Alcohol Consumption and Carotid Artery Structure in Older French Adults
The Three-City Study

Mahmoud Zureik, MD, PhD; Jérôme Gariépy, MD; Dominique Courbon MS; Jean-François Dartigues, MD; Karen Ritchie, PhD; Christophe Tzourio, MD, PhD; Annick Alpérovitch, MD; Alain Simon, MD; Pierre Ducimetière, PhD

Background and Purpose—Several epidemiological studies have suggested a U-shaped association between alcohol consumption and cardiovascular risk. However, the modifications of vascular structure associated with alcohol consumption are largely unknown.

Methods—The study population sample comprised 6216 subjects (3780 women and 2436 men) aged 65 years or older who were recruited from 3 French cities (Bordeaux, Dijon, and Montpellier, which are located in the 3 principal wine-growing regions). Usual alcohol consumption was assessed by a standardized questionnaire. Carotid ultrasound examination included measurements (at sites free of plaques) of intima-media thickness (IMT) at the common carotid arteries (CCA), CCA–lumen diameter, and assessment of atherosclerotic plaques in the extracranial carotid arteries.

Results—Neither CCA–IMT nor carotid plaques were associated with alcohol consumption categories in the overall population. Weak and marginal positive associations were observed between categories of alcohol consumption and carotid plaques in men ($P<0.02$ for linear trend). CCA–lumen diameter was positively and independently associated with alcohol consumption in overall population and in men and in women. Similar results were found between alcohol consumption and carotid measurements in subjects free of cardiovascular disease (90.1% of the population).

Conclusions—This very large population sample of French older adults shows no marked relationships of alcohol consumption with atherosclerosis. The positive association of alcohol intake with carotid arterial diameter may reflect the ability of alcohol to maintain adaptive enlargement to preserve lumen area. (Stroke. 2004;35:2770-2775.)

Key Words: alcohol ■ atherosclerosis ■ carotid arteries ■ epidemiology

Accumulated results from several prospective studies suggest that moderate alcohol drinkers have a lower risk of mortality, coronary artery disease, and stroke.1,2 This is further supported by the observation that the French population has one of the highest alcohol intakes in the world, whereas cardiovascular mortality rates are lower than in most other developed countries.3

The modifications of vascular structure associated with alcohol consumption remain unclear. Recent technological advances in high-resolution B-mode carotid ultrasonography have enabled us to evaluate directly minimal peripheral arterial wall or structure abnormalities (intima-media thickness [IMT], lumen diameter, and focal atherosclerotic plaques).4–6 The few studies that have directly examined the association between alcohol consumption and arterial structural modifications have yielded inconsistent findings.7–11 However, most of these studies may be limited by the use of carotid IMT as the only marker of vascular alterations and, to our knowledge, only one previous study has focused on the association of alcohol consumption with carotid atherosclerosis in elderly individuals who are at greater risk for cardiovascular disease.11

In this population-based cross-sectional study of 6216 subjects aged 65 years and older, we report the associations of carotid structure assessed by B-mode ultrasound with reported alcohol consumption.

Materials and Methods
The design of the Three-City Study, an ongoing longitudinal study aiming to evaluate the risk of dementia and cognitive impairment attributable to vascular factors, has been reported elsewhere.12 Briefly, between 1999 and 2001, 9294 subjects (3649 men and 5645 women), aged 65 years and older, and noninstitutionalized were recruited from the electoral rolls of 3 French cities, ie, Bordeaux, Dijon, and Montpellier. The study protocol was approved by the Ethical Committee of the University Hospital of Kremlin-Bicêtre.
and each participant signed an informed consent. The first step of the sampling procedure was to select administrative districts. Eligible inhabitants of the selected districts were then invited to participate in the study. The acceptance rate was 37%.

The practical organization of the different components of the data collection varied slightly between centers. In Bordeaux and Dijon, participants were first examined at home (interview, cognitive testing). They were then invited to the study examination center (a community medical center in Dijon and a mobile center in a specially equipped vehicle in Bordeaux) for completing the other parts of the study protocol; those who refused or were unable to visit the center had a second visit at home. In Montpellier, all subjects were asked to attend a half-day examination at a research clinic established within the regional neurology hospital.

**Medical History and Standard Biological Procedures**

Data were collected during a face-to-face interview using a standardized questionnaire administered by trained psychologists or nurses. Information about demographic background, occupation, medical history, drug use, and personal habits such as alcohol consumption and cigarette consumption were collected. Blood pressure was measured by one trained reader. To ensure reliability and validity of these measurements, programs of centralized training and regular quality-control were implemented for the sonographers (n=7) and the reader.

