Association Between Lipid Profile and Risk of Atrial Fibrillation
– Niigata Preventive Medicine Study –
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Background: Dyslipidemia, an important risk factor for cardiovascular disease, may be associated with atrial fibrillation (AF). Cross-sectional studies that have examined this association, however, have produced controversial results, and few longitudinal studies have been conducted.

Methods and Results: Using annual health examinations in Japan, the association between lipid profile and the risk of new-onset AF was investigated in the general population. A total of 28,449 individuals who did not have AF at baseline were included in the study. During a follow-up of 4.5±2.7 years, 265 individuals (0.9%) developed AF. In multivariate models, low high-density lipoprotein (HDL) cholesterol was associated with the development of AF in women (hazard ratio [HR], 2.86; 95% confidence interval [CI]: 1.49–5.50) but not in men (HR, 1.35; 95%CI: 0.77–2.38). Women had a 28% higher risk of AF with each 10% decrease in HDL cholesterol. Neither triglycerides nor lipid ratios were associated with AF. After excluding individuals with risk factors for AF, including those who were taking anti-hypertensive drugs, had diabetes, and structural heart disease, the association between low HDL cholesterol and AF remained significant in women.

Conclusions: Low HDL cholesterol was associated with an increased risk of new-onset AF in women, but not in men. (Circ J 2011; 75: 2767–2774)

Key Words: Atrial fibrillation; Cholesterol; Dyslipidemia; Epidemiology; Risk factors

Atrial fibrillation (AF) is the most common sustained arrhythmia observed in clinical practice, with a lifetime risk of 1 in 6 for people ≥40 years of age, even in the absence of antecedent congestive heart failure or myocardial infarction. The incidence of AF has grown with the rise in number of the elderly population and the increasing prevalence of chronic heart disease. AF is associated with increased risks of ischemic stroke, heart failure, all-cause mortality, and lower quality of life. Due to its high prevalence and serious complications, AF is a significant public health problem. AF is a progressive disease that results in more frequent and severe episodes and then perpetuation, a phenomenon known as “AF begets AF”. Anti-arrhythmic drugs that maintain sinus rhythm, however, do not decrease the incidence of severe complications compared to therapy for heart rate control. The indications for the recently developed catheter ablation techniques for AF need to be clarified. Therefore, the prevention of AF and the early intervention for the arrhythmogenic substrate of AF are important.

Multiple risk factors have been identified for the development of AF, and atherosclerotic risk factors, including age, male gender, hypertension, obesity, and type II diabetes, have also been implicated as prominent risk factors for AF. Dyslipidemia, which is an important risk factor for atherosclerotic disease, has also been suggested to increase the risk of AF. Cross-sectional studies that have examined the association between dyslipidemia and AF, however, have produced controversial results, and few longitudinal studies have been conducted. Our previous study has suggested that high-density lipoprotein (HDL) cholesterol levels are associated with risk of AF, and the purpose of the present study was to conduct further analyses to investigate the association between lipid profile and the risk of new-onset AF.
Table 1. Subject Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All subjects (n=28,449)</th>
<th>Men (n=9,805)</th>
<th>Women (n=18,644)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59±11</td>
<td>61±11</td>
<td>58±11</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>22.9±3</td>
<td>22.8±2.8</td>
<td>23±3.1</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>130±18</td>
<td>133±18</td>
<td>128±18</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78±11</td>
<td>80±11</td>
<td>76±11</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>211±35</td>
<td>201±34</td>
<td>216±35</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>128±33</td>
<td>118±32</td>
<td>133±32</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>62±16</td>
<td>59±16</td>
<td>64±15</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dl)</td>
<td>142±35</td>
<td>153±35</td>
<td>149±36</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>104±71</td>
<td>117±92</td>
<td>97±56</td>
</tr>
<tr>
<td>High TC (≥220 mg/dl), n (%)</td>
<td>10,650 (37)</td>
<td>2,571 (26)</td>
<td>8,079 (43)</td>
</tr>
<tr>
<td>High LDL-C (≥140 mg/dl), n (%)</td>
<td>9,522 (33)</td>
<td>2,244 (23)</td>
<td>7,278 (39)</td>
</tr>
<tr>
<td>Low HDL-C (&lt;40 mg/dl), n (%)</td>
<td>1,306 (5)</td>
<td>699 (7)</td>
<td>607 (3)</td>
</tr>
<tr>
<td>High triglycerides (&lt;150 mg/dl), n (%)</td>
<td>4,301 (15)</td>
<td>2,042 (21)</td>
<td>2,259 (12)</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>95±16</td>
<td>97±18</td>
<td>93±15</td>
</tr>
<tr>
<td>Anti-hypertensive drug, n (%)</td>
<td>5,779 (20)</td>
<td>2,143 (22)</td>
<td>3,636 (20)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>3,444 (12)</td>
<td>1,326 (14)</td>
<td>2,118 (11)</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>2,014 (7)</td>
<td>652 (7)</td>
<td>1,362 (7)</td>
</tr>
</tbody>
</table>

