Alcohol Consumption and Mortality in Men With Preexisting Cerebrovascular Disease

Vicki A. Jackson, MD; Howard D. Sesso, ScD; Julie E. Buring, ScD; J. Michael Gaziano, MD

Background: In counseling patients with a history of stroke, clinicians have limited information regarding the risks and benefits of alcohol consumption.

Objective: To examine the relationship between alcohol intake and risks of total and cardiovascular mortality in men with a history of stroke.

Methods: The study population consisted of 112,528 men from the enrollment cohort of the Physicians’ Health Study, 1320 of whom reported a baseline history of stroke. Men provided self-reported data on alcohol consumption, which was classified into 1 of 4 categories: rarely or never drink, very light (≤1 drink per week), light (1-6 drinks per week), or moderate (≥1 drink per day). Cox proportional hazards models were used to assess the relative risks of mortality associated with alcohol consumption, after adjustment for major coronary risk factors.

Results: During a mean follow-up of 4 1/2 years, 369 men died, 267 of whom died of cardiovascular disease. Compared with men with a history of stroke who drank rarely or never, those with a very light to moderate alcohol intake had multivariate relative risks for total mortality of 0.88 (95% confidence interval [CI], 0.60-1.28), 0.64 (95% CI, 0.48-0.85), and 0.71 (95% CI, 0.54-0.94), respectively (P = .03 for trend); and relative risks for cardiovascular mortality of 0.89 (95% CI, 0.58-1.36), 0.56 (95% CI, 0.40-0.79), and 0.64 (95% CI, 0.46-0.88) (P = .008 for trend). Compared with age-adjusted models, adjustment for major coronary risk factors did not significantly change risk estimates for total or cardiovascular mortality.

Conclusions: These data indicate a possible inverse association between light to moderate alcohol intake and risks of total and cardiovascular mortality in men with a history of stroke. More data are needed to confirm or refute these results.

Arch Intern Med. 2003;163:1189-1193
aspirin taken on alternate days decreases mortality from cardiovascular disease and whether beta carotene taken on alternate days decreases the incidence of cancer.\textsuperscript{6,7} In 1982, 261,248 US male physicians aged 40 to 84 years were identified from the mailing lists of the American Medical Association, Chicago, Ill, and were invited to participate in the PHS.\textsuperscript{8,9} The enrollment cohort for the PHS consisted of 112,528 men who responded with fully or partially completed questionnaires by December 31, 1983.

For this study, we focused our analyses on the 1320 men who indicated a history of stroke on the baseline questionnaire and provided information on alcohol consumption. These men did not participate in the randomized portion of the PHS, as stroke was among the baseline exclusions. The confirmation rate of self-reported nonfatal strokes in the randomized portion of the PHS is 98.6%.

**DATA COLLECTION**

The baseline questionnaire asked each subject to indicate his history of medical conditions such as myocardial infarction, stroke, transient cerebral ischemia, and diabetes mellitus. Information on several lifestyle, dietary, and medical factors was also collected, as described in this subsection. Alcohol intake was ascertained by a 7-level categorical variable that was a priori collapsed into 4 exposure categories: rarely or never drink, very light (\(<1\) drink per week), light (1-6 drinks per week), or moderate (\(\geq 1\) drink per day). Self-reported data on alcohol consumption have been shown to be reliable and valid in populations of health professionals.\textsuperscript{10-12}

Data were also collected on potential confounders, including age (in years) and body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters), and dichotomized into categories: BMI (<25 or \(\geq 25\)), history of diabetes mellitus (yes or no), treatment for hypertension (current, past, or never), smoking history (current, past, or never), history of angina pectoris (yes or no), history of myocardial infarction (yes or no), history of cancer (yes or no), current multivitamin use (yes or no), vigorous exercise at least once a week (yes or no), current liver disease (yes or no), and treatment for hypercholesterolemia (never or ever).

**OUTCOME ASCERTAINMENT**

The primary outcomes of interest were times to total and cardiovascular mortality. Deaths were identified through the National Death Index and were classified by trained nosologists, using the International Classification of Diseases, Ninth Revision, to select a cause of death. In addition to total mortality, we considered cardiovascular causes of death, which included ischemic coronary heart disease, acute myocardial infarction, stroke, and other cardiovascular disease. Person-time was defined as the number of years between the date the baseline questionnaire was returned and the date of death, or February 1, 1988, whichever occurred first.

**DATA ANALYSIS**

We computed descriptive statistics comparing means or proportions of baseline characteristics according to the level of alcohol consumption. Cox proportional hazards models tested the associations between alcohol consumption and total or cardiovascular mortality, with the group consuming alcohol rarely or never as the referent. Relative risks (RRs) and 95% confidence intervals (CIs) were computed.

