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# Alcohol Use and Risk of Ischemic Stroke Among Older Adults

## The Cardiovascular Health Study

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**Background and Purpose**—The association of light to moderate alcohol consumption with risk of ischemic stroke remains uncertain, as are the roles of potentially mediating factors and modification by apolipoprotein E (apoE) genotype.

**Methods**—We studied the prospective association of alcohol consumption and risk of ischemic stroke among 4410 participants free of cardiovascular disease at baseline in the Cardiovascular Health Study, a population-based cohort study of older adults from 4 US communities. Participants reported their consumption of alcoholic beverages yearly.

**Results**—During an average follow-up period of 9.2 years, 434 cases of incident ischemic stroke occurred. Compared with long-term abstainers, the multivariate relative risks of ischemic stroke were 0.85 (95% CI, 0.63 to 1.13), 0.75 (95% CI, 0.53 to 1.06), 0.82 (95% CI, 0.51 to 1.30), and 1.03 (95% CI, 0.68 to 1.57) among consumers of <1, 1 to 6, 7 to 13, and  $\geq 14$  drinks per week (*P* quadratic trend 0.06). ApoE genotype appeared to modify the alcohol–ischemic stroke relationship (*P* interaction 0.08), with generally lower risks among drinkers than abstainers in apoE4-negative participants but higher risks among drinkers than abstainers among apoE4-positive participants. We could not identify candidate mediators among lipid, inflammatory, and prothrombotic factors.

**Conclusions**—In this study of older adults, the association of alcohol use and risk of ischemic stroke was U-shaped, with modestly lower risk among consumers of 1 to 6 drinks per week. However, apoE genotype may modify this association, and even moderate alcohol intake may be associated with an increased risk of ischemic stroke among apoE4-positive older adults. (*Stroke*. 2005;36:000-000.)

**Key Words:** alcohol ■ cerebral infarction

Although light to moderate alcohol consumption is associated with a lower risk of myocardial infarction,<sup>1</sup> its relationship with risk of ischemic stroke is less clear. Some studies suggest that intake of even 2 drinks per day may increase risk of hypertension and atrial fibrillation, 2 important stroke risk factors.<sup>2,3</sup> A recent meta-analysis suggested that alcohol intake of <12 g per day was associated with a lower risk of ischemic stroke but found weaker effects in cohort studies than in case-control studies.<sup>4</sup> Importantly, previous studies have not focused on older adults, despite their greater risk for ischemic stroke.

Apolipoprotein E (apoE) is a key component of high-density lipoprotein particles, and high-density lipoprotein cholesterol (HDL-C) appears to mediate much of the cardiovascular effect of moderate drinking.<sup>5</sup> We reported previously that apoE genotype modifies the effects of alcohol on carotid atherosclerosis.<sup>6</sup> Whether apoE genotype modifies the asso-

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ciation of alcohol use with ischemic stroke and the degree to which biomarkers mediate this association are uncertain.

Therefore, we studied participants in the Cardiovascular Health Study (CHS),<sup>7</sup> a cohort of community-dwelling older adults. We assessed how baseline and follow-up measures of alcohol consumption, apoE genotype, and potential mediators influence the association of alcohol consumption with risk of incident ischemic stroke.

## Methods

### Study Population and Design

The CHS is a prospective study of 5888 men and women  $\geq 65$  years of age selected randomly from Medicare-eligibility lists in 4 US communities. Participants were not institutionalized or wheelchair-dependent, did not require a proxy for consent, were not under treatment for cancer, and were expected to remain in their respective

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regions for 3 years. In 1989 and 1990, 5201 participants were recruited (the original cohort); in 1992 and 1993, 687 additional black participants were recruited. The institutional review board at each center approved the study, and each participant gave informed consent.

The CHS study design has been published.<sup>7</sup> The baseline examination included standardized questionnaires, physical examination, resting electrocardiography, and laboratory examination. Follow-up contact occurred every 6 months, alternating between telephone calls and clinic visits.

We excluded 1437 participants with pre-existing myocardial infarction, angina, bypass surgery, angioplasty, transient ischemic attack, stroke, and carotid endarterectomy, and 41 participants missing baseline information on alcohol use, leaving 4410 eligible participants.

