Alcohol and Risk of Atrial Fibrillation or Flutter

A Cohort Study

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Background: The evidence for an association between alcohol consumption and risk of atrial fibrillation is conflicting.

Methods: We prospectively examined the association between alcohol consumption and risk of atrial fibrillation or flutter among 47,949 participants (mean age, 56 years) in the Danish Diet, Cancer, and Health Study. The consumption of alcohol was analyzed as sex-specific quintiles by Cox proportional hazards regression models.

Results: The mean ± SD consumption of alcohol per day was 28.2 ± 25 g in men and 13.9 ± 15 g in women. During follow-up (mean, 5.7 years), atrial fibrillation or flutter developed in 556 subjects (374 men and 182 women). After adjusting for established risk factors, there was a modest increase in risk of atrial fibrillation or flutter by increasing alcohol consumption in men. When using the lowest quintile of alcohol consumption in men as a reference, the adjusted hazard rate ratios in men in quintiles 2, 3, 4, and 5 were 1.04, 1.44, 1.25, and 1.46, respectively (*P* for trend, .04). When using the lowest quintile of alcohol consumption in women as a reference, the adjusted hazard rate ratios in women in quintiles 2, 3, 4, and 5 were 1.09, 1.27, 1.23, and 1.14, respectively (*P* for trend, .69). Inclusion of information on the frequency of alcohol consumption and the preferred source of alcohol did not change these associations.

Conclusions: Consumption of alcohol was associated with an increased risk of atrial fibrillation or flutter in men. In women, moderate consumption of alcohol did not seem to be associated with risk of atrial fibrillation or flutter.

cancer Registry and other population-based registries, including the Danish National Registry of Patients and the Danish Civil Registration System, using the civil registry number, which is a unique number given to everyone living with an address in Denmark since 1968. The Civil Registration System has electronic records of all changes in vital status for the Danish population since 1968, including change in address, date of emigration, and date of death. The Danish National Registry of Patients was established in 1977 and records 99.4% of all discharges from nonpsychiatric hospitals in Denmark. The data include the civil registry number, dates of admission and discharge, surgical procedures performed, and up to 20 discharge diagnoses per discharge, classified until 1993 according to the Danish version of the International Classification of Diseases, Eighth Revision (ICD-8) and thereafter according to the national version of ICD, 10th Revision (ICD-10). The physician who discharged the patient coded all discharge diagnoses. To study incident cases of atrial fibrillation and to reduce confounding, we excluded participants who had been hospitalized before baseline with endocrine diseases or cardiovascular diseases other than hypertension, recorded in the National Registry of Patients; ICD-8 codes 240-279, 390-398, and 410-419; and ICD-10 codes E00-E59, I00-I09, and I16-I99. We did not exclude patients with hypertension before or at baseline for several reasons. First, the diagnostic criteria for hypertension have changed over the past decades. Second, the validity of a diagnosis of hypertension in the Danish National Register of Patients is low. Third, if we used a definition of hypertension as a systolic blood pressure greater than 140 mm Hg at baseline, we would exclude more than 50% of subjects from the cohort. Finally, we did not a priori believe that the relation between blood pressure and risk of atrial fibrillation included a threshold function allowing us to exclude any subjects from the cohort because of a specific level of blood pressure.

The Danish Diet, Cancer, and Health Study and the present study were approved by the regional ethics committees in Copenhagen and Aarhus and by The Danish Data Protection Agency.

**BASELINE DATA**

Height, weight, systolic and diastolic blood pressure, and total serum cholesterol level were measured at baseline. Body weight was measured by the use of a Soehnle-Waagen (Murrhardt, Germany) digital scale weight and recorded to the nearest 100 g. Systolic and diastolic blood pressure was measured by an automatic blood pressure measurement devise (Takeda UH 751; A & D Company, Tokyo, Japan). Nonfasting total serum cholesterol was measured according to national guidelines.

All participants filled out a questionnaire about medical diseases, including myocardial infarction, angina, stroke, hypertension, hypercholesterolemia, and diabetes, as well as drug treatment of those conditions. Subjects who reported having ischemic heart disease, stroke, diabetes, and/or were receiving medication for those conditions were excluded from the present study. The participants also completed a questionnaire about smoking habits, alcohol intake, physical activity, health, and duration of education.

