Alcohol Consumption and Risk of Heart Failure in the Physicians’ Health Study I

Luc Djoussé, MD, MPH, DSc; J. Michael Gaziano, MD, MPH

Background—Heart failure (HF) is the leading cause of hospitalization among the elderly, and 1 in 5 adults aged 40 years will develop HF in their lifetime. Data on the effects of moderate alcohol consumption on the risk of HF have been sparse and inconsistent. This study sought to evaluate the association between moderate alcohol consumption and incident HF.

Methods and Results—A total of 21,601 participants of the Physicians’ Health Study I who were free of HF and provided data on alcohol intake at baseline were prospectively followed up from 1982 to 2005. Incident HF cases were ascertained through annual follow-up questionnaires and validated with the use of Framingham criteria. During an average follow-up of 18.4 years, 904 incident cases of HF occurred. The crude incidence rates of HF were 25.0, 20.0, 24.3, and 20.6 cases per 10,000 person-years for alcohol categories of 1, 1 to 4, 5 to 7, and >7 drinks per week, respectively. Corresponding hazard ratios (95% CI) were 1.0 (reference), 0.90 (0.76 to 1.07), 0.84 (0.71 to 0.99), and 0.62 (0.41 to 0.96), respectively, with $P$ for trend = 0.012 adjusted for age, body mass index, smoking, and history of valvular heart disease. There was no evidence for a strong association between moderate alcohol consumption and HF without antecedent coronary artery disease.

Conclusions—Although heavy drinking should be discouraged, our data indicate that moderate drinking may lower the risk of HF. The lack of an association between moderate alcohol intake and HF without antecedent coronary artery disease suggests that possible benefits of moderate drinking on HF may be mediated through beneficial effects of alcohol on coronary artery disease. (Circulation. 2007;115:34-39.)

Key Words: alcohol ■ epidemiology ■ heart failure ■ risk factors
trial in which a 2×2 factorial design was used to study low-dose aspirin and beta carotene for the primary prevention of cardiovascular disease and cancer among US male physicians. A detailed description of the PHS I has been published previously. Briefly, in 1981, 261 248 US male physicians aged 40 to 85 years were invited to participate in the trial. After exclusion criteria (history of myocardial infarction, stroke, transient ischemic attack, cancer [except nonmelanoma skin cancer], gout, current liver or kidney disease, peptic ulcer, current use of trial treatments), 33 223 participants were enrolled in an 18-week run-in period. After the run-in period, 22 071 subjects were randomized to low-dose aspirin, beta carotene, both agents, or placebo. For the present study, 470 participants because of (1) missing information on baseline alcohol intake, or (2) prevalent HF at baseline (n=18), and (3) missing covariates (n=254). Each participant gave written informed consent, and the study protocol was approved by the institutional review board at Brigham and Women’s Hospital, Boston, Mass.

Alcohol Consumption
Information about usual alcohol consumption was self-reported on a standard questionnaire. Participants were asked, “How often do you usually consume alcoholic beverages?” Possible response categories included “rarely/never,” “1 to 3/mo,” “1/wk,” “2 to 4/wk,” “5 to 6/wk,” “daily,” and “2+/d.” The response was interpreted as number of alcoholic drinks consumed during the specified period.

Ascertainment of Incident HF
A questionnaire was mailed to each participant every 6 months during the first year and has been mailed annually thereafter to obtain information on compliance with the intervention and the occurrence of new medical diagnoses including HF. In a pilot study, a total of 100 participants who reported a HF diagnosis on a follow-up questionnaire were contacted by mail. The mailing included a HF questionnaire with detailed questions about time and place of HF diagnosis, clinical signs and symptoms, medical treatment, and diagnostic methods (echocardiography, angiography, and radionuclide imaging). Of the 100 physicians, 4 had died, and 8 participants had a routine follow-up method that deviates from the normal mailing procedure (eg, some participants have requested to be contacted by telephone only). After 2 mailings, we obtained a completed questionnaire from 73 of 88 participants (83%). Among respondents, 90% of the HF cases (66 of 73) were confirmed with the use of the Framingham criteria.

Other Variables
Information on age, height, weight, body mass index, cigarette smoking, parental history of myocardial infarction, history of angina, hypertension, atrial fibrillation, valvular disease, diabetes mellitus, and physical activity was collected at baseline. Incident CAD (angina pectoris, myocardial infarction, coronary angioplasty, and coronary bypass surgery) was ascertainment through annual follow-up questionnaires.