### Alcohol Consumption

At baseline and annually until 1999, participants separately reported their usual frequency of consumption of beer, wine, and liquor, and the usual number of 12-ounce cans or bottles of beer, 6-ounce glasses of wine, and shots of liquor that they drank on each occasion. Alcohol consumption was not updated at the 1990 to 1991 or 1995 to 1996 visits. At baseline, participants reported whether they changed their consumption during the past 5 years and whether they ever regularly consumed  $\geq 5$  drinks daily. Participants who reported abstinence at baseline but responded yes to either question were classified as former drinkers.

We categorized weekly ethanol consumption as follows: none, former, <1 drink, 1 to 6 drinks, 7 to 13 drinks, and  $\geq 14$  drinks. For regression analyses, abstainers without former use were the reference category.

### Determination of Incident Ischemic Stroke

The CHS protocol for classification of incident stroke has been published.<sup>8</sup> A panel of neurologists, blinded to CHS entry data, reviewed hospital notes, test results, and imaging studies, verified the diagnosis of stroke and its type (ischemic, hemorrhagic, or unclassifiable), and, when necessary, spoke with the patient's physician. To be categorized as a stroke, a new neurologic deficit had to persist for 24 hours, or imaging studies had to demonstrate a lesion appropriate to the clinical deficit. Ischemic strokes were further subclassified as described,<sup>9</sup> but only 49% could be subtyped further (25% cardioembolic, 17% small vessel, and 7% large vessel), too small for separate analyses.

### Other Covariates

We defined hypertension and diabetes as in previous analyses.<sup>6</sup> Field center staff directly measured body mass index, which we grouped as <25, 25 to 29, and  $\geq 30$  kg/m<sup>2</sup>. We categorized exercise intensity into 4 groups on the basis of a weighted sum of kilocalories expended in specific physical activities.<sup>10</sup> We categorized smoking as current, former, and never, and dichotomized education (completion of high school or less versus some vocational school or college) and marital status (married versus other). Aspirin use included the use of any aspirin-containing medication for  $\geq 10$  days in the previous 2 weeks;<sup>11</sup> alternate definition as any use of aspirin did not change our results. We classified participants in the original cohort into 5 dietary patterns on the basis of cluster analysis.<sup>12</sup> Participants reported their general health at baseline. Depressive symptoms were assessed at baseline with the Center for Epidemiological Studies Depression scale.<sup>13</sup>

ApoE genotype testing was performed as described.<sup>14</sup> Written informed consent specifically for genetic studies was updated in 1998, when genetic analyses were performed. Of the 4410 eligible participants, 223 declined consent for genetic testing for cardiovascular diseases, and 266 did not have necessary stored DNA or were not successfully genotyped, yielding 3921 participants with apoE genotype.

### Statistical Analysis

Participants accrued person years from the date of entry into CHS to the date of first stroke, death, or June 2001. Using Cox models, we controlled for age, sex, race, smoking, marital status, and education (the basic model). We performed analyses that additionally controlled for exercise intensity, diabetes, depression score, aspirin use, and body mass index (the full model), which excluded 121 participants with missing covariate information. We included systolic blood pressure as a covariate only in sensitivity analyses because it may mediate a higher risk of ischemic stroke among heavy drinkers; analyses using hypertension instead were similar.

Our primary analyses used updated measures of alcohol consumption, in which we assessed the relative risk of ischemic stroke in yearly increments on the basis of consumption derived from the preceding questionnaire. We separated participants who stopped drinking from long-term abstainers using a time-varying covariate.

We assessed individual beverage types after separating former drinkers. We simultaneously controlled for the standard covariates in other models and intake of each of the other beverage types. We created a single category of  $\geq 7$  servings of each beverage per week because the number of participants in categories of 7 to 13 and  $\geq 14$  was small, and the hazard ratios were similar in the 2 categories. We also categorized participants by the beverage that they consumed preferentially ( $\geq 80\%$  of total alcohol intake); if no beverage constituted 80% of total intake, we classified participants as mixed drinkers.

