Alcohol Consumption and Atherosclerosis: What Is the Relation?
Prospective Results From the Bruneck Study
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Background and Purpose—Potential effects of regular alcohol consumption on atherogenesis are still controversial mainly due to the lack of prospective population-based studies.

Methods—The Bruneck Study is a prospective population-based survey of atherosclerosis and its risk factors. The study population comprises a sex- and age-stratified random sample of men and women aged 40 to 79 years. Participation and follow-up were more than 90% complete. Changes in carotid atherosclerosis between the 1990 baseline and the first follow-up in 1995 were monitored by high-resolution duplex ultrasonography. Alcohol intake was quantified with a standardized questionnaire and prospective diet records.

Results—Alcohol consumption less than once a week (occasional drinking) had no effect on atherogenesis. The association between regular alcohol intake and incident carotid atherosclerosis (early atherogenesis) was J-shaped, with light drinkers facing a lower risk than either heavy drinkers or abstainers. Protection offered by alcohol consumption of <50 g/d appeared to act through inhibition of the injurious action of high levels of low-density lipoprotein (LDL) cholesterol. Excess risk of incident atherosclerosis observed among heavy alcohol consumers (>100 g/d) clearly surpassed the risk burden afforded by heavy smoking. The association between regular alcohol intake and incident carotid stenosis (advanced atherogenesis) was U-shaped. Odds ratios were generally shifted toward protection and did not rely on LDL cholesterol levels. We failed to find any differential effects of alcohol from various sources. All associations remained independently significant when we adjusted for lifestyle, coincidental smoking, and the metabolic complex associated with drinking.

Conclusions—Our findings support the view that adverse and beneficial effects of alcohol on arterial disease are mediated in part by a dose-dependent promotion or deceleration of atherogenesis. The protection afforded by light drinking may possibly be attributed to antithrombotic effects and inhibition of the atherogenic action of high levels of LDL cholesterol. (Stroke. 1998;29:900-907.)

Key Words: alcohol drinking • atherosclerosis • carotid artery disease • lipid peroxidation • lipoproteins, LDL

Alcohol is an important constituent of the European and American diets. The weight of previous epidemiological evidence suggests a U- or J-shaped association between alcohol consumption and various types of ischemic illness, including myocardial infarction1,2 and ischemic stroke.3 Low amounts of alcohol when taken on a regular basis have been shown to protect against cardiovascular disease and death,4,5 whereas heavy drinking constitutes a severe risk condition. Dose-dependent atherogenic and antiatherogenic properties may constitute a main pathophysiological link between alcohol consumption and arterial disease.6 However, this hypothesis is still challenged due to a lack of prospective epidemiological surveys in this field. The current population study may well be the first to investigate the effects of alcohol consumption on incidence and progression of atherosclerosis over a 5-year period (1990 to 1995). Our main focus was on the following questions: (1) Does the cross-sectional U-shaped association between alcohol consumption and carotid atherosclerosis observed in this cohort7 hold true in the prospective evaluation? If so, what is the approximate threshold for the switch from favorable to injurious effects of regular alcohol intake? (2) Which stage of atherogenesis is the main target of alcohol effects? Is it of relevance which type of alcoholic beverage is consumed and how? (3) Do putative beneficial effects of light drinking act by modifying the injurious (atherogenic) potential of LDL cholesterol, as recently postulated8?

Subjects and Methods

Study Subjects
Population recruitment was performed as part of the Bruneck Study.7,8 The survey area is located in northern Italy, in the province...
of Bolzano. Agriculture, tourism, commerce, and light industry are the main sources of income. Geographic remoteness causes low population mobility (<1% per year). The study population constitutes a sex- and age-stratified random sample of 1000 men and women aged 40 to 79 years (125 women and 125 men, all in the fifth to eighth decades). A total of 93.6% participated, with data assessment completed in 919 subjects. During the follow-up period between summer 1990 and 1995, a subgroup of 62 individuals died, and one moved away and could not be traced. In the remaining population, follow-up was 96.5% complete (n = 826). All participants gave their informed consent before entering the study.

