Alcohol Consumption and Carotid Atherosclerosis: Evidence of Dose-Dependent Atherogenic and Antiatherogenic Effects

Results From the Bruneck Study

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Background and Purpose
Although a variety of epidemiological studies have suggested a U-shaped association between alcohol and cardiovascular disease, controversy still surrounds the role of atherogenesis in the mediation of alcohol effects.

Methods
Carotid atherosclerosis was measured with a sensitive and reproducible B-mode score in a random sample of 460 men drawn from the Bruneck Study (baseline examination in 1990).

Results
The age-adjusted relation between alcohol and carotid artery disease was U shaped, with light drinkers facing a lower atherosclerosis risk (odds ratio, 0.44; 95% confidence interval, 0.23 to 0.85; \( P = 0.01 \)) than either abstainers (odds ratio, 1.00) or heavy drinkers (odds ratio, 2.78; 95% confidence interval, 1.32 to 5.84; \( P < 0.01 \)). The association was not explained by the lifestyle of alcohol consumers (smoking) or inclusion of former (heavy) drinkers in the reference group. The effect of alcohol was modified by drinking behavior (type of beverage). Approximately a quarter of the atherosclerosis risk caused by severe alcohol consumption was mediated by the risk profile associated with drinking, whereas the apparent beneficial effect of low alcohol intake emerged independent of conventional risk attributes.

Conclusions
Our results support the hypothesis that adverse and beneficial effects of alcohol on cerebrovascular disease are mediated in part by analogous atherogenic and antiatherogenic properties. (Stroke. 1994;25:1593-1598.)

Key Words: • alcohol drinking • atherosclerosis • carotid arteries • epidemiology • ultrasonics

Study Population and Survey Area
Population recruitment was performed as part of the Bruneck Ischemic Heart Disease and Stroke Prevention Study.7,8 Bruneck and its suburbs constitute a semiurban area located in the north of Italy (Bolzano province). On the prevalence day (May 1, 1990) 4793 residents aged 40 to 79 years were registered in the survey area. Agriculture, commerce, and light industry are the main sources of income. Geographic remoteness determines low population mobility and maintenance of a traditional lifestyle. The population register is based on information available from the national census and is continuously updated for births, deaths, and changes of residence. The study population of the current survey constitutes a stratified random sample of 500 men aged 40 to 79 years (125 subjects from each decade). A total of 474 men participated. Data acquisition was complete in all but six subjects. To identify a population free of cerebrovascular disease we excluded men with a history or clinical symptoms of transient ischemic attack or stroke, which left 460 subjects for analysis.

Clinical History and Examination
Data on current alcohol consumption and drinking behavior were obtained as part of a standardized questionnaire on candidate vascular risk factors. Subjects were instructed to indicate their customary drinking frequency (days per week) and the average amount of alcoholic beverage ingested on a typical occasion or during a typical day. Beer (500-mL bottle, equivalent to about 25 g ethyl alcohol), wine (250-mL glass, 25 g alcohol), and spirits and liquors (standard drinks, 8 to 10 g alcohol each) were included as separate items. Average alcohol consumption was quantified in terms of grams per day and classified in four categories: (1) no current alcohol use, (2) ≤50 g/d, (3) 51 to 99 g/d, and (4) ≥100 g/d. Reliability of
## Odds Ratios of Current Alcohol Consumption for Carotid Atherosclerosis Before and After Sequential Addition of Associated Risk Attributes

<table>
<thead>
<tr>
<th>Alcohol, g/d</th>
<th>Model 1 (Adjusted for Age)</th>
<th>Model 2 (Plus Smoking/Lifestyle*)</th>
<th>Model 3 (Plus SBP)</th>
<th>Model 4 (Final Model)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1-50</td>
<td>0.44 (.01)</td>
<td>0.46 (.04)</td>
<td>0.47 (.07)</td>
<td>0.47 (.05)</td>
</tr>
<tr>
<td>51-99</td>
<td>0.80 (.05)</td>
<td>0.75 (.06)</td>
<td>0.70 (.09)</td>
<td>0.70 (.07)</td>
</tr>
<tr>
<td>≥100</td>
<td>2.78 (.0007)</td>
<td>2.61 (.01)</td>
<td>2.23 (.04)</td>
<td>2.20 (.05)</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; SBP, systolic blood pressure. Values in parentheses indicate relative changes in ORs.

