Metabolic Syndrome and Risk of Development of Atrial Fibrillation

The Niigata Preventive Medicine Study

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Background—The metabolic syndrome consists of a cluster of atherosclerotic risk factors, many of which also have been implicated in the genesis of atrial fibrillation (AF). However, the precise role of the metabolic syndrome in the development of AF is unknown.

Methods and Results—This prospective, community-based, observational cohort study was based on an annual health check-up program in Japan. We studied 28,449 participants without baseline AF. We used 2 different criteria for the metabolic syndrome—the guidelines of the National Cholesterol Education Program Third Adult Treatment Panel (NCEP-ATP III) and those of the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI)—to study the risk of development of new-onset AF. The metabolic syndrome was present in 3716 subjects (13%) and 4544 subjects (16%) using the NCEP-ATP III and AHA/NHLBI definitions, respectively. During a mean follow-up of 4.5 years, AF developed in 265 subjects (105 women). Among the metabolic syndrome components, obesity (age- and sex-adjusted hazard ratio [HR], 1.64), elevated blood pressure (HR, 1.69), low high-density lipoprotein cholesterol (HR, 1.52), and impaired fasting glucose (HR, 1.44 [NCEP-ATP III] and 1.35 [AHA/NHLBI]) showed an increased risk for AF. The association between the metabolic syndrome and AF remained significant in subjects without treated hypertension or diabetes by the NCEP-ATP III definition (HR, 1.78) but not by the AHA/NHLBI definition (HR, 1.28).

Conclusions—The metabolic syndrome was associated with increased risk of AF. The metabolic derangements of the syndrome may be important in the pathogenesis of AF.

Key Words: arrhythmia ■ diabetes mellitus ■ hypercholesterolemia ■ hypertension ■ metabolic syndrome X ■ risk factors ■ obesity
hensive Health Promotion and Research (Niigata, Japan). In the prefecture, annual health examinations supported by the administration are available to residents ≥20 years of age. The annual examination consists of a detailed medical history; physical examination; blood examination, including blood cell count and biochemical markers; chest x-ray; and a 12-lead ECG. This report includes subjects who lacked exclusion criteria, had at least 1 fasting blood test between 1996 and 1998 as the baseline examination of this study, and subsequently received at least 1 annual examination through 2005. AF was diagnosed from the 12-lead ECG recorded at a follow-up visit. Exclusion criteria included a history of AF (or atrial flutter), presence of AF, or permanent pacemakers at the time of their initial examination. Subjects who received antihyperlipidemic drugs were excluded because detailed data on individual drug regimens were not available.

Definition of the Metabolic Syndrome
The metabolic syndrome was defined according to the guidelines of the National Cholesterol Education Program Third Adult Treatment Panel (NCEP-ATP III) and American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) with modification for body size. On the basis of the baseline examination, the metabolic syndrome was diagnosed when at least 3 of the following criteria were met. The first criterion was elevated body mass index (BMI) (in lieu of waist measurement, which was not available in our database). BMI was calculated by dividing weight in kilograms by the square of the height in meters. The frequency of BMI ≥30 kg/m² is 2% to 3% in Japan and 20% to 30% in Western countries. Because of the differences in BMI between Japanese and Western populations, values ≥25 kg/m² were considered elevated (in contrast to ≥30 kg/m² in Western populations) according to criteria of the Japan Society for the Study of Obesity. The second criterion was elevated triglycerides (≥150 mg/dL); the third, low high-density lipoprotein (HDL) cholesterol (<40 mg/dL in men, <50 mg/dL in women); the fourth, elevated blood pressure (systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg, and/or a history of treated hypertension); and the fifth, impaired glucose tolerance (≥110 mg/dL by the NCEP-ATP III definition, ≥100 mg/dL by the AHA/NHLBI definition, and/or a history of diabetes).

