baseline Characteristics
A total of 21,981 men were enrolled in the cohort analysis. The mean age was 45.9±5.3 years. At baseline, MetS was present in 2,529 subjects (11.5%). Table 1 shows the baseline characteristics of this study population by baseline MetS status. Subjects with MetS were older, and had higher values for BMI, WC, SBP, DBP, pulse pressure, and had more comorbidities (HTN, DM, dyslipidemia, and impaired renal function) than subjects without MetS. Table 2 shows the prevalence of MetS and of the individual components of MetS.

Association Between MetS and the Incidence of AF
During a mean follow-up of 8.7 years, AF (including AFL) occurred in 168 subjects (0.8%, AF=166, AFL=2). Figure 2 depicts the cumulative incidence rates of AF by baseline MetS status. Although overall AF incidence rates were low (8.81/10,000 person-years), AF incidence rates were higher in subjects with MetS (13.32/10,000 person-years) than in subjects without MetS (8.25/10,000 person-years). This trend was consistently observed after age-adjustment. The age-adjusted AF incidence rates were 5.94 and 4.29/10,000 person-years in subjects with and without MetS, respectively (Table 3).

Effect of MetS on the Risk of New-Onset AF
As shown in Table 4, MetS was associated with an increased risk of AF. In the Cox proportional hazard regression model, the age-adjusted HR for AF in subjects with MetS was 1.62 (95% CI 1.08–2.44, P=0.02). In multivariate models adjusted for age, smoking status, regular exercise, drinking status, and CKD, the HR for AF in subjects with MetS was 1.57 (95% CI 1.04–2.38, P=0.03). Among the components of MetS, central obesity (HR 1.62, 95% CI 1.14–2.29, P<0.01) and raised BP (HR 1.43, 95% CI 1.05–1.94, P=0.02) were associated with an increased risk of AF. Among the components of MetS, central obesity (HR 1.62, 95% CI 1.08–2.44, P=0.02) remained significantly associated with an increased risk of AF regardless of BMI (Table S1).

Discussion
In the present study, we have shown that middle-aged East Asian men with MetS had a 57% increased risk for the development of AF during a mean follow-up of 8.7 years. Among the components of MetS, central obesity was the strongest predictor for the development of AF. Other components of MetS were not significantly associated with an increased risk of AF.
Study Strengths and Limitations

The strengths of our study are the large sample size and the well-organized cohort design characterized by consistent follow-up because of very low turnover rates in employment, the long average length of service (>18 years), and the obligation for health examinations, including ECGs (at least once every 2 years). Another advantage of our study is that AF was identified purely by 12-lead ECG, not by self-reported questionnaire or a code defined by the International Classification of Disease.

However, our study had several limitations. First, it was a retrospective cohort study with inherent limitations. Second, information regarding smoking, exercise, alcohol intake, and medical history were self-administered, thus allowing recall bias. Third, the study population was not representative of the general population because all subjects were working individuals and middle-aged men. However, this was also a strength of our study because there are few data regarding middle-aged men. AF constitutes a significant economic burden worldwide. From an economic standpoint, prevention of AF in this group is important because middle-aged men are the main agents of economic activity. Finally, the diagnosis of AF was based only on annual or biennial 12-lead ECGs. Thus, the diagnosis of AF, especially paroxysmal AF, may have been underestimated.

Conclusions

This large and long-term follow-up cohort study demonstrated that MetS was associated with an increased risk of AF in middle-aged East Asian men. Among the components of MetS, central obesity was the most potent risk factor for the development of AF. These findings suggested that strategies to reduce the development of MetS, especially central obesity, might reduce the risk of AF in middle-aged East Asian men.

Acknowledgment

We acknowledge the efforts of the health screening group at Ulsan University Hospital, Ulsan, Republic of Korea.

Conflict of Interest

The authors have no conflicts of interest to declare.

References


Supplementary Files

Supplementary File 1

Table S1. Risk of AF by central obesity using time-dependent Cox proportional hazard regression model

Please find supplementary file(s);