To test linear and quadratic trends, we excluded former drinkers and treated the categories of alcohol use as a simple continuous variable.<sup>6</sup> Alternate analyses that assigned median alcohol intake to each category or assessed alcohol intake as a continuous variable yielded similar results. We squared a centered linear trend variable to assess quadratic trend. To test for interaction, we used the Wald  $\chi^2$  test statistic on the basis of models with and without appropriate interaction terms. We performed all analyses using Stata Intercooled version 8 and SPSS version 12.

## Results

### Baseline Characteristics

On average, heavier alcohol consumption was associated with a greater likelihood of being a current smoker, married, and physically active (Table 1). Average blood pressure and prevalence of hypertension were lowest among light drinkers and highest among heavier drinkers.

### Average Alcohol Consumption and Ischemic Stroke

During a mean of 9.2 years of follow-up (median 11.1 years), 434 cases of incident ischemic stroke occurred. In basic and fully adjusted analyses using updated alcohol consumption, alcohol consumption had a U-shaped relation with risk, with the lowest risk among consumers of 1 to 6 drinks per week (Table 2). The magnitude of the risks was closer to 1 in the fully adjusted model. With the exception of the 7 to 13 drinks per week category, analyses using baseline alcohol consumption gave very similar risk estimates to those using updated alcohol use.

Table 2 also shows the results of models that include systolic blood pressure to test its role as a mediator. This changed the risk estimate for consumers of  $\geq 14$  drinks per week from 1.03 to 0.96, suggesting that their higher blood pressure mediates little of their apparently higher risk relative to light drinkers. At the same time, adjustment for systolic blood pressure did not alter the risk estimate for consumers of 1 to 6 drinks per week.

**TABLE 1. Characteristics of 4410 CHS Participants Free of Clinical Cardiovascular Disease According to Usual Alcohol Consumption**

|                                      | Weekly No. of Drinks |                   |               |                |                 |                |
|--------------------------------------|----------------------|-------------------|---------------|----------------|-----------------|----------------|
|                                      | None<br>(n=1791)     | Former<br>(n=371) | <1<br>(n=853) | 1–6<br>(n=763) | 7–13<br>(n=272) | ≥14<br>(n=360) |
| Weekly drinks                        |                      |                   |               |                |                 |                |
| Wine                                 | 0                    | 0                 | 0.1           | 0.7            | 2.9             | 3.9            |
| Beer                                 | 0                    | 0                 | 0.1           | 0.5            | 1.8             | 5.6            |
| Liquor                               | 0                    | 0                 | 0.1           | 0.8            | 3.2             | 11.3           |
| Age, y                               | 73.0                 | 72.7              | 72.3          | 71.8           | 72.6            | 72.0           |
| Female, %                            | 72.9                 | 43.9              | 67.1          | 51.2           | 45.2            | 41.7           |
| Black, %                             | 18.6                 | 25.6              | 12.4          | 10.2           | 7.0             | 8.9            |
| Some vocational school or college, % | 30.8                 | 34.8              | 50.9          | 57.9           | 64.4            | 59.9           |
| Married, %                           | 62.0                 | 60.4              | 65.2          | 71.3           | 75.4            | 75.5           |
| Smoking, %                           |                      |                   |               |                |                 |                |
| Never                                | 63.6                 | 29.4              | 47.8          | 36.9           | 37.1            | 19.8           |
| Former                               | 27.3                 | 56.1              | 39.3          | 49.1           | 50.7            | 59.6           |
| Current                              | 9.1                  | 14.6              | 12.9          | 14.0           | 12.1            | 20.6           |
| Exercise intensity, %                |                      |                   |               |                |                 |                |
| None                                 | 8.7                  | 10.2              | 7.5           | 5.2            | 7.0             | 7.2            |
| Low                                  | 56.2                 | 52.0              | 42.8          | 39.2           | 36.2            | 39.8           |
| Moderate                             | 29.5                 | 30.5              | 37.9          | 41.6           | 41.0            | 38.2           |
| High                                 | 5.6                  | 7.3               | 11.8          | 13.9           | 15.9            | 14.8           |
| Diabetes, %                          | 18.1                 | 24.7              | 9.9           | 9.7            | 5.9             | 9.7            |
| Hypertension, %                      | 59.2                 | 61.2              | 54.2          | 49.2           | 45.2            | 61.1           |
| Systolic blood pressure, mm Hg       | 137.0                | 138.8             | 135.6         | 133.9          | 133.8           | 139.0          |
| Diastolic blood pressure, mm Hg      | 70.6                 | 71.5              | 70.5          | 71.6           | 71.5            | 72.6           |
| Aspirin use, %                       | 16.7                 | 17.2              | 16.3          | 15.2           | 15.7            | 17.1           |
| Body mass index, %                   |                      |                   |               |                |                 |                |
| <25 kg/m <sup>2</sup>                | 36.8                 | 37.8              | 38.5          | 40.4           | 44.5            | 46.5           |
| 25–30 kg/m <sup>2</sup>              | 38.7                 | 41.4              | 42.8          | 43.8           | 47.1            | 41.8           |
| ≥30 kg/m <sup>2</sup>                | 24.5                 | 20.8              | 18.7          | 15.8           | 8.5             | 11.7           |
| Depression score                     | 4.7                  | 5.1               | 4.5           | 4.2            | 3.5             | 4.0            |
| ApoE4 positive, %                    | 25.1                 | 27.2              | 23.6          | 24.4           | 19.9            | 28.3           |
| HDL-C, mg/dL                         | 54                   | 53                | 55            | 57             | 58              | 63             |
| Fibrinogen, mg/dL                    | 327                  | 329               | 323           | 315            | 309             | 295            |

