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QUARTERLY FOCUS ISSUE: PREVENTION/OUTCOMES

Editorial Comment

Alcohol and Cardiovascular Mortality

Common Sense and Scientific Truth*

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"Noah, the tiller of the soil, was the first to plant a vineyard. He drank of the wine and became drunk, and he uncovered himself within the tent."

—Genesis 9:20–21

Noah is thus identified both as the first winemaker and the first to suffer embarrassment from inebriation. It has been evident for millennia that heavy alcohol drinking could cause social and bodily harm. The probability that moderate intake was less harmful or innocuous led to guidelines for a reasonable upper drinking limit. Probably the most famous

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of these was Anstie's Rule of a "sensible limit" of 45 ml of ethyl alcohol/day, or approximately 3 standard-sized drinks (1). In the mid-19th century, Anstie, a prominent public health activist, no doubt intended his guideline for mature men, but he recognized variation in alcohol tolerance. The use of "sensible" rather than "safe" acknowledges that no amount of alcohol is safe for everyone.

Scientific Evidence Develops

Evidence of possible benefit from moderate alcohol drinking was a 20th century development. One population report (2) of an alcohol–mortality J-curve relationship preceded others by one-half century. In Pearl's Baltimore study of 5,248 subjects, "heavy/steady" drinkers had the highest mortality, "abstainers" were next, and "moderate" drinkers had the lowest mortality. With no explanation, and in U.S. Prohibition days, his predictably cautious interpretation was that moderate drinking was "not harmful." A major contribution was the realization that comparing all drinkers with abstainers masked the J-curve. Memorably, he said, "one cannot judge the role of diet by starvation or excess" (2).

More recent observational population studies (3,4) consistently show lower risk among lighter drinkers than abstainers for atherothrombotic vascular disease, most notably coronary artery disease (CAD). Points favoring a causal protective effect of moderate alcohol drinking include proper time sequence, consistency in diverse healthy or unhealthy populations, plausible biological mechanisms, relative specificity for atherothrombotic conditions, controlled trial data for surrogate end points, and weakness of data supporting alternative explanations (3–6). Because CAD dominates statistics for all cardiovascular (CV) disease, the alcohol relation is similar for CAD and CV.

The alcohol–CAD reports have been examined intensely for methodological flaws (7–9). Reasonable fear of problems consequent to encouragement of moderate drinking contributes to reluctance to accept that there is any benefit from alcohol. Skepticism is fueled because some studies failed to separate ex-drinkers, including "sick quitters," from lifelong abstainers in the referent group, thus exaggerating apparent benefits of lighter drinking. Although studies using lifelong abstainers or infrequent drinkers as referents confirmed apparent protection (4), the absence of prospective randomized trials with CV events as the outcome allows residual uncertainty about CAD protection by alcohol. Consequently there has been a point-counterpoint debate in the published medical reports (8–11).

A National Study

The analysis reported by Mukamal et al. (12) in this issue of the *Journal* fits nicely into this context. This characteristically elegant presentation from a leading group in the alcohol epidemiology field confirms a U-shaped relationship between alcohol intake and CV mortality in a large nationwide study population. As expected, most of the apparent benefit in light–moderate drinkers is due to lower risk of CAD death.

The analysis (12) adds to the case that the inverse relationship of light–moderate drinking to CV mortality is scientifically valid. One important consideration is the use of a national sample. This aspect contributes strength to the scientific validity of the data by countering the argument that data in narrower study populations might not be generalizable. Another important strength is directly relevant to the much-debated issue of the most appropriate reference group. In the present report (12) there is little

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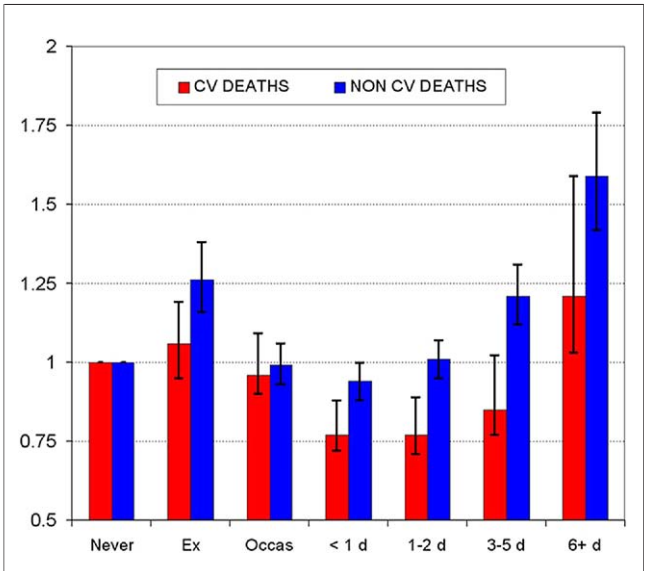

