To Drink or Not to Drink? That Is the Question

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Abstract—Numerous studies have used a J-shaped or U-shaped curve to describe the relationship between alcohol use and total mortality. The nadir of the curves based on recent meta-analysis suggested optimal benefit at approximately half a drink per day. Fewer than 4 drinks per day in men and fewer than 2 per day in women appeared to confer benefit. Reductions in cardiovascular death and nonfatal myocardial infarction were also associated with light to moderate alcohol intake. Although some studies suggested that wine had an advantage over other types of alcoholic beverages, other studies suggested that the type of drink was not important. Heavy drinking was associated with an increase in mortality, hypertension, alcoholic cardiomyopathy, cancer, and cerebrovascular events, including cerebrovascular hemorrhage. Paradoxically, light-to-moderate alcohol use actually reduced the development of heart failure and did not appear to exacerbate it in most patients who had underlying heart failure. Numerous mechanisms have been proposed to explain the benefit that light-to-moderate alcohol intake has on the heart, including an increase of high-density lipoprotein cholesterol, reduction in plasma viscosity and fibrinogen concentration, increase in fibrinolysis, decrease in platelet aggregation, improvement in endothelial function, reduction of inflammation, and promotion of antioxidant effects. Controversy exists on whether alcohol has a direct cardioprotective effect on ischemic myocardium. Studies from our laboratory do not support the concept that alcohol has a direct cardioprotective effect on ischemic/reperfused myocardium. Perhaps the time has come for a prospectively randomized trial to determine whether 1 drink per day (or perhaps 1 drink every other day) reduces mortality and major cardiovascular events. (***Circulation*. 2007;116:1306-1317.**)

Key Words: alcohol ■ arrhythmia ■ cardiomyopathy ■ heart failure ■ myocardial infarction

Alcohol is an old drug that has attracted human interest for thousands of years. Evidence of wine making was depicted on the walls of the temples of the pharaohs in Egypt and the Sumerians of Mesopotamia. Scientific debate about the risks and benefits of alcohol started in Europe several centuries ago and continues today. How much alcohol should people drink, what should they drink, and who should be doing the drinking are important questions that need definitive answers. This article provides an in-depth analysis of the effect of alcohol on the human heart and its clinical relevance to patient care.

A recurring theme is that although high doses of alcohol are harmful to the heart (cardiomyopathy, arrhythmias, and hypertension), mild to moderate alcohol consumption has been associated with reductions in coronary artery disease and even total mortality.

When we reviewed the literature, it became very evident that definitions describing how much alcohol is in a drink vary remarkably by article and country, and terms such as light, moderate, and heavy drinking are variably defined. Table 1 provides some of the definitions we could find from the US government, but readers should be aware that the definitions are not well standardized in the literature and are not agreed on by all researchers (Tables 1 and 2).[1–5]

Alcohol and Total and Cardiovascular Mortality

Numerous studies have used J-shaped or U-shaped curves to describe the relationship between alcohol use and total mortality. An excellent and very recent updated meta-analysis of 34 prospective studies was published by Di Castelnuovo and associates[6] to show the relationship between alcohol dosing and total mortality. The 34 studies in men and women included information on >1 million subjects and >94 500 deaths. The authors described a J-shaped relationship between alcohol intake and mortality in which after an initial reduction in mortality, as alcohol intake was increased, the curve reached a plateau and then demonstrated an increase in mortality at higher doses of alcohol. In the Di Castelnuovo updated meta-analysis, the lowest mortality was observed at 6 g of alcohol per day (approximately half a drink per day; relative risk=0.81; 95% confidence interval [CI], 0.80 to 0.83), but lower mortality compared with zero alcohol consumption was observed with up to ≈4 drinks per day (Figures 1 and 2). Differences in response by sex existed, in that whereas up to 4 drinks per day in men was protective, only up to 2 drinks per day in women was protective. Doses of alcohol of >4 drinks per day in men and >2 in women were

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TABLE 1. Common Definition of a Standard Alcoholic Drink in the United States[1]

≈0.6 fl oz of alcohol
≈17.74 mL of alcohol
≈14 g of alcohol
≈12 oz of beer
≈5 oz of wine
≈1.5 oz or a "shot" of 80-proof distilled spirits or liquor (gin, rum, vodka, whiskey)

Note: Another definition in the US literature places an alcoholic drink at ≈0.5 fl oz or ≈12 g of alcohol. Definition of a standard drink differs among countries. For example, in England it is ≈8 g of alcohol; in Japan it is ≈19.75 g.

associated with an increase in mortality. Maximum protection was 17% in men and 18% in women. The basic shape of the curves persisted after adjustment for confounding variables. The authors concluded that low levels of alcohol intake were "inversely associated with total mortality in both men and women." The authors speculated on why this inverse association disappears at a lower dose in women than in men. Possibilities included an increased risk of cancer in women. In addition, for equal amounts of alcohol consumption, women are exposed to a higher blood level of alcohol compared with men, perhaps because of differences in the way alcohol is metabolized between women and men (women have lower gastric alcohol dehydrogenase activity). Additionally, the benefits of alcohol on total mortality in women may be blunted by the fact that premenopausal women have a low incidence of coronary artery disease mortality.

Gaziano et al[7] studied 89 299 men in the Physician's Health Study who at enrollment were aged 40 to 84 years and were free of myocardial infarction. Usual alcohol consumption was determined by questionnaire, and patients were followed over 5.5 years for mortality. This study was also included in the aforementioned large meta-analysis. The investigators observed a U-shaped curve describing the relationship between alcohol intake and death from any cause. Those who drank 1 to 3 drinks per month, 1 drink per week, 2 to 4 drinks per week, 5 to 6 drinks per week, 1 drink per day, and ≥2 drinks per day demonstrated a reduction in risk of all-cause mortality of 0.86, 0.74, 0.77, 0.78, 0.82, and 0.95, respectively, compared with those who did not drink. The relationship between light to moderate alcohol intake and