*Social status, activity, and body-mass index.
†Plus triglycerides, glucose, fibrinogen, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol.

categorization and relevancy of a nondifferential response error were ascertained by reassessing (at an interval of 3 weeks after the initial inquiry) 10-MHz imaging with 20-item diet records in 250 men (50% of the original sample). Since day-to-day variation of alcohol consumption is substantial, diet and alcohol records were collected over an extended period of 7 days. In addition to recent drinking behavior, previous alcohol intake (same categories) and trends in the amount of regular alcohol consumption over the past decade were assessed. Subjects were classified in three categories according to the type of alcoholic beverage preferred: (1) wine drinkers (wine consumption less than once per week), (2) beer drinkers (wine consumption less than once per week), and (3) consumers of beer and wine and/or considerable amounts of spirits (more than 5 drinks per week). Qualitative features of drinking were derived from a structured in-person interview, which was uniformly conducted by a single experienced physician. The number of cigarettes smoked per day was recorded for current and ex-smokers, as were history of coronary artery disease, medication, and social status. Systolic and diastolic blood pressures were calculated from two independent measurements, each of which was taken after 10 minutes of rest. The body mass index was used as an obesity index, determined as weight (kilograms)/height^2 (meters^2). The activity score consisted of the calculated average of the scores for work, leisure, and sports activities. Venous blood samples were drawn after 12 hours of fasting and abstinence from smoking. High-density lipoprotein (HDL) cholesterol and triglycerides were analyzed by means of commercial enzymatic assays (CHOD-PAP and GOD-PAP methods, Merck). Low-density lipoprotein (LDL) cholesterol was calculated from the Friedewald formula. Apolipoproteins A-I and B, fasting glucose, serum fibrinogen, and γ-glutamyl transferase (GGT) were measured with standard procedures.

### Evaluation of Vascular Status

Sonographic assessment of the carotid arteries was performed using a duplex ultrasound system (ATL UM8, Advanced Technology Laboratories) with a 10-MHz imaging probe. Carotid atherosclerosis was quantified with a sensitive and reproducible plaque scoring system, as previously described in detail. The score was composed of 16 different measurements, each of which represented the maximum axial diameter of atherosclerotic lesions on the near or far wall at eight well-defined imaging sites (right/left proximal common carotid artery, 15 to 30 mm proximal to the carotid bulb; distal common carotid artery, <15 mm proximal to the carotid bulb; proximal internal carotid artery, carotid bulb and the initial 10 mm of the vessel; and distal internal carotid artery, >10 mm above the flow divider). The outcome variable used in the analysis was dichotomized according to the vascular status (0, no atherosclerosis; 1, plaque score >0 mm). The interobserver agreement of this binary variable was considerably high (κ coefficient=0.85, n=50).

### Statistical Analysis

Statistical evaluation of the association between risk factors and alcohol intake (grams per day) was based on the calculation of partial correlation coefficients with age and smoking used as covariates. Log-transformed variables were used for computation in the event of a skewed distribution. Regarding the accuracy of self-reported alcohol consumption, agreement was calculated in the alcohol categorization (0 to 3) between both assessments (κ statistics). To examine the potential relation of alcohol and carotid atherosclerosis, logistic regression models were developed with the hypothesis test based on likelihood-ratio statistics. Since log-odds for atherosclerosis relate to aging in a linear fashion, we used a continuous variable (years) for age adjustment. Changes in the odds ratios (ORs) for alcohol with advancing age were within the range of random variability. Thus, all analyses refer to the entire population sample aged 40 to 79 years. To estimate the extent to which alcohol effects were mediated by other risk attributes, we sequentially added concurrent behavioral factors (such as smoking) (Table, model 2) and risk factors associated with drinking (Table, models 3 and 4) to a base model including age as a single covariate. Interaction among age, alcohol use, and risk variables was calculated but gave no evidence of effect modification (not explicitly mentioned in the text).