Statistical Analyses
Because the initial analyses conducted with the original 7 alcohol categories showed an inverse association between alcohol consumption and HF (hazard ratio, 1.0, 0.99, 0.82, 0.91, 0.75, 0.81, 0.61 from lowest to the highest category of alcohol intake, respectively, adjusted for age, smoking, and history of valvular heart disease; P for trend=0.005), we collapsed adjacent categories to obtain stable estimates. Additional adjustment for exercise (categories) did not alter the findings. We calculated person-time of follow-up from baseline until the first occurrence of (1) HF, (2) death, or (3) censoring date (date of receipt of last follow-up questionnaire). Within each alcohol category, incidence rate was computed by dividing the number of HF cases by the corresponding person-time. Actuarial analyses were performed by the Kaplan-Meier method, and the statistical significance was determined with the log-rank test. We used Cox proportional hazard models to compute multivariable adjusted hazard ratios with corresponding 95% CIs using subjects in the alcohol category of “rarely/never” as reference group. We assessed confounding by using 10% change in hazard ratio. Assumptions for the proportional hazard models were tested (by including main effects and product terms of covariates and time factor) and were met (all P>0.05). We obtained the probability value for linear trend by assigning the midpoint of each alcohol group to a new open-ended alcohol category. Age was a major confounding factor, and because we did not have adequate overlap across categories of alcohol consumption, we conducted stratified analyses by age categories (<50, 50 to 59, 60 to 69, and ≥70 years). In addition, we controlled for age as a continuous variable within age strata when fitting Cox regression models. Smoking was entered in the model as never, past, and current smoker. We also examined whether the effects of alcohol were mediated by myocardial infarction by adjusting additionally for myocardial infarction as a time-dependent covariate. We updated myocardial infarction at the end of 1989, 1994, and 1999. To assess whether alcohol influences the risk of HF without antecedent CAD, we censored noncases at the time of diagnosis of CAD. HF cases that occurred after CAD were also censored at the time of diagnosis of CAD and recoded as noncases. To examine a possible “sick quitter” effect (subjects may have stopped drinking shortly after a diagnosis of a chronic condition), we conducted sensitivity analyses by excluding individuals whose person-times were <2 years and by using person consuming 1 to 4 drinks per week as the reference group. We also verify that alcohol intake was inversely related to myocardial infarction in this cohort. All analyses were completed with the use of SAS, version 9.1 (SAS Institute, NC). The significance level was set at 0.05.

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

Results
Among 21 601 participants in the PHS I, the mean age at randomization was 53.8±9.5 years (range, 40 to 86 years). Table 1 presents baseline characteristics of the study participants. Frequent alcohol consumption was associated with older age; current smoking; higher prevalence of

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Frequency of Alcohol Intake, Drinks per Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>53.7±9.8</td>
<td>52.4±9.0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>250.0±3.0</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>62.8</td>
<td>52.0</td>
</tr>
<tr>
<td>Current smokers</td>
<td>9.2</td>
</tr>
<tr>
<td>Exercise, %</td>
<td>67.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23.3</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.3</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>0.3</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>0.1</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>2.0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Values are mean±SD or %.
hypothesis, atrial fibrillation, and valvular disease; and lower prevalence of angina pectoris and diabetes mellitus. During an average follow-up of 18.4 years, 904 new cases of HF occurred. The crude incidence rates of HF were 25.0, 20.0, 24.3, and 20.6 cases per 10,000 person-years for usual alcohol consumption of <1, 1 to 4, 5 to 7, and >7 drinks per week, respectively. There was evidence for increased event-free survival from the lowest to the highest category of alcohol consumption (P = 0.02, log-rank test). From the multivariable Cox regression model, hazard ratios (95% CI) for HF were 1.0 (reference), 0.88 (0.75 to 1.05), 0.80 (0.68 to 0.94), and 0.62 (0.40 to 0.95) for alcohol consumption of <1, 1 to 4, 5 to 7, and >7 drinks per week, respectively, after adjustment for age and smoking (3 categories) (P for linear trend = 0.002; Table 2). Additional adjustment for body mass index (<25, 25 to 29, ≥30 kg/m²) and history of valvular heart disease had only a minimal effect on the results (Table 2). Further adjustment for physical activity did not alter these findings (data not shown). Additional adjustment for myocardial infarction, as a time-dependent covariate, led to a modest attenuation of the main effect of alcohol on HF: Corresponding hazard ratios (95% CI) were 1.0, 0.91 (0.76 to 1.07), 0.87 (0.73 to 1.02), and 0.63 (0.41 to 0.97) from the lowest to the highest alcohol group (P for trend = 0.02). Exclusion of individuals whose follow-up times were <2 years made the association slightly stronger with fully adjusted relative risks (95% CI): 1.0, 0.90 (0.76 to 1.06), 0.83 (0.70 to 0.99), and 0.58 (0.37 to 0.91) from the lowest to the highest alcohol category, respectively (P for trend = 0.007). When we used drinkers of 1 to 4 per week as the reference group, our data showed similar results. Multivariable adjusted relative risks (95% CI) were 1.11 (0.94 to 1.32), 1.0 (reference), 0.94 (0.80 to 1.10), and 0.69 (0.45 to 1.06) from the lowest to the highest alcohol group, respectively (P for trend = 0.003).