TABLE 2. Definitions of Alcoholic Drinking

Moderate drinking: Low-risk or responsible drinking.[2] From *Dietary Guidelines for Americans*[3]: no more than 1 drink per day for women and no more than 2 drinks per day for men
Heavy drinking: Consuming an average of >2 drinks per day for men and >1 drink per day for women[2]
Light drinking: No standard definition; presumably less than moderate drinking
Binge drinking: Pattern of alcohol consumption that achieves blood alcohol concentration to ≥0.08%; usually corresponds to >4 drinks on a single occasion for men or >3 drinks for women within ≈2 hours
Alcohol abuse: A pattern of drinking that causes harm to a person's health, relationships, or ability to work[5]

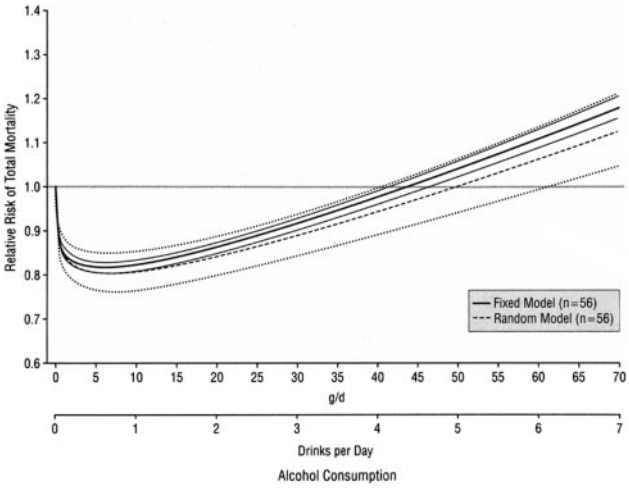

Figure 1. Risk of total mortality and 95% CIs for drinks of alcohol per day taken from 56 curves as part of a meta-analysis, using fixed and random-effects models. Reprinted from Di Castelnuovo et al,[6] with permission from the publisher. Copyright © 2006, the American Medical Association.

cardiovascular mortality was L-shaped, with decreased risk starting at 1 drink per week. Even at ≥2 drinks per day, a decrease in cardiovascular mortality could be seen compared with nondrinkers. The relationship between alcohol intake and death from myocardial infarction was also L-shaped, with decreased risk of dying from a myocardial infarction of 32% to 47% for those taking ≥1 drink per week. In contrast, an increase in RR for cancer was present at the highest drinking level (relative risk=1.53; 95% CI, 1.15 to 2.05), although much of this excess risk was confounded by smoking.

Grønbaek et al[8] described a U-shaped curve for stable alcohol intake and total mortality. Compared with light drinkers (1 to 6 drinks per week), nondrinkers (<1 drink per week) had a relative risk of dying of 1.29 (95% CI, 1.13 to 1.48), and heavy drinkers (>13 drinks per week) had a relative risk of 1.32 (95% CI, 1.15 to 1.53). In contrast, the risk of death from coronary heart disease decreased across the levels of stable drinking. Thus, compared with light drinkers (1 to 6 drinks per week), nondrinking was associated with a relative risk of dying from coronary heart disease of 1.32 (95% CI, 0.97 to 1.79), moderate drinking (7 to 13 drinks per week) with a relative risk of 0.95 (95% CI, 0.66 to 1.38), and heavy drinking (>13 drinks per week) with a relative risk of 0.86 (95% CI, 0.62 to 1.20). The increase in total mortality with heavy drinking thus was not related to coronary artery disease but appeared to be related to an increase in cancer deaths.

This same group of researchers[9] also showed that the type of alcoholic beverage may make a difference. Those who drank 8 to 21 glasses of wine per week had a relative risk of death of 0.76 (95% CI, 0.67 to 0.86), whereas those who drank a light to moderate intake of beer or spirits showed only a small effect on all-cause mortality. People who were light drinkers and drank wine had a lower relative risk of death (0.66; 95% CI, 0.55 to 0.77) compared with nondrinkers versus light drinkers who avoided wine (relative risk for death=0.90; 95% CI, 0.82 to 0.99). Wine drinkers also had a

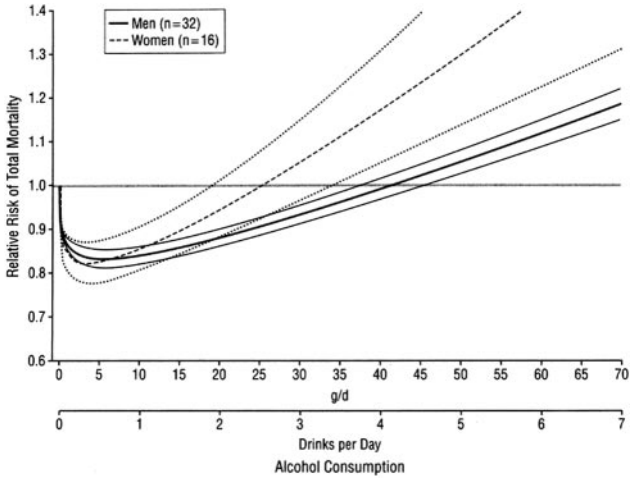

Figure 2. Relative risk of total mortality (99% CI) and alcohol consumption in men and women. Reprinted from Di Castelnuovo et al,[6] with permission from the publisher. Copyright © 2006, the American Medical Association.

lower mortality from cancer compared with those who did not drink wine.

Other studies have shown that light drinking is associated with lower rates of nonfatal acute myocardial infarction and coronary death compared with nondrinkers and heavy drinkers.[10,11] Mukamal and associates[12] explored the effect that prior alcohol intake had on long-term survivors of acute myocardial infarction. They studied 1913 adults hospitalized for acute myocardial infarction and observed all-cause mortality over ≈4 years, comparing it with self-reported weekly consumption of beer, wine, and liquor in the year before the acute coronary event. Forty-seven percent of the cohort abstained from alcohol, whereas 36% drank <7 drinks per week and 17% drank ≥7 drinks per week. Patients who drank ≥7 drinks per week had a lower all-cause mortality rate (2.4 per 100 person-years) compared with those who abstained (6.3 deaths per 100 person-years; hazard ratio=0.38; 95% CI, 0.25 to 0.55; $P<0.001$); in addition, patients who consumed <7 drinks per week had a lower all-cause mortality rate (3.4 per 100 person-years) compared with those who abstained (6.3 deaths per 100 person-years; hazard ratio=0.55; 95% CI, 0.43 to 0.71). Even after adjustment for other potential confounders, alcohol consumption predicted lower morality. This finding held true for total and cardiovascular mortality and for both men and women. Of note, no difference existed in benefit dependent on the type of alcoholic beverage that was consumed: Wine, beer, and liquor all appeared to confer benefit.