The examination involved scanning of the common carotid arteries (CCA), the carotid bifurcations, and the origin of the internal carotid arteries. The near and far walls of these arterial segments were scanned longitudinally and transversally to assess, at the time of the examination, the presence of plaques. The presence of plaques was defined as previously reported. 13

For IMT and lumen diameter measurements, far and near walls of the right and the left CCAs 2 to 3 cm proximal to bifurcation were imaged. For each side, at least one optimal longitudinal image was frozen in end-diastole by electrocardiogram R-triggering. All frozen images were transferred to a computer system (IoTEC) and digitized into 640x580 peak cells with 256 gray levels.14 They were stored on CD-ROMs that were sent to the reference center weekly. The IMT was measured at a site free of any discrete plaques along a 10-mm-long segment of the far wall of the CCA and measured as the distance between the lumen–intima interface and the media–adventitia interface using an automated edge detection algorithm. A mean of more of the ultrasound measurements, giving a final sample of 192 subjects per center and on each side. Lumen diameter was defined as the average of the distances between the 2 leading edges of far wall and near wall lumen–intima interfaces along at least 0.5 cm of length using a computerized validated program. 15

**Reproducibility Study**

A reproducibility study was conducted. One hundred fourteen subjects underwent 2 ultrasound examinations performed blindly by 2 different sonographers during the same visit. The mean absolute difference and correlation coefficient between repeated examinations of CCA–IMT were, respectively, 0.06 mm and 0.71. For lumen diameter, they were, respectively, 0.16 mm and 0.91. For carotid plaque, the Kappa coefficient for agreement between the 2 examinations was 0.78.

**Statistical Analyses**

Standard procedures from the Statistical Analysis System (SAS) were used for statistical analyses. Ultrasound parameters used in this report were CCA–IMT, lumen diameter, and carotid plaques. Differences in cardiovascular risk factors and in ultrasound parameters according to alcohol consumption categories were adjusted for gender and tested by analysis of covariance for quantitative variables and by Mantel–Haenszel χ2 test for qualitative variables. Multivariate associations between alcohol consumption categories and ultrasound parameters were tested using analysis of covariance and multiple logistic regressions. To test the linear trends of associations between alcohol consumption and ultrasound parameters, the categories of alcohol consumption were treated as a continuous variable, excluding former drinkers. To test the quadratic trend, the linear trend variable was squared. Of the 6631 participants who had ultrasound examinations, 415 were excluded from the statistical analyses because of missing data on alcohol consumption and/or one or more of the ultrasound measurements, giving a final sample of 6216 subjects. There were no statistical significant differences between subjects who were included in the analyses and those who were excluded for the studied cardiovascular risk factors.

**Results**

Mean levels of alcohol consumption were 12.8 g/d (median 9.6, standard deviation, 14.7 g/d); 86.8% of alcohol consumption was wine, 3.1% beer, and 10.1% liquor. The main clinical characteristics of the study population according to alcohol consumption categories are presented in Table 1. Smoking habits, total cholesterol, and high-density lipoprotein cholesterol were positively associated with alcohol consumption.
Alcohol consumption was not associated with CCA–IMT in sex-adjusted and multivariate-adjusted analyses (Table 2). Adding quadratic terms did not modify these results. When CCA–IMT values were divided into 3 or 4 categories according to sex-specific tertile or quartile values, similar patterns of results were observed confirming the lack of an association between CCA–IMT and alcohol consumption.

CCA–lumen diameter was positively associated with alcohol consumption (Table 2). Multivariate adjustment for potential cardiovascular risk factors (including high-density lipoprotein cholesterol) did not alter these findings (Table 2). When CCA–IMT and/or carotid plaques were added to the multivariate models, the associations of alcohol consumption with CCA–lumen diameter remained significant. In addition, substitution of weight and height for body mass index in the multivariate models did not alter the results (data not shown).

No association between alcohol consumption and carotid plaques was observed. Multivariate analyses confirmed these findings (Table 2). When analyses were separately performed according to sex, the lack of association between alcohol consumption and CC–IMT and the positive association between alcohol consumption and CCA–lumen diameter were confirmed in men and in women (Table 3). For carotid plaques, weak positive associations with categories of alcohol consumption were observed in men (Table 3), and the interaction term to test the differential associations of alcohol consumption with plaques according to gender was statistically significant ($P=0.02$). This was not the case for CCA–IMT ($P=0.23$) and CCA–lumen diameter ($P=0.34$).

When all analyses were limited to subjects without cardiovascular disease ($n=5602$) or to those with stable alcohol consumption ($n=3850$), similar results to those observed in the whole population were found (data available from the authors).

**Discussion**

In this large-scale study conducted in older adults, we found no significant association of alcohol consumption with common carotid IMT and carotid plaques (in women) and a modest association between alcohol consumption and carotid plaques in men. The magnitude of the latter association may be of little biological importance. Common carotid lumen diameter was positively associated with alcohol consumption independently of major known cardiovascular risk factors.

