Alcohol, Ischemic Stroke, and Lessons From a Negative Study
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As one reviews a study with a negative outcome, there may be a sense of the role of a medical examiner at an autopsy, particularly if the expectation was a positive result and the data were from the renowned Framingham Study. Was the cohort too small? Were assumptions or analyses of the study flawed? Or should the natural death of the null hypothesis be accepted, rather than merely not rejected? In their article, Djoussé et al have found no overall association of alcohol consumption to ischemic stroke, although some preventive benefit was noted in the 60-to-69 age group. This was a novel but proficient analysis, and the latest of many observational studies that have addressed this question. A “J-shaped” curve of alcohol use compared with ischemic stroke risk has been demonstrated in at least 2 large prospective studies and at least 2 case-control studies, showing a positive benefit in moderate alcohol consumption in ischemic stroke prevention.

Other studies have had negative results, particularly in Japanese cohorts, or have demonstrated the harm of excessive alcohol use, either chronically or as “binge” drinking. These studies have been very well reviewed by Camargo. There are difficulties measuring the exposure of alcohol, particularly with underreporting that occurs at higher levels of drinking. It is also difficult to control for the various confounders of alcohol exposure, including smoking, hypertension, age, and gender. Moreover, advancing age is associated with both higher risk of stroke and factors that alter or stop alcohol consumption, such as heart disease, institutionalized lifestyle, and stroke itself. Finally, there is uncertainty regarding mechanisms of stroke protection or risk with alcohol, including reduction of atherogenesis, altered hemostasis, and blood pressure effects. Common to most studies of alcohol and stroke is the consideration of ischemic stroke as a relatively homogeneous manifestation of atherosclerosis, analogous to coronary artery disease, from which moderate alcohol consumption has been more firmly shown to confer protection.

Djoussé et al sampled drinking behavior and the occurrence of ischemic stroke in 4198 subjects of the Framingham cohort over a 20-year period from approximately 1962 (visit 7) to 1982 (visit 17). The alcoholic beverages were separated as wine, beer, and spirits as well in a secondary analysis. Because of low numbers, subjects of age <50 were excluded, and drinking behaviors of more than 2 drinks per day were collapsed into a single category. Djoussé et al combined their observations in a “pooling method,” so that if a subject survived stroke-free for the 10-year epoch, the drinking behavior was again sampled, and he or she participated again as a new subject. In this way 9171 samplings, or virtual subjects, for a single virtual 10-year epoch were generated. These strokes were categorized as atherothrombotic versus embolic in origin, although the occurrences in each category were not given. Note that much of the actual observation time occurred before advanced imaging studies, including computed tomography.

The results of the study include a total of 441 ischemic strokes, for a stroke rate of 4.62/1000 person-years for women and 5.06/1000 person-years for men. The virtual cohort was well balanced overall in each of the drinking behavior categories, although drinkers smoked considerably more than never-drinkers, and former drinkers were older, with higher rates of coronary artery disease, atrial fibrillation, and antihypertensive medication use. The adjusted hazard ratios for stroke were near unity in all categories for both genders, except in former drinkers, although this latter ratio was not adjusted for coronary artery disease and perhaps other important variables. Thus the single positive aspect of the study, as pointed out in the abstract, is that in the age group 60 to 69 years, some protective effect was noted with drinking in all categories, especially 12 to 23 grams (1 to 2 drinks) per day. The authors also point to a modest protective effect of wine consumption, with a hazard ratio of 0.8, although its CI included 1.0.

There are significant weaknesses of this study, as noted by the authors. One such weakness is insufficient numbers for many analyses, even in the “virtual” cohort. Thus we see a trend toward benefit of alcohol by hazard ratios even in the crude data of Table 2, but with wide CIs. The effect of alcohol cannot be assessed in ages <50, nor can the deleterious effect of heavy alcohol use, especially binge drinking, be assessed. Although wine drinking suggested a benefit, one would not be able to differentiate the effect of red wine, with its putative benefit of phenols. A second type of weakness involves issues of classification bias and confounding, for example, former drinkers were older, smoked more, and were generally less healthy, while healthier patients who lived through 2 or all 3 epochs were multiply sampled. There seems to be a lesson elucidated by these weaknesses and by those of many other negative alcohol-stroke studies of the past: that the effect of alcohol is variable and highly prone to modification or confounding with stroke risk factors, including not only age but also smoking, hypertension, and cardiac disease.
But I believe there is a third type of weakness, which involves the majority of studies of the benefit or risk of alcohol with ischemic stroke, namely an inability to differentiate the effect of alcohol on atherothrombotic versus other ischemic stroke subtypes. This weakness is due to an historical lack of ability to reliably diagnose these subtypes, and the epidemiological perspective of stroke as predominantly a cerebral atherosclerosis. This perspective was supported by an earlier review of the Framingham Study, in which 83% of ischemic strokes were categorized as atherothrombotic, so defined to include both large-artery disease and lacunes. This is contrasted with more recent and image-based assessments such as the TOAST Study, in which large-artery atherothrombosis is a mere 28% of “determined” ischemic stroke. While studies to date suggest that moderate alcohol consumption is protective of ischemic stroke, perhaps it is so by virtue of being protective to those at higher risk of developing cerebral atherothrombosis, while neither deleterious nor beneficial to those who are not at such risk. A few smaller cohort studies have specifically illustrated this explanation with respect to carotid atherogenesis, although it remains for the Djoussé et al study and most predecessors a speculation.

There are certainly large overlaps in the risk factor profiles of the 3 major etiologic categories of ischemic stroke, that is, atherothrombosis, cardiac embolism, and lacunar disease. In turn, such overlaps largely justified consideration of ischemic stroke as a homogeneous entity in the past, particularly given limitations in the diagnostic technology. However, with the current (and future) improvement in stroke diagnosis, I think it will be increasingly important for epidemiologic studies to consider ischemic stroke as it actually is, not as much a disease as a syndrome with multiple etiologies. I take this to be the more important lesson from this negative study.

References
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