Heavy Alcohol Consumption and Risk of Atrial Fibrillation
– The Circulatory Risk in Communities Study (CIRCS) –

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Background: Evidence regarding the relationship between different levels of alcohol consumption and the risk of atrial fibrillation (AF) is currently limited in Asian populations.

Methods and Results: Between 1991 and 1995, a total of 8,602 Japanese men and women aged 30–80 years took part in the first examination of the Circulatory Risk in Communities Study (CIRCS), a population-based cohort study in Japanese communities. An interviewer obtained detailed information on weekly alcohol intake. During the follow-up period, the incidence of AF was ascertained from annual ECG records, the subject’s medical history of AF, and cardiovascular disease surveillance. The hazard ratios (HRs) of incident AF and the 95% confidence intervals (CIs) relative to the never-drinking group were calculated with adjustment for potential confounding factors by using the Cox proportional hazard model. During a median follow-up period of 6.4 years, 296 incidents of AF occurred. A higher incidence of AF was observed among participants with an ethanol intake >69 g/day, compared with never-drinkers. Compared with the never-drinkers, the multivariable-adjusted HRs (CIs) of past, light (<23 g/day), light–moderate (23–46 g/day), moderate (46–69 g/day), and heavy (>69 g/day) drinkers were 1.30 (0.68–2.49), 0.89 (0.60–1.32), 1.19 (0.73–1.95), 1.36 (0.79–2.35), and 2.90 (1.61–5.23), respectively.

Conclusions: Heavy alcohol consumption is associated with a higher risk of AF. (Circ J 2014; 78: 955–961)

Key Words: Alcohol; Atrial fibrillation; Epidemiology; Risk factors

Atrial fibrillation (AF) is one of the most commonly diagnosed cardiac arrhythmias in clinical practice, affecting 2.3 million people in the United States. Individuals with AF are at substantially increased risk of stroke and have double the mortality rate from cardiovascular disease and overall mortality, compared with those with normal sinus rhythms. Epidemiological studies have identified several risk factors for AF, including hypertension, diabetes mellitus, obesity, heavy alcohol drinking, and cardiac dysfunction. Although several previous studies have found significant associations between heavy alcohol consumption and increased risk of AF in Western countries, few have shown an association between alcohol consumption and AF among Japanese. Furthermore, there is a paucity of data demonstrating the dose-response relationship between alcohol consumption and AF incidence. Alcohol consumption may have significant effects on the incidence of AF among Japanese in comparison with Western populations, as Japanese people do not have sufficient levels of alcohol dehydrogenase.

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To examine the relationship between alcohol consumption and risk of AF, we used data from follow-up of men and women in the Circulatory Risk in Communities Study (CIRCS). Although previous studies conducted in Western countries have detected most AF cases from information derived from discharge records, the CIRCS is able to detect symptomatic AF and asymptomatic AF not only from AF treatment information but also from annual ECG records, as this survey has...
Methods

Study Design and Subjects

The CIRCS is a population-based study of cardiovascular risk factors, disease incidence, and their respective trends in Japanese communities. Details of the study design and procedures have been previously reported.26–28 In brief, participants in this study were Japanese men and women living in the north-eastern rural community of Ikawa (total census population of 6,206 in 1995), the southwestern rural community of Noichi (total census population of 15,828 in 1995), the central rural community of Kyowa (total census population of 17,322 in 1995), and the Minami Takayasu district of Yao, which is a southwestern urban suburb (total census population of 23,654 in 1995). All analyses were limited to men and women aged 30–80 years. Annual cardiovascular risk surveys have been conducted in the district of Yao City, Ikawa, and Noichi since 1963, and in Kyowa since 1981, by a research team from the Osaka Medical Center for Health Science and Promotion, University of Tsukuba, Ehime University, and Osaka University.