Figure 1 CV and Non-CV Deaths

Adjusted relative risk (RR) of death through 2002 by alcohol intake among 127,212 persons who supplied alcohol data at health examinations in 1978 to 1985. **Red bars** = RR cardiovascular (CV) death (n = 8,439); **blue bars** = RR non-CV death (n = 13,044). Never drinkers are referent with the following other categories: ex-drinkers; occasional (<1 drink/month); and <1, 1 to 2, 3 to 5, and 6+ drinks/day. Covariates are age, sex, ethnicity, body mass index, marital status, education, and smoking. Adapted, with permission, from Klatsky and Udaltsova (13).

relationship of CV death to past or infrequent drinking. If acknowledged past drinkers are not at increased risk, it is less likely that misclassification of others as lifelong abstainers is a factor in results.

There are published data (13) showing that increased total mortality among ex-drinkers is due primarily to non-CV causes. An example (Fig. 1) shows that apparent benefit of lighter alcohol intake is essentially limited to CV deaths and that increased risk among ex-drinkers is primarily seen for non-CV deaths. These specificities strengthen the likelihood that CAD protection by alcohol has scientific validity.

Confounding Might Act Both Ways

Skeptics emphasize flaws in methodology that might spuriously produce apparent benefit of moderate drinking, either via increased risk of "sick quitters" or reduced risk of "healthy drinkers." Less attention has been given to sources of bias that might reduce apparent benefit. One is residual confounding by smoking, a correlate of alcohol drinking in most populations. Mukamal et al. (12) nicely control for smoking, but completeness of control is always uncertain. Imprecise categorization of alcohol intake because of under-reporting by heavy drinkers is another source of bias against apparent benefit by moderate intake (14). By placing some heavy drinkers in lighter categories, under-reporting distorts alcohol-health curves. If the true relation of a harmful effect has a threshold (i.e., no effect at light drinking but increasing harm at heavier intake), under-reporting lowers or obliterates the threshold. With a J-curve, as in the CV mortality association reported here (12), under-reporting lessens apparent benefit and, as for a threshold relationship, spuriously lowers the apparent threshold for harm.

The Randomized Controlled Trial (RCT) Issue

The RCT with pre-specified end points is considered the best path to scientific truth in medical matters. Randomization is the best method of controlling for known and unknown confounders. Blinding, often part of the process, minimizes bias. The logistics of RCTs are more difficult for study of lifestyle changes than for pharmacologic or procedural interventions. We have no RCTs of moderate alcohol drinking with CAD or other fatal event end points. For ethical reasons the effects of heavy drinking are not amenable to an RCT, but the wish for such studies of chronic disease effects of moderate drinking is often expressed. Generally there has been little discussion of practical considerations. The hypothesized fractional benefits would require large numbers in a costly multicenter trial of long duration. Even assuming such an effort, could a representative study group, after exclusions, be recruited? If an appropriate population was acquired, could compliance with randomization to daily/almost daily moderate drinking or none be maintained for years? Is blinding possible? What alcohol dose(s) should be used? How many arms are needed (e.g., beer, liquor, white wine, red wine, alcohol-water mixture, placebo)? These are formidable problems. We do have studies relevant to intermediate "surrogate" markers, such as high-density lipoprotein cholesterol, antithrombotic effects, and endothelial function. There is also promise in "natural' experimental randomization by metabolic genetic polymorphisms related to alcohol metabolism. Unfortunately, it is likely that we will be left much-dependent upon observational epidemiology.