Data Analysis
Differences in baseline characteristics between groups were determined by the unpaired t test for continuous variables and the χ² test for categorical variables. Hazard ratios and 95% CIs were calculated from Cox proportional-hazards models to study the contribution of age as a continuous value and sex to the development of AF. Cox models were adjusted for age as a continuous value and sex to evaluate the contribution of the metabolic syndrome, the components of the metabolic syndrome, and the number of fulfilled metabolic syndrome components to AF development. All statistical analyses were performed with SPSS, version 12.0 (SPSS Inc, Chicago, III). Two-sided values of P<0.05 were considered statistically significant. Values are expressed as mean±SD.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Characteristics of Study Subjects
Baseline characteristics of the 28,449 subjects in this study are shown in Table 1. The mean age of the entire cohort was 59.2±11.0 years, and 66% of the subjects were women. Antihypertensive treatment was given in 20% of the subjects, and diabetes was present in 12% of the subjects. The metabolic syndrome was present in 3716 subjects (13%) according to the NCEP-ATP III definition and in 4544 subjects (16%) according to the AHA/NHLBI definition. Subjects with the metabolic syndrome were older by either definition (P<0.001 for each) and more likely to be male when diagnosed by the AHA/NHLBI definition but not by the NCEP-ATP III definition (P=0.008 for the AHA/NHLBI definition, P=0.31 for the NCEP-ATP III definition). The prevalence of the metabolic syndrome was higher in subjects ≥65 years of age compared with those <65 years of age (NCEP-ATP III definition, 15% versus 12%; AHA/NHLBI definition, 18% versus 15%; P<0.001 for each). The criterion for elevated blood pressure was fulfilled in more than half of the subjects and was the most common of the 5 metabolic syndrome components (Table 2). About 70% of the subjects fulfilled at least 1 component of the metabolic syndrome.
AF and the Metabolic Syndrome

During a mean follow-up of 4.5±2.7 years, AF developed in 265 subjects (105 women; mean age, 67.5±7.4 years; incidence, 4.1 and 1.3 per 1000 person-years in men and women, respectively). The age-adjusted incidence rates of AF were higher in subjects with than in those without the metabolic syndrome (Table 3). The mean number of components fulfilled for the metabolic syndrome was 1.6±1.1 and 1.2±1.1 in subjects with and without AF (P<0.001), respectively, according to the NCEP-ATP III definition and 1.8±1.1 and 1.4±1.1 in subjects with and without AF (P<0.001), respectively, according to the AHA/NHLBI definition.

In Cox proportional-hazard models, increasing age (hazard ratio, 1.10 per year; 95% CI, 1.08 to 1.12; P<0.001) and male gender (hazard ratio, 3.06; 95% CI, 2.39 to 3.91; P<0.001) were associated with new-onset AF. In multivariable models adjusted for age and sex, the presence of metabolic syndrome as defined by either the NCEP-ATP III or AHA/NHLBI definition was associated with the development of AF (Table 4). The risk of AF was higher, however, with the NCEP-ATP III definition compared with the AHA/NHLBI definition. The association between the metabolic syndrome and AF remained significant in subjects without treated hypertension or diabetes by the NCEP-ATP III definition but not by the AHA/NHLBI definition.

We also evaluated the contribution of the metabolic components to the development of AF. All of the metabolic syndrome components except elevated triglycerides were related to development of AF in Cox models adjusted for age

Table 2. Prevalence of Individual Metabolic Syndrome Components and Number of Fulfilled Components