Means are shown for continuous variables and proportions for categorical variables.

Further controlling for dietary pattern (among 3382 participants with available information) did not change the effect of consumption of 1 to 6 drinks per week, nor did controlling for fiber, energy, and fish intake, self-reported general health, or atrial fibrillation.

### Stratified Analyses of Ischemic Stroke

ApoE genotype appeared to modify the effect of alcohol on risk of ischemic stroke (*P* interaction 0.08 with updated and baseline alcohol intake; Figure). Ischemic stroke risk was lower among drinkers compared with abstainers who were apoE4-negative, but higher among apoE4-positive drinkers relative to apoE4-positive abstainers. This interaction was similar among participants older and younger than the median age.

Other than apoE genotype, other variables did not markedly influence the association of alcohol use with ischemic

stroke risk. Relationships were consistent when stratified by sex, age (<75 and >75 years of age), aspirin use, baseline hypertension, and baseline atrial fibrillation (*P* interaction 0.45 to 0.96).

### Beverage Type and Ischemic Stroke

Intake of ≥7 glasses of wine and 1 to 6 servings of beer per week were associated with lower risk of ischemic stroke, whereas heavier intake of spirits at baseline was associated with higher risk (supplemental Table I, available online at <http://www.strokeaha.org>). Further adjustment for dietary pattern did not substantially change any of the individual beverage type estimates.

In sensitivity analyses of participants who preferentially consumed a single beverage, no beverage type was consistently associated with lower risk, and mixed drinkers tended

**TABLE 2. Relative Risk of Ischemic Stroke According to Usual Alcohol Consumption Among CHS Participants**

|   | Weekly No. of Drinks |           |           |           |           |           | P Value‡    |
|---|----------------------|-----------|-----------|-----------|-----------|-----------|-------------|
|   | None                 | Former    | <1        | 1–6       | 7–13      | ≥14       |             |
| Updated alcohol use                       |                      |           |           |           |           |           |             |
| Cases                                     | 179                  | 90        | 68        | 45        | 22        | 30        |             |
| Person years                              | 14 311               | 7950      | 7155      | 6030      | 2515      | 2795      |             |
| Basic model*                              | 1.0                  | 0.86      | 0.80      | 0.66      | 0.72      | 0.95      | 0.17 (0.02) |
| 95% CI                                    | ...                  | 0.66–1.11 | 0.60–1.06 | 0.47–0.92 | 0.45–1.13 | 0.63–1.43 |             |
| Full model†                               | 1.0                  | 0.87      | 0.85      | 0.75      | 0.82      | 1.03      | 0.52 (0.06) |
| 95% CI                                    | ...                  | 0.67–1.15 | 0.63–1.13 | 0.53–1.06 | 0.51–1.30 | 0.68–1.57 |             |
| Also adjusted for systolic blood pressure | 1.0                  | 0.84      | 0.85      | 0.75      | 0.80      | 0.96      | 0.39 (0.10) |
| 95% CI                                    |                      | 0.64–1.11 | 0.63–1.13 | 0.53–1.06 | 0.50–1.28 | 0.63–1.47 |             |
| Baseline alcohol use                      |                      |           |           |           |           |           |             |
| Cases                                     | 202                  | 32        | 74        | 58        | 30        | 38        |             |
| Person years                              | 16 409               | 3069      | 8017      | 7343      | 2540      | 3378      |             |
| Full model†                               | 1.0                  | 0.83      | 0.88      | 0.75      | 1.13      | 1.10      | 0.90 (0.05) |
| 95% CI                                    | ...                  | 0.55–1.25 | 0.66–1.16 | 0.55–1.03 | 0.74–1.72 | 0.76–1.61 |             |

