Alcohol and Coronary Heart Disease
The Answer Awaits a Randomized Controlled Trial

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In this issue of *Circulation*, Mukamal and colleagues report that frequent moderate consumption of alcohol is inversely associated with incident myocardial infarctions for both men and women.[1] This finding is consistent with numerous studies conducted in the course of 3 decades that have documented this inverse relationship. It has been described as a "J-" or "U-" shaped phenomenon, with moderate drinkers having a lower risk of myocardial infarctions as compared with abstainers and heavy drinkers.[2] A substantial contribution of this study is the results suggesting that the observed "benefits" of alcohol on myocardial infarction outcomes, particularly in men, are mediated in large part by only 3 factors: HDL-cholesterol, glucose intolerance (HbA_{1C}), and fibrinogen.

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Previous studies have examined the potential causes for the observed benefits of moderate alcohol consumption and are consistent with these findings. Serum HDL-cholesterol concentrations, for example, increase in a dose-dependent response to alcohol consumption.[3] Prospective studies have reported a reduced incidence of type 2 diabetes mellitus[4] and 1 randomized controlled trial showed increased insulin sensitivity levels with moderate alcohol consumption.[5] Heavy drinking and binge drinking have been associated with an increased incidence of type 2 diabetes.[6] Similarly, moderate alcohol consumption is associated with lower levels of inflammatory and hemostatic markers as compared with never or occasional consumption.[7,8] Heavy alcohol drinkers, in contrast, have higher levels of the inflammatory marker C-reactive protein, as compared with moderate drinkers.[8] Even when risk factors are examined in aggregate, as in the case of the metabolic syndrome, current moderate consumers of alcohol have a lower prevalence of the syndrome than current nondrinkers.[9]

This abundance of evidence supporting the hypothesis that alcohol itself leads to lower incident coronary heart disease (CHD) events is not, however, definitive. Because the majority of the data describing the relationship between alcohol and CHD risk comes from observational studies, albeit well-established cohorts, the possibility that confounding may be partially or even entirely responsible for these observed effects remains controversial. Some contend that nondrinkers have a higher burden of CHD risk factors than do moderate drinkers and consequently have higher incidence rates of CHD events. In a recent study examining 30 cardiovascular-associated risk factors, 90% of the risk factors were significantly more prevalent in nondrinkers as compared with moderate drinkers.[10] It should be noted, however, that former drinkers and potentially some "sick quitters" were included in the abstainer group, thereby potentially increasing the risk burden in nondrinkers. Nevertheless, issues of confounding can be critical, as was recently appreciated in the highly publicized examples of hormone replacement, β-carotene, and vitamin E therapies. In each of these cases, the clinical adoption by some individuals of these potential therapies was proven premature when randomized controlled trials did not demonstrate the beneficial cardiovascular events that were found in observational studies.

Even beyond the important potential issue of uncontrolled or residual confounding in this case, the therapeutic cardioprotective use of alcohol raises serious concerns. Alcohol has considerable toxicities including abuse and dependence. In the United States, 17.6 million adults abuse alcohol or are dependent on alcohol.[11] Among current drinkers, 8% exceed weekly consumption criteria for risky drinking, defined by the National Institute on Alcohol Abuse and Alcoholism as >14 drinks for men or 7 drinks for women per week.[12] Binge drinking, which is associated with substantial morbidity, is common: 32% of current drinkers consumed ≥5 drinks on 1 occasion in the past year and 15% reported such behaviors on ≥12 days in the past year.[12] A recent study comparing the prevalence of alcohol abuse in the US population from 1990 to 1991 and 2000 to 2001 showed that alcohol abuse had significantly increased, from 3.03% to 4.65%.[11] Similarly, binge drinking increased from 1.2 billion episodes in 1993 to 1.5 billion episodes in 2001.[13] Although the prevalence of alcohol problems pales when compared with the prevalence of CHD, it is important to note that alcohol consumption was the third leading actual cause of death in the United States in 2000,[14] and in 1998 alone it was associated with economic costs totaling $184.6 billion.[15] Moreover, other side effects to be considered include the unfavorable associations between alcohol and violent crime, unintentional injuries including death and suicide, and myriad other health conditions includ-

ing certain forms of cancer.[16] Of particular importance with respect to the use of alcohol as a cardioprotective strategy, some investigators estimate that 5% to 7% of current abstainers and/or infrequent drinkers could develop diagnosable alcohol problems on beginning regular moderate alcohol-consumption regimens.[17] These estimates, however, are based on the general population and not on a particular subgroup of drinkers (eg, moderate drinkers consuming alcohol within "safe" limits).