### Results

#### Prevalence

Of 460 men eligible for analysis, 34% reported that they consumed alcoholic beverages containing up to a maximum of 50 g of ethyl alcohol per day, and 26% reported more than 50 g/d but less than 100 g/d. The groups of teetotalers and heavy drinkers (≥100 g/d) accounted for 24% and 16%, respectively (Fig 1). We achieved 89% participation in the 1-week assessment of diet records, and therefore results are probably not biased by selective responding. A comparison of both assessments exhibited low rates of misclassification across quantitative alcohol strata (κ coefficient=0.87; Fig 2) and categories of main alcoholic beverages (κ coefficient=0.79). When diet records were used as a reference standard, the nondifferential response error for those consuming less than 100 g/d alcohol was low at 6.5%. Heavy drinkers tended to underestimate their daily alcohol intake by 13% on average, which essentially did not affect correct classification in the top category of alcohol use (≥100 g/d).
As expected, we found evidence for a strong association between alcohol consumption and smoking (Fig 3a). There was a clear trend toward an increased prevalence and severity (categories 0 to 3) of cigarette smoking among drinkers ($\chi^2=18.1, df=9, P<.05$). HDL cholesterol (partial correlation coefficient $r=+0.35, P<.001$) and apolipoprotein A-I ($r=+0.32, P<.001$) correlated positively with increasing levels of alcohol intake (Fig 3b and 3c). Our data confirm and amplify the previously reported relation between hypertension and alcohol consumption (Fig 3d). Increasing amounts of alcohol consumed correlated positively with mean diastolic and systolic blood pressures ($r=+.14, P<.01$) and negatively with serum fibrinogen levels ($r=-.15, P<.01$). Other risk variables, including fasting glucose and triglyceride levels, were distributed equally between abstainers and drinkers.

**Alcohol and Carotid Atherosclerosis**

In a first analysis alcohol consumption was scaled in terms of grams per day and treated as a continuous variable. In the logistic regression equation the age-adjusted overall effect of drinking was moderate disease promotion (slope coefficient $\beta=+.0067, df=1, P<.01$) (Fig 4a). Next, alcohol consumption was classified in four equally spaced groups at 50 g/d each, and separate risk estimates were calculated for these categories. Visual inspection of the ORs (Fig 4a) strongly suggested the occurrence of a U-shaped trend. Atherosclerosis risk in men who consumed $\geq 100$ g/d was more than twice that of abstainers; light drinkers fared best, with an OR of 0.44 ($P=.01$). The use of orthogonal polynomials confirmed the excellent fit of the quadratic model (quadratic component, $P<.001$). Restricting analysis to alcohol estimates obtained with the diet record method further improved the predictive significance of alcohol consumption ($\leq 50$ g/d: OR, 0.38; $\geq 100$ g/d: OR, 3.67). When past alcohol use was analyzed in place of recent drinking habits, the association with carotid atherosclerosis remained U shaped but the strength of the relation was less pronounced, which may reflect an equally lower accuracy in the evaluation of previous drinking. Analyses based on self-reported drinking were supplemented by corresponding equations that included GGT, a valid biochemical marker of alcohol intake. Men with a GGT value of 21 to 25 U/L showed a tendency toward a reduced atherosclerosis risk (OR, 0.72; reference group, GGT $\leq 20$ U/L), whereas GGT at the upper end of the observed range ($>30$ U/L) indicated a significantly enhanced risk (OR, 1.95; 95% confidence interval [CI], 1.01 to 3.79; $P=.05$) (Fig 4d). Results were adjusted for medication and hepatitis (B and C) as additional major causes of liver damage and enzyme induction. In a female population from the same survey area, the relation between low amounts of alcohol ($\leq 50$ g/d, $n=112$ [25%]) and carotid atherosclerosis was similar to that of a male population (OR, 0.47; $P=.01$).

