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# Alcohol and Acute Ischemic Stroke Onset: The Stroke Onset Study

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## Abstract

**Background and Purpose—**Previous research suggests that regular heavy alcohol consumption increases the risk for ischemic stroke, whereas frequent light to moderate alcohol intake may decrease the risk. However, the risk of ischemic stroke associated with transient exposure to alcohol remains unclear. In this study, we used a case-crossover approach to test the hypothesis that alcohol consumption affects the acute risk of ischemic stroke, to determine the length of time between alcohol intake and the onset of symptoms (induction time) and to examine whether the risk varies by the type of alcohol.

**Methods—**In this multi-center study, we interviewed 390 patients (209 men, 181 women) between January 2001 and November 2006 (median 3 days after stroke). Alcohol consumption in the hour before stroke symptoms was compared with its expected frequency based on the usual frequency of alcohol consumption over the prior year.

**Results—**Of the 390 patients, 248 (64%) reported alcohol consumption in the prior year, 104 within 24 hours and 14 within 1 hour of stroke onset. The relative risk of stroke in the hour after consuming alcohol was 2.3 (95% confidence interval [CI], 1.4 to 4.0; p=0.002). The relative risks were similar for different types of alcoholic beverages and when the sample was restricted to those who were not simultaneously exposed to other potential triggers.

**Conclusions—**The risk of stroke onset is transiently elevated in the hour following alcohol ingestion.

### Keywords

cerebrovascular disorders; stroke; alcohol; case-crossover; epidemiology

## Introduction

Moderate[1] and high[2–4] intakes of alcohol have been documented to have acute potentially deleterious physiologic effects within hours after consumption, including impaired

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fibrinolysis[2, 3] and increased platelet activation[4], blood pressure and heart rate[1]. On the other hand moderate consumption of alcohol has been associated with protective effects within hours[5–7], weeks[8–12] or years[13–15], including enhanced fibrinolytic activity[7, 8] and improvements in lipid profile[12], inflammatory markers[8, 11], flow-mediated vasodilatation[5, 6], soluble vascular adhesion molecules[11, 14], insulin sensitivity[9, 15] and adipokines[9, 14]. However, only a few studies[16–18] have examined the risk of ischemic stroke associated with transient exposure to alcohol.

In this study, we used a case-crossover approach to test the hypothesis that alcohol consumption affects the acute risk of ischemic stroke, to determine the length of time between alcohol intake and the onset of symptoms (induction time) and to examine whether the risk varies by the type of alcohol.

## Methods

### Study population

The Stroke Onset Study was conducted in three medical centers (Beth Israel Deaconess Medical Center, Boston, MA; University of North Carolina Hospitals, Chapel Hill, NC; Vancouver Island Health Authority, Victoria, BC). Between January 2001 and November 2006, 390 patients (209 men and 181 women) were interviewed a median of 3 days (range 0 to 14) after sustaining an acute ischemic stroke. Research staff identified eligible patients by reviewing admission logs and charts of patients admitted to each hospital's Stroke Service. Additionally, patients with new onset of an acute neurological syndrome compatible with stroke were screened upon admission to emergency departments. Presumed stroke etiology was classified using an abbreviated Trial of Org 10172 in Acute Stroke Treatment (TOAST) system[19].

Study personnel using standardized abstraction forms recorded data on demographics, medical history and admission laboratory results. Eligible, participants had a neurologist-confirmed diagnosis of acute ischemic stroke, either by clinical diagnosis or appropriate imaging studies, were English speaking, and free of dementia prior to the index event. Patients were excluded if they could not identify the time of onset of their stroke symptoms or if the treating clinician deemed them unable to complete the structured interview, either because they were cognitively impaired, had poor memory around the time of the stroke, experienced aphasia or they were too ill to complete the structured interview that lasted 30 to 45 minutes. Across all sites, 43% of patients with confirmed ischemic stroke met all inclusion criteria. Of these, 83% agreed to participate, 5.5% refused and 12.5% were discharged from the hospital before the interviewers were able to approach them. The protocol was approved by the institutional review board at each participating center and informed consent was obtained from each patient.