Thun et al[11] reported the results of a very large trial of 490 000 men and women who recorded their use of alcohol in 1982 and were followed for 9 years. Rate of death for all cardiovascular disease was 30% to 40% lower for those who drank at least 1 drink per day compared with nondrinkers in men (relative risk=0.7; 95% CI, 0.7 to 0.8) and in women (relative risk=0.6; 95% CI, 0.6 to 0.7). Overall death rates were lowest in men and women who drank ≈1 drink per day. However, the mortality from breast cancer was 30% higher in women who drank 1 drink per day versus nondrinkers (relative risk=1.3).

Klatsky et al[13] reported the results of 128 934 adults in the San Francisco area who were part of a comprehensive healthcare program. These investigators also showed that light drinkers were at lower risk from death from coronary artery disease (relative risk for 1 to 2 drinks per day=0.7; 95% CI, 0.6 to 0.9). This observation occurred independent of baseline risk for coronary disease. A preference for wine consumption resulted in a lower relative risk for cardiovascular death compared with liquor, whereas beer did not differ from liquor. Heavy drinkers (≥6 drinks per day) had a greater risk from noncardiovascular deaths compared with people who did not drink (relative risk=1.6; 95% CI, 1.3 to 2.0). Cirrhosis, unnatural death, and tobacco-related cancers were especially more common causes of death in heavy drinkers. This increased risk was higher in women and people aged <50 years.

Goldberg et al[14] reported a prospective study of the heath effects of alcohol consumption in middle-aged (aged 51 to 64 years) and elderly men (aged 65 to 75 years) as part of the Honolulu Heart Program. This study was a prospective analysis of Japanese American men who at baseline were free of known coronary heart disease, cerebrovascular disease, and cancer. Alcohol consumption was determined at baseline and 6 years later. After adjustment for confounding variables, the investigators reported that total mortality followed a J-shaped pattern in relationship to alcohol in those men aged 51 to 75 years. Total mortality was lowest in light drinkers (1 to 14 mL of alcohol per day) for middle-aged men and in moderate drinkers (15 to 39 mL of alcohol per day) for elderly men. Death from coronary artery disease was actually lowest for heavy drinkers (≥40 mL of alcohol per day) in middle-aged men and lowest for moderate drinkers (15 to 39 mL of alcohol per day) in elderly men. Death from cerebrovascular disease was increased in moderate to heavy drinkers in middle-aged men and in heavy drinkers in elderly men. This study is important in that it shows a benefit of moderate alcohol intake on coronary artery death, even in the elderly. Another study (Valmadrid et al[15]) verified a benefit of alcohol consumption in patients with older-onset diabetes mellitus. They examined the relationship between alcohol consumption and coronary artery disease mortality in patients diagnosed with diabetes mellitus after age 30 years. Mortality rates for coronary heart disease in never and former drinkers were substantially higher than the rates for patients who had mild consumption of alcohol. Hence, an inverse relationship existed between alcohol use and coronary heart disease mortality in these older-onset diabetic subjects. After controlling for a host of confounding factors, the benefit of alcohol on coronary heart disease mortality persisted.

Alcohol and Sudden Cardiac Death

The benefit of light to moderate intake of alcohol has also been examined in relationship to sudden cardiac death. Albert et al[16] pointed out that heavy drinking of alcohol (>5 drinks per day) was associated with increased risks of ventricular arrhythmias and sudden deaths as established in older studies,[17,18] but data on light to moderate alcohol consumption

have been inconsistent. Albert et al prospectively determined the effect of light to moderate alcohol intake on the risk of sudden cardiac death among 21 537 male participants in the Physicians' Health Study who at study entry were free of cardiovascular disease. After adjustment for confounding variables, men who had 2 to 4 drinks per week had a decreased risk of sudden cardiac death compared with men who never or rarely drank (relative risk=0.40; 95% CI, 0.22 to 0.75; P=0.004). Furthermore, men who drank 5 to 6 drinks per week had an even lower relative risk of sudden death compared with nondrinkers (relative risk=0.21; 95% CI, 0.08 to 0.56; P=0.002). A U-shaped relationship existed between alcohol intake and sudden cardiac death, with the lowest risk at 5 to 6 drinks per week and unity at <1 drink per month and ≥2 per day. The relationship between alcohol intake and the relative risk for nonfatal myocardial infarction was inversely linear such that the lowest risks were found in men who took ≥2 drinks per day (Figure 3). The relationship of alcohol intake and nonsudden coronary heart death was L-shaped.

Therefore, a large number of studies suggest that light to moderate alcohol intake reduces total mortality compared with nondrinking and that a portion of this benefit is a reduction in coronary artery disease deaths, including sudden cardiac death. Heavy drinking is associated with increase in mortality, including an increase in cancer and cerebrovascular events; some studies suggest that even heavier drinking may be associated with reduced coronary artery disease. Although some studies suggest that wine has an advantage over other types of alcohol, others suggest that the type of alcohol may not be that important.

Alcohol and Coronary Artery Disease, Angina, and Nonfatal Myocardial Infarction

Alcohol may have a favorable impact on the development of coronary artery disease. Yano et al[19] followed 7705 apparently healthy men of Japanese descent living in Hawaii for 6 years. Two hundred ninety-four developed coronary artery disease. Moderate alcohol consumption of up to 40 mL of absolute alcohol per day was associated with decreased incidence of coronary artery disease, irrespective of whether the beverage was beer, wine, or hard liquor. A reduction in nonfatal myocardial infarction and death from coronary artery disease in patients who had moderate alcohol intake remained significant after adjustment for other cardiovascular risk factors. A larger study of 22 071 male physicians in the United States confirmed that compared with men who had <1 drink per week, those who drank 1 drink per day had a lower relative risk of developing angina pectoris (relative risk=0.69; 95% CI, 0.59 to 0.81) and myocardial infarction (0.65; 95% CI, 0.52 to 0.81).[20] Similar benefit was shown in other population-based studies.[21,22] The benefit of alcohol in reducing the incidence of coronary artery disease was consistently shown in both high-risk populations such as those with diabetes mellitus[23] and low-risk populations with healthy lifestyles.[24]

