

Alcohol and Cardiovascular Health: The Dose Makes the Poison...or the Remedy

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Abstract

Habitual light to moderate alcohol intake (up to 1 drink per day for women and 1 or 2 drinks per day for men) is associated with decreased risks for total mortality, coronary artery disease, diabetes mellitus, congestive heart failure, and stroke. However, higher levels of alcohol consumption are associated with increased cardiovascular risk. Indeed, behind only smoking and obesity, excessive alcohol consumption is the third leading cause of premature death in the United States. Heavy alcohol use (1) is one of the most common causes of reversible hypertension, (2) accounts for about one-third of all cases of nonischemic dilated cardiomyopathy, (3) is a frequent cause of atrial fibrillation, and (4) markedly increases risks of stroke—both ischemic and hemorrhagic. The risk-to-benefit ratio of drinking appears higher in younger individuals, who also have higher rates of excessive or binge drinking and more frequently have adverse consequences of acute intoxication (for example, accidents, violence, and social strife). In fact, among males aged 15 to 59 years, alcohol abuse is the leading risk factor for premature death. Of the various drinking patterns, daily low- to moderate-dose alcohol intake, ideally red wine before or during the evening meal, is associated with the strongest reduction in adverse cardiovascular outcomes. Health care professionals should not recommend alcohol to nondrinkers because of the paucity of randomized outcome data and the potential for problem drinking even among individuals at apparently low risk. The findings in this review were based on a literature search of PubMed for the 15-year period 1997 through 2012 using the search terms *alcohol*, *ethanol*, *cardiovascular disease*, *coronary artery disease*, *heart failure*, *hypertension*, *stroke*, and *mortality*. Studies were considered if they were deemed to be of high quality, objective, and methodologically sound.

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It is true, that even then, it was known and acknowledged, that many were greatly injured by it; but none seemed to think the injury arose from the use of a bad thing, but from the abuse of a very good thing.

Abraham Lincoln¹

The consumption of alcohol (specifically ethanol), which is commonly referred to as “drinking,” has been an integral part of many cultures since the beginning of recorded human history. Yet, alcohol is analogous to the proverbial double-edged sword: perhaps no other health or lifestyle factor can cut so deeply in either direction—toxic or beneficial—depending on how it is used. According to the World Health Organization, alcohol kills approximately 2.5 million people each year worldwide, causing 4% of all deaths—more than violence, AIDS, or tuberculosis.² The harmful use of alcohol is the world's leading risk factor for death among males between

ages 15 and 59 years, mainly due to injuries, violence, and cardiovascular (CV) diseases.² Excessive drinking has been linked to cirrhosis, seizures, stroke, poisonings, accidents, violence, and many malignancies including cancers of the colon and rectum, breast, larynx, and liver.² The yearly health care and economic costs associated with alcohol are staggering, exceeding \$234 billion in the United States alone.³ In stark contrast to the devastation wrought by excessive alcohol consumption are the benefits associated with light to moderate drinking, including substantial reductions in CV disease—the leading cause of death in the United States.⁴ Responsible habitual alcohol use also appears to be linked to lower risks for diabetes mellitus (DM), stroke, heart failure (HF), and total mortality.⁵

The purposes of this review article are to (1) outline the CV risks and benefits associated with alcohol, (2) detail the mechanisms of action whereby alcohol confers protection and/or causes harm, and (3) make recommendations

regarding ideal drinking patterns, beverages, and quantities for maximizing the likelihood of benefit while minimizing the risk of harm from alcohol consumption. The findings in this review were based on a literature search of PubMed for the 15-year period 1997 through 2012 using the search terms *alcohol*, *ethanol*, *cardiovascular disease*, *coronary artery disease*, *heart failure*, *hypertension*, *stroke*, and *mortality*. Studies were considered if they were deemed to be of high quality, objective, and methodologically sound.

AMERICANS' DRINKING HABITS

Among all American adults, about two-thirds report that they at least on occasion consume alcohol, and 44% are regular drinkers, defined as someone who has at least 1 drink per week.⁶ These regular drinkers consume an average of 4.2 alcoholic drinks per week. While a similar proportion of men and women consume alcohol, men on average ingest 6.2 alcoholic beverages per week compared with 2.2 drinks per week for women. Whites are more likely to consume alcohol than nonwhites, and on average, white drinkers also consume more drinks—4.5 per week compared with 3.3 among nonwhites.⁶ The favorite drink for men is beer, whereas most women prefer wine. One in 5 drinkers admits to sometimes ingesting too much alcohol, with rates of excessive drinking higher among men and younger adults.⁶

WHAT CONSTITUTES A DRINK?