Interviewers used a structured questionnaire and asked patients to report the date and time of their first symptoms heralding their stroke. Patients were asked if they had consumed any alcoholic beverage in the year preceding their stroke. Patients who reported any alcohol consumption were also asked to report the last time that they had consumed an alcoholic beverage, their usual frequency of alcohol consumption over the prior year, the usual number of servings consumed each time they drank an alcoholic beverage and the types of alcohol consumed (beer, wine or liquor). A serving size of alcohol was defined as 12 ounces of beer, 4 ounces of wine or 1.5 ounces of liquor straight or in a mixed drink. Patients were also asked to report the timing of their last exposure to other potential triggers and usual frequency of these factors over the prior year, including caffeine, cigarette smoking, marijuana, cocaine, stress, anger and physical activity. Other information collected from the interview included medication use and symptoms on the day of the stroke.

### Reliability and Validity of the Questionnaire

The test-retest reliability of the Stroke Onset Study questionnaire was assessed in 25 patients who were re-interviewed up to 6 days after their initial interview. The intraclass correlation for the usual frequency of alcohol consumption was excellent (0.84), and there was perfect agreement for reporting of any alcohol consumption during the past year and during each of the first 2 hours preceding stroke onset ($\kappa = 1.0$). In the subset of 181 subjects interviewed at Beth Israel Deaconess Medical Center who had HDL-cholesterol levels measured at the time of hospitalization, the partial correlation between estimated alcohol consumption and HDL-cholesterol level adjusting for sex, age, race, smoking, education and physical activity was 0.35 ($p=0.003$), comparable to that found in the Second National Health and Nutrition Examination Survey[20].

### Study Design

The Stroke Onset Study utilized a case-crossover study design to assess the change in risk of acute ischemic stroke onset during a brief "hazard period" following consumption of alcohol. In the case-crossover design control information for each patient is based on his or her own past exposure experience. Self-matching eliminates confounding by risk factors that are constant within individuals over the sampling period but differ between subjects. Alcohol use in the hazard period, the 1-hour period immediately preceding the onset of ischemic stroke symptoms, was compared with its expected frequency based on control data obtained from the patients. We used the usual frequency of alcohol consumption over the year prior to stroke to estimate its expected frequency in an average 1-hour period.

### Statistical Analysis

Each patient in a case-crossover study forms his or her own stratum and thus is his or her own control[21, 22]. The ratio of the observed exposure frequency in the hazard period to the expected frequency was used to calculate estimates of the rate ratio as a measure of relative risk (RR). We multiplied the usual annual frequency of alcohol consumption by the hypothesized window of its physiologic effect (one hour in the primary analysis) to estimate the amount of person-time exposed to alcohol. The unexposed person-time was calculated by subtracting this value from the number of hours in one year. The data were analyzed using methods for cohort studies with sparse data in each stratum.

To estimate the length of time from alcohol consumption to the onset of ischemic stroke, RRs were calculated by comparing exposure within different hypothesized windows of its physiologic effect to the estimated person-time exposed to alcohol in the previous year. We conducted stratified analyses to assess the effect of drink type (beer, wine, liquor), sex, age (<65 years of age vs 65 years of age), smoking status (current smokers vs. nonsmokers) and stroke etiology and compared the RRs by means of a test for homogeneity[23].

To evaluate whether potential triggers could account for the observed association, we conducted a sensitivity analysis excluding patients who engaged in other potentially triggering activities (i.e., vigorous physical exertion and anger) in the hour preceding their stroke. In another sensitivity analysis we used the number of drinks consumed in the week preceding the stroke as the control information. We were not able to examine the association between binge drinking and ischemic stroke, since only one person reported drinking more than 2 servings of alcohol in the hour before stroke onset. All reported p-values are two-sided.