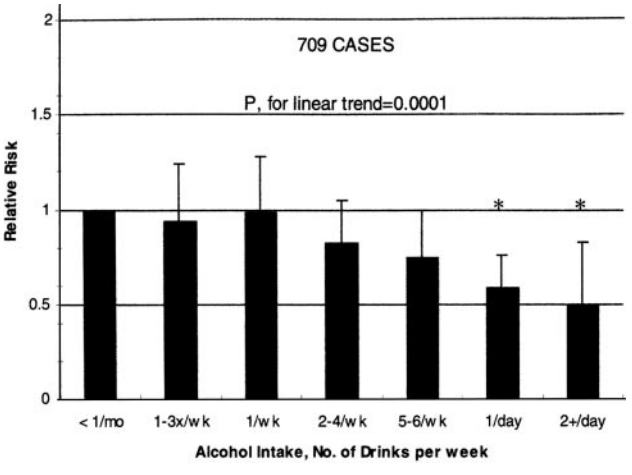

Figure 3. Relative risk (multivariate) of nonfatal myocardial infarction vs alcohol consumption. Vertical bars represent 95% CIs. The asterisks show those relative risks that were significantly <1. Reprinted from Albert et al,[16] with permission from the publisher. Copyright © 1999, the American Heart Association.

The effect of alcohol was investigated in a group of patients with well-documented coronary artery disease. A total of 1351 stable patients who had undergone coronary artery bypass surgery were followed for 4.3 years. Patients who had 1 to 6 drinks per week did not show a clear trend, but those who had between 7 and 13 drinks per week had a 30% reduction in clinical events. Part of this benefit appears to be due to a higher high-density lipoprotein (HDL) cholesterol level.[25]

Reduction in both incidence of clinical coronary artery disease and severity of angiographically documented coronary artery disease has been documented with moderate alcohol drinking.[26,27] The benefit was consistently shown with various types of alcoholic drinks.

Recently, coronary calcium scores determined by computed tomography have emerged as a surrogate for the presence of atherosclerotic coronary artery disease. Studies of coronary calcium scores and their relationship to alcohol drinking patterns are less consistent.[28,29] However, in 1 well-designed study by Vliegenthart et al,[30] the authors documented that consumption of 1 to 2 alcoholic drinks per day was associated with a 50% reduction in extensive coronary calcification, defined as a score of >400.

Few studies were conducted to test whether a sex difference is associated with drinking alcohol and the incidence of coronary artery disease; some studies showed that women are expected to benefit from moderate alcohol drinking.[31,32] In a large study of 53 500 subjects by Tolstrup et al,[33] men demonstrated an increased benefit in association with increase in the frequency of drinking. Optimal benefit was noted in men who drank daily. In women, however, almost any alcohol use was beneficial. Women who drank 1 day per week had a lower risk of developing coronary artery disease than women who drank less frequently.[33]

Does the type of a drink correlate with the beneficial outcomes relative to the incidence and extent of coronary artery disease? Although intuitive thinking and laboratory studies would suggest an advantage to red wine,[34] large-scale studies failed to substantiate this hypothesis. In a 12-year follow-up to 38 077 male health professionals who were free of coronary artery disease at baseline, benefit was related to

moderate alcohol drinking. Neither the type of drink nor its relation to meals had a significant impact on reducing the risk of nonfatal myocardial infarction or fatal coronary heart disease.[35] Of note, although, in general, studies in Europe have often shown a cardiovascular advantage of wine, most studies in the United States have not shown much difference according to the type of alcohol. Perhaps this finding is related to the confounding variable of differences in patterns of drinking. In the United States, it is more common for little or no drinking to occur during the week, with heavy drinking on the weekend. Clearly, a definite answer for a specific recommendation can only arise from well-designed prospective, randomized studies.[36]

Tavani et al[37] identified 507 cases of acute, nonfatal myocardial infarction during a period of 5 years of observation. Cases were compared with a similar control group admitted to the same hospital with noncardiac complaints. Drinking >3 drinks per day resulted in a 50% reduction in the incidence of nonfatal myocardial infarction. The greatest benefit was noted in patients with the longest duration of drinking. Other studies conducted in other countries yielded similar results.[38–40] No differences were attributable to drinking pattern or type of drinks, and the benefit of wine was similar to that of alcoholic drinks other than wine for fatal and nonfatal myocardial infarction. A meta-analysis confirmed the benefit, which was distributed equally between men and women and which was similar between different types of alcoholic drinks.[10]

Mukamal et al[41] investigated whether recent alcohol consumption affected the clinical course of acute myocardial infarction. Of the cohort of patients who experienced acute myocardial infarction, 18.5% had consumed alcohol within 24 hours of the onset of infarction. Alcohol consumption had no effect on infarction size or on the incidence of ventricular fibrillation and various cardiac arrhythmias. Light to moderate drinking after the infarction did not alter the risk for development of congestive heart failure, even in the group of patients with significant left ventricular dysfunction.[42]

Mechanisms of Alcohol Benefit

What are some of the mechanisms whereby alcohol could have a benefit on the heart, specifically, a reduction in mortality, sudden death, and coronary heart disease events? Alcohol raises HDL cholesterol, as described in further detail below. Healthy volunteers who consumed 1 glass of red wine daily had a significant reduction in plasma viscosity as well as fibrinogen concentration.[43] Increased alcohol consumption has also been associated with an increase in fibrinolysis and a decrease in platelet aggregation and coagulation.[44–46] Evidence also exists that wine may have beneficial effects on endothelial function,[47,48] reduces inflammation,[49] and contains antioxidants.[50] Nonalcoholic substances in wine such as flavonoids and resveratrol may play an important protective role.[48]

Effects on the Vascular Endothelium

Alcohol consumption by healthy subjects results in improved flow-mediated vasodilation, an accepted measure of endothelial function.[47] More importantly, this benefit may be secondary to components other than alcohol. Karatzi et al[48] studied 15 male subjects with angiographically documented coronary artery disease. Subjects ingested 250 mL of either red wine or alcohol-free red wine. The red wine that contained no alcohol resulted in higher flow-mediated vasodilatation than regular red wine. Another study suggests that the benefit on vascular endothelium may be mediated by wine flavonoids and polyphenols rather than alcohol.[51]