Clinical History

Data on alcohol consumption and drinking behavior were obtained twice in 1990 and 1995 with use of the same standardized questionnaire. Subjects were instructed to indicate their customary drinking frequency (days per week) and the average amount of alcoholic beverages ingested on a typical occasion or during a typical day. Beer (500-mL bottle, equivalent to about 25 g ethyl alcohol), white or red wine (250-mL glass, 25 g ethanol), and spirits and liqueurs (standard drink, 8 to 10 g alcohol each) were included as separate items. Average alcohol consumption was quantified in terms of grams per day and classified into four categories: (1) no regular alcohol use, (2) ≤50 g/d, (3) ≥51 to 99 g/d, and (4) ≥100 g/d. In addition, diet records, which resembled those developed and validated by Willett and coworkers, were collected as part of the follow-up evaluation. Nine frequency response categories ranged from consumption less than once a month or never to 6 times or more per day. Data were recorded by study subjects over the 4-week period prior to the follow-up examination, and the records were completed with the assistance of 1 specially trained physician. The prospective analysis was restricted to men and women who either remained in the same or a neighboring category of alcohol consumption (n = 780). In the latter event we calculated a weighted average of alcohol intake between 1990 and 1995, using the time intervals with consistent alcohol intake as weights, and categorized accordingly. Alternative approaches, which either applied the baseline category of alcohol intake or further excluded subjects with slight changes in alcohol quantities, yielded similar results (data not presented).

Qualitative features of drinking were derived from a structured in-person interview. According to the type of alcoholic beverage preferred, subjects were classified as (1) red wine drinkers, (2) beer drinkers (consumption of other beverages less than once a week), or (3) consumers of alcohol from other or mixed sources. Despite the high average alcohol intake in the survey area, binge drinking (defined as occasional uncontrolled ingestion of >75 to 100 g/d alcohol) was rare (<1%) and thus not considered in the analysis.

The average number of cigarettes smoked per day and the pack-years as a measure of cumulative exposure were noted for each smoker and ex-smoker. Systolic and diastolic blood pressure readings were taken with a standard mercury sphygmomanometer after at least 10 minutes of rest, while the subject was in a sitting position. The values used in the current analysis are means of three measurements taken by the same investigator at about 1-hour intervals. A standardized oral glucose tolerance test (75 g glucose in 10% solution) was performed in all subjects except those with well-established diabetes mellitus. Diabetes mellitus was coded present for subjects with fasting glucose levels of >7.8 mmol/L (140 mg/dL) and/or a 2-hour value of >11.1 mmol/L (200 mg/dL). Body mass index and waist-to-hip ratio were used as obesity indices.

Laboratory Methods

Blood samples were taken from the antecubital vein after subjects had fasted and abstained from smoking for at least 12 hours. Apolipoproteins were measured by a nephelometric fixed-time method (apolipoproteins A1 and B, Behring; CV, 5.7% and 2.4%). HDL cholesterol and triglyceride levels were determined enzymatically (CHOD-PAP and GPO-PAP methods, Merck; CVs, 2.2% to 2.4% and 4.3% to 5.4%, respectively). LDL cholesterol was calculated with the Friedewald formula except in subjects with triglyceride levels of >4.52 mmol/L. Fasting insulin level was measured according to the method of Hales and Randale (CV, 3.2% to 4.8%) and with a human insulin–specific radioimmunoassay (Linco Research; CV, 3.9%). Lipoprotein(a) (enzyme-linked immunosorbent assay, Baxter Diagnostics; CV, 2.1% to 4.9%), and fibrinogen (method of Clauss) were assessed according to standard procedures.