Data given as mean±SD or n (%).

Methods

Subjects
This community-based observational cohort study was based on a program of voluntary annual health examinations in the Niigata prefecture of Japan. In this prefecture, annual health examinations supported by the administration are available to residents aged ≥20 years. The population of the prefecture is approximately 2,400,000, and approximately 250,000 residents (approximately 10%) receive the examinations at Niigata Health Foundation every year. The annual examination consists of a detailed medical history obtained through interviews; physical examinations; blood examinations including blood cell count and biochemical markers; urine tests; chest X-rays; and a 12-lead electrocardiogram (ECG). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula (LDL cholesterol = total cholesterol – HDL cholesterol – 0.2 x triglycerides). The HDL cholesterol was subtracted from the total cholesterol to obtain the non-HDL cholesterol. The present study cohort included individuals who did not meet the exclusion criteria, who had had at least one fasting blood test between 1996 and 1998 (which constituted the baseline examination for the present study), and who subsequently received at least one annual examination from the baseline examination to 2005. AF was diagnosed from a 12-lead ECG recorded at an annual follow-up visit. The ECG diagnoses were made by physicians, and any abnormalities were confirmed by cardiologists. Exclusion criteria included a past and/or current history of AF (or atrial flutter), the presence of AF, and having a permanent pacemaker at the initial examination. To study the effects of lipid profile on the development of AF, we excluded individuals who received anti-dyslipidemia drugs that might have affected baseline serum lipid levels. Development of atrial flutter during the follow-up period was included as an endpoint equivalent to AF. The cut-offs for the lipid levels (total cholesterol, 220 mg/dl; LDL cholesterol, 140 mg/dl; HDL cholesterol, 40 mg/dl; and triglycerides, 150 mg/dl) were defined according to the guidelines of the Japanese Atherosclerotic Society.

Data Analysis
Differences in the baseline characteristics between the groups were determined using the unpaired t-test for continuous variables and the chi-square test for categorical variables. The hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated using Cox proportional hazards models to study the contributions of sex and age, as a continuous variable, to the development of AF. For the initial analysis, the Cox models were adjusted for sex and age as continuous variables to evaluate the contribution of the lipid profile to AF development. We found no significant interaction between the follow-up time and the lipid levels to predict the development of AF in the primary Cox model adjusted for age and sex, which indicates the appropriateness of the proportional hazards assumption. The Cox models were then adjusted for the following variables: age, sex, body mass index (BMI), systolic and diastolic blood pressure, and fasting blood sugar. All the statistical analyses were performed using SPSS version 12.0 (SPSS, Chicago, IL, USA). Two-sided P<0.05 was considered statistically significant. Data are given as mean±SD.

Results

Baseline Characteristics
A total of 28,449 individuals (59±11 years of age; 18,644 women) were included in the study (Table 1). Total cholesterol, LDL cholesterol, and HDL cholesterol levels were higher in women than in men, whereas triglyceride levels were higher in men than in women. Men received anti-hypertensive treatment more frequently than women. Diabetes was more common in men than in women.