We first used univariate proportional hazards models to test relevant predictors of death, as listed in the “Data Collection” subsection of this section. Variables with \(P<.05\) were considered significant predictors of cardiovascular mortality on univariate analysis or a priori established risk factors; therefore, potential confounders were included in the initial multivariate model.

Next, we used Cox proportional hazards models to estimate the RRs of total and cardiovascular death associated with increasing levels of alcohol consumption. Hypertension and hypercholesterolemia were excluded from the models, as they may be in the causal pathway between alcohol consumption and subsequent cardiovascular mortality.\textsuperscript{13} To evaluate possible effect modification, interaction terms for alcohol consumption with myocardial infarction, BMI, diabetes mellitus, and age were tested and models with stratum-specific results were assessed. Tests for linear trend were performed by including alcohol consumption as an ordinal variable, using the median value from each alcohol use category. The assumption of proportional hazards was satisfied for our multivariate models for total and cardiovascular mortality (\(P>0.05\) for both).

**RESULTS**

**COHORT CHARACTERISTICS**

During a mean follow-up of 4 1/2 years in this cohort of 1320 men who reported a history of stroke, there were 369 deaths, 267 (72.4%) from cardiovascular causes (myocardial infarction, 90 subjects; stroke, 55; ischemic coronary heart disease, 69; and other cardiovascular disease, 53). Characteristics of the cohort, by level of alcohol consumption, are presented in Table 1. Overall, the mean age of the cohort was 67.4 years, with a mean BMI of 25. A greater percentage of men in the highest alcohol consumption category reported current smoking, while self-reported history of myocardial infarction was similar across all of the alcohol consumption categories.

**TOTAL AND CARDIOVASCULAR MORTALITY**

We observed statistically significant decreases in age-adjusted total mortality (369 deaths) among men who consumed 1 to 6 drinks per week (RR, 0.67; 95% CI, 0.51-0.88) and more than 6 drinks per week (RR, 0.73; 95% CI, 0.56-0.94) compared with those who reported drinking rarely or never (\(P=0.03\) for trend) (Table 2). Relative risks for multivariate models were nearly identical to those computed in the age-adjusted models. Significant decreases in total mortality (355 deaths) were observed in multivariate models (\(P=0.03\) for trend).

We also observed statistically significant decreases in age-adjusted cardiovascular mortality (267 deaths) among men who consumed 1 to 6 drinks per week (RR, 0.57; 95% CI, 0.42-0.79) and more than 6 drinks per week (RR, 0.64; 95% CI, 0.47-0.86) compared with those who reported drinking rarely or never (\(P=0.008\) for trend). Again, the RRs for multivariate models were nearly identical to those computed in the age-adjusted models. We observed no significant change in risk estimates for men who consumed less than 1 drink per week (Table 2).

**OTHER ANALYSES**

History of cancer, multivitamin use, and history of liver disease were not significant predictors of death (\(P>0.05\)
for all) on univariate analyses or found to be confounders; therefore, these variables were not included in the final multivariate model. We evaluated models with and without hypertension and hypercholesterolemia and found no difference in predictive ability. Because hypertension and hypercholesterolemia are potentially in the causal pathway of the development of cardiovascular disease, these conditions were not included in multivariate models.13 Finally, inclusion or exclusion of men with missing data on covariates other than alcohol intake did not alter risk estimates.

We found a statistically significant decrease in age-adjusted ischemic coronary heart disease mortality (69 deaths) in men who consumed 1 to 6 drinks per week compared with those who reported drinking rarely or never ($P = .09$ for trend) (Table 3). For the risks of stroke (55 deaths) and myocardial infarction (90 deaths) mortality, we observed nonsignificant decreases with wide 95% CIs, perhaps because of the small numbers of events, which limited our power. Cancer mortality (43 deaths) was not significantly increased in any of the alcohol consumption groups (Table 2).

We then evaluated the interaction between alcohol consumption and age, history of myocardial infarction, history of diabetes mellitus, and BMI on cardiovascular mortality in men with a history of stroke. We found possible interaction between alcohol consumption of 1 to 6 drinks per week or more than 6 drinks per week and age.
In this cohort of 1320 male physicians with a history of stroke, we found a lower mortality among those with light to moderate alcohol consumption, with a 33% reduction in the risk of total mortality and a 43% reduction in the risk of cardiovascular mortality in men who consumed 1 to 6 drinks per week, compared with a reference group that never or rarely drank. This effect was independent of major coronary risk factors. There were also trends toward lower rates of stroke and myocardial infarction death among light to moderate drinkers. We were unable to differentiate between a history of ischemic and hemorrhagic stroke. We did not observe a significantly increased risk of death from cancer in this cohort of men who consumed 1 to 6 drinks per week.