Alcohol and Markers of Inflammation

Imhof et al[52] studied a random cross-sectional sample of ≈8000 men and women representative of the general population of 3 European countries: Germany, Scotland, and France. The study population represented largely moderate consumers of a variety of alcoholic drinks including beer, wine, and spirits. Overall, the group representing moderate alcohol consumers exhibited lower levels of white blood cell counts and inflammatory markers including fibrinogen and C-reactive protein compared with nondrinkers and heavy drinkers, after adjustment for potential confounders. Maraldi et al[53] followed 2487 subjects without known history of heart disease for 5.6 years. Patients classified as mild drinkers, defined by 1 to 7 drinks per week, had a significant reduction in all-cause mortality. This benefit was more marked among men with high baseline interleukin-6, a proinflammatory cytokine. Thus, mild alcohol consumption decreases inflammatory markers in the subjects, and this seems to be an important mechanism related to the beneficial effects of alcohol.

Impact of Alcohol on Lipids

A substantial body of data strongly suggests a favorable effect of alcohol consumption on serum lipid levels, notably an increase in HDL cholesterol[54,55] (Figure 4). This increase in HDL has been postulated to be a major mechanism whereby alcohol benefits the heart. Genetic variations may alter this relationship. Hines et al[55] showed that moderate alcohol drinkers who are homozygous for the alcohol dehydrogenase Type 3 gene have a higher level of HDL and a lower incidence of myocardial infarction. Veenstra et al[56]

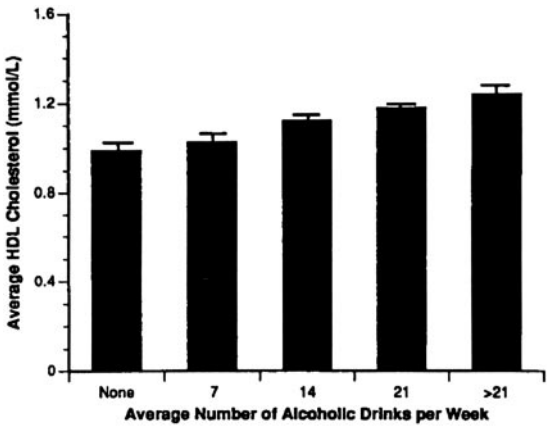

Figure 4. Average HDL cholesterol increases with alcohol consumption. Reprinted from Suh et al,[54] with permission from the publisher. Copyright © 1992, the American College of Physicians.

studied the effect of a single dose of moderate alcohol drinking on blood lipids. Individuals received 3 glasses of red wine with dinner. One hour later, increases in HDL of 11.5% and in apolipoprotein A_2 of 7.3% were noted. However, the favorable effect was transient and was attenuated by the following day. Gaziano et al[57] examined the effect of moderate daily alcohol consumption (1 to 3 drinks per day) on 680 patients with known coronary artery disease compared with healthy subjects. An inverse relationship between alcohol consumption and the risk of developing myocardial infarction was observed. This benefit was associated with a statistically significant increase in both HDL_2 and HDL_3. Apolipoprotein A-I and A-II levels were also positively associated with alcohol consumption. When this relation was examined in 7052 male smokers in Finland, similar findings were seen only with moderate drinking, whereas heavy drinkers exhibited a higher total cardiovascular mortality rate.[58] In this study, higher levels of alcohol intake blunted the inverse relationship between HDL and coronary mortality. The potential benefit of moderate drinking on lipids appears to be more important in patients with a higher risk profile, such as men with metabolic syndrome.[59] Heavy alcohol consumption, on the other hand, will lead to loss of the beneficial effect with worsening of the metabolic syndrome[60,61] and elevation in plasma homocysteine levels.[62] Thus, drinking in moderation is beneficial to serum lipid levels and decreases risk of cardiovascular mortality, whereas excessive drinking exerts the opposite effect.

Does Alcohol (or Components of Wine) Have a Direct Cardioprotective Effect?

Yet another potential mechanism exists by which light to moderate alcohol consumption may be associated with a reduced rate of coronary events: the concept that alcohol has a direct cardioprotective effect on ischemic myocardium. Some studies have examined short-term dosing of alcohol with coronary events, and others have examined more long-term dosing before the event. Both positive and negative data can be found in the literature, as described in more detail in the online-only Data Supplement, which describes various preclinical trials.[63–85]

Alcohol and Heart Failure

Alcoholic Cardiomyopathy

Alcoholic cardiomyopathy has been well described in heavy drinkers, ie, patients who abuse alcohol.[86–89] Those who stop using alcohol may have an improved ejection fraction over the course of 3 years.[87]

Although the primary functional abnormality of alcoholic cardiomyopathy was thought to be a depression in systolic function,[90] it is now appreciated that an impairment in diastolic function is present in one third of alcoholics who have a normal systolic function; in many, systolic and diastolic dysfunction coexist.[91] Excess alcohol consumption affects not only the cardiomyocytes but striated skeletal muscle as well.[92] A greater risk of alcoholic cardiomyopathy, as well as skeletal myopathy, exists in women than in men for any given lifetime amount of alcohol.[93,94]

Incident Congestive Heart Failure Related to Alcohol Use

In the Physician's Health Study I, 21 601 male physicians who were free of congestive heart failure at baseline and who provided data on alcohol were followed for an average of 18.4 years.[95] For the alcohol categories of <1, 1 to 4, 5 to 7, and >7 drinks per week, the hazard ratios for heart failure were 1.0 (reference), 0.90 (0.76 to 1.07), 0.84 (0.71 to 0.99), and 0.62 (0.41 to 0.96), respectively; $P=0.012$ after adjustment for age, body mass index, smoking, and valvular heart disease. Therefore, in this study, moderate drinking actually lowered the risk of heart failure.