\*The basic model adjusted for age, sex, race, education, marital status, and smoking; †the full model adjusted for the covariates in the basic model and exercise intensity, depression score, frequent aspirin use, body mass index, and diabetes at baseline.

‡P values are derived from tests of linear (quadratic) trend.

to have the lowest risks. For example, among consumers of 1 to 6 drinks per week, the risk of ischemic stroke was lowest for mixed drinkers (hazard ratio, 0.62; 95% CI, 0.38 to 1.02), with no heterogeneity across beverages ( $P=0.61$ ).

### Potential Mediators of the Alcohol–Ischemic Stroke Relationship

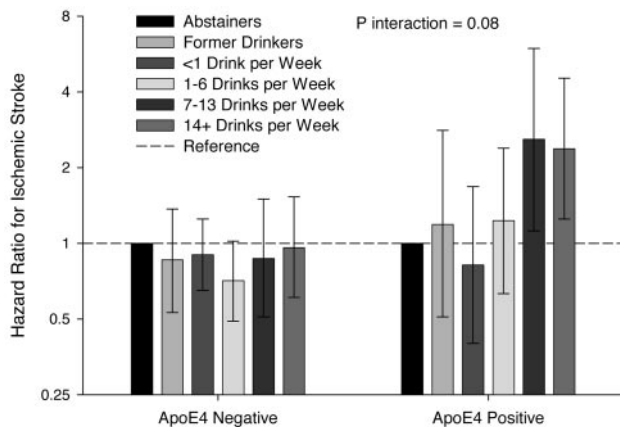
We assessed a series of potential mediators of the lower risk of stroke among consumers of 1 to 6 drinks per week. These included baseline levels of lipids, measures of glucose metabolism (fasting glucose and insulin), inflammatory markers (C-reactive protein, white blood cell count, platelet count, and albumin), coagulation factors (factor VII and factor VIII coagulant activity and fibrinogen), and potassium level. No factor

substantially changed the risk estimate associated with baseline consumption of 1 to 6 drinks per week (hazard ratio, 0.75), with risk estimates that varied from 0.74 to 0.79. These results were similar when assessed among apoE4-negative participants.

### Discussion

Despite the lower risk of coronary heart disease among moderate drinkers, the link between moderate alcohol use and ischemic stroke is less consistent.<sup>15–17</sup> For example, one study reported that alcohol intake has a U-shaped association with hospitalization for ischemic stroke, with relative risks of 0.8 among consumers of 1 drink monthly to daily and 1.0 among consumers of  $\geq 3$  drinks per day<sup>18</sup> but a simple inverse association with risk of coronary heart disease hospitalization, with relative risks of 0.6 to 0.7 among consumers of  $\geq 3$  drinks per day.<sup>19</sup> A similar disparity exists in the Health Professionals Follow-Up Study.<sup>20,21</sup> A meta-analysis of cohort studies found relative risks for ischemic stroke of 0.82 and 0.94 among consumers of <12 and 12 to 24 g of alcohol per day.<sup>4</sup> Our results extend these findings to older adults and confirm that consumption of 1 to 6 drinks per week is associated with an  $\approx 20\%$  lower risk of ischemic stroke than abstinence; alcohol consumption heavier than that leads to higher risk.