By definition, a standard drink, regardless of the variety, contains 14 g of ethanol (0.6 fl oz of pure alcohol).^{7,8} This equates to 12 oz of beer (about 5% ethanol), 5 oz of table wine (about 12% ethanol), or 1.5 oz of hard liquor or distilled spirits (about 40% ethanol).^{7,8} Alcohol consumption can also be quantitated in units, whereby 1 U equals 10 mL or 8 g of ethanol, which corresponds to the amount of alcohol an average adult can metabolize in 1 hour. Thus, for example, 25 mL of whiskey, or 6 oz of beer, or one-half of a standard (5-6 oz) glass of wine would each contain about 1 U of alcohol.^{7,8}

PRIMARY PREVENTION

The health effects of drinking are determined by the quantity and pattern of ethanol consumption.⁵ Observational studies consistently report

ARTICLE HIGHLIGHTS

- Habitual light to moderate alcohol intake is associated with lower rates of death, coronary artery disease, diabetes mellitus, congestive heart failure, and stroke.
- Excessive alcohol intake is the third leading cause of premature death in the United States; alcohol abuse is the single strongest risk factor for premature death among males aged 15 to 59 years.
- Excessive alcohol consumption, in a dose-dependent fashion, commonly causes both reversible hypertension and atrial fibrillation and accounts for one-third of all cases of nonischemic dilated cardiomyopathy.
- The risk-to-benefit ratio of light to moderate drinking is more favorable for people older than age 50 compared with those younger than age 50.
- The ideal drinking pattern for reducing risk of adverse cardiovascular outcomes is daily consumption of one 5- to 6-oz glass of red wine immediately before or during the evening meal.
- The cardioprotective effects of light to moderate drinking have not been apparent in most epidemiological studies of populations from India and China.
- People who abstain from alcohol should not be advised to begin light to moderate drinking because of the paucity of randomized outcome data and the potential for escalation into problem drinking.

that light to moderate drinkers are at lower risk for CV diseases than abstainers, and heavy drinkers are at the highest risk. A meta-analysis involving 1 million individuals reported that light to moderate alcohol consumption was associated with highly significant decreases in death during follow-up, with maximum protection noted at one-half to 1 drink daily for women (18% decrease in total mortality; 99% CI, 13%-22%).⁹ For men, maximal benefit was seen at 1 to 2 drinks daily, with a total mortality decrease of 17% (95% CI, 15%-19%) (Figure 1). However, intakes above 2.5 drinks per day in women and 4 drinks per day in men were associated with progressively higher death rates in a dose-dependent relationship. In another large and statistically rigorous study of 245,000 US adults, alcohol intakes of both light (3 drinks per week or less) and moderate (4 to 7 drinks per week for women, 4 to 14 drinks per week for men) levels were associated with lower CV

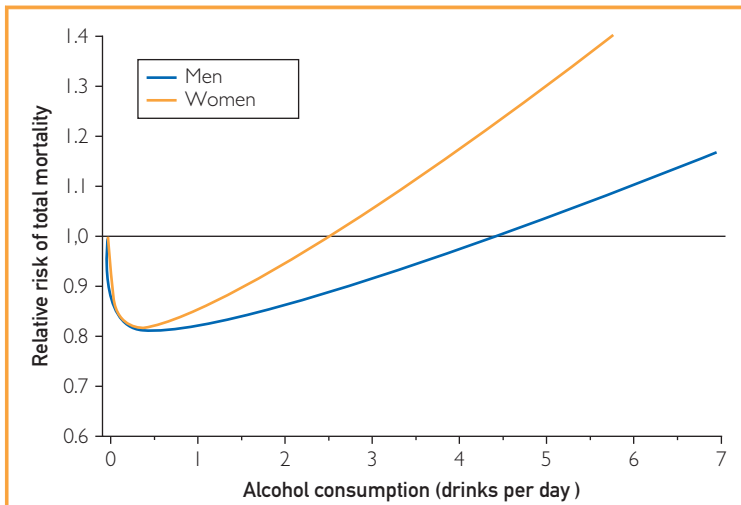


FIGURE 1. Alcohol intake and total mortality. Data from *Arch Intern Med*.⁹

mortality compared with either heavy users (>7 drinks per week in women or >14 drinks per week in men) or lifetime abstainers (Figure 2).¹⁰

The risk-benefit ratio of habitual moderate alcohol intake appears to be more favorable for middle-aged and older people compared with younger individuals. In a pooled analysis of 8 prospective studies from North America and Europe including 192,067 women and 74,919 men, an inverse association was found between alcohol intake and risk of coronary artery disease (CAD) events.¹¹ However, the