The Cardiovascular Health Study[96] was a prospective cohort study of cardiovascular disease risk factors and outcomes in 5888 subjects aged ≥65 years followed for 7 to 10 years. The adjusted risk of congestive heart failure was lower in people reporting intake of 1 to 6 drinks per week compared with nondrinkers (hazard ratio=0.82; 95% CI, 0.67 to 1.00; $P=0.05$; Figure 5). In addition, people who drank 7 to 13 drinks per week had an even lower hazard ratio than those who abstained (hazard ratio=0.66; 95% CI, 0.47 to 0.91; $P=0.01$). The hazard ratio remained lower in drinkers even after adjustment for incident myocardial infarctions. The investigators concluded that moderate alcohol use among older adults was associated with a lower risk of heart failure. Similar results were reported by Abramson et al.[97] A study from the Framingham Heart Study[98] also concluded that moderate alcohol intake protected against congestive heart failure.

Effects of Continued Alcohol Consumption Among Patients With Known Congestive Heart Failure

Several studies suggested that moderate drinking in patients with known congestive heart failure did not cause acute deterioration of cardiac function.[99,100] In 1 of these studies of alcoholic cardiomyopathy (in patients who drank a minimum of 100 g of ethanol per day for 10 years), either abstinence or controlled drinking (20 to 60 g of ethanol per day) showed comparable improvements in left ventricular ejection fraction.[100] In the Studies of Left Ventricular Dysfunction (SOLVD) trial, in which all patients had a baseline left ventricular ejection fraction of <0.35, mortality rates were

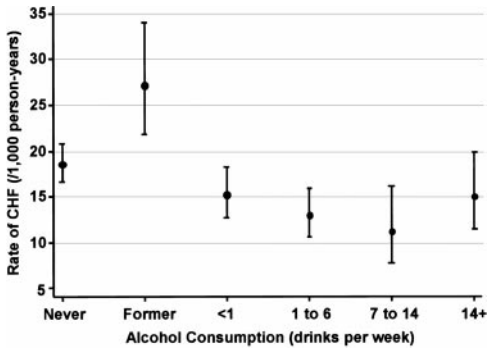

Figure 5. Rate of incident congestive heart failure (CHF) by alcohol consumption in the Cardiovascular Health Study. Reprinted from Bryson et al,[96] copyright © 2006, with permission from the American College of Cardiology Foundation.

lower at 7.2 deaths per 100 person-years in light to moderate drinkers (1 to 14 drinks per week) than in nondrinkers (9.4 deaths per 100 person-years; $P<0.001$).[101] In patients with ischemic left ventricular dysfunction, light to moderate drinking was also associated with decreased all-cause mortality (relative risk=0.85; $P=0.01$) and death from myocardial infarction (relative risk=0.55; $P<0.001$). Light to moderate drinking did not decrease mortality in patients with nonischemic left ventricular dysfunction in this trial. Klatsky et al[102] also showed that alcohol intake was inversely related to the risk of heart failure due to ischemic heart disease. One to 2 drinks per day was associated with a lower relative risk of heart failure in this group of patients (0.6; 95% CI, 0.5 to 0.7).

The reason that alcohol can paradoxically decrease the incidence of heart failure includes the possibility of reducing the risk of myocardial infarction in patients with ischemic heart disease. Another possibility is that mild to moderate alcohol use can lower blood pressure and reduce vascular resistance, thus decreasing afterload.[99] In addition, low-dose alcohol may reduce the effects of norepinephrine and arginine vasopressin and increase plasma levels of atrial natriuretic peptide.[97]

Thus, whereas heavy intake of alcohol is associated with dilated cardiomyopathy, light to moderate alcohol intake may actually protect the heart from developing heart failure. In addition, light to moderate alcohol administered to patients who already have heart failure does not appear to exacerbate the heart failure.

Alcohol and Hypertension

Numerous studies have suggested that excess alcohol intake causes an increase in blood pressure.[103–113] Klatsky et al[103] studied 83 947 men and women as part of a Kaiser-Permanente Multiphasic Health Examination study and reported that men and women who drank ≥3 drinks per day had both higher systolic and diastolic blood pressure compared with nondrinkers. In addition, those who drank ≥3 drinks a day had a greater prevalence of blood pressure ≥160/95 mm Hg. They also showed[104] that excess alcohol contributed to elevated blood pressure after controlling for other variables and that beginning within days of abstinence, alcohol-related hypertension regresses. In the International Study of Sodium, Potassium, and Blood Pressure (INTERSALT), alcohol consumption for 7 days before a standard blood pressure measurement was obtained in >4800 men and 4800 women.[106] After correction for confounding variables, men who drank 300 to 499 mL alcohol per week had an increase of systolic/diastolic blood pressure 2.7/1.6 mm Hg greater than that of nondrinkers; those men who drank ≥500 mL alcohol per week had an increase of systolic/diastolic blood pressure of 4.6/3.0 mm Hg. Women who drank ≥300 mL per week had an increase in systolic/diastolic blood pressure of 3.9/3.1 mm Hg. Binge drinking was associated with higher blood pressure than regular constant drinking. The authors concluded that a significant association existed between heavy drinking (3 to ≥4 drinks per day) and blood pressure; furthermore, this relationship was observed in both sexes and in both younger and older individuals.

Paulin et al[107] reported that in 901 adults, after adjustment for age and body mass index, men who used ≥300 g of alcohol per week had a systolic blood pressure that was 9.8 mm Hg higher and diastolic blood pressure that was 8.9 mm Hg higher than men who did not drink. Of note, in this study, in contrast to others, alcohol intake in women was not associated with an increase in blood pressure. As pointed out by Cushman,[108] decreasing intake of alcohol by 1 drink per day decreases systolic and diastolic blood pressure by ≈1 mm Hg.[109]

Gillman et al[110] reported an interesting study of young adults (n=316; aged 18 to 26 years) comparing alcohol intake with blood pressure measurements. They described a J-shaped curve whereby the lowest systolic blood pressure occurred in subjects taking 1 to <2 drinks per day.

The mechanism whereby excess alcohol raises blood pressure may be related to stimulation of the sympathetic nervous system. Certainly, when heavy drinkers withdraw from alcohol, marked sympathetic stimulation is produced. The same phenomenon may occur at a lower level on a daily basis after a person stops drinking for the day (a mini-withdrawal phenomenon). That blood pressure tends to be higher with binge drinking supports this notion.