Few large studies have specifically evaluated the effects of regular alcohol intake on large artery structure and conflicting results have been reported. In the ARIC Study of 45- to 64-year-old subjects with considerable proportions of nondrinkers (from 29% to 78% according to gender and ethnicity) and drinkers of less than once per week (from 44% to 80% among drinkers), no cross-sectional association between current alcohol consumption and carotid IMT was observed. In the Bruneck Study, conducted in adults and older subjects ($n=919$) with very high alcohol consumption (57 g/d in men and 25.9 g/d in women), showed J-shaped cross-sectional and
TABLE 2. Associations of Daily Alcohol Consumption Categories With Common Carotid Intima Media Thickness (mm), Lumen Diameter (mm), and Prevalence of Carotid Plaques

<table>
<thead>
<tr>
<th>Categories of Daily Alcohol Consumption</th>
<th>CCA-IMT</th>
<th>Lumen diameter</th>
<th>Carotid plaques</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sex-adjusted</td>
<td>Multivariate-adjusted</td>
<td>Sex-adjusted</td>
</tr>
<tr>
<td>None</td>
<td>0.72±0.004†</td>
<td>0.73±0.01</td>
<td>0.71±0.02</td>
</tr>
<tr>
<td>Former</td>
<td>0.73±0.005</td>
<td>0.74±0.01</td>
<td>0.73±0.004</td>
</tr>
<tr>
<td>≤1 Drink</td>
<td>0.73±0.005</td>
<td>0.74±0.01</td>
<td>0.73±0.004</td>
</tr>
<tr>
<td>&gt;1–2 Drinks</td>
<td>0.73±0.005</td>
<td>0.74±0.01</td>
<td>0.73±0.004</td>
</tr>
<tr>
<td>&gt;2–3 Drinks</td>
<td>0.73±0.005</td>
<td>0.74±0.01</td>
<td>0.73±0.004</td>
</tr>
<tr>
<td>&gt;3 Drinks</td>
<td>0.73±0.005</td>
<td>0.74±0.01</td>
<td>0.73±0.004</td>
</tr>
<tr>
<td>p*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR indicates odds ratios.

*P for difference was calculated by analysis of covariance using all categories of alcohol consumption; P for linear trend (and quadratic trend) was calculated after excluding former drinkers by analysis of covariance using the categories of alcohol consumption as a continuous variable (and squared the linear trend variable for quadratic trend).

†Mean±standard error of mean.

‡Adjusted for age, sex, center, body mass index, smoking habits, hypertension, diabetes, hypercholesterolemia, HDL cholesterol, and presence of cardiovascular disease.

longitudinal relationships of alcohol consumption with carotid atherosclerosis determined by the presence (incidence) of plaques and stenosis.8,9

To the best of our knowledge, only the Cardiovascular Health Study (CHS) has specifically reported the association of alcohol use with carotid atherosclerosis in the elderly.11 Relative to older subjects who abstain from alcohol, consumption of 1 to 6 drinks per week had an inverse association with common carotid IMT, whereas consumption of ≥14 drinks had a positive association. The discrepancy of these results with ours is difficult to explain. Two-fifths of the subjects were nondrinkers, and beer and liquor were the predominant types of alcoholic beverages consumed by the CHS population.11 However, we do not think that types of alcoholic beverages can explain the discrepancy because accumulated findings support the hypothesis that the beverage most widely consumed by a given population is the one most likely to be inversely associated with the risk of myocardial infarction and stroke in that population.1,16 Nevertheless, the inconsistency in the results provided by the different studies may suggest that the effects of alcohol consumption on carotid atherosclerosis, if they exist, are modest.

In our study, common carotid lumen diameter increased with increasing alcohol consumption, independently of classical cardiovascular risk factors. These findings extend those of 2 other population-based studies.4,17 Arterial enlargement

TABLE 3. Multivariate* Associations of Daily Alcohol Consumption Categories With Common Carotid Intima-Media Thickness (mm), Lumen Diameter (mm), and Prevalence of Carotid Plaques

<table>
<thead>
<tr>
<th>Categories of Daily Alcohol Consumption</th>
<th>CCA-IMT</th>
<th>Lumen diameter</th>
<th>Carotid plaques</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In men</td>
<td>In women</td>
<td>In men</td>
</tr>
<tr>
<td>None</td>
<td>0.76±0.01†</td>
<td>0.72±0.01</td>
<td>6.55±0.07</td>
</tr>
<tr>
<td>Former</td>
<td>0.75±0.01</td>
<td>0.73±0.01</td>
<td>6.67±0.04</td>
</tr>
<tr>
<td>≤1 Drink</td>
<td>0.74±0.01</td>
<td>0.72±0.01</td>
<td>6.72±0.04</td>
</tr>
<tr>
<td>&gt;1–2 Drinks</td>
<td>0.74±0.01</td>
<td>0.72±0.01</td>
<td>6.72±0.04</td>
</tr>
<tr>
<td>&gt;2–3 Drinks</td>
<td>0.75±0.01</td>
<td>0.73±0.01</td>
<td>6.77±0.05</td>
</tr>
<tr>
<td>&gt;3 Drinks</td>
<td>0.74±0.01</td>
<td>0.71±0.02</td>
<td>6.82±0.05</td>
</tr>
<tr>
<td>p*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OR indicates odds ratios.