Clinicians considering the use of alcohol as a treatment modality for CHD in clinical practice must also carefully consider the issues of dosing and duration of therapy and the needs of individual patients. Past research is not particularly informative about these issues. Observational data has consistently shown that 1 to 2 drinks per day is associated with lower cardiovascular risk, yet most studies did not ascertain and therefore did not consider risky patterns of alcohol consumption (eg, binge drinking) in the study design or subsequent analyses. For example, among people with infrequent episodes of heavy drinking, the risk of CHD is higher as compared with abstainers even when the overall volume of alcohol consumed is low.[18] None of the major prospective studies, including the present study, used measurement tools such as the Timeline Followback, the gold standard for ascertaining alcohol consumption in the past 30 days.[19] Other measurement tools only allow investigators to average daily patterns of consumption based on weekly, monthly, or annual reports. The Timeline Followback, however, specifically asks subjects to recall the amount of alcohol consumed during each of the past 30 days, thereby quantifying daily volumes and patterns of consumption.[19] Another issue of concern is the lack of adjustment for duration of alcohol consumption or the consideration of past quantities of consumption in the predictive models. Also, the alcohol data collected prospectively during the follow-up period in these studies are sparse. Assumptions of stable, unchanging alcohol consumption over time may simply not be accurate. Previous studies clearly show, for example, that younger adults tend to consume higher quantities of alcohol and demonstrate increased risky behavior associated with alcohol (eg, binge drinking) than do older adults.[13] Because the alcohol exposure for participants most likely predates their enrollment into established cohorts, not accounting for this past quantity or pattern of alcohol exposure may be problematic. Another concern, as in the case of the present study, is that participants in these established cohorts may not be necessarily generalizable to the overall population. They typically do not represent the minority of the population with risky alcohol consumption behavior patterns, nor are they designed to provide information pertaining to an individual's metabolic, dietary, or genetic make-up, which may affect alcohol metabolism and subsequent CHD risk. Consequently, the available observational data, although important, still do not answer important questions for physicians and patients such as: Is/are 1 to 2 drinks several days a week the appropriate amount of alcohol and pattern of consumption that is required to be cardioprotective? How long should this therapy continue? Does this therapy need to be lifelong? Is there an amount or lifetime quantity of alcohol consumption that needs to be consumed to achieve the "observed benefit?"

The important limitations of these observational studies do not diminish the significance of these studies for identifying important associations that make the compelling case for pursing clinical trials that can direct clinical care. The abundance of favorable data associated with alcohol consumption in relation to CHD juxtaposed with a side effect profile that includes risk of dependence, comorbid medical conditions, or even death compounded by the absence of specific dose or duration for the therapy to achieve a well-defined cardiovascular outcome presents the practicing physician with somewhat of a dilemma. Current recommendations are clear that if high-risk drinking behavior is present, patients should be asked to cut back or seek treatment.[20] If a patient is currently drinking within "safe" limits, then physicians can delineate and discuss the potential benefits of such behavior and the risks of drinking beyond such limits with patients.[21] For those who do not drink or only occasionally consume alcohol, recommendations for alcohol use as a protective agent should not be broadly endorsed. It is true that some proponents such as Dr R. Curtis Ellison of the Boston University School of Medicine argue that, "For appropriate patients without any contraindications (eg, history of abuse, medical conditions, religious or ethical inhibitions, etc) who do not drink or do so only occasionally, and who wish to do so, encouraging a glass of wine or other alcoholic beverage with dinner every evening may be the best advice you can give them."[22] Others, including the present editorialists, believe that observational studies are not enough to make a prescription.

Although no large prospective studies have examined the role of alcohol as a cardioprotective agent for CHD, some randomized controlled trials involving alcohol do show a beneficial effect on insulin and triglyceride concentrations among those who consume 30 g (2 drinks)/day,[5] and numerous trials have shown beneficial effects of moderate alcohol intake on lipids, clotting factors, and other intermediaries.[7] Primary prevention trials have been considered previously but judged doubtful for several important reasons: high costs, difficulty with blinding subjects, the need to find large numbers of people who have no contraindications to alcohol use (eg, medical reasons) and who are willing to forgo or continue alcohol use for an extended period of time, and the possibility of eventual alcohol abuse or dependence.[23] Others, however, have suggested that large secondary prevention trials among those at highest risk (eg, history of CHD) and on appropriate therapy may not only be possible but are also arguably justifiable.[24]

Consequently, given the importance and prevalence of CHD, the potential benefits of alcohol use, the risks of alcohol abuse, and the inherent limits of observational studies, it is time for serious consideration of the usual next step in the assessment of a prevention intervention: performance of a randomized controlled trial.
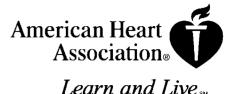
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