**ASCERTAINMENT OF ALCOHOL CONSUMPTION**

All cohort members completed a detailed semiquantitative food- and drink-frequency questionnaire. Descriptions of the development and validation of this questionnaire have been published previously. The study participants were asked to fill out a questionnaire about type of alcohol: light beer, ordinary beer, strong beer, wine, fortified wine, and spirits, and frequency of consumption (never, less than once per month, once per month, 2-3 times per month, once per week, 2-4 times per week, 5-6 times per week, once per day, 2-3 times per day, 4-5 times per day, 6-7 times per day, and ≥ 8 times per day). We converted this information into 3 exposure variables:

- Variable 1: Amount of alcohol consumed (grams of alcohol consumed per day). The amount of alcohol consumed was evaluated as sex-specific quintiles.
- Variable 2: Preference for wine, beer, or mixed drinking (50% or more consumed alcohol from wine and fortified wine or from beer; otherwise, the subject was categorized as a mixed drinker).
- Variable 3: Frequency of alcohol consumption (<2 times or ≥ 2 times per week).

**ATRIAL FIBRILLATION AND ATRIAL FLUTTER**

We identified probable cases of atrial fibrillation or flutter within the cohort in The Danish National Registry of Patients (ie, cases with the discharge diagnoses 427.93 and 427.94 [ICD-8] and 148 [ICD-10]) through December 31, 2001. Beginning January 1, 1993, patients who were only seen in an outpatient hospital clinic were also coded into the Danish National Registry of Patients. A change from ICD-8 to ICD-10 occurred in Denmark in 1994. Atrial fibrillation and atrial flutter were coded separately in ICD-8 (codes 427.93 and 427.94), but in ICD-10, atrial fibrillation and flutter have the same ICD code (148).

A single reviewer (L.F.), using a standardized form, reviewed the medical records of the subset of study participants living in the county of Aarhus, Denmark, with an incident diagnosis of atrial fibrillation or flutter recorded in the Danish National Registry of Patients through December 1999. Of 116 subjects with an incident diagnosis of atrial fibrillation or flutter on electrocardiogram, a printout from telemetry or a printout from a Holter recording could verify atrial fibrillation or atrial flutter in 112 individuals. Thus, 112 (97%) of 116 diagnoses could be verified. Among the 112 subjects with a verified diagnosis, 103 subjects (92%) had atrial fibrillation, 3 (3%) had both atrial fibrillation and atrial flutter, and 6 (5%) had atrial flutter.

**FOLLOW-UP**

The study participants were followed-up in the National Registry of Patients and in the Central Person Registry. Linking was done by use of the civil registry number. Follow-up for atrial fibrillation or flutter began on the date of visit to one of the study centers and ended on the date of an event or a censoring (ie, a diagnosis of atrial fibrillation or flutter, death, emigration, or December 31, 2001, whichever came first).

**STATISTICAL ANALYSIS**

We used piecewise linear regression to examine the relationship between a continuous variable and the hazard of atrial fibrillation or flutter. We kept a continuous variable as continuous in the Cox proportional hazards regression model, when appropriate, according to these analyses.

We computed a multivariate Cox proportional hazards regression model in men and women by an initial forced entry of known risk factors for atrial fibrillation, namely, age, systolic blood pressure, and treatment for hypertension, together with information for body height and body mass index, followed by forward selection of the other variables of interest. Thereafter, we confirmed our model by doing a Cox proportional hazards regression analysis with backward elimination of variables. We performed supplementary analyses by adding product terms to test for interaction. The relevance of a variable in the model was further assessed by the change-in estimate method.
The variables included in our final models in men and women were age (years), body height (centimeters), body mass index (calculated as weight in kilograms divided by the square of height in meters), systolic blood pressure (millimeters of mercury), treatment for hypertension (no/yes), total serum cholesterol level greater than 232 mg/dL (>6 mmol/L) (no/yes), and sex-specific quintiles of alcohol consumption. Therefore, we assessed further potential confounders: smoking (never, former, or current) and length of education after elementary school (0, <3, 3-4, and >4 years) to evaluate the potentials for a change in the estimate of the hazards for atrial fibrillation or flutter associated with consumption of alcohol.

Correlation was evaluated by Spearman nonparametric correlation analysis. Tests for linear trend were calculated by assigning the medians of intake in quintiles treated as a continuous variable.

The assumption of proportional hazards in the Cox models was evaluated using graphical assessment and found appropriate in all models. We calculated 95% confidence intervals throughout the analyses. All reported P values are 2 sided. We used SPSS statistical software version 11.5 (SPSS Inc, Chicago, Ill).

**RESULTS**

The cohort included 57 053 subjects at baseline. We excluded 9022 subjects who reported having or taking medicine for endocrine or cardiovascular diseases (hypertension was not excluded) and/or had a diagnosis of endocrine or cardiovascular disease (hypertension was not excluded) in the Danish National Registry of Patients before or at baseline. Eighty-two subjects were excluded because of missing information on amount of alcohol consumption. Thus, the study population included in the cohort consisted of 47 949 subjects (22 528 men and 25 421 women). The men provided a total of 128 131 person-years of risk (mean, 5.7 years [range, 0-8.1 years]) and the women contributed 147 251 person-years of risk (mean, 5.8 years [range, 0-8.1 years]). During follow-up, 374 men (1.7%) and 182 women (0.7%) had an incident diagnosis of atrial fibrillation or flutter in the National Registry of Patients, corresponding with incidence rates of 29.1 per 10 000 person-years at risk in men and 12.4 per 10 000 person-years at risk in women.