Incidence of AF
During a follow-up of 4.5±2.7 years, AF developed in 265 individuals (0.9%; 160 men, 105 women), and the age-adjusted incidence of AF was 2.07 per 1,000 person-years (95% CI: 1.82–2.32). The age-adjusted incidence of developing AF over time was higher in men (3.28 per 1,000 person-years; 95% CI: 2.75–3.81 per 1,000 person-years) than in women (1.39 per...
The incidence of AF was increased across age (Figure 1). Table 2 lists the incidence of AF according to lipid level quartiles. The incidence of AF was decreased with increasing quartiles of total cholesterol, LDL cholesterol, and HDL cholesterol. Low levels of total cholesterol, LDL cholesterol, and HDL cholesterol were associated with increased risk of developing AF (Figure 2). Triglyceride levels were not associated with the incidence of AF.

Table 2. Incidence of AF vs. Dyslipidemia

<table>
<thead>
<tr>
<th>Quartiles</th>
<th>All participants</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events (n/person-years)</td>
<td>Incidence per 1,000 person-years (95% CI)</td>
<td>Events (n/person-years)</td>
</tr>
<tr>
<td>TC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4, highest</td>
<td>45/31,698</td>
<td>1.42 (1.01–1.83)</td>
<td>29/10,437</td>
</tr>
<tr>
<td>3</td>
<td>53/32,501</td>
<td>1.63 (1.19–2.07)</td>
<td>41/10,805</td>
</tr>
<tr>
<td>2</td>
<td>81/31,402</td>
<td>2.58 (2.02–3.14)</td>
<td>44/10,627</td>
</tr>
<tr>
<td>1, lowest</td>
<td>86/32,060</td>
<td>2.68 (2.12–3.25)</td>
<td>46/10,745</td>
</tr>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4, highest</td>
<td>53/31,782</td>
<td>1.67 (1.22–2.12)</td>
<td>31/10,504</td>
</tr>
<tr>
<td>3</td>
<td>56/32,273</td>
<td>1.74 (1.28–2.19)</td>
<td>42/10,937</td>
</tr>
<tr>
<td>2</td>
<td>70/32,463</td>
<td>2.16 (1.65–2.66)</td>
<td>40/10,844</td>
</tr>
<tr>
<td>1, lowest</td>
<td>86/31,089</td>
<td>2.77 (2.18–3.35)</td>
<td>47/10,282</td>
</tr>
<tr>
<td>HDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4, highest</td>
<td>46/30,534</td>
<td>1.51 (1.07–1.94)</td>
<td>41/10,849</td>
</tr>
<tr>
<td>3</td>
<td>59/31,077</td>
<td>1.90 (1.41–2.38)</td>
<td>45/10,659</td>
</tr>
<tr>
<td>2</td>
<td>76/33,926</td>
<td>2.24 (1.74–2.74)</td>
<td>40/10,665</td>
</tr>
<tr>
<td>1, lowest</td>
<td>84/32,124</td>
<td>2.61 (2.06–3.17)</td>
<td>34/10,441</td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4, highest</td>
<td>68/30,029</td>
<td>2.26 (1.73–2.80)</td>
<td>28/10,023</td>
</tr>
<tr>
<td>3</td>
<td>63/31,012</td>
<td>2.03 (1.53–2.53)</td>
<td>45/10,511</td>
</tr>
<tr>
<td>2</td>
<td>67/31,934</td>
<td>2.10 (1.60–2.60)</td>
<td>41/10,836</td>
</tr>
<tr>
<td>1, lowest</td>
<td>67/34,686</td>
<td>1.93 (1.47–2.39)</td>
<td>46/11,244</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; CI, confidence interval. Other abbreviations see in Table 1.

1,000 person-years; 95% CI: 1.13–1.66 per 1,000 person-years. The incidence of AF was increased across age (Figure 1).
Figure 2. Cumulative risk of developing atrial fibrillation (AF) according to (A) baseline total cholesterol (TC), (B) low-density lipoprotein (LDL) cholesterol, (C) high-density lipoprotein (HDL) cholesterol, and (D) triglycerides (TG).