Scanning Protocol and Definition of Ultrasound End Points

The ultrasound protocol involves the scanning of the internal (bulbous and distal segments) and common carotid arteries (proximal and distal segments) of either side with a 10-MHz imaging probe and a 5-MHz Doppler probe. Atherosclerotic lesions were defined by two ultrasound criteria: (1) wall surface (protrusion into the lumen or roughness of the arterial boundary) and (2) wall texture (echogenicity). The maximum axial diameter of plaques, the vessel diameter in the diastole, and Doppler frequency spectra were assessed in each of the 8 vessel segments. Scanning was performed twice (in 1990 and 1995) by the same experienced sonographer, who was unaware of the subjects’ clinical and laboratory characteristics. Based on the follow-up evaluation we assessed 5-year changes in the vascular status (overall progression). The scanning protocol also permitted a differentiation of various stages in atherogenesis.

The analysis focused on incident atherosclerosis (early atherogenesis) defined by the occurrence of new plaques in previously normal segments and on the development of vessel stenosis as a crucial event in advanced atherogenesis. The latter process was defined by a relative increase in the maximum diameter of preexisting plaques that exceeded the double measurement error of the method (distal internal carotid artery, 35%; bulbous, 30%; common carotid artery, 20%) and resulting narrowing of the lumen of >40%. The cutoff of 40% appeared to be a biological threshold in our population, at which marked changes in growth kinetics, risk profiles, and vascular remodeling occurred, indicating a shift in the underlying pathological mechanisms from continuous step-by-step mechanisms toward occasional disease progression by plaque thrombosis. This concept is substantiated by the fact that the occurrence of stenosis >40% did not rely on conventional risk factors but emerged as a domain of a procoagulant state involving high levels of fibrinogen, lipoprotein(a), and low levels of antithrombin III. Reproducibility of the ultrasound outcome categories was “nearly perfect,” as indicated by (weighted) κ coefficients >0.8 for agreements between double measurements (n = 100).

Statistical Analysis

Agreement in alcohol quantities assessed with the standardized questionnaire or diet records was calculated using the κ statistics. The association between regular alcohol intake and various stages of atherogenesis was examined by logistic regression analysis, with the hypothesis test based on likelihood ratio statistics. The alcohol categories were modeled either as a set of indicator variables to assess the strength of association (ORs) or as a set of trends (orthogonal polynomials) to characterize the scale. To estimate the extent to which alcohol effects were mediated by other risk attributes, we added behavioral factors and risk factors associated with drinking to a base model that was adjusted for age and sex only. The forced entry of all covariates yielded results virtually identical to those of a forward stepwise selection procedure. Thus, for ease of presentation we present data derived from the primary simpler
light drinkers facing a lower risk than either abstainers or heavy alcohol consumers (n=780, Figure 3a and 3b). Excess risk of atherosclerosis observed among heavy alcohol consumers (adjusted OR, 3.41) clearly surpassed the risk burden afforded by heavy smoking (≥20 cigarettes/d) (OR, 2.20). Restriction of the study population to nonsmokers (n=610) yielded similar results (adjusted ORs [95% CI] for the alcohol categories: 1.0, 0.54 [0.31 to 0.93], 2.81 [1.22 to 6.05], and 3.88 [1.38 to 9.77]; P<0.001), as did the exclusion of subjects who stopped drinking before 1990 (n=34) or who experienced symptomatic cardiovascular disease (1.0, 0.65 [0.44 to 0.97], 1.85 [0.88 to 3.89], and 3.22 [1.21 to 8.57]; P=0.005).

Differential effects of regular alcohol consumption on various stages of atherogenesis are visualized in Figure 3c and 3d. Notably, effects of low alcohol intake on early atherogenesis were apparently different in subjects with high (≥66th percentile=3.88 mmol/L; 150 mg/dL) and low-to-normal LDL cholesterol levels (adjusted ORs, 0.39 versus 1.07, P=0.009 for effect modification, Figure 3c). When these results were viewed in light of the LDL atherogenicity, high level of LDL was a prominent risk factor in abstainers and even more pronounced in moderate-to-heavy drinkers but not in light drinkers (Figure 4). Advanced atherogenesis and alcohol consumption showed a U-shaped relation (Figure 3d). ORs were generally shifted toward protection and were not influenced by LDL levels.