For the present study, we analyzed data from 8,602 Japanese men and women aged 30–80 years who participated in the CIRCS between 1991 and 1995. The main aim was to examine the association between cardiovascular risk factors, particularly

Table 1. Age and Sex-Adjusted Means or Prevalence of Baseline Characteristics of Participants According to Habitual Alcohol Consumption Category (Cross-Sectional Survey) in the Circulatory Risk in Communities Study (CIRCS)

| Alcohol consumption (ethanol g/day) | Never | Past | Light (<23) | Light-moderate (23–46) | Moderate (46–69) | Heavy (>69) | P for difference |
|-------------------------------------|-------|------|-------------|------------------------|------------------|-------------|-----------------|
| Men                                 |       |      |             |                        |                  |             |                 |
| n                                   | 640   | 202  | 758         | 749                    | 582              | 227         |                 |
| Ethanol intake, g/day                |       |      |             |                        |                  |             |                 |
| Men                                 |       |      |             |                        |                  |             |                 |
| Past                                | 0     | 32.4 | 11.9        | 29.4                   | 49.0             | 75.9        |                 |
| Light (<23)                         | 59.1  | 64.0 | 55.9        | 57.1                   | 55.9             | 52.7        |                 |
| Light-moderate (23–46)              | 0.9   | 2.3  | 0.8         | 0.8                    | 1.6              | 1.9         | 0.28            |
| Moderate (46–69)                    | 47.1  | 44.7 | 42.2        | 52.3                   | 63.9             | 70.0        | <0.0001         |
| Heavy (>69)                         | 23.4  | 23.4 | 23.3        | 23.0                   | 23.1             | 22.9        | 0.77            |

Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or use of antihypertensive medication. Hyperglycemia was defined as a fasting glucose level ≥110 mg/dl, a non-fasting glucose level ≥140 mg/dl or use of medication for diabetes.

BMI, body mass index; BP, blood pressure; MI, myocardial infarction.
alcohol intake and AF incidence, using data from the prospective observational cohort study.

Informed consent was obtained from community representatives to conduct an epidemiological study based on guidelines established by the Council for International Organizations of Medical Science. This study was approved by the Ethics Committee of the Osaka Medical Center for Health Science and Promotion.

Surveillance for AF
Trained interviewers obtained information about past and present history of physician-diagnosed AF from the participants in the annual risk factor surveys. A 12-lead ECG tracing was obtained in the supine position in the risk factor surveys and coded with the Minnesota Code (2nd version) by trained physician-epidemiologists. Information on embolic stroke because of AF was obtained from systematic hospital surveillance of stroke. Of the 8,602 participants, 8,516 who were free of clinical AF were followed up to determine incident AF that occurred by the end of 2000. The majority of participants (7,206, 84.6%) received a follow-up examination at least once during the follow-up period. During this follow-up period, 296 cases of AF were identified; 254 cases (85.8%) diagnosed by ECG during the annual risk factor surveys, 36 cases (12.2%) of physician-diagnosed AF from the risk factor surveys, and 6 cases (2.0%) by hospital surveillance of stroke.

### Table 2. Age and Sex-Adjusted Means or Prevalence of Baseline Characteristics of Participants With Incident Atrial Fibrillation (AF) and Those Without AF (Longitudinal Survey) in the Circulatory Risk in Communities Study (CIRCS)