Table 3. Dyslipidemia and Risk of Development of AF

<table>
<thead>
<tr>
<th></th>
<th>All subjects (n=28,449)</th>
<th>Men (n=9,805)</th>
<th>Women (n=18,644)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>P value</td>
<td>HR (95%CI)</td>
</tr>
<tr>
<td>Male gender</td>
<td>2.28 (1.77–2.92)</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td>Age (10-year increase)</td>
<td>2.35 (2.03–2.72)</td>
<td>&lt;0.001</td>
<td>2.02 (1.67–2.44)</td>
</tr>
<tr>
<td>TC (per 10-mg/dl increase)</td>
<td>0.94 (0.9–0.97)</td>
<td>&lt;0.001</td>
<td>0.95 (0.91–1.00)</td>
</tr>
<tr>
<td>LDL-C (per 10-mg/dl increase)</td>
<td>0.94 (0.91–0.98)</td>
<td>0.005</td>
<td>0.95 (0.90–1.00)</td>
</tr>
<tr>
<td>HDL-C (per 10-mg/dl decrease)</td>
<td>1.09 (1–1.18)</td>
<td>0.04</td>
<td>1.00 (1.00–1.18)</td>
</tr>
<tr>
<td>Non-HDL-C (per 10-mg/dl increase)</td>
<td>0.96 (0.92–0.99)</td>
<td>0.02</td>
<td>0.95 (0.91–1.00)</td>
</tr>
<tr>
<td>Triglycerides (per 10-mg/dl increase)</td>
<td>1.01 (0.99–1.02)</td>
<td>0.55</td>
<td>1.00 (0.98–1.02)</td>
</tr>
<tr>
<td>TC/LDL (per 1-unit increase)</td>
<td>1.06 (0.95–1.19)</td>
<td>0.28</td>
<td>1.06 (0.95–1.18)</td>
</tr>
<tr>
<td>TC/HDL (per 1-unit increase)</td>
<td>1.02 (0.9–1.14)</td>
<td>0.80</td>
<td>0.95 (0.81–1.11)</td>
</tr>
<tr>
<td>LDL/HDL (per 1-unit increase)</td>
<td>0.99 (0.85–1.15)</td>
<td>0.90</td>
<td>0.92 (0.75–1.11)</td>
</tr>
<tr>
<td>Triglycerides/HDL (per 1-unit increase)</td>
<td>1.03 (0.97–1.09)</td>
<td>0.30</td>
<td>1.00 (0.93–1.09)</td>
</tr>
<tr>
<td>High TC (≥220 mg/dL)</td>
<td>0.66 (0.5–0.88)</td>
<td>0.005</td>
<td>0.69 (0.46–1.03)</td>
</tr>
<tr>
<td>High LDL-C (≥140 mg/dL)</td>
<td>0.75 (0.56–1)</td>
<td>0.046</td>
<td>0.74 (0.49–1.11)</td>
</tr>
<tr>
<td>Low HDL-C (&lt;40 mg/dL)</td>
<td>1.78 (1.16–2.74)</td>
<td>0.008</td>
<td>1.35 (0.77–2.38)</td>
</tr>
<tr>
<td>High non-HDL-C (≥160 mg/dL)</td>
<td>0.86 (0.66–1.13)</td>
<td>0.27</td>
<td>0.85 (0.59–1.24)</td>
</tr>
<tr>
<td>High triglycerides (≥150 mg/dL)</td>
<td>1.13 (0.81–1.57)</td>
<td>0.48</td>
<td>0.90 (0.57–1.40)</td>
</tr>
</tbody>
</table>

Models were adjusted for sex and age.
HR, hazard ratio. Other abbreviations see in Tables 1, 2.
AF and Dyslipidemia

In the univariate Cox proportional hazard model, increasing age (HR, 2.35; 95%CI: 2.03–2.72; per 10-year increase; P<0.001) and male gender (HR, 2.28; 95%CI: 1.77–2.92; P<0.001) were associated with increased risk of AF. In multivariate models adjusted for age and sex, total cholesterol as a continuous variable was inversely associated with AF in women, but not in men (Table 3). LDL cholesterol levels were inversely associated with risk of AF in both genders. Low HDL cholesterol was associated with AF in women, but not in men.