The Figure shows the proportion of men and women by alcohol consumption. More than half of the women had a consumption of alcohol that was lower than 1 U/d (<10 g/d). The mean±SD consumption of alcohol per day was 28.2±25 g in men and 13.9±15 g in women. The proportions of men and women who were total abstainers at baseline were 2.1% and 3.0%, respectively. The proportions of subjects (men and women) who preferred wine were 41.1% and 62.2%; who preferred beer were 36.6% and 8.5%; and who preferred spirits were 3.0% and 3.1%. Many subjects could not be categorized with respect to the preferred source of alcohol because they consumed an equal amount of alcohol from beer and wine.

**Table 1** gives the characteristics of men and women at baseline according to sex-specific quintile of alcohol consumption. Among men, the mean consumption of alcohol was 4.1 g/d in the lowest quintile compared with 38.8 g/d in the top quintile. The mean age decreased slightly by an increasing category of alcohol intake. The proportion of current smokers increased by an increase in alcohol consumption. The systolic blood pressure and the proportion receiving treatment for hypertension increased by an increasing intake of alcohol. The proportion of subjects with a nonfasting total serum cholesterol level greater than 232 mg/dL (>6 mmol/L) increased by increasing category of alcohol intake.

In women, the mean consumption of alcohol was 1.1 g/d in the lowest quintile compared with 38.8 g/d in the top quintile. The mean age decreased slightly by increasing alcohol consumption. Body height increased by increasing quintile of alcohol consumption, and body weight decreased by increasing quintile of alcohol consumption, as did the body mass index. The proportion of current smokers was highest in the lowest and in the top quintiles. The systolic blood pressure and the proportion receiving treatment for hypertension did not change much by category of intake of alcohol. The proportion of subjects with a nonfasting total serum cholesterol level greater than 232 mg/dL (>6 mmol/L) decreased by an increasing category of alcohol intake.

**Table 2** gives the incidence rates of atrial fibrillation or flutter in men and women according to sex-specific quintiles of alcohol consumption. The number of men with an incident diagnosis of atrial fibrillation or flutter increased over quintiles of alcohol consumption from 61 subjects in the lowest quintile to 63 (quintile 2), 86 (quintile 3), 75 (quintile 4), and 89 (quintile 5) subjects, corresponding with incidence rates of 23.7, 24.7, 33.8, 29.3, and 34.6, respectively, per 10 000 person-years of follow-up. The number of women with an incident diagnosis of atrial fibrillation by quintile of alcohol intake was 36 (quintile 1), 35 (quintile 2), 39 (quintile 3), 37 (quintile 4), and 35 (quintile 5). Thus, in women, there did not seem to be any association between consumption of alcohol and risk of atrial fibrillation.

**Table 3** gives the hazard rate ratios in men and women for atrial fibrillation or flutter according to sex-specific quintiles of alcohol consumption. When using the lowest quintile of alcohol consumption as a reference, the adjusted hazard rate ratios in men in quintiles 2, 3, 4, and 5 were 1.04, 1.44, 1.25, and 1.46, respectively (P for trend, .04). In women the adjusted hazard...
Cardiovascular Health Study reported that alcohol consumption reduced the risk of atrial fibrillation in a dose-response–related manner. Conversely, a case-control study recently reported an adjusted relative risk of 2.4 (95% confidence interval, 1.4–4.1) for atrial fibrillation among subjects who consumed more than 42 U (>420 g) of alcohol per week. Thus, the discussion on alcohol as a risk factor for atrial fibrillation remains open.

The potential risk for atrial fibrillation associated with alcohol can have many causes. The “Holiday Heart Syndrome” was defined by Ettinger et al in 1978 as an acute cardiac rhythm and/or conduction disturbance associated with heavy ethanol consumption in a person without other clinical evidence of heart disease and disappearing, without evident residual, with abstinence.