|             | Incident AF | No AF     | P value |
|-------------|-------------|-----------|---------|
| **Men**     |             |           |         |
| n           | 110         | 2,465     | –       |
| Age, years  | 59.3        | 57.1      | –       |
| Ethanol intake, g/day | 32.5        | 25.7      | 0.0025  |
| Heavy drinker (ethanol intake ≥69 g/day), % | 15.0        | 6.4       | 0.0005  |
| Current smoking, % | 54.2        | 50.1      | 0.40    |
| BMI, kg/m²  | 23.4        | 23.2      | 0.45    |
| Obesity (BMI ≥30), % | 3.8         | 2.1       | 0.26    |
| Systolic BP, mmHg | 131.3       | 130.6     | 0.72    |
| Diastolic BP, mmHg | 79.7        | 79.7      | 0.99    |
| Antihypertensive medication, % | 19.5        | 18.6      | 0.82    |
| Hypertension, % | 36.0        | 36.3      | 0.95    |
| Blood glucose, mg/dl | 127.9       | 120.8     | 0.07    |
| Hyperglycemia, % | 32.3        | 21.9      | 0.01    |
| Total cholesterol, mg/dl | 192.7       | 192.9     | 0.94    |
| Total cholesterol ≥220 mg/dl, % | 25.7        | 21.1      | 0.24    |
| Major ST-T abnormality, % | 3.2         | 3.3       | 0.95    |
| Previous MI, % | 2.6         | 0.9       | 0.07    |
| Heart failure, % | 0           | 0.2       | –       |
| **Women**   |             |           |         |
| n           | 186         | 4,445     |         |
| Age, years  | 56.7        | 55.2      | –       |
| Ethanol intake, g/day | 1.61        | 1.49      | 0.79    |
| Heavy drinker (ethanol intake ≥69 g/day), % | 0.54        | 0.07      | 0.03    |
| Current smoking, % | 3.4         | 5.4       | 0.24    |
| BMI, kg/m²  | 23.7        | 23.1      | 0.005   |
| Obesity (BMI ≥30), % | 8.0         | 3.4       | 0.0009  |
| Systolic BP, mmHg | 128.0       | 129.8     | 0.17    |
| Diastolic BP, mmHg | 77.7        | 79.0      | 0.10    |
| Antihypertensive medication, % | 15.3        | 16.3      | 0.74    |
| Hypertension, % | 31.3        | 34.1      | 0.43    |
| Blood glucose, mg/dl | 118.0       | 112.3     | 0.01    |
| Hyperglycemia, % | 15.7        | 12.5      | 0.20    |
| Total cholesterol, mg/dl | 203.2       | 204.7     | 0.58    |
| Total cholesterol ≥220 mg/dl, % | 28.2        | 32.4      | 0.22    |
| Major ST-T abnormality, % | 2.9         | 4.7       | 0.25    |
| Previous MI, % | 0           | 0.3       | –       |
| Heart failure, % | 0.5         | 0.3       | 0.63    |

Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or use of antihypertensive medication. Hyperglycemia was defined as a fasting glucose level ≥110 mg/dl, a non-fasting glucose level ≥140 mg/dl or use of medication for diabetes.

Abbreviations as in Table 1.
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**Table 3. Hazard Ratios (HR) and 95% Confidence Intervals (CI) of Atrial Fibrillation (AF) According to Habitual Alcohol Consumption (Longitudinal Survey) in the Circulatory Risk in Communities Study (CIRCS)**

| Alcohol consumption (ethanol g/day) | Men               | Women             | Total             |
|------------------------------------|-------------------|-------------------|-------------------|
| n                                 | 524               | 3,949             | 4,473             |
| AF cases                           | 18                | 164               | 182               |
| Person-years                       | 3,289             | 25,633            | 28,922            |
| Incidence (1/1,000)                | 5.47              | 6.40              | 6.29              |
| Age-adjusted HR                    | 1.00              | 1.00              | 1.00              |
| Multivariate-adjusted*HR           | 1.00              | 1.00              | 1.00              |
| Age and sex-adjusted HR            | 1.00              | 1.00              | 1.00              |
| Multivariate-adjusted**HR          | 1.00              | 1.00              | 1.00              |

*HRs were adjusted for age, cigarette smoking status, BMI, hypertension, hyperglycemia, hyperlipidemia, major ST-T abnormality, previous MI and heart failure.