Once the effect of all potential confounders had been accounted for, associations shown in Figure 3 remained unchanged in shape and emerged as independently significant. Elevated HDL cholesterol levels and improved insulin sensitivity in light drinkers accounted for an albeit small part (≈10%) of the inverse association with incident atherosclerosis. Application of orthogonal polynomials revealed a significant quadratic (P=0.012) and positive linear component (P<0.001) for the relation between alcohol and early atherogenesis and a purely quadratic type of relation for advanced atherogenesis (P=0.02).

All analyses were repeated using six equally spaced alcohol categories of 25 g/d each instead of three. This approach was more precise although less reproducible. It established upper quantitative thresholds for significant protection against early and advanced atherogenes at 50 and 25 g/d, respectively.

All of the results shown above were not substantially different for alcohol from wine, beer, or other and mixed sources. For example, ORs for the beneficial effects of alcohol on advanced atherogenesis were 0.41, 0.48, and 0.54 for red wine, beer, and combinations of both or other beverages, respectively. Alcohol consumption during meals tended to offer more protection against advanced atherogenesis than did other types of drinking (P=0.09 for effect modification) but did not modify the relation between drinking and early atherogenesis.

Finally, ORs of incident atherosclerosis for quitters were a good match for those of current heavy drinkers (adjusted OR [95% CI], 3.75 [1.47 to 9.55]). Occasional drinking (less than once a week) affected neither early nor advanced atherogenesis (adjusted ORs, 0.97 and 1.01).
**Discussion**

**Alcohol and Atherosclerosis: What Is the Relation?**

Controversy still surrounds the role of alcohol consumption as a potential risk factor for atherogenesis. In our population-based prospective study, the association between regular alcohol intake of various quantities and 5-year progression of carotid atherosclerosis was J-shaped, with light drinkers facing a lower risk than either heavy drinkers or abstainers (Figure 3a). The relation was not materially different in men and women (Figure 3b), even though interpretation of moderate-to-heavy alcohol intake in females requires caution because of the low number of subjects in these categories. A J- or U-shaped association applied to both early and advanced atherogenesis (Figure 3c and 3d). Occasional drinking, ie, alcohol intake less than once a week, had essentially no effect on incidence and progression of atherosclerotic lesions. Our findings support the view that adverse

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**Table 2a**

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<tr>
<th>Alcohol categories</th>
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<td>1990 0</td>
<td>+3.3 (n=354)</td>
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<td>+4.3 (n=29)</td>
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<td>+2.8 (n=29)</td>
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<td>-0.2 (n=26)</td>
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<tr>
<td>1</td>
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<td>+0.1 (n=25)</td>
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<td>-36.9 (n=6)</td>
<td>-41.1 (n=16)</td>
<td>+3.3 (n=18)</td>
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</table>

**Figure 2.** Panels a and b, Changes in HDL cholesterol levels and systolic blood pressure according to changes and amounts of regular alcohol consumption during follow-up (1990 to 1995) (n=826). Panels c and d, Changes in antithrombin III and γ-glutamyl transferase according to changes and amounts of regular alcohol consumption during follow-up (1990 to 1995) (n=826).
and beneficial effects of regular alcohol consumption on arterial disease are mediated in part by a dose-dependent promotion or deceleration of atherogenesis. Alcohol-induced hypertension and excess smoking among alcohol consumers may be potentially important intermediate components in the association between moderate-to-heavy alcohol intake and atherosclerosis risk. On the other hand, the presence of an elevated HDL cholesterol level has been suggested to be of relevance in mediating the beneficial effects of light drinking. In our survey, when the effects of these and other risk variables were accounted for and/or smokers were excluded, the association between alcohol consumption and atherogenesis risk.
esis remained independently significant. Thus, our study is indicative of direct effects of alcohol and/or nonalcoholic components of wine and beer, even if some residual confounding does exist.