This form of atrial fibrillation is most often seen in younger subjects and is not related to organic heart disease, although a recent study has suggested the existence of a preexisting atrial pathologic condition evaluated by P-wave signal averaging in patients with alcohol-induced paroxysmal atrial fibrillation and controls.
A study involving 6 patients with alcohol-induced atrial fibrillation and 6 controls showed a tendency toward an increased sympathetic reaction among patients with alcohol-induced atrial fibrillation compared with controls evaluated by heart rate variability analysis.18

Small-scale experimental human and animal studies have not been able to document any changes in the atrial refractory period by acute exposure to alcohol.22

A study of patients with paroxysmal atrial fibrillation showed that the risk of recurrences of atrial fibrillation was not associated with recent consumption of alcohol, the amount of alcohol consumed during the week before, or the daily consumption of alcohol.23

Excess consumption of alcohol may induce cardiomyopathy leading to heart failure and risk of atrial fibrillation. However, data from the Framingham Heart Study has shown that moderate consumption of alcohol protects against the development of heart failure.24 It is also known that consumption of alcohol is associated with a lower risk of coronary atherosclerosis,25,26 which is associated with risk of atrial fibrillation.

The main strengths of our study are the large number of cases with atrial fibrillation, the detailed information on potential confounding factors, the complete follow-up through nationwide, population-based registries (which limit selection and surveillance bias), and the standardized assessment of a sample of the registered outcome events.

We were only able to include atrial fibrillation or flutter that was symptomatic and led to hospitalization or clinical investigation in an outpatient hospital clinic. However, given the age profile of our study cohort, it is likely that patients with clinical symptoms of atrial fibrillation were referred to a hospital for further evaluation. We relied on self-reported data on consumption of alcohol. Underreporting of the amount of consumed alcohol among heavy consumers may have caused us to underestimate the risk of atrial fibrillation in the top quintile of alcohol consumption. On the other hand, heavy alcohol consumption may be a risk factor for hospitalization for any reason, and this would introduce biased follow-up,27 as any hospitalization will increase the probability of the diagnosis of asymptomatic atrial fibrillation. Conversely, heavy alcohol consumption may also lead to ignorance of health-related problems, and this would bias follow-up in the opposite direction.

Most of the study participants were frequent drinkers (intake of alcohol twice or more per week). Therefore, we could not evaluate if binge drinking was associated with risk of atrial fibrillation or flutter. We also believe that the question of binge drinking and risk of atrial fibrillation is best evaluated in a case-crossover design.

We had limited statistical power, especially in women, so we cannot exclude the possibility that we would have found an excess risk of atrial fibrillation associated with intake of alcohol in women given that we had more outcomes among women.

We could not differentiate atrial fibrillation from atrial flutter, because atrial fibrillation and atrial flutter

<table>
<thead>
<tr>
<th>Variable</th>
<th>Quintile 1</th>
<th>Quintile 2</th>
<th>Quintile 3</th>
<th>Quintile 4</th>
<th>Quintile 5</th>
<th>P Value for Trend</th>
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<td>Total No. of person-years of follow-up</td>
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<td>25430</td>
<td>25581</td>
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<tr>
<td>No. of subjects with atrial fibrillation or flutter</td>
<td>61</td>
<td>63</td>
<td>86</td>
<td>75</td>
<td>89</td>
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<tr>
<td>Incidence rate per 10,000 person-years</td>
<td>23.7</td>
<td>24.7</td>
<td>33.8</td>
<td>29.3</td>
<td>34.6</td>
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<td>Mean duration of follow-up, d</td>
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<td>Total No. of person-years of follow-up</td>
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<td>29318</td>
<td>29363</td>
<td>29253</td>
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<tr>
<td>No. of subjects with atrial fibrillation or flutter</td>
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<td>35</td>
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<tr>
<td>Incidence rate per 10,000 person-years</td>
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<td>11.9</td>
<td>13.3</td>
<td>12.6</td>
<td>12.0</td>
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*Data are given as hazard ratio (95% confidence interval) unless otherwise specified.
†Reference category.
‡Adjusted for age, body height, body mass index, smoking, systolic blood pressure, treatment for hypertension, total serum cholesterol, and level of education.
had the same ICD code. However, from the evaluation of hospital files of a sample of cases participating in Danish Diet, Cancer, and Health Study and recorded in the Danish National Registry of Patients with an incident diagnosis of atrial fibrillation or flutter, we know that approximately 5% of the recorded cases had atrial flutter. If alcohol is not associated with risk of atrial flutter, inclusion of atrial flutter in the present study may have caused us to underestimate the risk of atrial fibrillation by an increase in the consumption of alcohol. However, given the low proportion of patients with atrial flutter, this bias would be modest.

Accepted for publication November 28, 2003.

This study was supported by grant 22-02-0582 from The Danish Medical Research Council and by The Danish Cancer Society, Copenhagen, Denmark.

We thank Katja Boll, programmer, and Jytte Fogh Larsen, secretary, from The Danish Cancer Society, for assisting in data collection; Anne Tjønneland, MD, PhD, and Kim Overvad, MD, PhD, for assisting in data access; and Lone Juul Hansen, MSc, statistician, UNI-C, The Danish IT Centre for Education and Research, Aarhus, for assisting in data management and statistical analyses.

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