## Results

The characteristics of the Stroke Onset Study patients are presented in Table 1. Of the 390 patients with acute ischemic stroke, 248 (64%) reported that they had consumed alcohol in the

prior year (wine n=45; beer n=29; liquor n= 32; more than one type n=142). Compared to non-drinkers, subjects who reported alcohol consumption were more likely to be male and to have ever smoked cigarettes. Among the 248 subjects who drank alcohol in the prior year, 47 (12%) reported drinking at least 1 serving of alcohol per day, 38 (10%) reported drinking at least once per week and 163 (66%) reported drinking at least once per month. The median frequency of consumption among drinkers in the prior year was 2.0 times per week. Subjects reported that they typically drank small amounts each time (median=1 drink) and only 13 reported typically drinking more than two servings.

There were 169 subjects who reported exposure during the week prior to stroke, 104 subjects drank alcohol within 24 hours of stroke onset and 14 drank within 1 hour of stroke onset. We found that within 1 hour after alcohol consumption, the risk of stroke onset was 2.3-fold higher (95% CI, 1.4 to 4.0; p= 0.002)compared with periods of nonuse. The RR was 1.6 (95% CI, 1.0 to 2.5; p=0.05) in the second hour after drinking, and returned to baseline thereafter (Figure 1). By 24 hours, there was a 30% lower risk (RR=0.7, 95%CI 0.5–0.9; p=0.02).

Among the 14 participants who consumed alcohol in the hour prior to stroke onset, 7 drank liquor, 5 drank beer and 2 drank wine. The RR for alcohol consumption in the hour prior to stroke onset was strongest for liquor and weakest for wine, though the difference was not statistically significant (p for interaction=0.28; Figure 2). The RRs for alcohol consumption in the hour prior to stroke did not vary by sex, age, smoking status or stroke etiology (p for interaction=0.62, 0.62, 0.12, 0.43 respectively).

Among the 248 participants exposed to alcohol in the prior year, 63 participants were exposed to other potential triggers in the hour prior to stroke onset. Of the 14 people exposed to alcohol in the hour prior to stroke onset, 4 were also exposed to vigorous physical activity and one drank a caffeinated beverage. When we conducted an analysis excluding the 63 people exposed to any potential stroke trigger in the hour preceding stroke onset, the results remained similar.

The mean usual frequency of alcohol consumption during the past year was 4.42 times per week, similar to the mean frequency of reported alcohol consumption during the past week (4.23). In a sensitivity analysis using each patient's reported frequency of consumption in the past week as the control information, the risk of ischemic stroke onset was 3.3-fold higher (95% CI 1.2 to 9.3; p=0.03) within 1 hour of consuming at least 1 serving of alcohol compared to periods with no alcohol intake. Excluding the one person who reported drinking more than 2 servings of alcohol in the two hours before stroke onset did not meaningfully alter the results.

## Discussion

In this study, alcohol consumption was associated with a transient increased risk of ischemic stroke in the subsequent hour that was 2.3 times higher than the risk during periods with no alcohol consumption. This finding is consistent with previous research indicating an acute detrimental effect of alcohol consumption[17, 18]. The risk returned to baseline by three hours and there was a modestly lower risk by 24 hours.

Few studies have evaluated the role of alcohol as a trigger of ischemic[16–18, 24] and hemorrhagic stroke[25]. For instance, Hillbom et al[18] found that moderate (151–300 grams) and heavy (>300 grams) consumption of alcohol within the week before stroke onset is associated with a significantly higher risk of stroke, with adjusted odds ratios of 3.6 (95% CI 1.7 to 7.8) and 3.7 (95% CI 1.6 to 8.7), respectively. Consistent with our data, Gorelick et al[24] reported that after accounting for co-exposures including smoking, there was no statistically significant increase in risk of ischemic stroke in the 24 hours after alcohol consumption.