Previous reports on alcohol and carotid atherosclerosis are sparse and cross-sectional in design. Two small studies revealed an inverse association between carotid atherosclerosis and low alcohol intake.\textsuperscript{15,19} In contrast, another large cross-sectional evaluation failed to find beneficial effects of regular alcohol intake on intima-media thickening, a precursor lesion of atherosclerosis.\textsuperscript{16} As a potential explanation for these inconsistencies, it is important to note that mean alcohol consumption in the latter study was low at 3 to 10 g/d and that a considerable proportion of study subjects reported alcohol intake less than once a week (occasional drinking). Finally, in a population from the Friuli-Venezia Giulia area (northern Italy), a high lifetime load of alcohol in terms of kilograms of ethanol consumed predicted an elevated risk of prevalent carotid artery disease.\textsuperscript{21} In our survey, when alcohol consumption was treated as a continuous variable (grams per day), the emerging overall association with atherosclerosis progression showed a positive slope as well (data not shown).

Threshold
The weight of previous studies on cardiovascular disease reported beneficial effects of low alcohol intake up to 20 to 50 g/d ethanol, and a smaller body of evidence suggests similar thresholds for ischemic stroke.\textsuperscript{4–6,22} Corresponding limits for atherogenesis in our survey amounted to 25 to 50 g/d, depending on given stages, and thus fit well into the above range. However, all limits should be interpreted as population averages and do not necessarily reflect correct individual thresholds. Actually, intestinal degradation, absorption, metabolism, and blood clearance of ethanol are subject to high interindividual variability.

Effects of Drinking Behavior
Consumption of alcohol during meals has been postulated to offer more protection against atherosclerotic disease than other drinking patterns.\textsuperscript{23,24} In our population this hypothesis may hold true for effects of alcohol on advanced atherogenesis. Previous population surveys revealed that wine, beer, and spirits in moderation are all protective against cardiovascular disease.\textsuperscript{3,24,25} Thus far, no consistent evidence has emerged that any of these beverages is actually superior to others. The current study revealed analogous results for atherosclerosis, ie, it did not find differential effects of alcohol from various sources. This result should be viewed in light of the fact that red wine and beer accounted for 90% of overall alcohol intake in the survey area. Accordingly, results are reliable for either of these beverages but may be insufficient to settle the issue for white wine or spirits.

Pathophysiological Background

**LDL Oxidation**
Recently, marked inhibitory effects of nonalcoholic components of red wine on oxidation of LDL have been documented in vitro.\textsuperscript{26–29} Relevance of such a mechanism in vivo has been proposed,\textsuperscript{30} but was initially challenged owing to the lack of precise knowledge of the pharmacokinetics of the phenolic substances.\textsuperscript{31} Meanwhile, an emerging body of evidence suggests that at least some are readily absorbed and that they occur in circulation at concentrations able to suppress LDL oxidation.\textsuperscript{30,32,33} However, beneficial effects of phenolic acids, which are contained in various amounts in all alcoholic beverages,\textsuperscript{28} must be considered in the light of a potential opposite effect of ethanol. Actually, there is some experimental support for a pro-oxidant action of ethanol\textsuperscript{14,35} that has been ascribed to LDL modification by acetaldehyde, its primary metabolite,\textsuperscript{21,36} to an alcohol-induced increase in the NADH-dependent generation of free oxygen radicals,\textsuperscript{37} and to mobilization of highly reactive Fe$^{2+}$ ions.\textsuperscript{38} The net impact of the consumption of alcoholic beverages on lipid peroxidation and lipid-induced atherogenesis has been postulated to dependently change from protection to disease promotion.\textsuperscript{26–39} In our survey, injuries effects of high LDL levels on early atherogenesis were indeed inhibited by light drinking (<50 g/d) (Figures 3c and 4), whereas consumption of more than 50 g/d tended to further enhance the atherogenic capacity of high LDL cholesterol ($P=0.009$ for effect modification). Owing to the multiple analyses performed, however, we cannot rule out the possibility that this new and potentially important finding is simply a chance finding even though biological plausibility, internal consistency of the finding in sexes and different age groups (data not presented) and the emergence of a similar conjecture in a British study on alcohol intake and myocardial infarction\textsuperscript{3} all argue against this interpretation.