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Table 4. Dyslipidemia and Risk of Development of AF (Multivariate Analysis)

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (per 10-mg/dl increase)</td>
<td>0.92 (0.88–0.96)</td>
<td>&lt;0.001</td>
<td>0.93 (0.88–0.98)</td>
</tr>
<tr>
<td>HDL-C (per 10-mg/dl decrease)</td>
<td>1.08 (1.18–0.98)</td>
<td>0.11</td>
<td>0.99 (1.10–0.89)</td>
</tr>
<tr>
<td>Triglycerides (per 10-mg/dl increase)</td>
<td>0.98 (0.96–1.00)</td>
<td>0.08</td>
<td>0.98 (0.96–1.01)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>High LDL-C (≥140 mg/dl)</td>
<td>0.69 (0.52–0.92)</td>
<td>0.01</td>
<td>0.68 (0.45–1.03)</td>
</tr>
<tr>
<td>Low HDL-C (&lt;40 mg/dl)</td>
<td>1.58 (1.00–2.48)</td>
<td>0.048</td>
<td>1.28 (0.70–2.32)</td>
</tr>
<tr>
<td>High triglycerides (≥150 mg/dl)</td>
<td>0.84 (0.59–1.19)</td>
<td>0.33</td>
<td>0.70 (0.43–1.12)</td>
</tr>
</tbody>
</table>

Models were adjusted for sex, age, body mass index, systolic and diastolic blood pressure, and fasting blood sugar.

Abbreviations see in Tables 1–3.

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Figure 3. Cumulative risk of developing atrial fibrillation (AF) according to (A) baseline total cholesterol (TC), (B) low-density lipoprotein (LDL) cholesterol, (C) high-density lipoprotein (HDL) cholesterol, and (D) triglycerides (TG) in individuals who were not taking anti-hypertensive drugs, and who did not have diabetes or heart disease.
Non-HDL cholesterol levels were inversely associated with the risk of AF in the analyses that included all the individuals, but the association became non-significant when it was assessed by gender. Triglycerides or various lipid ratios were not associated with AF.

The multivariate models adjusted for sex, age, BMI, systolic and diastolic blood pressure, and fasting blood sugar provided similar results to the initial analyses (Table 4). LDL cholesterol levels were inversely associated with the development of AF in both genders. We found an 8% reduction in AF risk with each 10% increase in LDL cholesterol levels. The HDL cholesterol levels were inversely associated with AF in women, but not in men. In women, there was a 28% increase in AF risk with each 10% decrease in HDL cholesterol levels, and the women with an HDL cholesterol level <40 mg/dl had an approximately 2.4-fold higher risk of AF compared to those with an HDL cholesterol level ≥40 mg/dl.

Excluding the individuals who received anti-dyslipidemia drugs may have affected the present results. Therefore, we studied the association between the lipid levels and the risk of AF in the cohort prior to the exclusion and succeeded in producing similar results to prior analyses. The risk of AF increased as HDL cholesterol decreased in women (HR, 1.08 per 10-mg/dl decline; 95% CI: 1.05–1.10 per 10-mg/dl decline; P=0.01). The risk of HDL increased as LDL cholesterol increased in women (HR, 1.08 per 10-mg/dl increase; 95% CI: 1.02–1.14 per 10-mg/dl increase; P=0.01) and men (HR, 1.06 per 10-mg/dl increase; 95% CI: 1.02–1.11 per 10-mg/dl increase; P=0.007). The risk of AF was not associated with changes in triglycerides. Because the present cohort included more women than men, we randomly selected 9,805 women (the same number of men) and repeated the analysis. We found that the association between HDL cholesterol and risk of AF remained significant in this cohort (HR, 1.39; 95% CI: 1.09–1.79; P=0.009).

In 1,712 individuals ≥75 years of age (875 women), LDL cholesterol levels were inversely associated with risk of AF in women (HR, 0.79 per 10-mg/dl increase; 95% CI: 0.65–0.95 per 10-mg/dl increase; P=0.01), but not in men (HR, 0.94 per 10-mg/dl increase; 95% CI: 0.83–1.07 per 10-mg/dl increase; P=0.35). The levels of other lipids or lipid ratios were not associated with the risk of AF in that cohort.