*Adjusted for age, center, body mass index, smoking habits, hypertension, diabetes, hypercholesterolemia, HDL cholesterol, hormonal replacement therapy (in women), and presence of cardiovascular disease.

†Mean±standard error of mean.

‡Odds ratios (95% confidence interval).
is considered as an adaptive response of the arterial wall to atherosclerosis. Ultrasonographic studies have also suggested that compensatory enlargement of the carotid arteries might occur in response to arterial wall thickening and plaque progression.\textsuperscript{17,18} When we added CCA–IMT and/or carotid plaques in the multivariate analyses, the associations between alcohol consumption and CCA–lumen diameter remained significant, suggesting that the differences in arterial dimensions according to alcohol consumption categories are independent of atherosclerosis.

The mechanisms, which may link alcohol intake to carotid enlargement, are largely unknown. Blood flow and wall shear stress are the major determinants of vascular lumen diameter.\textsuperscript{19,20} Adaptive changes in arterial diameter produced by changes in blood flow or shear stress are in part endothelium-dependent.\textsuperscript{19,21} Because ethanol and nonalcoholic components of alcoholic beverages have possible favorable effect on endothelium (reducing intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin expression of vascular endothelium, as well as monocyte adhesion), these adaptive changes in arterial diameter may be preserved with aging in subjects with increasing alcohol intake. Alcohol (particularly red wine) could also enhance nitric oxide synthase expression and subsequent nitric oxide release from endothelial cells, leading to vasoprotective impact.\textsuperscript{23,24} Other possible mechanisms of the vasodilator effects of alcohol may be that ethanol can potentiate contractions mediated by the noradrenergic component of sympathetic nerves that play a role in maintaining vascular tone and regulation of blood flow.\textsuperscript{25} All these potential mechanisms may suggest the ability of alcohol to maintain adaptive arterial enlargement preserving lumen area. However, our findings obtained from a cross-sectional study should be confirmed by longitudinal studies.

Our population consisted of an elderly population who were able to come to the study examination centers. This may explain the differences in cardiovascular risk factors between participants who had ultrasound examinations and those who had not. This fact and the potential effects of selective survival, as well as self-selection biases leading to an under-representation of persons in poor health, should be considered as a methodological limitation of the study. We assessed the effects on carotid structure of average amounts of alcohol consumed rather than drinking habits. The Kuopio Ischemic Heart Disease Risk Factor Study showed that binge-drinking men with heavy alcohol consumption have the greatest progression of carotid atherosclerosis.\textsuperscript{10} However, binge-drinking habits are uncommon in France. Analyses were conducted adjusting for major known cardiovascular risk factors. The potential confounding effects of unknown and, to a lesser extent, unmeasured factors could not be ruled out, although these factors would need to be strongly associated with both alcohol and carotid structure.\textsuperscript{11} Self-reported current usual alcohol consumption was assessed by a standardized questionnaire. Nondifferential and differential measurement errors (because of underreporting consumption, especially by heavy drinkers, and recall bias in older subjects) might also have occurred. Because alcohol drinking is socially accepted in France, we think that error measurements of alcohol would not be higher that those occurring in other comparable population-based studies. In addition, the associations of alcohol intake with smoking habits and high-density lipoprotein cholesterol were virtually equivalent to those found in other studies,\textsuperscript{11} suggesting that alcohol intake of our study is reasonably valid.

In conclusion, this very large population sample of older adults showed no marked relationships of alcohol consumption with CCA–IMT and carotid plaques. The results also suggest that alcohol intake and carotid arterial diameter are positively associated, independently of conventional cardiovascular risk factors. The potential ability of alcohol to maintain adaptive enlargement to preserve lumen area should be investigated in longitudinal studies.

Acknowledgments
The 3C Study is mainly supported by the Fondation pour la Recherche Médicale and the Sanofi-Synthelabo Company.

References


Alcohol Consumption and Carotid Artery Structure in Older French Adults: The Three-City Study
Mahmoud Zureik, Jérôme Gariépy, Dominique Courbon, Jean-François Dartigues, Karen Ritchie, Christophe Tzourio, Annick Alpérovitch, Alain Simon and Pierre Ducimetière

Stroke. 2004;35:2770-2775; originally published online October 28, 2004;
doi: 10.1161/01.STR.0000147968.48379.c3
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/35/12/2770

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/