**Baseline Examination**

Systolic and 5th-phase diastolic blood pressure (BP) was measured by trained technicians using a standard mercury sphygmomanometer on the right arm of the seated participant after a rest period of at least 5 min. Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or use of antihypertensive medication. Serum total cholesterol was measured via an enzymatic method at the laboratory of the Osaka Medical Center for Health Science and Promotion, an international member of the US National Cholesterol Reference Method Laboratory Network.** Hyperlipidemia was defined as a total cholesterol level ≥220 mg/dl (5.69 mmol/L) or use of lipid-lowering medication. Body mass index (BMI) was calculated as the weight (kg)/height (m)2. Hyperglycemia was defined as a fasting glucose level ≥110 mg/dl, a non-fasting glucose level ≥140 mg/dl or use of medication for diabetes. Major ST-T abnormality was defined as a past history of either.

**Statistical Analysis**

Prevalence of heavy alcohol drinking, current smoking habit, obesity, hyperglycemia, and hyperlipidemia was different between men and women, so we analyzed the data stratified by sex.

The age-adjusted and sex-adjusted incidences of AF were calculated from the number of new cases appearing between 1991 and 2000 in the 4 Japanese communities studied. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazard regression models. Risk factors were selected based on previous prospective findings for AF, which included excess ethanol intake (ethanol intake ≥69 g/day), smoking status (current or never/former), obesity (BMI ≥30 kg/m2, yes or no), hypertension (yes or no), hyperglycemia (yes or no), hyperlipidemia (yes or no), major ST-T abnormality in ECG, previous myocardial infarction (yes or no), and heart failure (yes or no). SAS version 9.2 (SAS Institute, Cary, NC, USA) was used for analyses. All probability values for statistical tests were 2-tailed and P<0.05 was regarded as statistically significant.

**Results**

Table 1 shows the baseline characteristics of the participants with respect to the categories of alcohol consumption. In men, the prevalence of current smoking, hyperglycemia, major ST-T abnormality, and the mean value of total cholesterol differed among alcohol consumption categories. In contrast, the prevalence of current smoking and mean BMI differed among the
alcohol consumption categories for women. There were no significant differences in AF, hypertension, hyperlipidemia, previous myocardial infarction, or heart failure among the alcohol consumption categories for either sex.

Median follow-up period was 6.4 years and the follow-up rate was 84.6%. The mean number of examinations for the participants was 5.2 (2 examinations, 21.3%; 3 examinations, 20.7%; 4 examinations, 11.3%; and >5 examinations, 46.7%). During the follow-up period, 296 cases of incident AF occurred. Table 2 shows the means and prevalence of risk characteristics for previous examinations of the participants with and without AF. For men, the mean values of ethanol intake and the prevalence of heavy alcohol drinking and hyperglycemia were higher among participants with AF than for those without AF. For women, however, the mean BMI and blood glucose values, as well as the prevalence of heavy drinking and obesity, were higher among the participants with AF than for those without AF. There were no significant differences in current smoking status, BP levels, total cholesterol levels, or major ST-T abnormality for either sex.

A higher incidence rate of AF was observed among participants with an ethanol intake >69 g/day compared with never-drinkers, especially among men (Table 3). Relative to the never-drinking group, the multivariable-adjusted HRs (95% CIs) of past, light (<23 g/day), light—moderate (23–46 g/day), moderate (46–69 g/day), and heavy (>69 g/day) drinking groups were 1.30 (95% CI, 0.68–2.49), 0.89 (0.60–1.32), 1.19 (0.73–1.95), 1.36 (0.79–2.35), and 2.90 (1.61–5.23), respectively. Age, excess ethanol intake (≥69 g/day), obesity, and hyperglycemia were associated with risk of AF (Table 4), whereas BP, hyperlipidemia, current smoking, major ST-T abnormality, previous myocardial infarction and heart failure were not. The multivariable-adjusted HRs (95% CIs) were 1.02 (1.01–1.03) for age, 2.61 (1.55–4.39) for excess ethanol intake (≥69 g/day), 2.24 (1.41–3.58) for obesity (BMI ≥30 kg/m²), and 1.35 (1.02–1.78) for hyperglycemia. When we analyzed the associations stratified by sex, the associations between risk factors and AF were virtually unchanged. Although obesity was significantly associated with AF among women, and hyperglycemia was significantly associated with AF among men, interactions between obesity, hyperglycemia and sex were not statistically significant (P for interaction>0.30).