Because changes in lipoprotein levels occur after menopause, we divided the women into 2 groups according to age. In the 14,297 women ≥50 years of age, HDL cholesterol levels (HR, 1.08 per 10-mg/dl decrease; 95% CI: 1.07–1.09 per 10-mg/dl decrease; P=0.006) and LDL cholesterol levels (HR, 1.10 per 10-mg/dl decrease; 95% CI: 1.03–1.18 per 10-mg/dl decrease; P=0.005), but not triglyceride levels (HR, 1.03 per 10-mg/dl increase; 95% CI: 0.99–1.08 per 10-mg/dl increase; P=0.09) were associated with the risk of AF. The lipid levels, however, were not associated with AF in the 4,347 women <50 years of age.

### Analyses in Individuals Without Treated Hypertension, Diabetes, or Heart Disease

To address the possibility that these results were driven by other risk factors for AF rather than dyslipidemia, the analyses were repeated in 21,321 individuals who were not taking anti-hypertensive drugs, nor had diabetes, and heart disease at baseline (mean age, 58±11 years; female, 67%). During a follow-up of 4.6±2.7 years, AF developed in 136 individuals (0.6%, 83 men and 53 women), and the age-adjusted incidence of AF was 1.57 (95% CI: 1.31–1.84) per 1000 person-years. The incidence of AF decreased in individuals with high total cholesterol (Figure 3). The incidence of AF increased in individuals with low HDL cholesterol. LDL cholesterol and triglyceride levels were not associated with the incidence of AF. In the multivariate models adjusted for sex, age, BMI, systolic and diastolic blood pressure, and fasting blood sugar, the association between HDL cholesterol and the risk of AF remained significant in women, but not in men (Table 5).

### Discussion

In this large Japanese cohort, we found that lower HDL cholesterol levels were strongly associated with an increased risk of developing AF. The association was strong in women, but it was weak in men. Total cholesterol and LDL cholesterol levels were inversely associated with AF.

Dyslipidemia is associated with atherosclerosis and is a well-established independent risk factor for cardiovascular diseases, such as coronary artery disease and stroke, as well as heart failure. Several factors, including age, gender, obesity, metabolic syndrome, and hypertension, have been associated with an increased risk of developing AF, suggesting a strong association between AF and atherosclerosis. The association between dyslipidemia and AF, however, has been controversial. In 1 cross-sectional study, total cholesterol, triglycerides, and HDL cholesterol levels were lower in patients with paroxysmal AF than in those without AF. In another study, total cholesterol levels were lower in patients with AF than in those without AF, but HDL cholesterol levels were not different between the groups. In another cross-sectional study, there was no relationship between the lipid levels and AF. To address this issue, we conducted this longitudinal study and found that low total cholesterol, low LDL cholesterol, and low HDL cholesterol levels were associated with the development...
of AF in the general population. The inconsistent results for the association between lipid levels and AF in previous studies may have been driven by the cross-sectional study design;5-8 the present results are consistent with those of a previous longitudinal study of patients with hypertension, which were that there was a higher incidence of AF in individuals with low HDL cholesterol than in those with high HDL cholesterol.9 Triglyceride levels or several lipid ratios that have been proposed as biomarkers for atherosclerotic diseases were not associated with AF. Moreover, the effects of lipid levels on AF were more significant in women than in men.

**Potential Mechanisms**

There are some potential mechanisms by which HDL cholesterol levels are associated with AF. Reduced levels of HDL cholesterol are associated with increased left ventricular mass, cardiac dysfunction, and the development of heart failure, all of which are risk factors for AF.16-19 Therefore, abnormal HDL cholesterol levels may predispose an individual to AF through a structural change in the atrium. The association between HDL cholesterol levels and increased risk of AF, however, remained significant in individuals without heart disease, suggesting mechanisms other than structural cardiac abnormalities. Inflammation and oxidative stress may also play critical roles in the initiation and perpetuation of AF.20,21 and low HDL cholesterol levels may increase the risk of AF via these derangements. Recent studies have suggested that anti-inflammatory drugs (eg, glucocorticoids) and statin therapy reduce the risk of developing AF.22-25 Further studies are needed, however, to clarify whether therapies for low HDL cholesterol may decrease the risk of AF. Evidence that intake of fish-derived or fish-oil supplement-derived ω-3 polyunsaturated fatty acids, which have antioxidant effects, is associated with a lower incidence of AF, further supports the hypothesis.