Previous studies on the acute effects of alcohol consumption indicate that heavy alcohol intake is associated with impaired fibrinolysis[2, 3], increased platelet activation[4], and increases in blood pressure and heart rate[1]. Furthermore, heavy consumption may acutely lead to dehydration, further increasing the transient risk of stroke. However, such heavy consumption was rare and unlikely to explain our findings.

Even moderate drinking may have acutely adverse consequences. In a clinical trial of eight healthy men, Hendriks and colleagues[7] found that plasminogen activator inhibitor was significantly higher after 40 grams of alcohol than water after one, three, and five hours, but was not significantly different after nine hours.

On the other hand, there is evidence that moderate drinking may provide transient health improvements[5–9, 11, 12, 26]. Short-term randomized trials indicate that moderate alcohol consumption may have beneficial effects via changes in flow-mediated vasodilatation[5, 6] within minutes to hours and improvements in lipid profile[12], inflammatory markers[11] soluble vascular adhesion molecules[11] and adipokines[9, 26] within weeks.

In contrast to the evidence on acute effects of alcohol consumption, there is consistent evidence that habitual heavy alcohol consumption is associated with an increased risk of ischemic [27, 28] and hemorrhagic stroke[28–30]. However, the evidence regarding light to moderate consumption is mixed. While some studies reported no association with ischemic or hemorrhagic stroke[31–35], recent comprehensive reviews [28, 36] indicate a decreased risk of ischemic stroke and a higher risk of hemorrhagic stroke associated with light to moderate consumption.

Integrating the short-term effects observed here with other studies on alcohol use and long-term risk is difficult. Although speculative, it is possible that the transiently increased stroke risk from moderate alcohol consumption may be outweighed by the health benefits for the following 24 hours, but consuming multiple drinks at once may result in a sharp increase in acute risk with potential increased long-term risk as well. Mukamal and colleagues[27] found that, compared to complete abstention from alcohol, light consumption (<1 drink daily) is not associated with stroke risk, moderate alcohol consumption (1 to 2 drinks daily) is protective, and intake of more than 2 drinks per day is associated with an increased risk of ischemic stroke. Our finding of an acute detrimental effect and a suggestion of a decreased risk over the 24 hour period after alcohol consumption seem consistent with these findings. For example, one may hypothesize that over time, individuals who drink large amounts infrequently primarily experience the acute detrimental effect, while subjects who drink small amounts frequently may still experience a transient increase in risk, but this may be offset in part by the subsequent reduction in risk that follows.

There are some limitations to our study. Since the case-crossover design uses subjects as their own controls, there can be no confounding by risk factors that are stable over time[22]. Confounding by factors that change over time within individuals can occur. However, excluding subjects reporting other potential triggers in the hour preceding stroke onset did not materially alter the results. In an effort to minimize reporting bias, efforts were made to ensure the patient's privacy during the interview. We used a standardized structured interview and patients were not informed of the duration of the hypothesized hazard period. Because most of the participants drank small amounts of alcohol in the hour prior to stroke onset, we could not examine the acute effects of different doses of alcohol. We had limited power to evaluate the effect of beverage type since few participants were exposed to each type. A larger study would help elucidate such effects. Finally, our results may not be generalizable to patients presenting with a severe or fatal stroke.

## Summary

In conclusion, we found that the risk of ischemic stroke was transiently elevated for 2 hours after drinking as little as 1 serving of alcohol. The risk rapidly returned to baseline and was modestly lower by 24 hours. When examined in the context of long-term studies of alcohol consumption, the net clinical impact on ischemic stroke risk appears to depend on the frequency and quantity of alcohol consumption. Definitive evidence would require a long-term clinical trial, although such a trial would be logistically difficult and is unlikely to be carried out in the near future.