Could light to moderate alcohol consumption actually benefit the hypertensive patient? Malinski et al[114] explored this issue as part of the Physicians' Health Study. The investigators identified 14 125 men who provided self-reported information about alcohol intake, had known hypertension, and were free of myocardial infarction, stroke, and cancer. Men who reported monthly, weekly, and daily alcohol consumption had adjusted relative risks of cardiovascular disease mortality compared with those who never drank of 0.83 (95% CI, 0.62 to 1.13), 0.61 (95% CI, 0.49 to 0.77), and 0.56 (95% CI, 0.44 to 0.77; $P<0.001$ for trend). In addition, the relative risks for mortality were also reduced in the groups who drank (0.86, 0.72, and 0.73; $P<0.001$, respectively). The benefit for cardiovascular mortality held true for weekly and daily drinkers who had blood pressures of ≥140/90 mm Hg. The authors concluded that light to moderate alcohol intake reduced the risk of total and cardiovascular disease mortality in men with hypertension.

Palmer et al[115] studied >6000 hypertensives attending hospital clinics in the United Kingdom. Both men and women hypertensives who drank had a reduced risk for stroke mortality; men also had a trend toward lower ischemic heart disease mortality if they drank. Beulens et al[116] recently reported the result of 11 711 men with hypertension who participated in the Health Professionals Follow-up Study. The authors observed that in this cohort of men with hypertension, moderate alcohol consumption decreased the risk of myocardial infarction; it did not, however, decrease risk of total mortality.

Bulpitt[117] recently reviewed the issue of whether older persons with hypertension should drink alcohol. After reviewing the results of various studies, he concluded that patients with hypertension aged >60 years who drink >16 drinks per week should decrease their alcohol intake but not stop drinking entirely; a daily drink may be beneficial. However, he did not advise those who do not drink to start

drinking. An accompanying editorial by Beilin[118] pointed out some of the limitations of trials that have investigated the effects of alcohol on cardiovascular outcomes, including the following: unreliable self-reporting of alcohol use, failure to always take into account the effects of alcohol on noncardiovascular morbidity and mortality, lack of cost/benefit analysis, changes in alcohol use over time (ie, some patients who may initially drink a supposed safe dose of alcohol [≤1 drink per day] from a cardiovascular viewpoint may increase their dose over time), failure to take into account lifelong risk, and differences in ethnicity or culture. Still, this author states that for the majority of those in a Western environment who control their drinking and its circumstances, up to 1 drink per day in women or 1 to 2 drinks per day in men appears to be associated with the greatest net health benefits and the lowest risks.[118]

Alcohol and Stroke

Findings for associations between alcohol and stroke have been variable in the literature. Although light to moderate drinking consistently reduces cardiovascular events, effects on stroke have not been as consistent. In a study of 38 156 male professionals, Mukumal et al[119] showed that, compared with nondrinkers, light drinkers (0.1 to 9.9 g/d) had an adjusted relative risk of 0.99 (95% CI, 0.72 to 1.37) for ischemic stroke, moderate drinkers (10.0 to 29.9 g/d) had a relative risk of 1.26 (95% CI, 0.90 to 1.76), and heavier drinkers (≥30 g/d or ≥3 drinks per day) had a relative risk of 1.42 (95% CI, 0.97 to 2.09; $P=0.01$). Although red wine was inversely related to risk, other beverages were not. Patterns of drinking also affected outcome: Consuming moderate alcohol on 3 to 4 days per week was associated with the lowest relative risk of ischemic stroke (0.68; 95% CI, 0.44 to 1.05).

Stampfer et al[120] studied 87 526 female nurses over ≈4 years. Moderate alcohol intake was associated with a decrease in coronary heart disease. Five to 14 g of alcohol per day (≈3 to 9 drinks per week) was associated with a decreased relative risk of ischemic stroke (0.3; 95% CI, 0.1 to 0.7), and for ≥15 g per day the relative risk was 0.5 (95% CI, 0.2 to 1.1). However, 5 to 14 g of alcohol per day increased the relative risk of subarachnoid hemorrhage (3.7; 95% CI, 1.0 to 13.8). In a very large trial, Klatsky et al[121] studied the association between alcohol use in 128 934 members of a health plan and hemorrhagic stroke. Only persons who drank ≥6 drinks per day had an increase in hemorrhagic stroke (relative risk=1.9; 95% CI, 1.0 to 3.5). Elkind et al[122] also recently reported in a multiethnic population of both sexes that moderate drinking (≥1 drink in the past month to ≤2 per day) was associated with a reduced risk of ischemic stroke (0.67; 95% CI, 0.46 to 0.99) compared with patients who did not drink in the prior year (Figure 6). When the reference group was people who never drank, results were the same. In contrast, a 2007 study by Beulens[116] reported that the relative risk of ischemic stroke for hypertensive patients consuming 10 to 29.9 g alcohol per day was 1.55 (95% CI, 0.90 to 2.68) versus abstainers.

Although Berger et al[123] also reported that light to moderate alcohol (as little as 1 drink per week) reduced the risk of ischemic stroke in male physicians, they did not observe an

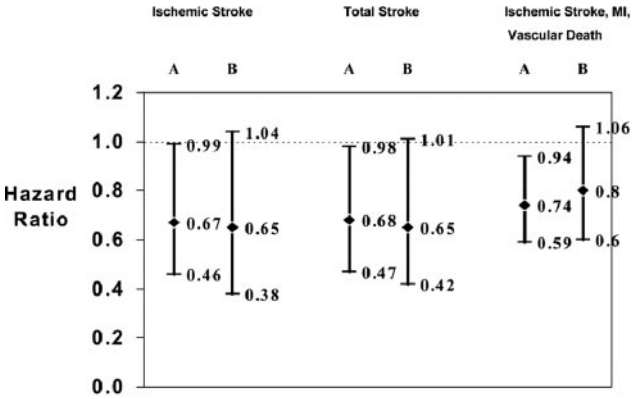

Figure 6. Association between moderate alcohol intake (≥1 drink per month and ≤2 drinks per day) and the risk of ischemic stroke, total stroke, and other vascular events. The reference group consists of those who did not drink within the past year (A) and those classified as never drinkers (B). The diamonds represent the hazard ratios and the vertical lines the 95% CIs. These analyses were adjusted for age, sex, race, education, hypertension, diabetes mellitus, smoking, atrial fibrillation, and HDL levels. MI indicates myocardial infarction. Reprinted from Elkind et al,[122] with permission from the publisher. Copyright © 2006, the American Heart Association.