Although it is well known that hypercholesterolemia is associated with oxidative stress and inflammation, both of which increase the susceptibility to AF,20,21,26 the dyslipidemia paradox has been observed in patients with AF for more than a decade.6,7 Previous studies have shown that total cholesterol and triglyceride levels are lower in patients with AF than in those without AF.6,7 and we found that low HDL cholesterol levels were associated with an increased risk of development of AF. A previous study found a U-shaped relationship between LDL cholesterol and all-cause mortality; it suggested that the presence of appropriate LDL cholesterol levels minimizes the risk of fatal events.27 We found a linear relationship, however, between increasing LDL cholesterol levels and decreasing risk of AF; this result was similar to the finding in another study that found an inverse relationship between LDL cholesterol levels and the risk of intraparenchymal hemorrhage.28 But it is difficult to explain the mechanism that underlies the association between low LDL cholesterol and the increased risk of AF. Clinical and subclinical hyperthyroidism may be a cause of both low cholesterol levels and the development of AF. Unfortunately, the annual examination at Niigata Health Foundation did not include thyroid function tests and thus we could not investigate that association. In experimental studies, a hypercholesterolemic diet, which leads to higher LDL cholesterol levels, may reduce angionecrosis and provide antioxidant protection, which could prevent the development of AF.29,30

**Gender Differences**

Previous studies have found gender-related differences in the clinical characteristics of AF, although the reason for these differences is not clear.31-35 In the present and other studies, the risk of developing AF is lower in women than in men,31,32 while the risk of recurrent or frequent episodes of paroxysmal AF is higher in women than in men.36 Women are also at a higher risk of mortality attributed to AF compared to men.34 The impact of atherosclerotic risk factors on the development of AF may be different between men and women. Women have been found to be more likely than men to have diabetes,33 and we found that the impact of lipid levels on AF was significant in women, but was weak in men. The electrophysiological properties of the atria are different between men and women, and could possibly account for these gender-related differences.37 The lipid levels were associated with a risk of AF in women ≥50 years of age but not in those <50 years of age, suggesting a role for sex hormone in the risk of AF. Changes in lipid levels after menopause may increase the effects of lipid levels on AF susceptibility in women.

**Study Limitations**

The present subjects included more women than men, although the opportunity for the annual health examination was provided equally to men and women. The manner and frequency of the evaluation for the diagnosis of AF may lead to an underestimation of the incidence of AF, but the incidence of AF in the present study was similar to that reported by another study in Japan.38 Because AF was diagnosed from an ECG recorded at an annual follow-up, it was difficult to distinguish between paroxysmal AF and persistent AF. Atrial flutter was included as an endpoint, similar to the previous studies.33,39 Medical histories were collected during an interview, and we had limited information on baseline structural heart disease. Treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may have beneficial effects on AF,40,41 but individual drug regimens were not available in our database. The characteristics of the Japanese population may have affected the present results. AF is less common in Japan than in Western countries,38,41-43 and HDL cholesterol levels are higher in Japan than in other countries.44,45 Further studies in other populations are necessary to generalize the present results.

**Conclusions**

AF is a progressive disease; thus, early intervention for the arrhythmogenic substrate of AF is important.4 There are multiple risk factors for AF, including heart disease and atherosclerotic risk factors,4 and we found that decreased HDL cholesterol levels were associated with an increased risk of developing AF and that the association was strong in women but was weak in men. Furthermore, the present finding of an inverse association between total cholesterol and LDL cholesterol levels and risk of AF supports the dyslipidemia paradox, but the underlying mechanism is unclear.

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**Disclosures**

None.

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