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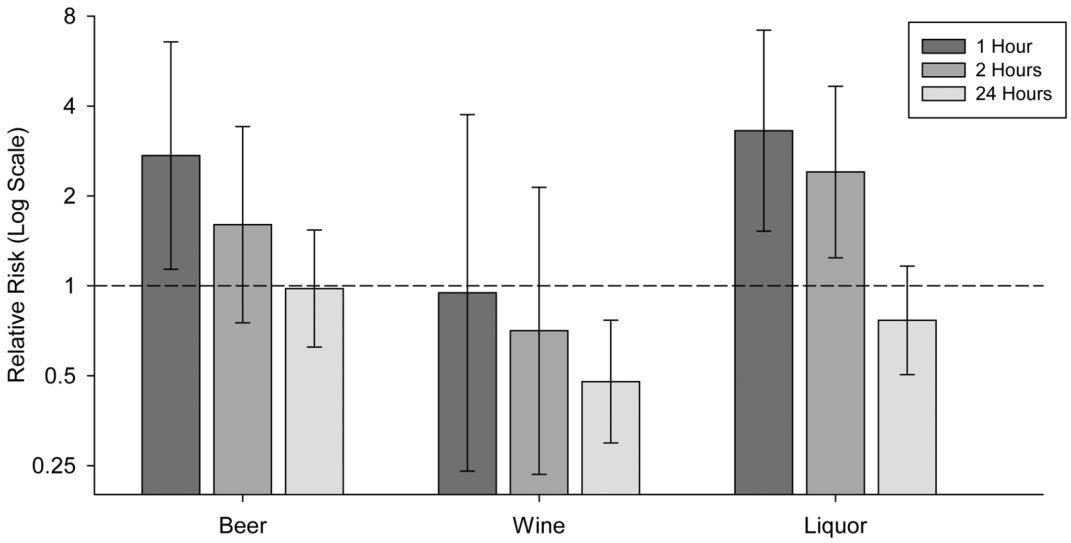


**Figure 1.**

Time of Onset of Stroke after an Episode of Alcohol Consumption. Each of the three hours before the onset of stroke was assessed as independent hazard periods, and drinking during each hour was compared with that during the control period. The error bars indicate the 95 percent confidence limits. The dashed line indicates the baseline risk.