Of the total of 904 incident cases of HF, 143 (15.8%) and 346 (38.3%) had antecedent myocardial infarction and CAD, respectively. We examined the association between alcohol intake and HF without antecedent CAD and found no evidence for a strong association. Compared with the lowest alcohol category, hazard ratios (95% CI) for HF without antecedent CAD were 0.93 (0.74 to 1.16), 0.97 (0.79 to 1.21), and 0.84 (0.51 to 1.37) in subjects consuming 1 to 4, 5 to 7, and >7 drinks per week, respectively (P for trend = 0.73; Table 3). There was evidence for a weaker inverse association between moderate alcohol intake and HF without antecedent myocardial infarction (hazard ratio, 1.0, 0.93 [95% CI, 0.77 to 1.12], 0.91 [95% CI, 0.76 to 1.09], and 0.66 [95% CI, 0.10 to 1.04] from the lowest to the highest alcohol category, respectively; P for trend = 0.13). In a multivariable model adjusted for age, body mass index, smoking, and history of hypertension, atrial fibrillation, and valvular heart disease, alcohol consumption was inversely associated with the risk of myocardial infarction in this cohort with corresponding hazard ratio (95% CI) of 1.0, 0.86 (0.76 to 0.98), 0.67 (0.59 to 0.77), and 0.61 (0.43 to 0.86) from the lowest to the

### TABLE 2. Incidence Rate and Hazard Ratios (95% CI) of HF According to Alcohol Consumption

<table>
<thead>
<tr>
<th>Frequency of Alcohol Intake</th>
<th>Cases</th>
<th>Crude Incidence Rate, Cases/10 000 Person-Years</th>
<th>Hazard Ratio (95% CI) Model 1*</th>
<th>Model 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 drink per week</td>
<td>256</td>
<td>25.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1–4 drinks per week</td>
<td>295</td>
<td>20.0</td>
<td>0.88 (0.75–1.05)</td>
<td>0.90 (0.76–1.07)</td>
</tr>
<tr>
<td>5–7 drinks per week</td>
<td>330</td>
<td>24.3</td>
<td>0.80 (0.68–0.94)</td>
<td>0.84 (0.71–0.99)</td>
</tr>
<tr>
<td>&gt;7 drinks per week</td>
<td>23</td>
<td>20.6</td>
<td>0.62 (0.40–0.95)</td>
<td>0.62 (0.41–0.96)</td>
</tr>
</tbody>
</table>

*Adjusted for age (continuous within stratified Cox regression using age strata of <50, 50–59, 60–69, and ≥70) and smoking (never, past, and current smokers).
†Adjusted for variables in model 1 plus body mass index (<25, 25–29, ≥30 kg/m²) and valvular heart disease.

### TABLE 3. Hazard ratios (95% CI) of HF Without Antecedent Myocardial Infarction and CAD

<table>
<thead>
<tr>
<th>Alcohol, Drinks per Week</th>
<th>HF Without Antecedent Myocardial Infarction</th>
<th>HF Without Antecedent CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>205</td>
<td>148</td>
</tr>
<tr>
<td>1–4</td>
<td>246</td>
<td>173</td>
</tr>
<tr>
<td>5–7</td>
<td>290</td>
<td>219</td>
</tr>
<tr>
<td>&gt;7</td>
<td>20</td>
<td>18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (95% CI)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>0.93 (0.77–1.12)</td>
<td>0.93 (0.74–1.16)</td>
</tr>
<tr>
<td></td>
<td>0.91 (0.76–1.09)</td>
<td>0.97 (0.79–1.21)</td>
</tr>
<tr>
<td></td>
<td>0.66 (0.10–1.04)</td>
<td>0.84 (0.51–1.37)</td>
</tr>
</tbody>
</table>