ApoE4-positive participants had a generally higher risk with alcohol consumption in CHS, whereas others did not. This finding closely parallels our results on carotid atherosclerosis and inflammatory markers.<sup>6,22</sup> The National Heart, Lung, and Blood Institute (NHLBI) Family Heart Study found a similar interaction for carotid atherosclerosis that was not statistically significant.<sup>23</sup> Importantly, the NHLBI Family Heart Study also found that the higher levels of HDL-C among drinkers were blunted substantially in carriers of the apoE4 allele,<sup>24</sup> which may explain the higher risks of ischemic stroke associated with



Risk of ischemic stroke according to baseline alcohol intake and apoE genotype. The hazard ratios are adjusted for age, sex, race, education, marital status, smoking, exercise intensity, depression score, aspirin use, body mass index, and diabetes. The I-bars indicate 95% CIs.

alcohol use among apoE4 carriers in this study. Surprisingly, apoE4 genotype attenuated the positive association of heavier drinking and blood pressure in one study.<sup>25</sup>

Limitations of our study warrant discussion. As in any observational study, unmeasured confounding factors could influence our results. For example, we did not have information on migraine headache, although its prevalence is low among older adults.<sup>26</sup> We may also have misclassified participants who stopped drinking >5 years before baseline, although risk was not higher among former drinkers.

Alcohol use is less common in older than in younger adults. As a result, some findings were of borderline statistical significance, and our power to detect differences by beverage type was clearly limited. The number of strokes with confirmed subtypes was also too small to separately analyze embolic, thrombotic, and hemorrhagic strokes, which may relate differently with alcohol use.<sup>27</sup>

Although we used self-reported alcohol intake, previous studies of older adults suggest that they report alcohol consumption as accurately as other populations,<sup>28</sup> and we confirmed previously the expected correlation of alcohol use and HDL-C levels in CHS.<sup>6</sup> The CHS nutritional questionnaire also did not collect information on overall drinking patterns; a recent study suggested that intake of 1 to 2 drinks 3 to 4 days per week may be associated with the lowest risk of ischemic stroke.<sup>20</sup>

In summary, we found a U-shaped association of alcohol intake with risk of ischemic stroke in this population-based study of older adults. There was a particularly higher risk associated with alcohol intake among apoE4 carriers. Our findings provide direct support for public health admonitions against consumption of >1 drink daily for older adults<sup>29</sup> and suggest that even limited consumption might increase risk of ischemic stroke among genetically susceptible individuals.

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## Editorial Comment

### Alcohol and Stroke An Epidemiological Labyrinth

According to the seventh edition of Webster's *New Collegiate Dictionary*, the definition of labyrinth is "something extremely tortuous or complex in structure, arrangement, or character." The investigator who studies the relations of alcohol drinking to stroke chooses a tortuous path. Multiple issues need consideration. (1) Stroke is not one disease. There are disparities in risk factors of the major stroke types, hemorrhagic stroke (HS), and ischemic stroke (IS), and of their subdivisions.<sup>1-5</sup> (2) Several cardiovascular conditions have independent relations to alcohol drinking and also to  $\geq 1$  stroke types; these include systemic hypertension (HTN), dilated cardiomyopathy, atrial arrhythmias, and coronary heart disease.<sup>6,7</sup> (3) As always with respect to alcohol, light-moderate and heavy drinking play quite different roles. (4) Cigarette smoking, a strong adverse predictor of HS and IS, is correlated with alcohol drinking and must be carefully controlled. (5) Drinking pattern and beverage choice play a role; binge drinking, in particular, increases risk.<sup>1</sup> (6) Drinking habits change. (7) Nonalcohol components of specific beverages might play a role. (8) There are potential interactions of alcohol with antithrombotic treatment, perhaps especially with warfarin anticoagulation. (9) Under-reporting by heavy drinkers could produce a spuriously low threshold for harmful effects or an apparent continuous relation when a true threshold effect exists.

Considering the potentially labyrinthine interactions between these factors, it is hardly surprising that reports about alcohol and "stroke" are conflicting.

