

## Wine and Your Heart

### A Science Advisory for Healthcare Professionals From the Nutrition Committee, Council on Epidemiology and Prevention, and Council on Cardiovascular Nursing of the American Heart Association

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Data regarding the incidence of coronary heart disease (CHD) in different populations have generated a series of hypotheses that protective substances in the diet may counteract the harmful effects of high-cholesterol, high-saturated-fat diets. One such potential food substance is wine, especially red wine. The purpose of this advisory is to summarize the current literature on wine intake and cardiovascular disease. As stated in a previous advisory on alcohol and CHD,<sup>1</sup> recommendations for use of a nonessential dietary component with significant health hazards require definitive evidence of benefit. Although population surveys and in vitro experiments show that wine may have limited beneficial effects, more compelling data exist for other less-hazardous approaches to cardiovascular risk reduction.

#### Epidemiological Association of Wine Intake and Cardiovascular Disease

##### Do Epidemiological Data Support a Role for Alcoholic Beverages (Wine in Particular) as a Cardioprotective Substance?

There are more than 60 prospective studies that suggest an inverse relation between moderate alcoholic beverage consumption and CHD.<sup>2</sup> A consistent coronary protective effect has been observed for consumption of 1 to 2 drinks per day of an alcohol-containing beverage; however, higher intakes are associated with increased total mortality.<sup>3,4</sup> Although ecological studies support an association between wine intake and lower CHD risk, these studies are confounded by lifestyle, diet, and other cultural factors.<sup>4,7</sup> Most cohort studies do not support an association between type of alcoholic beverage and prevention of heart disease; however, a few have suggested that wine may be more beneficial than beer or spirits.<sup>8,9</sup> It remains unclear whether red wine confers any advantage over white wine or other types of alcoholic beverages.

A synthesis of the observational studies is difficult because of wide variations in methodology, measurement error in alcohol consumption, and biological variability in response to

alcohol consumption (which tends to underestimate effect). Moreover, consumption may vary over time, and this is often not taken into consideration in observational studies. Consumption of alcohol is associated with age, race, smoking, ethnic background, and education level. Wine drinkers tend to be less fat, to exercise more, and to drink with meals. Statistical modeling that includes potential confounders does not mitigate the beneficial effect of alcohol consumption on CHD. Furthermore, the residual protective effect of wine may be due to unmeasured factors or differences between drinkers and nondrinkers that cannot be adequately controlled for in statistical analyses. Because of these limitations, epidemiological data can be considered to be supportive of the alcohol-CHD hypothesis, but not definitive. More data are needed to clarify the effects of specific types of beverages in diverse populations.

The mortality rate from CHD in France is perhaps half the rate in the United States despite similar intakes of animal fats.<sup>10</sup> This has been coined the "French paradox." When potential confounders and differences in reporting are taken into consideration, the gap is narrowed but probably not eliminated. Regional variation in CHD rates and risk factors in both the United States and France makes a simple explanation for the paradox unlikely. Nevertheless, one explanation for the lower risk of CHD among the French is an increased intake of wine, especially red wine.<sup>11</sup> An inverse association between moderate consumption of alcoholic beverages (1 to 2 glasses per day) and CHD has been documented. However, data regarding the specific effects of red wine are less consistent, possibly for the reasons discussed above. Moreover, the protective effect appears to be influenced by whether the wine is consumed with meals.<sup>4</sup> This hypothesis deserves further investigation, because the pattern of consumption of alcoholic beverages may be a marker for other lifestyle factors related to CHD risk.<sup>7</sup> A number of dietary factors, such as consumption of fresh fruits, vegetables, and fish and reduced intake of milk products, differ between European populations and can be readily associated with reduced CHD risk.<sup>12,13</sup>

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## The Biological Basis for a Protective Effect of Alcohol and Red Wine