increase in hemorrhagic stroke with alcohol use. A study by Wannamethee and Shaper[124] from the United Kingdom observed that men who drank >6 drinks per day had an increased risk of stroke within 8 years of follow-up (relative risk=1.9; 95% CI, 1.0 to 3.5), the effects of which were attenuated after adjustment for systolic blood pressure. Occasional drinkers, regular weekend drinkers, and those who drank daily (1 to 6 drinks per day) had similar risk that was lower than that of nondrinkers (including ex-drinkers and lifelong abstainers). One of the conclusions of the investigators was that heavy drinking is associated with increased risk of total stroke that could be related largely to an increase in blood pressure. Several reports from Japan also warned of an increase in cerebral hemorrhage among hypertensive individuals who drank heavily.[125–127] One recent study from Japan found that ≤2 drinks per day did not raise the risk of total stroke, but for those drinking ≥450 g ethanol per week, a 60% increase in total stroke occurred compared with occasional drinkers. This increased risk was primarily due to hemorrhagic stroke and in this study was not entirely dependent on hypertension.[128] The Honolulu Heart Program[129] also described a correlation between alcohol intake and hemorrhagic stroke. In their study of 8006 men followed for ≈12 years, the risk of hemorrhagic stroke more than doubled even for light drinkers and nearly tripled for heavy drinkers, and these associations remained independent of hypertension. Also of note in this study is the fact that no significant relationship existed between alcohol and ischemic (thromboembolic) stroke. Drinking habits may play a role in the development of strokes, in that binge drinking was more likely to be associated with strokes.[130] Thus, in general, most but not all studies suggest that light to moderate drinking is safe and is not associated with an increase in stroke, but heavy drinking may be associated with hemorrhagic stroke.

Alcohol and Arrhythmias

The term *holiday heart syndrome* was coined by Ettinger et al[131] as "an acute cardiac rhythm and/or conduction disturbance associated with heavy ethanol consumption in a person without other clinical evidence of heart disease and disappearing, without evident residual, with abstinence." However, the literature is inconsistent on the association of alcohol and atrial fibrillation, as recently discussed.[132] Some studies suggest that >3 to 5 drinks per day but not light to moderate alcohol intake is associated with atrial fibrillation in men, but the association between alcohol and atrial fibrillation was less clear in women.[132,133] A 2004 report from the Framingham Study[134] stated that it was not until consumption of alcohol was >36 g/d that an association with atrial fibrillation was observed; alcohol intake above these levels resulted in a 34% increased risk of atrial fibrillation (95% CI, 1.01 to 1.78). This increase was seen in both men (relative risk=1.33; 95% CI, 0.89 to 2.00) and women (relative risk=1.34; 95% CI, 1.01 to 1.78). The potential mechanisms for this phenomenon include hyperadrenergic state associated with drinking followed by withdrawal, reduced vagal tone, and prolongation of the QT interval. That alcohol can induce arrhythmias in some patients (including those with heart disease) was further suggested by a study in which 14 patients with histories of rhythm disturbances associated with alcohol underwent electrophysiological testing. After administration of 90 mL (≈2 to 2.5 drinks) of 80-proof whiskey, 10 of 14 patients who were alcoholics developed arrhythmias, including sustained or nonsustained atrial or ventricular tachycardias. Alcohol resulted in a shortening of cycle length and a prolongation of the H-V interval.[135] Although 1 group showed that alcohol could precipitate new-onset atrial fibrillation in a case-control study,[136] the same group concluded that alcohol was not associated with induction of other supraventricular arrhythmias, including paroxysmal atrial tachycardia and flutter.[137] Other studies had lumped atrial fibrillation and flutter into 1 diagnosis, making it less clear whether flutter alone was associated with alcohol.[132,134] Although light to moderate alcohol consumption has been associated with a reduction in sudden cardiac death, as described earlier in this review, heavy drinking has sometimes been associated with ventricular arrhythmias and sudden death, as reviewed by Kupari and Koskinen.[138]

Alcohol and the Heart: What Is Missing?

Although numerous studies have described a J-shaped or U-shaped curve to describe the relationship between alcohol intake versus total mortality and cardiovascular mortality, these studies have all been observational and epidemiological in nature. Most reviews warn of not prescribing alcohol for those who do not drink. However, a large, multicenter, prospective, randomized study in which 1 group of patients receives alcohol long term versus another has not been done because of ethical, behavioral, and logistic challenges. Is this really the correct approach? The observational data collected thus far appear consistent that light to moderate alcohol has a cardiovascular benefit even when corrected for confounding factors, and 0.5 to 1 drink per day appears protective. Perhaps the time has arrived for a long-term prospective, randomized trial in which 1 group of people abstain totally and a second group receives 1 glass of alcohol, perhaps in the form of red wine, per day (or perhaps every other day). The patients are then followed long term for total mortality, cardiovascular events (including cardiovascular death, nonfatal myocardial infarction, development of angina, congestive heart failure), cerebrovascular events, and noncardiovascular/noncerebrovascular disease. Obviously, inclusion and exclusion criteria will need to be strict and probably complex. Former alcohol abusers, those with liver disease, and those with esophagitis, gastrointestinal ulcers, or bleeding should not be included. The patient cohort must be very compliant; liver function tests would need to be performed, and clinical monitoring would need to be of the highest quality. Methods would be needed to ensure that the control group had not started drinking. On the other hand, perhaps such a trial should not be very restricted and have broad inclusion criteria so as to be applicable to the types of patients usually seen by physicians, including the very elderly, diabetics, and those patients on various medicines. Any randomized controlled study would need to be large, on the order of at least ≈7500 patients, and would need to be conducted over at least ≈4 years. However, in a prospective trial, if 1 glass of wine per day could reduce mortality by the same 17% to 18% suggested in a recent meta-analysis,[1] these data would provide strong evidence that a glass of wine per day is a major and cost-effective therapeutic intervention.

To drink or not to drink? What should the answer to this question be in 2007? Until large, prospective, randomized trials are available, the preponderance of data suggests that drinking 1 to 2 drinks in men and 1 in women will benefit the cardiovascular system. However, this statement is tempered by the observation in 1 large study of an increase in breast cancer among women who drank.[11]

Disclosures

None.

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