In our study, men with a history of stroke and diabetes mellitus who consumed at least 1 drink per day had a significantly lower risk of cardiovascular mortality. These findings are consistent with recent results observed among subjects without previous stroke. In the Nurses’ Health Study and the PHS enrollment cohort, coronary heart disease mortality risk reductions of approximately 20% to 50% were observed, depending on levels of alcohol consumption, after adjusting for cardiac risk factors.

The protective effects of alcohol in men with a history of stroke were observed more strongly in men younger than 65 and in men with a BMI of less than 25, compared with the reference group. These results are intriguing but must be interpreted with caution as these findings have not been reported in other similar cohorts. These results may be caused by unknown mechanisms by which alcohol intake affects younger and leaner men, or by chance.

Alcohol consumption has been shown to reduce cardiovascular mortality through its beneficial effects on lipids. Alcohol use has also been shown to reduce platelet aggregation and alter clotting factors. Tissue plasminogen activator and nitrous oxide production also appear to be affected by alcohol intake.

Higher levels of alcohol consumption are thought to increase the risk of hemorrhagic stroke via decreased clotting time, an increase in blood pressure, and direct vascular damage. Heavy alcohol use may increase the risk of development of ischemic stroke by increased blood pressure. In our analyses, we demonstrated an association between light to moderate alcohol intake and decreased risks of cardiovascular and total mortality, despite these biologically plausible mechanisms by which alcohol could reduce this effect in men with a history of stroke.

Our analyses had several limitations. We did not have access to information about severity of stroke, rates of depression, and use of β-blockers, angiotensin-converting enzyme inhibitors, or statins, all of which can affect the course of disease. Some coronary risk factors, such as exercise, were not equally represented in all alcohol consumption categories. Although these known factors were adjusted for in multivariate models, other unknown and unadjusted factors affecting our RRs may have been present in this nonrandomized sample.

Our ascertainment of alcohol consumption relied on self-reported levels, which may have introduced misclassification in our primary exposure. However, self-reported alcohol consumption has been shown to be reliable in groups of health professionals. Misclassification could also occur if participants change their drinking habits or patterns over time, for which we had no follow-up measurements of alcohol intake. These types of misclassification bias would tend to underestimate the magnitude of any effect of alcohol intake on mortality.
Our highest alcohol consumption category included subjects who consumed more than 2 drinks per day. Previous research has demonstrated higher mortality in men who consume heavy amounts of alcohol. It would have been preferable to exclude heavy drinkers from the moderate intake category. Their inclusion may underestimate the true effect or association.

Finally, our cohort predominantly consists of white males, and we were unable to examine these results in women and other ethnic groups. However, other studies have found no difference in the effects of alcohol intake based on sex or ethnicity. Sacco et al10 found decreased odds of ischemic stroke in those who consumed moderate amounts of alcohol among men and women and among whites, blacks, and Hispanics.

Light to moderate alcohol intake has been demonstrated to be beneficial in reducing cardiovascular mortality after myocardial infarction and in primary prevention of stroke, and herein is associated with reduced all-cause and cardiovascular mortality in men with a history of stroke. Heavy alcohol consumption of more than 5 drinks per day, however, is known to increase the risk of ischemic and hemorrhagic stroke. For women, 2 drinks per day is considered at-risk drinking.

The beneficial effects of light to moderate alcohol consumption in our population outweighed any increased risk of death from recurrent stroke. The dose-dependent effects of alcohol on mortality complicate the recommendation of alcohol consumption, as excessive consumption carries medical and societal risks. As a result, physicians must carefully individualize their recommendations, taking into consideration a patient's past and current patterns of alcohol intake.

Accepted for publication August 15, 2002.

We acknowledge Eugenia Chan, MD, Sokja Janket, MD, and Eli Perencevich, MD, for their technical expertise in the development of the manuscript. In addition, we acknowledge the contributions of the staff of the PHS, under the leadership of Charlene Belanger, and Mary Breen, Vadim Babes, Jean MacFadyen, Geneva McNair, David Potter, Leslie Power, Harriet Samuelson, Miriam Schwartz, Michelle Sheehy, Joanne Smith, and Phyllis Johnson Wojciechowski. We are also indebted to the dedicated and committed participants who provided us with health information.

Corresponding author and reprints: Vicki A. Jackson, MD, Dana-Farber Cancer Institute, 44 Binney St, SW 411, Boston, MA 02115 (e-mail: vjackson@partners.org).

REFERENCES