**Antithrombotic Effects**
In our study population, low alcohol intake halved the risk of incident carotid stenosis, most likely by counteracting plaque thrombosis. Antithrombotic effects of low amounts of alcohol are experimentally well founded: alcohol reduces thrombocyte aggregability, postprandial hypercoagulability, and activity of various coagulation factors while enhancing thrombocyte survival time and, possibly, fibrinolytic capacity.\textsuperscript{32,40–45} Furthermore, prostacyclin levels and the ratio of prostacyclin to thromboxane A$_2$ have been found to increase after low doses of ethanol.\textsuperscript{46} This observation may be relevant to atherosclerotic tissue, where a decline in prostacyclin usually predisposes to thrombus formation. Alcohol ingestion during meals tended to offer more protection, probably due to a delayed absorption and prolonged mode of action at a time when platelet reactivity increases under the influence of alimentary lipids.\textsuperscript{47} Potential antithrombotic effects continuously leveled off beyond a threshold of 25 g/d ethanol, which was paralleled by a marked decrease in antithrombin III levels,\textsuperscript{15} a reversal of some of the antithrombotic mechanisms mentioned above, and, possibly, reactive thrombocyte hyperaggregability during periods of alcohol withdrawal (“platelet rebound”\textsuperscript{39,49}).

**Methodological Considerations**
In the interpretation of our results it must be remembered that alcohol consumption is self-reported and is thus subject to various sources of bias.\textsuperscript{7,50} The nondifferential response error, which is believed to be the major source of incorrect ascertainment of alcohol consumption, has been estimated...
and found to be considerably low according to diet records used as a reference standard.7 The second important type of error, the deliberate denial of alcohol use or selective nonresponse by heavy drinkers, may also be lower than in most previous comparable studies owing to the high participation, the availability of medical records on alcohol-related diseases, and the high boundaries of socially accepted drinking in the survey area.7 Accuracy in the assessment of alcohol intake is further substantiated by the expected strong relation with several risk factors.7,15

The category of alcohol abstinence may not represent an ideal reference group as it subsumes nondrinkers, past heavy drinkers (sick quitters),4,50,51 and, possibly, a few current drinkers who deny their alcohol intake. Inclusion of the latter groups could theoretically introduce a bias in terms of a pretended beneficial effect of low alcohol consumption. In the current analysis, subjects who quit drinking during follow-up were excluded before analysis. Further exclusion of subjects who stopped previously heavy drinking before 1990 did not affect any conclusion drawn from the original population sample and neither did the exclusion of “non-drinkers” with elevated γ-glutamyl transferase and subjects with cardiovascular disease, cancer, or cirrhosis of the liver, who may have changed drinking habits due to disease status.

Conclusions
Regular consumption of more than 50 g/d ethanol emerged as a prominent risk factor for early atherogenesis, surpassing even the effect of heavy smoking. On the other hand, low alcohol intake was beneficial in that the risk of incident vessel stenosis was cut in half. Light drinking may suppress the injurious action of high LDL levels on early atherogenesis; however, this awaits confirmation in future research.

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Appendix
The Bruneck Study Group included Stefan Brandt, Paula Eder, Arno Gasperi, Martin Oberhollenzer, Klaus Oberlechner, and Harald Steiner at the Department of Internal Medicine and Agnes Mair and Peter Santer at the Department of Laboratory Medicine, Bruneck Hospital, Bruneck, Italy; Franz Spögl at the Department of Neurology, Brixen Hospital, Brixen, Italy; Elmar Jarosch and Maria Schober at the Department of Laboratory Medicine, Innsbruck University Hospital, Innsbruck, Austria; and Michele Muggeo at the Department of Endocrinology and Metabolism, Verona University, Verona, Italy.

References


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