*Adjusted for age (continuous within stratified Cox regression using age strata of <50, 50–59, 60–69, and ≥70), body mass index (<25, 25–29, ≥30 kg/m²), smoking (never, past, and current smokers), and history of valvular heart disease.
highest category of alcohol, respectively (P for trend <0.0001). In secondary analyses, moderate alcohol consumption was associated with a lower risk of HF (although this was not statistically significant) in people with and without diabetes (data not presented). Furthermore, we did not find evidence for an interaction between moderate alcohol consumption and diabetes on the risk of HF (P for interaction=0.53).

Discussion

In observational studies, moderate alcohol consumption has been associated with lower rates of coronary heart disease,21–23 a major determinant of HF. Although many researchers have shown that heavy alcohol consumption is associated with cardiomyopathy,10,24 limited data are available on the influence of moderate alcohol consumption (up to 2 drinks per day for men and 1 drink per day for women) on the development of HF in a community setting. In the present prospective study, we demonstrated that moderate alcohol consumption was inversely associated with the risk of HF in a dose-response manner and independent of major confounding factors. We did not find a statistically significant association between moderate alcohol consumption and HF without antecedent CAD, however.

Our findings are consistent with many of the previously published data suggesting a reduced risk of HF with moderate alcohol consumption. Abramson et al14 first reported an inverse association between alcohol consumption and HF among 2235 elderly subjects with a mean age of 74 years; in that cohort, alcohol intake was inversely associated with HF incidence (P for trend=0.02) with a 47% lower risk of HF in subjects consuming 21 to 70 oz of alcohol per month (=1.5 to 4 drinks per day) compared with abstainers.14 We have previously reported an inverse association between alcohol consumption and all-cause incident HF in 2796 men and 3493 women of the Framingham Heart Study who reported light to moderate amounts of alcohol per month (1.5 to 4 drinks per day) compared with abstainers.14 We have previously reported an inverse association between alcohol consumption and all-cause incident HF in 2796 men and 3493 women of the Framingham Heart Study who reported light to moderate amounts of alcohol consumption13; in addition, the Framingham data showed a lower risk of HF without antecedent myocardial infarction among men who consumed 1 to 7 drinks per week (relative risk, 0.41 [95% CI, 0.21 to 0.79]) and suggestive evidence for women consuming 3 to 7 drinks per week (relative risk, 0.55 [95% CI, 0.25 to 1.20]) after adjustment for age, smoking, body mass index, diabetes, valvular disease, and hypertension. Recent data from the Cardiovascular Health Study found a 34% lower risk of HF among elderly people consuming 7 to 13 drinks per week but little effect with heavy alcohol consumption.15

In contrast, data from the Kaiser Permanente Medical care Program reported 40% to 60% lower risk of HF hospitalization for drinkers of at least 1 drink per day among 126,235 individuals.25 This apparent risk reduction for HF hospitalization was restricted to CAD-related HF with only a borderline statistically significant 20% reduction in HF hospitalization risk among individuals consuming <1 drink per day. In contrast, heavy alcohol consumption was associated with a significant increased risk of non–CAD-related HF hospitalization in that cohort (relative risk, 1.7 [95% CI, 1.1 to 2.6]). Specifically, among 55,658 male participants in the Kaiser Permanente Study, consumption of 1 to 2 drinks per day was associated with 40% lower risk of CAD-related HF hospitalization (P=0.001) and a modest 10% increased risk of non–CAD-related HF hospitalization (P=0.7). Our study did not find a statistically significant association between moderate alcohol consumption and HF without antecedent CAD.

On the other hand, other investigators did not find an association between alcohol intake and HF. In a sample of subjects with myocardial infarction, recent alcohol consumption was associated with HF in a crude model, but this association became statistically nonsignificant after controlling for potential confounders.11 In the SAVE trial, light to moderate alcohol consumption was not related to incident HF after 42 months of follow-up among 2231 patients with left ventricular systolic dysfunction who were randomized to angiotensin-converting enzyme inhibitor or placebo.12 The discrepancy with our findings merits some comments. Whereas we assessed long-term alcohol consumption, Mukamal et al assessed the immediate effects of alcohol on HF, namely, whether alcohol ingestion can trigger the development of HF. The PHS I included subjects with normal left ventricular function in contrast to the SAVE trial,12 in which subjects had an ejection fraction <40%. In addition, the shorter mean follow-up in the SAVE trial (3.5 years compared with 19 years in the PHS I) and relative small sample size may have been insufficient for observation of any major effects of alcohol.