Heavy drinking (defined here as  $>2$  standard-sized drinks per day) is related to increased prevalence of HTN,<sup>7,8</sup> and alcohol has antithrombotic effects.<sup>9,10</sup> Thus, it is easy to understand why heavy drinking is associated with increased HS risk, and there is some consensus about this relation in relevant reports.<sup>1-4,11</sup> The antithrombotic actions of alcohol might also result in increased HS risk at moderate drinking levels, but reports differ about whether lighter drinking increases HS risk or is unrelated.<sup>1,11,12</sup> The alcohol-HS relation seems similar for subarachnoid and intracerebral hemorrhage.<sup>1,11</sup>

Reports are less concordant about alcohol-IS relations, but several analyses suggest a U-shaped or J-shaped curve of drinking amount to IS risk.<sup>13-16</sup> Data are sparse about alcohol relations to specific IS subsets such as cardioembolic events, aortic arch/great vessel emboli, or intracerebral thrombi. Associations of alcohol with these IS subgroups might vary.<sup>5</sup> For example, plausible interactions of heavy drinking with cardiomyopathy, atrial fibrillation, and HTN might increase risk of cardioembolic stroke and account for some of the upturn at heavy intake in the U- or J- shaped alcohol-IS curve. Simultaneously, protection against atherothrombotic

disease processes by light-moderate drinking might reduce risk of aortic arch embolism or intracerebral thrombosis.

The insightful analysis of alcohol drinking and IS risk in older persons by Mukamal et al in this issue of *Stroke*<sup>18</sup> confirms a lower IS risk among light drinkers, although the strength of this apparent protection is not robust. The investigators introduce another level of sophistication by demonstrating an interaction of the alcohol-IS relationship with the apolipoprotein E gene epsilon4 (APOE4). Lowered risk of IS among drinkers is limited to APOE4-negative persons. Because this allele has been associated with increased risk of vascular disease, lower high-density lipoprotein (HDL) cholesterol, and blunted alcohol-HDL effect,<sup>19</sup> these data offer tantalizing possible perception of a plausible biological mechanism by which light-moderate alcohol drinking might protect against IS.

Laudably, Mukamal et al<sup>18</sup> attempted to study IS subsets. Yet, despite expert advice and presumed widespread use of modern imaging methods, they were able to assign a specific etiology to  $<50\%$ . In their older population, half of those who could be classified were considered cardioembolic, a subtype with less hypothetical basis for protection by alcohol. Less protection by alcohol against cardioembolic IS was indirectly suggested by a 2001 Kaiser Permanente cohort report<sup>17</sup> that presented data according to presence or absence of atrial fibrillation. In that analysis of 2014 IS subjects, there was a U-shaped relationship between alcohol drinking and risk, with a nadir at usual intake of 1 to 2 drinks per day (relative risk [RR; 95% CI] versus lifelong abstainers=0.8 [0.6 to 0.9]). Among 257 patients in atrial fibrillation at the time of IS, the RR (CI) was 1.1 (0.7 to 1.7) versus 0.7 (0.6 to 0.8) among 1757 persons without atrial fibrillation.<sup>17</sup> A substantial preponderance of the atrial fibrillation subjects presumably had a cardioembolic event.

Results may depend on models used. For example, as a possible intermediary in alcohol-stroke relations, HTN should not be controlled except, as was done in the Mukamal et al analysis,<sup>18</sup> to see its effect on the data. It is noteworthy that introduction of HTN into the model had little effect on risk estimates,<sup>18</sup> presumably because there were few heavy drinkers. Persons with known baseline cardiovascular disease were eliminated from the study population,<sup>18</sup> properly so because such history could influence drinking habits. If included among the nondrinking reference group, "sick quitters" might spuriously increase their risk of IS. Yet persons with pre-existent atherothrombotic disease represent a high-risk group that, hypothetically, might benefit most from protective effects of alcohol and might be the best choice for a randomized, controlled trial.

The health professional looking for advice guidelines will not find a simple message suitable for all.<sup>20,21</sup> Intrepid epidemiologists will continue to explore the alcohol–stroke labyrinth. Ultimately, answers will be found, but one can reliably predict that the path will be neither easy nor straight.

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