### Does Red Wine Decrease Atherosclerotic Cardiovascular Disease Because It Is an Antioxidant?

A widely held theory is that development of atherosclerotic plaque involves oxidation of lipoproteins within the artery wall. A large amount of *in vitro* data has shown that lipoprotein oxidation increases its uptake by cells and can cause cholesterol loading of macrophages, a process thought to be analogous to the evolution of lesional “foam cells.” Some *in vivo* studies in rabbits and transgenic mice have suggested that antioxidants decrease atherosclerotic plaque formation. However, the studies are not conclusive; the intake of the antioxidant drug probucol by apolipoprotein (apo) E knockout mice<sup>14</sup> and humans with peripheral vascular disease was not associated with reduced atherosclerosis.<sup>15</sup> Moreover, several recent clinical intervention studies<sup>16,17</sup> have failed to show a cardioprotective effect of vitamin E, a presumed antioxidant. Wine, especially red wine, contains a number of polyphenol compounds, such as resveratrol, and flavonoids that prevent lipoprotein oxidation *in vitro*.<sup>18</sup> Flavonoids also occur in other alcoholic beverages, such as dark beer. Antioxidant compounds in wine are also found in non-alcohol-containing grape juice.<sup>19</sup> Studies of the effects of resveratrol on atherosclerosis in animals are conflicting.<sup>20,21</sup> Alcohol itself may be a pro-oxidant, and this effect of alcohol is thought to be associated with the increase in cancers of the oropharyngeal cavity in alcohol abusers. In contrast, alcohol addition to the diets of several strains of atherosclerosis-prone mice decreased atherosclerosis.<sup>22,23</sup> In summary, wine consumption as a means of cardiovascular protection because of its antioxidant content is an unproven strategy. It is still unclear what the effects of other antioxidants on human disease may be. Fresh fruits and vegetables, including non-alcoholic grape beverages, should have a similar antioxidant action as red wine.

### How Does Alcohol Ingestion Change Lipoproteins?

Alcohol leads to 2 well-established changes in lipoproteins; wine, as a source of alcohol, has no other known effects. Like any other source of carbohydrates, alcohol can increase plasma triglyceride levels and can serve as a source of excess calories. In patients with underlying hypertriglyceridemia, the triglyceride elevations can be marked.<sup>24,25</sup> The association between alcohol-related hypertriglyceridemia and exacerbation of pancreatitis is well known. The source of the increase in triglyceride is an increase in triglyceride production and secretion in very-low-density lipoprotein (VLDL). The best-known effect of alcohol is to increase circulating levels of high-density lipoprotein (HDL) cholesterol. One to 2 drinks per day increase HDL by  $\approx 12\%$  on average.<sup>26</sup> This increase is similar to that seen with several other interventions, including exercise programs<sup>27</sup> and fibric acid medications. Niacin therapy is a more effective method to raise HDL and leads to an  $\approx 20\%$  increase in HDL cholesterol. Approximately half of the beneficial effects of alcohol on cardiovascular disease have been ascribed to the increase in HDL

cholesterol.<sup>1</sup> No clinical trials have provided verification that alcohol can be used to increase HDL cholesterol levels. In contrast, treatment of patients with low HDL with statins as primary prevention<sup>28</sup> and with fibric acids as secondary prevention<sup>29</sup> has been shown to be beneficial.

### Do Wine and Other Alcoholic Beverages Have Significant Antithrombotic Actions?

For light to moderate intakes (up to 60 mL of alcohol per day), the answer appears to be yes. Numerous studies have shown statistically significant decreases in platelet aggregation (measured *in vitro*) associated with the consumption of alcoholic beverages.<sup>30</sup> However, controversy surrounds the issue of whether some forms of alcoholic beverages, particularly red wine, are more effective than others. There is some evidence that resveratrol and other polyphenolic compounds found in red wine can have an independent and additive effect on the reduction of platelet aggregation.<sup>31-33</sup> Other studies<sup>34</sup> suggest that most of the effects on platelets can be explained by the alcohol component of the beverage. Primarily on the basis of *in vitro* studies, inhibition of prostaglandin synthesis has been determined to be the apparent mechanism by which alcoholic beverages decrease platelet aggregation; aspirin works by a similar mechanism. Less well studied than the effects on platelets are the effects of alcoholic beverages on other aspects of coagulation. For example, there are occasional reports of potentially beneficial effects of alcohol or resveratrol on plasma fibrinogen levels (decreased<sup>34</sup>) and cellular tissue factor levels (also decreased<sup>35</sup>), but more data are needed to adequately evaluate these and related findings. Overall, light to moderate consumption of any type of alcohol-containing beverage appears to reduce platelet aggregation and thereby provides an antithrombotic benefit similar to that of aspirin.