There are several biological mechanisms to explain the observed association between alcohol consumption and HF. Previous studies have demonstrated beneficial effects of alcohol on high-density lipoprotein cholesterol,26,27 insulin sensitivity,28,29 inflammation and endothelial function,30 coagulation factors,31 and atrial natriuretic peptide,16–18 a cardiac hormone that plays a role in volume homeostasis. Consequently, several studies have reported that moderate alcohol intake may lower the risk of myocardial infarction and fatal coronary events. The attenuation of the hazard ratios on additional adjustment for myocardial infarction and the lack of an association between moderate alcohol intake and HF without antecedent CAD suggest that the observed lower risk of HF among moderate drinkers may be mediated through beneficial effects of alcohol on CAD.

The present study has some limitations. First, we did not collect data to allow separation of former drinkers from lifetime abstainers. The inclusion of former drinkers who stopped drinking because of HF-related events would increase the baseline rate of HF in the reference category and thus inflate the alcohol-HF association. The fact that exclusion of HF cases occurred during the first 2 years of follow-up did not alter our results suggests that we did not have a substantial number of presymptomatic HF cases who reduced or stopped alcohol consumption to be wrongfully classified with lifetime abstainers. Furthermore, the fact that using moderate drinkers as the reference group still showed lower risk of HF for subjects consuming 5 to
7 and >7 drinks per week suggests that our findings are not influenced by sick quitters. Second, we did not collect adequate data to further classify HF on the basis of left ventricular function. Third, there is a possibility of under-reporting of alcohol consumption, especially among heavy drinkers, because these data were self-reported. Such exposure misclassification in the highest alcohol group would lead to attenuation of the effects of moderate alcohol consumption on HF. Fourth, our sample consists of highly educated male physicians who may have different behaviors than the general population. It is thus possible that residual confounding in this cohort by unmeasured factors such as diet may partially explain our findings. The nature of our cohort also limits the generalizability of our findings. Fifth, because only 3% (n=665) of our participants reported consumption of ≥2 drinks per day, we did not have enough data to examine the effects of heavy drinking on HF, and our findings are mainly applicable to moderate drinkers. Finally, we did not have data on beverage types to examine the effects of wine, beer, and spirits consumption on HF. Nevertheless, the large sample size, the longer duration of follow-up, and the fact that participants were physicians who could recognize early signs of HF are strengths of the present study.

In conclusion, our data show an inverse association between moderate alcohol consumption and incident HF. Although individuals always need to be cautioned against the dangers of heavy alcohol drinking, these findings suggest that moderate alcohol consumption may lower the risk of HF, especially CAD-related HF.

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Disclosures

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References


Heart failure (HF) is the leading cause of hospitalization in the elderly population and is associated with higher costs and societal burden. Hypertension, myocardial infarction, obesity, and valvular heart disease are major risk factors for HF, and previous studies have suggested that modifiable lifestyle factors could lower these risk factors and thus prevent HF. Earlier data have reported beneficial effects of moderate alcohol consumption on coronary artery disease and mortality. Available data on the effects of moderate drinking on the risk of HF are limited and inconsistent, however. We examined prospectively the effects of moderate alcohol consumption on the risk of HF among 21,601 US male physicians. Compared with abstainers, the risk of HF was 10%, 16%, and 38% lower among individuals consuming 1 to 4, 5 to 7, and >7 drinks per week, respectively, after adjustment for major confounders. The fact that the relative risks for HF were attenuated on additional adjustment for myocardial infarction and the lack of an association between moderate alcohol intake and HF without antecedent coronary artery disease suggest that the observed lower risk of HF among moderate drinkers may be mediated through beneficial effects of alcohol on coronary artery disease. The most likely biological mechanism appears to be the increase in high-density lipoprotein cholesterol observed with moderate alcohol consumption. Although individuals always need to be cautioned against the dangers of heavy alcohol drinking (because such consumption could increase the risk of hypertension and cardiomyopathy), these findings suggest that moderate alcohol consumption may lower the risk of HF, especially coronary artery disease–related HF.
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