We next analyzed the effect of beer and wine separately; a U-shaped association with carotid artery disease was consistently obtained regardless of the type of beverage preferred (Fig 4b). In the top category of alcohol consumption ($\geq 100$ g/d), men who exclusively drank wine fared best, with an OR of 1.42 (95% CI, 0.46 to 4.45). Beer drinkers and those who consumed wine, beer, and occasionally spirits faced a clearly higher risk of carotid atherosclerosis (OR, 3.60; 95% CI, 1.56 to 8.30; $P<.01$).

**Biological Pathways and Potential Confounding**

The crude association between alcohol consumption and carotid atherosclerosis may be attributed as much to lifestyle and social behavior as to drinking itself. To estimate the extent of confounding by coincident smoking, the logistic regression model was carefully controlled for the number of cigarettes smoked daily. The OR associated with severe alcohol consumption ($\geq 100$ g/d) decreased by approximately 6%, whereas the apparent protection provided by low alcohol intake was unaffected. When analysis was restricted to actual nonsmokers ($n=310$), no major changes in adjusted ORs were observed. The addition of behavioral variables including social status, physical activity, and body mass index did not further improve the fit of the regression model and yielded similar risk estimates for alcohol intake (Table, model 2).

A variety of experimental and epidemiological studies, including ours, have indicated that alcohol consumption is associated with other risk factors such as hypertension and a disturbed lipid metabolism. The Table displays results of sequential addition of these factors to the logistic regression model. For example, adding systolic blood pressure moved the OR of severe alcohol consumption from 2.61 to 2.23. Once the effect of all attributes was accounted for, alcohol appeared to have a strong and independent residual relation to carotid artery disease (Table, model 4).
Ex-drinkers usually stopped drinking because of health problems or a desire for a more favorable lifestyle. On comparing lifetime abstainers with past (heavy) drinkers, the latter group had an enhanced atherosclerosis risk (+47%), which emerged independent of the vascular risk profile. Therefore, we explored whether the inclusion of past drinkers in the reference group (current nondrinkers) had introduced a bias in terms of a pretended beneficial effect of low alcohol quantities and a spurious U-shaped relation. The standard procedure to address this potential error is the exclusion of previous drinkers. In a second approach we reclassified ex-drinkers as light, moderate, or severe based on the self-reported amounts of previous alcohol consumption and ran separate equations. Both methods tended to lessen the beneficial effect of low amounts of alcohol (OR, 0.52 and 0.51, compared with 0.44 in the original model); the residual relation, however, remained statistically significant (P<.05). Finally, results did not change appreciably when excluding subjects with coronary artery disease, who might have changed their drinking behavior because of pre-existing disease status.

**Discussion**

The present population study yielded strong empirical evidence for a U-shaped relation between daily alcohol consumption and carotid atherosclerosis (df=3, P<.001) (Fig 4). Lifestyle and social behavior associated with drinking had little confounding effect and per se could not explain the relation between alcohol and atherosclerosis. The beneficial effect of low amounts of alcohol (≤50 g/d) was not an artifact because of the inclusion of former (heavy) drinkers in the reference group of nondrinkers. Our findings support the view that adverse and beneficial effects of alcohol on cerebrovascular diseases are mediated in part by a dose-dependent promotion or deceleration of atherogenesis.

Previous reports on the relation between carotid atherosclerosis and alcohol are sparse and controversial. Bogousslavsky and coworkers found patients with light-to-moderate alcohol intake (<40 g/d) to be at lower risk for carotid artery disease than nondrinkers, which is in close agreement with our observations. In the Honolulu Heart Program the prospective evaluation of 198 men yielded a weak inverse trend for the association between atherosclerosis and generally low alcohol intake. Prati and coworkers observed that a lifetime alcohol intake (in kilograms) strongly predicted moderate and severe carotid artery disease in the Friuli-Venice area. Palomäki et al reported a significant inverse association between low alcohol intake and atherosclerosis in a sample of 294 patients with transient ischemic attack or minor stroke. These studies...
Current Alcohol Consumption

