For more than 75 years, pathologists have recognized that alcohol consumption has a surprising link to atherosclerosis (1). In those early studies, postmortem examinations of deceased heavy drinkers identified less atherosclerosis than was expected from age and sex, suggesting that alcohol consumption is atheroprotective. In the ensuing 8 decades, investigators have made substantial strides in understanding this relationship, including confirmation of the strength and shape of the association of alcohol consumption with lower risk of coronary heart disease (CHD), its consistency across beverage types and in different populations, and its associations with various forms of cardiovascular disease.

One of the most important aspects of the alcohol–CHD relationship that continues to draw interest is its underlying mechanism. There are a number of reasons for this interest. First, because no long-term randomized trial of alcohol consumption on CHD incidence or prognosis is likely anytime in the near future, the evidence base will continue to be largely observational, with all of the attendant limitations therein. Consequently, the presence of a plausible mechanism provides reassurance that the observed association is not the result of confounding by such factors as baseline health or socioeconomic status. Second, given the many difficulties with recommending alcohol intake, even in moderation, a better understanding of the mechanisms involved could lead to safer therapies that harness these same pathways to prevent CHD. Finally, because the relationships of alcohol consumption with candidate pathways can be readily tested in randomized trials, even when its relationship with CHD cannot, identification of key pathways helps to direct trialists to the best biomarkers and intermediate outcomes to test in short-term feeding studies. For all of these reasons, studies attempting to draw the full links between alcohol consumption, CHD, and the pathways that connect them remain important.

Epidemiologists have taken 2 approaches to this challenge. One approach has been to determine the effect of alcohol consumption on candidate biomarkers in randomized trials and then to quantify the expected reduction in risk of CHD based on those changes. This approach is attractive because the first step—how alcohol changes biomarkers—comes from clinical trials that are not subject to confounding: We can confidently say that moderate alcohol consumption truly causes the observed changes in these biomarkers. This approach still requires extrapolation, however, from short-term biomarker changes to long-term risk reduction in the second step.

In the most comprehensive example of this approach, Rimm and colleagues systematically reviewed the short-term feeding studies that evaluated the effect of alcohol consumption on a wide variety of biomarkers (2). Alcohol consumption had its most prominent effects on 3 markers: increasing HDL cholesterol (HDL-C) and triglycerides but lowering of fibrinogen. On the basis of the previously observed associations of these 3 factors with the risk of CHD along with accounting for the natural variability in these measurements, the authors concluded that these 3 pathways alone would be anticipated to produce a 25% lower risk of CHD among consumers of 2 drinks per day—an estimate very close to that observed in epidemiologic studies.

The second approach that epidemiologists have adopted to understand the mechanisms linking alcohol and CHD relies on statistical adjustment in multivariable regression models. In this approach, investigators first evaluate the strength of the association (i.e., the relative risk) between some level of alcohol consumption and risk of CHD, typically when compared with abstinence. This step typically includes adjustment for standard confounding factors, such as age, sex, and smoking, but not for potentially mediating factors. Then, the modeling is repeated but with additional adjustment for one or more plausible mediators. If one of these potential mediators truly lies on the causal pathway between alcohol and CHD, then we anticipate that the magnitude of the alcohol–CHD association will weaken with this latter adjustment because it
vents” that mediator from influencing the risk of CHD. Furthermore, one can quantify the change in the association with this latter adjustment, thereby providing an estimate of how much of the original association is related to a specific mediator. At the extreme, if all of the association is driven by a single pathway, then adjustment should drive the relative risk to the null (i.e., to 1).