It is easy to perceive an analogy between the alcohol–CAD data and the observational data about the relation of CAD with post-menopausal hormone replacement therapy (HRT). Thus, the unexpected unfavorable outcome for HRT in the Women's Health Initiative (15) strengthens skepticism about the alcohol–CAD relation. There are considerations that make the alcohol–CAD relationship less likely to be spurious than the discredited HRT–CAD association. One is the absence of adverse CAD effects of moderate alcohol intake; this contrasts with the long-known pro-thrombotic action of HRT. Perhaps more important is the lower likelihood of selection bias by "knowledge" of benefit. For decades, health-conscious women with a favorable CAD lifestyle were more likely to seek HRT. However, before widespread media publicity about alcohol benefit in the 1990s, few persons drank alcohol primarily to reduce health risk.

Widespread current belief in potential benefit for CAD introduces a new selection bias problem. More recent observational studies are more susceptible to this problem

than older ones. The Mukamal et al. report (12) is probably free of this bias, because the alcohol data were collected in 1987 and 1992. Actually, this factor could introduce bias either way, because both those with known high CAD risk and the health-conscious with low CAD risk might be more likely to drink for presumed benefit. Reasons for drinking or not drinking will need to be incorporated in future analyses.

Conclusions

Although this writer believes the case compelling, absolute proof that persons at CAD risk obtain benefit from light–moderate drinking will not appear soon. In the 21st century a universal sensible limit would not accommodate serious public health issues such as the increased risk of female breast cancer risk associated with even moderate drinking or the consequences of the mixture of youthful drinking with the motor vehicle. The risks of moderate drinking differ by sex, age, personal history, and family history. As is often the case in medical practice, advice about lifestyle must be based on something less than certainty. There is no substitute for balanced judgment by a knowledgeable, objective health professional. What is required is a synthesis of common sense and the best available scientific facts.

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REFERENCES

1. Anstie FE. On the Uses of Wines in Health and Disease. New York, NY: JS Redfield, 1870:11–3.
2. Pearl R. Alcohol and Longevity. New York, NY: Knopf, 1926.
3. Corrao G, Bagnardi V, Zambon A, La Vecchia C. A meta-analysis of alcohol consumption and the risk of 15 diseases. Prev Med 2004;38:613–9.
4. Klatsky AL. Alcohol and cardiovascular diseases. Expert Rev Cardiovasc Ther 2009;7:499–506.
5. Zakhari S. Molecular mechanisms underlying alcohol-induced cardioprotection: contribution of hemostatic components. Alcohol Clin Exp Res 1999;23:1108–10.
6. Booyse FM, Parks DA. Moderate wine and alcohol consumption: beneficial effects on cardiovascular disease. Thromb Haemost 2001;86:517–28.
7. Shaper AG, Wannamethee G, Walker M. Alcohol and mortality in British men: explaining the U-shaped curve. Lancet 1988;2:1267–73.
8. Rehm J, Irving H, Ye Y, Kerr WC, Bond J, Greenfield TK. Are lifetime abstainers the best control group in alcohol epidemiology? On the stability and validity of reported lifetime abstention. Am J Epidemiol 2008;168:866–71.
9. Fillmore KM, Kerr WC, Stockwell T, Chikritzhs T, Bostrom A. Moderate alcohol use and reduced mortality risk: systematic error in prospective studies. Addict Res Theory 2006;14:101–32.
10. Klatsky AL. Errors in selection of "error-free" studies. Addict Res Theory 2007;15:8–16.
11. Klatsky AL. Invited commentary: never, or hardly ever? It could make a difference. Am J Epidemiol 2008;168:872–5.
12. Mukamal KJ, Chen CM, Sowmya RR, Breslow RA. Alcohol consumption and cardiovascular mortality among U.S. adults, 1987 to 2002. J Am Coll Cardiol 2010;55:1328–35.
13. Klatsky AL, Udaltsova N. Alcohol drinking and total mortality risk. Ann Epidemiol 2007;17:S63–7.
14. Klatsky AL, Gunderson EP, Kipp H, Udaltsova N, Friedman GD. Higher prevalence of systemic HTN among moderate alcohol drinkers: exploring the role of under-reporting. J Stud Alc 2006;67:421–8.
15. Rossouw JE, Anderson GL, Prentice RL, et al., for the Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33.

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