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
<th>NCEP-ATP III</th>
<th>AHA/NHLBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome components</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>5899 (21)</td>
<td>8103 (28)</td>
<td></td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>14 628 (53)</td>
<td>10 049 (35)</td>
<td></td>
</tr>
<tr>
<td>Low HDL cholesterol</td>
<td>3785 (13)</td>
<td>6581 (23)</td>
<td></td>
</tr>
<tr>
<td>Elevated triglycerides</td>
<td>4119 (15)</td>
<td>3716 (13)</td>
<td></td>
</tr>
<tr>
<td>Impaired fasting glucose (NCEP-ATP III)</td>
<td>2691 (9)</td>
<td>7298 (26)</td>
<td></td>
</tr>
<tr>
<td>Impaired fasting glucose (AHA/NHLBI)</td>
<td>6420 (23)</td>
<td>9232 (33)</td>
<td></td>
</tr>
<tr>
<td>Metabolic syndrome component, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCEP-ATP III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>8103 (28)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10 049 (35)</td>
<td>1.95 (1.30–2.93)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6581 (23)</td>
<td>2.05 (1.34–3.15)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>3716 (13)</td>
<td>3.27 (2.10–5.10)</td>
<td></td>
</tr>
<tr>
<td>Trend across number of components</td>
<td></td>
<td>1.38 (1.21–1.56)</td>
<td></td>
</tr>
<tr>
<td>AHA/NHLBI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7298 (26)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9232 (33)</td>
<td>2.33 (1.47–3.72)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7375 (26)</td>
<td>2.54 (1.59–4.07)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>4544 (16)</td>
<td>3.39 (2.08–5.53)</td>
<td></td>
</tr>
<tr>
<td>Trend across number of components</td>
<td></td>
<td>1.35 (1.19–1.53)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Incidence of AF by the Metabolic Syndrome Definitions

<table>
<thead>
<tr>
<th></th>
<th>NCEP-ATP III</th>
<th>AHA/NHLBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Metabolic Syndrome</td>
<td>209/112 222 (1.9 (1.6–2.2)</td>
<td>204/108 535 (1.9 (1.7–2.2)</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>56/15 439 (3.3 (2.4–4.2)</td>
<td>61/19 126 (2.9 (2.0–3.8)</td>
</tr>
<tr>
<td>Events, n/person-y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted incidence per 1000 person-y (95% CI)</td>
<td></td>
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</table>
and sex. Among the components of the metabolic syndrome, elevated blood pressure and obesity contributed the most to the increased risk of new-onset AF. We then studied the association between the number of fulfilled components of the metabolic syndrome and the development of AF. Multivariable models adjusted for age and sex revealed that the hazard ratios for developing AF increased across a number of the fulfilled metabolic syndrome components and that the trend was significant for either definition.

**Discussion**

In this community-based study, we have shown that subjects meeting the criteria for the metabolic syndrome are at increased risk for the development of AF. In addition to some components of the metabolic syndrome already established as risk factors for AF, we found that low HDL cholesterol increases the risk of AF.

In 2001, the NCEP-ATP III proposed now widely accepted criteria for the diagnosis of the metabolic syndrome. In 2005, the AHA and NHLBI modified the criteria by reducing the threshold for impaired glucose intolerance to optimize sensitivity and specificity for predicting future diabetes, cardiovascular disease, and death. Because type II diabetes is known to be a strong risk factor for AF, we used both diagnostic criteria for the metabolic syndrome. Although the metabolic syndrome according to either definition was associated with the development of AF, the hazard ratio was higher with the NCEP-ATP III definition than with the AHA/NHLBI definition. The higher risk for AF with the NCEP-ATP III definition can be explained by the higher hazard ratio of impaired glucose tolerance with the NCEP-ATP III compared with the AHA/NHLBI definition.

The metabolic syndrome is a cluster of interrelated risk factors robustly associated with the development of atherosclerotic cardiovascular disease. Because all components except elevated triglycerides are associated with the development of AF in our study and prior work, it is difficult to distinguish the influence of the metabolic syndrome on new-onset AF from that of individual components. However, the metabolic syndrome was associated with increased risk of developing AF in subjects without hypertension or diabetes, suggesting that the biochemical derangement underlying the metabolic syndrome may increase the susceptibility for AF.