## Adverse Effects of Alcohol Ingestion

### Are There Downsides to Moderate Alcohol Consumption?

The proposed health benefits of alcohol consumption must be evaluated against the adverse effects of alcohol consumption, which include fetal alcohol syndrome, cardiomyopathy, hypertension, hemorrhagic stroke, cardiac arrhythmia, and sudden death. Most of these adverse effects are associated with long-term alcohol consumption with chronic intake of  $>3$  servings of alcoholic beverages per day. Acute alcohol consumption may also have effects on the cardiovascular system that are primarily related to the negative inotropic and proarrhythmic effects of alcohol. Alcohol consumption should never be considered as a preventive measure for teenagers or young adults; automobile accidents, trauma, and suicide are leading causes of mortality in this age group, and use of alcohol can contribute to their incidence. Alcohol is an addictive substance, and adverse effects of drinking occur at more moderate levels in some individuals. An individual's risk for developing alcoholism is difficult, if not impossible, to determine. There is particular concern about “moderate” alcohol consumption in women. A recent American Heart Association/American College of Cardiology consensus panel statement, “Guide to Preventive Cardiology for Wom-

en,"<sup>36</sup> suggested that consumption of no more than 1 glass of alcohol per day is appropriate for women. In addition to concerns about prevention of CHD, there is some concern that alcohol intake >50 g/d may be associated with increased breast cancer risk.

### Hypertension

There are more than 50 cross-sectional and 10 prospective epidemiological population-based studies that have demonstrated a direct association of alcohol intake and hypertension in men and women of different ages and races. Data from the Nurses Health Study<sup>37</sup> demonstrate that >20 g of alcohol per day (2 drinks) in women who are between 30 and 55 years of age is associated with a linear increase in the incidence of hypertension. In men, alcohol consumption exceeding 20 g/d is also linked to the development of hypertension; however, the increase in blood pressure relative to the level of alcohol consumption is less linear. In the Kaiser Permanente study,<sup>38</sup> men and women drinking 6 to 8 drinks/d had a 9.1-mm Hg higher systolic blood pressure and 5.6-mm Hg higher diastolic blood pressure than nondrinkers. Daily intake of more than moderate amounts of alcoholic beverages is a clear risk factor for the development of hypertension. Patients who are hypertensive should avoid alcoholic beverages.

### Stroke

There appears to be consensus that long-term heavy alcohol consumption (>60 g/d) increases an individual's risk for all stroke subtypes, especially intracerebral and subarachnoid hemorrhage. The effects of moderate alcoholic beverage consumption (<2 drinks/d) are less clear because of conflicting reports. Some studies<sup>39</sup> suggest that moderate alcohol consumption may decrease the risk of ischemic stroke in specific populations, whereas others<sup>40</sup> have not found a protective association between alcohol intake and stroke. There may be numerous variables, such as race/ethnicity, age, sex, drinking patterns, and beverage type, that interact with the effects of alcohol on stroke risk. Data remain inconclusive in this area, and therefore specific recommendations are difficult to formulate.

### What Conclusions Can We Make About a Protective Effect of Wine Against Heart Disease?

Moderate intake of alcoholic beverages (1 to 2 drinks per day) is associated with a reduced risk of CHD in populations. There is no clear evidence that wine is more beneficial than other forms of alcohol, although further research is needed regarding the potential protective non-lipoprotein-altering effects of substances unique to wine. If wine does have additional effects, it appears that many of the same additional biological effects might be achieved with grape juice.<sup>19,41</sup> Despite the biological plausibility and observational data in this regard, it should be kept in mind that these are insufficient to prove causality. There are numerous examples in the cardiovascular literature of studies that have documented consistent population and mechanistic data that have not held up in clinical trials, eg,  $\beta$ -carotene, vitamin E, and hormone replacement therapy. It is impossible to adequately adjust for

factors related to human behavior that cannot be measured in observational designs. Although moderate use of wine and other alcohol-containing beverages does not appear to lead to significant morbidity, alcohol ingestion, unlike other dietary modifications, poses a number of health hazards. Without a large-scale, randomized, clinical end-point trial of wine intake, there is little current justification to recommend alcohol (or wine specifically) as a cardioprotective strategy. The American Heart Association maintains its recommendation that alcohol use should be an item of discussion between physician and patient.

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