### Discussion

In the present study, a higher incidence of AF was observed among participants with an ethanol intake exceeding 69 g/day compared with never-drinkers in the longitudinal survey. In contrast, however, light to moderate alcohol consumption was not associated with elevated risk of AF. Thus, the association between ethanol intake and AF is suggestive of a threshold pattern effect. Because the prevalence of heavy drinkers was still high among Japanese men (7.2%), to reduce heavy alcohol consumption may not only decrease the risk of AF but also prevent stroke and heart failure related to AF. This must be important from a public health point of view.

On the other hand, there were no significant differences between alcohol intake and the prevalence of AF for both sexes in the cross-sectional survey. In general, people who were diagnosed with AF might receive advice from physicians to reduce their alcohol intake. Therefore, the association between alcohol intake and AF may be underestimated in the cross-sectional survey.

The Framingham study showed that alcohol consumption >36 g/day was associated with 34% increased risk of AF during the follow-up of 50 years and more in a nested case–control study of 1,055 AF cases and covariate-matched controls. From the Copenhagen study of 16,415 women and men aged 25–75 years, more than 35 drinks/week (60 g/day) was associated with a 45% increased risk of AF among men. Furthermore, Frost et al demonstrated that when using the lowest quintile of alcohol consumption (alcohol consumption of 4.1±2.6 g/day) as a reference, the multivariable-adjusted HR (95% CI) in the highest quintile (alcohol consumption of 68.7±22.8 g/day) was 1.46 (1.05–2.04) for men and 1.14 (0.70–1.85) for women. Finally, Kodama reported a dose–response relationship between alcohol consumption and future AF by meta-analysis in a linear regression model, which found that the pooled estimate for increments of 10 g/day of alcohol intake was 1.08 (95% CI: 1.05–1.10).

In the present study, a higher risk of AF was observed among participants whose ethanol intake exceeded 69 g/day. This is

| Table 4. Multivariate-Adjusted Hazard Ratios (HR) and 95% Confidence Intervals (CI) of Atrial Fibrillation (AF) for Cardiovascular Risk Factors (Longitudinal Survey) in the Circulatory Risk in Communities Study (CIRCS) |
|-----------------|-----------------|-----------------|
|                 | Men | Women | Total |
| Age (male)      | 1.03 (1.01–1.05) | 1.02 (1.00–1.03) | 1.02 (1.01–1.03) |
| Sex (male)      | 1.02 (1.00–1.03) | 1.00 (0.98–1.02) | 0.98 (0.96–1.01) |
| Excess ethanol intake (≥69 g/day) | 2.68 (1.56–4.61) | 3.62 (0.49–26.8) | 2.61 (1.55–4.39) |
| Current smoking | 1.22 (0.83–1.79) | 0.63 (0.28–1.44) | 1.01 (0.73–1.41) |
| Obesity (BMI ≥30) | 1.72 (0.63–4.67) | 2.53 (1.48–4.31) | 2.24 (1.41–3.58) |
| Hypertension    | 1.02 (0.69–1.50) | 0.89 (0.66–1.22) | 0.93 (0.73–1.19) |
| Hyperglycemia   | 1.51 (1.01–2.25) | 1.24 (0.84–1.85) | 1.35 (1.02–1.78) |
| Hyperlipidemia  | 1.46 (0.95–2.26) | 0.79 (0.57–1.09) | 0.96 (0.74–1.25) |
| Major ST-T abnormality | 1.09 (0.40–2.99) | 0.69 (0.30–1.56) | 0.79 (0.42–1.50) |
| Previous MI     | 2.96 (0.92–9.52) | – | 2.13 (0.67–6.74) |
| Heart failure   | – | 1.85 (0.26–13.3) | 1.22 (0.17–8.73) |

Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or use of antihypertensive medication. Hyperglycemia was defined as a fasting glucose level ≥110 mg/dl, a non-fasting glucose level ≥140 mg/dl or use of medication for diabetes. Abbreviations as in Table 1.
in line with previous studies conducted in Western countries. Although Japanese people do not have sufficient levels of alcohol dehydrogenase or aldehyde dehydrogenase, the threshold dose of ethanol intake that induced AF among the Japanese was not lower than the threshold dose for people from Western countries.

Mechanisms by which heavy alcohol consumption increase the incidence of AF are unclear and multifactorial. Alcohol consumption gives rise to a hyperadrenergic state and impairs vagal tone.\textsuperscript{35–37} Excess alcohol consumption shortens the effective refractory period of the atrium and promotes the occurrence of atrial premature beats.\textsuperscript{38} Furthermore, long-term excess alcohol intake may also cause alcoholic cardiomyopathy and congestive heart failure.\textsuperscript{39} The major ethanol metabolite, acetaldelyde, may produce alcoholic cardiomyopathy that manifests as cardiac dysfunction, hypertrophy, and heart failure.\textsuperscript{40} Ethanol is metabolized into acetaldehyde by alcohol dehydrogenase, which is then further metabolized into acetate by aldehyde dehydrogenase.\textsuperscript{41} Polymorphisms in these 2 enzymes affect the elimination of ethanol and acetaldehyde, and have been reported to change the risk of alcoholic complications.\textsuperscript{42} Increased fibrosis of the atrium, indicative of the pathologic changes of alcoholic cardiomyopathy caused by long-term excess alcohol intake, is likely to block electric conduction and create re-entrant circuits in AF.\textsuperscript{43} In the present study, there was a significant difference in the prevalence of major ST-T abnormality among the categories of alcohol consumption in men. This may be supported, in part, by the aforementioned mechanisms, because ethanol intake produces major ST-T abnormality through alcoholic cardiomyopathy.\textsuperscript{44}

The strength of this study is that we conducted a population-based large cohort study, with a long-term follow-up (mean follow-up period: 6.4 years) and a very high follow-up rate (84.6%). The evaluation of alcohol consumption at baseline was precise and reliable.\textsuperscript{45} Furthermore, this study confirmed the association of alcohol intake with risk of AF among Japanese, who do not have sufficient levels of alcohol dehydrogenase.\textsuperscript{46}

Study Limitations
Firstly, although AF cases were identified using annual ECG surveys and AF treatment history reports (receiving catheter ablation therapy or medical therapy with anticoagulant and/or antiarrhythmic drugs), the majority of AF cases were detected by annual ECG records (85.8%). Therefore, the number of cases of asymptomatic paroxysmal AF may have been underestimated. Secondly, some participants did not undergo ECG examination every year. In the present study, the mean number of ECG examinations for participants was 5.2 (2 examinations, 21.3%; 3 examinations, 20.7%; 4 examinations, 11.3%; and >5 examinations, 46.7%). There is some possibility of detection bias for AF; although there was no difference in the mean number of ECG examinations between each of the alcohol consumption categories. Finally, our data did not include creatinine levels, therefore we could not analyze the association between chronic kidney disease and AF.

Conclusions
Heavy alcohol consumption may be associated with a higher risk of AF, although there is no association of light to moderate alcohol consumption with risk of AF among Japanese men and women. Although people of Japanese descent do not have sufficient levels of alcohol dehydrogenase and aldehyde dehydrogenase, the threshold ethanol intake that induces AF among Japanese was not lower than that for people from Western countries.

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Disclosures
None.

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