Although the pathogenesis of the metabolic syndrome is not well understood, it is likely that the condition represents a complex interplay between metabolic, genetic, and even environmental factors. Inflammation and oxidative stress have been proposed as common etiologic factors linking these processes and have likewise been implicated in the pathogenesis of AF. We found that low HDL cholesterol was strongly associated with the risk of AF, suggesting inflammation and oxidative stress as key substrates in the development of AF. Although not measured in this study, other studies have detected elevated levels of C-reaction protein and oxidants in patients with AF. Reductions in the incidence of AF not only by administration of antiinflammatory drugs (eg, glucocorticoids) but also by the use of drugs with antioxidant properties (such as atorvastatin) provide further evidence that inflammation and oxidant stress are etiologic factors for AF. Therefore, the increased risk of developing AF in the metabolic syndrome may be related in part to activation of signaling pathways important in inflammation and oxidative stress.

Another possible mechanism by which the metabolic syndrome may predispose to AF is mechanical stress in the atrium. Structural remodeling and electrophysiological remodeling are critical for AF to perpetuate. The structural substrate includes atrial stretch, dilatation, loss of muscle mass, fibrosis, and disruption of cell coupling at gap junctions. Hypertension and obesity, integral components of the metabolic syndrome, can cause atrial stretch and dilatation, resulting in a structural substrate predisposing to AF. Structural remodeling can alter the cellular electrophysiology and result in AF. The rapid atrial rates during episodes of AF can then lead to further atrial remodeling and more frequent and severe episodes of AF, a phenomenon known as “AF begets AF.”

Our study has several limitations. The study population included more women than men. Because waist circumferences were not available for our subjects, we used BMI to establish the diagnosis of obesity with adjustment to a Japanese population as a component of the metabolic syndrome. Subjects who received antihyperlipidemic drugs were excluded because of the lack of information about individual drug regimens. The medical history was self-reported. The manner and frequency of evaluation supporting AF diagnosis may lead to underestimation of AF, and the incidence of AF appears lower in this study compared with that in Western countries. However, AF is less common in Japan than in Western countries, and the incidence of AF in our study was similar to that in another study in Japan (3.8 and 1.9 per 1000 person-years in men and women ≥40 years of age, respectively). Further studies are needed to validate our results in Western populations.

**Conclusions**

Physicians should be aware that subjects with the metabolic syndrome are at increased risk for the development of AF, even in the absence of diabetes or hypertension. The syndrome has a strong association with stroke, myocardial infarction, and cardiovascular and all-cause mortality, and the increased incidence of stroke and higher mortality in subjects with the metabolic syndrome can be partially explained by its association with AF. Derangement of biochemical indexes associated with the metabolic syndrome may activate signaling pathways critical for the pathogenesis of AF, in addition to mechanical anomalies in atrium. Modulation of these signaling pathways not only may attenuate the risk of atherosclerotic cardiovascular disease but also may reduce the risk of AF. Further studies aimed at understanding the mechanisms underlying the metabolic syndrome-associated AF may yield clues to new therapeutic approaches.
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Disclosures
None.

References
The metabolic syndrome and atrial fibrillation (AF) are common disorders, and the prevalence of both disorders is currently increasing with a growing elderly population and changing lifestyle. Because many of the components of the metabolic syndrome also are risk factors for the development of AF, an association between the metabolic syndrome and AF has been proposed. Furthermore, inflammation and oxidative stress have been implicated in the pathogenesis of both the metabolic syndrome and AF. Therefore, we studied the association between the metabolic syndrome and new-onset AF in the general population. In the present study, subjects meeting the criteria for the metabolic syndrome were at increased risk of development of AF. Among the components of the metabolic syndrome, obesity, elevated blood pressure, impaired glucose tolerance, and reduced high-density lipoprotein cholesterol, but not elevated triglycerides, were associated with AF. The risk of developing AF increased across a number of the fulfilled metabolic syndrome components. Our data suggest that the metabolic syndrome increases not only the risk of atherosclerotic diseases but also the risk of AF. It is likely that an interaction between the metabolic syndrome and deranged biochemical indexes activates signaling pathways important in the pathogenesis of AF. Modulation of the pathways may be of therapeutic value for preventing AF.
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