Ex-Drinkers Excluded

Type of Beverage

Gamma-Glutamyl Transferase

were either restricted to low alcohol consumption (≤40 to 50 g/d) or did not differentiate between light and heavy drinkers. Past reports did not address potential differences in the relation of carotid atherosclerosis and various types of alcoholic beverages. In our population sample, wine drinkers tended to consume less alcohol than did drinkers of other types of alcohol and showed a lower OR for carotid atherosclerosis in the event of heavy alcohol consumption. Quantitative differences between alcohol from wine and other (or varying) sources approach statistical significance (df=3, P<.11). However, the possibility cannot be ruled out that the emergence of a lower risk among wine consumers is confounded by differences in drinking behavior: wine is mostly consumed during meals, giving rise to a prolonged absorption and possibly to lower peak alcohol levels in blood. The hypothesis that antioxidant phenolic components in wine decelerate LDL oxidation is preliminary and controversial. Evidence is still conflicting as to the extent to which the relation between alcohol and atherosclerosis is mediated by the metabolic complex associated with drinking. One of the proposed mechanisms by which low alcohol intake reduces the risk of cardiovascular disease is by raising HDL cholesterol concentrations. In our analysis the beneficial effect of low alcohol quantities emerged independent of an HDL cholesterol (apoliprotein A-1) pathway and of other risk attributes as well. Accordingly, our study is indicative of direct ethanol effects. As a promising clue, prostacyclin levels and the ratio of prostacyclin to thromboxane A2 were found to increase after moderate doses of ethanol. This observation may be relevant to atherosclerotic vascular tissue, where a decline in prostacyclin predisposes to thrombus formation and a further progression of atherosclerosis due to platelet-derived mitogenic and chemotactic factors. Potential antiatherogenic properties of low amounts of ethanol include a decrease in platelet aggregability and an enhanced release of plasminogen activator.

Insight into the underlying pathomechanism(s) of the high atherosclerosis risk of heavy drinking is limited. In our survey the risk profile associated with severe alcohol consumption accounted for approximately 25% of the relation between alcohol and carotid artery disease. Promotion of LDL oxidation by acetaldehyde, the primary metabolite in ethanol catabolism, may possibly achieve some relevance. As to the interpretation of results, some aspects demand further close consideration. (1) According to the study design used, the association evident between alcohol consumption and carotid atherosclerosis refers to prevalent rather than incident atherosclerotic disease. Some longitudinal aspects were introduced by exploring the effect of previous drinking habits, which
generally confirmed the results derived from responses on current alcohol consumption. (2) Categorization of quantitative alcohol intake (grams per day) is based primarily on customary portion sizes of alcoholic beverages consumed in the survey area. It bears the advantage of an accurate and reproducible classification and of a homogeneous distribution of study subjects across quantitative strata; however, it does not necessarily mirror the precise biological thresholds in the dose-response effect of drinking and atherosclerosis. (3) As a general problem confronting alcohol research, the ascertainment of customary alcohol consumption relies on self-reported information, which is subject to response error.1,19,29,30 Sample survey estimates based on self-reported data were found to be approximately 40% to 60% of the aggregate consumption computed separately through sales and tax statistics.30 This coverage problem is attributed primarily to a nondifferential recall error that affects all respondents similarly.1,19 In our study the application of diet records (over a 7-day period) as a reference standard and the assessment of drinking behavior as part of a general risk evaluation indicate a more complete response. Therefore, the comparatively high average alcohol consumption in the present population sample may reflect in part the precise evaluation of drinking behavior. Several lines of evidence argue against a relevant influence of a differential response error. Boundaries of socially accepted drinking in the survey area, which may determine the deliberate denial of alcohol use, are fairly broad. The U-shaped relation remained evident when substituting a valid biochemical marker (GGT) for self-reported drinking quantities.13 Behavioral risk conditions are of particular importance in the prevention of vascular disease. In the present study, a daily consumption of up to 50 g of alcohol was seen to be inversely associated with carotid atherosclerosis and may be medically safe. This potential beneficial effect of small amounts of alcohol, however, is restricted by the substantial social and health risks, including atherosclerosis, of heavy alcohol use. The net effect of alcohol consumption, when grouping all types of drinking together, was a positive predictive consumption and blood lipid levels: Kaisariane Multifaceted plasma lipoprotein responses. Proc Soc Exp Biol Med. 1992;200:67-77.

Acknowledgments

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