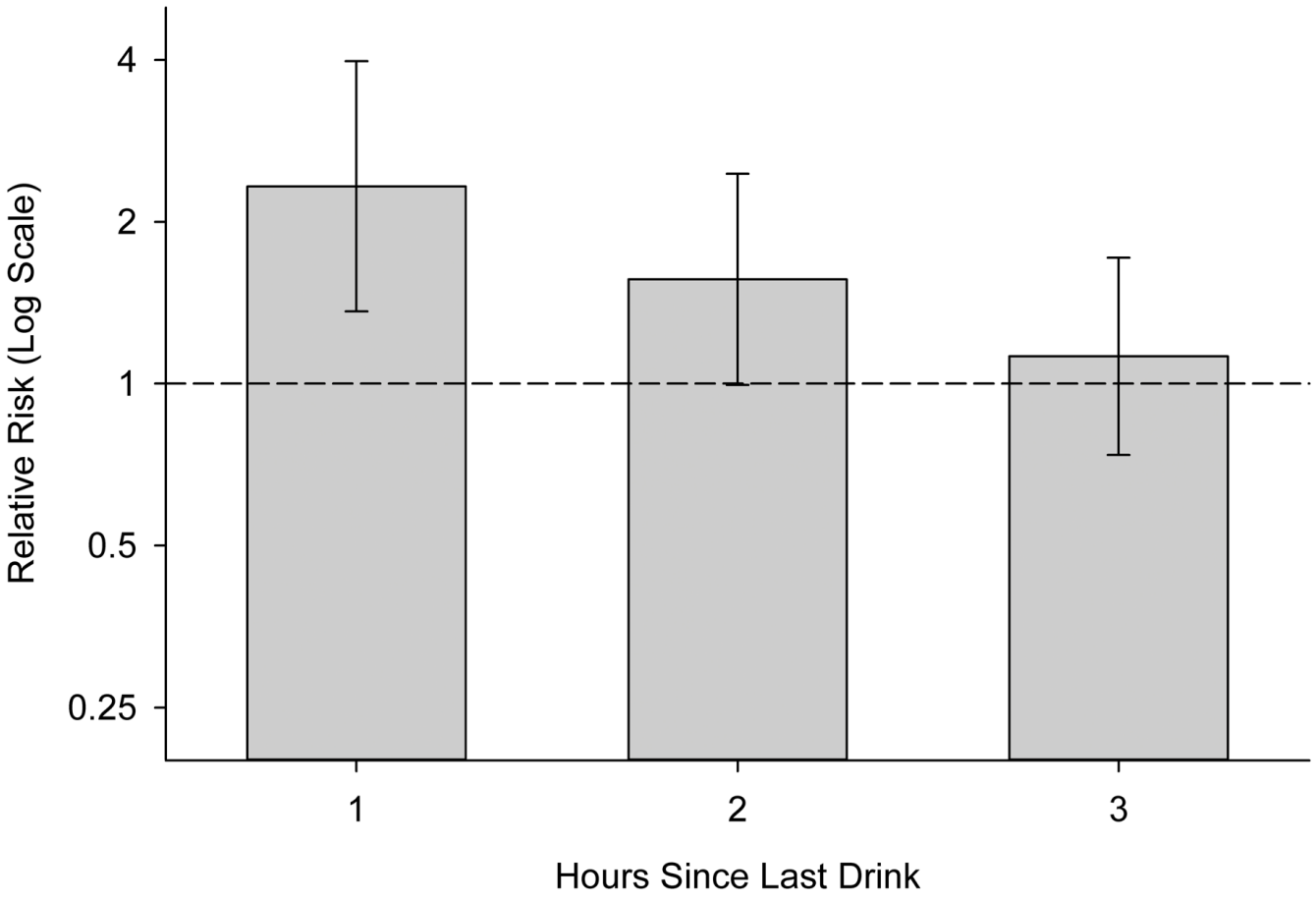


**Figure 2.**
Relative Risk of Stroke According to the Beverage Type. The error bars indicate the 95 percent confidence limits. The dashed line indicates the baseline risk.

## Table 1

Clinical Characteristics of the Stroke Onset Study Population. Mean±standard deviation or n (%)

| | Alcohol Drinkers (n =248) | Non-Drinkers (n =142) | P-Value |
|---|---|---|---|
| Age (years) | 68±14.5 | 69±13.7 | 0.11 |
| Male | 143 (58%) | 66 (47%) | 0.03 |
| Smoking status | | | 0.09 |
| Never | 72 (29%) | 56 (39%) | |
| Former | 122 (49%) | 63 (44%) | |
| Current | 54 (22%) | 23 (16%) | |
| Obesity (BMI ≥ 30 kg/m$^2$)* | 59 (24%) | 31 (22%) | 0.68 |
| Diabetes | 56 (23%) | 39 (27%) | 0.28 |
| Hypercholesterolemia | 101 (41%) | 45 (32%) | 0.08 |
| Hypertension | 152 (61%) | 100 (70%) | 0.07 |
| Atrial fibrillation | 32 (13%) | 22 (15%) | 0.48 |
| History of: | | | |
| MI† | 36 (15%) | 14 (10%) | 0.19 |
| Stroke | 41 (17%) | 32 (23%) | 0.14 |
| TIA‡ | 29 (12%) | 18 (13%) | 0.77 |
| Coronary revascularization | 11 (8%) | 31 (13%) | 0.15 |
| Carotid endarterectomy | 2 (1%) | 5 (2%) | 0.66 |
| Stroke etiology§ | | | 0.31 |
| Small Vessel | 67 (29%) | 44 (37%) | |
| Large Vessel | 46 (20%) | 21 (18%) | |
| Cardioembolic | 57 (25%) | 24 (20%) | |
| Other/Undetermined | 60 (26%) | 32 (26%) | |

*There was no data available on BMI for 7 subjects

†MI: myocardial infarction

‡TIA: transient ischemic attack

§At one of the centers, stroke etiology was not determined (n=39)