It is important to recognize the strengths and limitations of this approach. Although it is highly flexible, can be adapted to account for many types of relationships, and can evaluate multiple pathways simultaneously, it is strongly dependent on a number of assumptions. For example, the model should be fully adjusted for all possible confounders before adding the potential mediator; otherwise, the mediator may serve as a marker of an unadjusted confounder rather than just as a mediator. Likewise, a given biomarker may reflect more than one pathway if it tends to be correlated with other biomarkers. For example, inclusion of HDL-C also effectively tests not only reverse cholesterol transport but also insulin resistance, inflammation, and all of the other metabolic processes that influence HDL-C concentrations if they are not included separately. Perhaps most relevant, the 3 key factors in these models—in this case alcohol, HDL-C, and CHD—should all be measured well and have the expected relationships with each other. That is, moderate alcohol consumption should be associated with an approximately 25% to 30% lower risk of CHD, HDL-C should be associated with an approximately 25% lower risk for each 15-mg/dL (0.39-mmol/L) increment, and alcohol and HDL-C should have a correlation coefficient of approximately 0.25.

The first systematic effort to evaluate this association was performed in the Lipid Research Clinics Follow-up Study (3), which found that HDL-C accounted for approximately 58% of the association of alcohol consumption with cardiovascular mortality among men. Follow-up studies have generally suggested a similar level of mediation—typically finding that about half of the association of alcohol with CHD relates to HDL-C.

Not all studies have observed this magnitude of attenuation, however, and their differences are instructive. Two studies of older populations found no attenuation of the alcohol–CHD relationship with adjustment for HDL-C (4, 5). Of note, lipids are much weaker predictors of CHD in older adults than in middle-aged adults; hence, this difference likely reflects the lesser contribution of HDL-C to CHD in the elderly.

In the most recent such study, Magnus and colleagues examined these questions with approximately 150 000 Norwegian adults (6). The cohort was evaluated on a single occasion, when a nonfasting lipid profile was also obtained. Alcohol consumption was ascertained by asking 3 moderately similar questions about drinking frequency; drinking quantity was not ascertained. For both sexes, the authors found a 35% lower adjusted risk of CHD mortality among consumers of just 1 drink per week, compared with the nondrinking population, with essentially no change occurring after additional adjustment for HDL-C.

These results should be viewed with serious caution for several reasons. First, the correlation of alcohol with HDL-C was not reported, nor was the association of HDL-C with coronary mortality. If either of these associations is weaker than expected, whether because of chance or simply imprecise measurement, then HDL-C is unlikely to serve as a mediator in this population. Second, the observed association of alcohol with CHD mortality in this study has some unusual features. For both sexes, the association is improbably strong at a dose of alcohol that is unlikely to be biologically meaningful. Even if we assume that alcohol consumption was underreported, as the authors suggest was likely, there was a 30% lower risk among women who consumed alcohol 1 to 3 times per month, with almost no further decrease in risk with greater intake—a strong association with rare drinking that is implausible even with substantial underreporting. Were very light drinkers to have been used as the referent category, which might have been preferable given the absence of information on former drinking, alcohol consumption would clearly not have been associated with a lower risk in women at all. Thus, it is unclear how much of the lower risk was due to the biological effects of alcohol at all. Finally, statistical methods to quantify the change in risk with adjustment for a mediator have been developed recently, but the authors did not incorporate these analyses. Therefore, we cannot estimate how much mediation by HDL-C might be consistent with the observed findings due to chance alone.

By any account, HDL-C does not account for all of the association of alcohol consumption with lower risk of CHD in any previous study, and the current study, when considered with the previous studies of older populations, suggests that other pathways are likely to be involved, especially those in which lipids are less prominent risk factors. What might these factors be? The results of clinical trials clearly point to at least 3. First, alcohol has long been recognized as an antiplatelet agent, both for the good (preventing atherothrombotic events) and for the bad (leading to internal hemorrhage). Second, alcohol consumption raises concentrations of adiponectin, an insulin-sensitizing adipokine, and improves insulin sensitivity in some trials. Third, alcohol consumption lowers circulating concentrations of fibrinogen, an acute-phase reactant,
thus implicating alcohol as an antiinflammatory agent. Given the known immunosuppressive effects of heavy drinking, this effect is indeed plausible. Thus, several intriguing potential pathways beyond HDL-C may link alcohol consumption with a lower risk of CHD. It is now up to epidemiologists to harness the full range of study designs at their disposal to ascertain which of these pathways are truly at work in this long-observed but incompletely understood association.

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