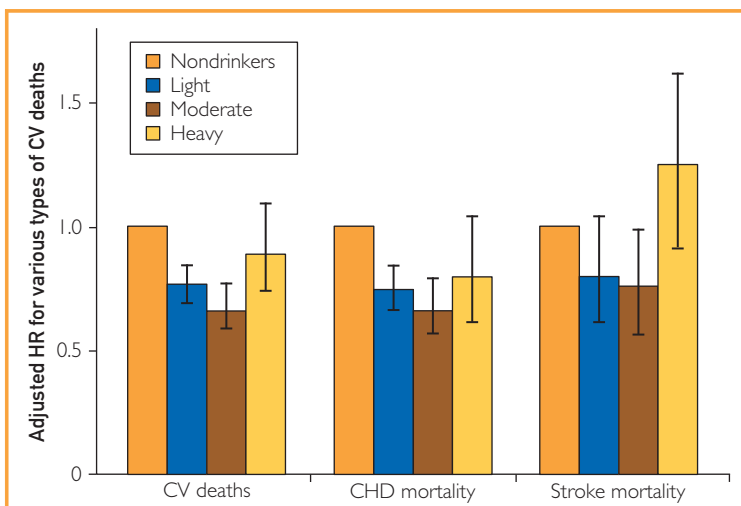


FIGURE 2. Adjusted risks for cardiovascular (CV) disease as a function of alcohol intake. CHD = coronary heart disease; HR = hazard ratio. Error bars indicate 95% CIs. Data from *Journal of the American College of Cardiology*.¹⁰

absolute reductions in CAD were not clinically significant for people younger than 50 years of age (Figure 3). Additionally, in a cohort study of 2074 young (aged 25 to 39 years) healthy adults, the carotid intima-media thickness (a surrogate CV risk marker) increased directly in proportion to amount of alcohol ingested.¹² Younger individuals are at a much lower risk for CAD but are more likely to engage in excessive and/or binge drinking and accordingly are at higher risk of alcohol-related accidents, violence, and overdoses.^{2,3} Thus, the risks of regular drinking may outweigh the benefits for many younger men and women. In contrast, studies focusing on middle-aged and older individuals generally show larger absolute CV risk reductions associated with light to moderate drinking.¹³

The alcohol-related CAD benefit in primary prevention was also seen in low-risk men. In the Health Professionals Follow-Up Study, a subgroup of participants was identified as being at low risk for CAD by virtue of meeting all 4 of the following criteria: normal weight, physically active, being a nonsmoker, and eating a healthy diet (Figure 4).¹⁴ Another study reported that moderate alcohol intake was identified as the single strongest contributor to the longevity conferred by the traditional Mediterranean diet,¹⁵ accounting for 25% of the total mortality benefit associated with the Mediterranean cuisine and being more important than vegetable intake, fruit and nut consumption, olive oil use, and fish intake.

SECONDARY PREVENTION

Light to moderate alcohol intake has also been shown to improve outcomes in patients with established CV disease. In a recent meta-analysis of 8 prospective studies involving 16,351 patients with a history of CV disease, the familiar J-shaped curve was observed with maximal protection by alcohol at approximately 26 g/d (or about 2 drinks daily).¹⁶ Studies evaluating alcohol's effects on patients who have had a myocardial infarction (MI) also report the typical J-shaped relationship between drinking and adverse events or total mortality.^{17,18} A large study involving 45 US hospitals with a median follow-up of 3.8 years found a reduced risk-adjusted post-MI total mortality rate for patients who were drinkers before their MI when compared with nondrinkers.¹⁹ Light to moderate drinking has also been correlated

with less atherosclerotic progression within coronary artery bypass grafts²⁰ and lower risk of peripheral arterial disease and its complications.²¹⁻²³

ALCOHOL AND ARRHYTHMIAS

Decades ago, the moniker “holiday heart” was suggested for acute cardiac arrhythmias, typically atrial fibrillation (AF), observed commonly in individuals drinking heavily during times of celebration.²⁴ Unquestionably, heavy alcohol use, whether short-term or long-term, can precipitate arrhythmias.²⁵ In the Copenhagen City Heart Study, consumption of more than 35 drinks per week correlated with higher risk of AF in men.²⁶ Above a “safe” threshold of about 1 drink per day, the relative risk of AF increases approximately 10% for each drink per day (Figure 5).^{27,28}

Excessive alcohol intake, whether acutely from binge drinking or from long-term heavy drinking, can also occasionally stimulate ventricular arrhythmias and rarely even sudden cardiac death.^{9,29} The proarrhythmic effects of excessive alcohol consumption may be due to its tendency to cause QT interval prolongation and shortening of the atrial effective refractory period.³⁰ Acute alcohol intoxication and withdrawal are both associated with the development of hypomagnesemia and hypokalemia.³¹ Alcohol withdrawal also increases cardiac sympathetic activity and reduces both heart rate variability and baroreflex sensitivity; these autonomic disturbances are all strongly linked to cardiac arrhythmias.³²

ALCOHOL AND HF

Ethanol at higher doses is a cardiotoxin. Habitual heavy alcohol consumption can result in a specific cardiac disease known as alcoholic cardiomyopathy, which accounts for about one-third of all cases of nonischemic dilated cardiomyopathy in the United States.³³ Individuals who consume more than 90 g of alcohol per day, which corresponds to about 7 drinks per day, for at least 5 years are at risk for the development of alcoholic cardiomyopathy and HF. Without complete abstinence, the 4-year mortality rate for alcoholic cardiomyopathy can be as high as 50%, and it is a common cause of death among long-term heavy drinkers.³⁴ Importantly, cessation of alcohol consumption and treatment of HF dramatically improve both cardiac function and prognosis.³³

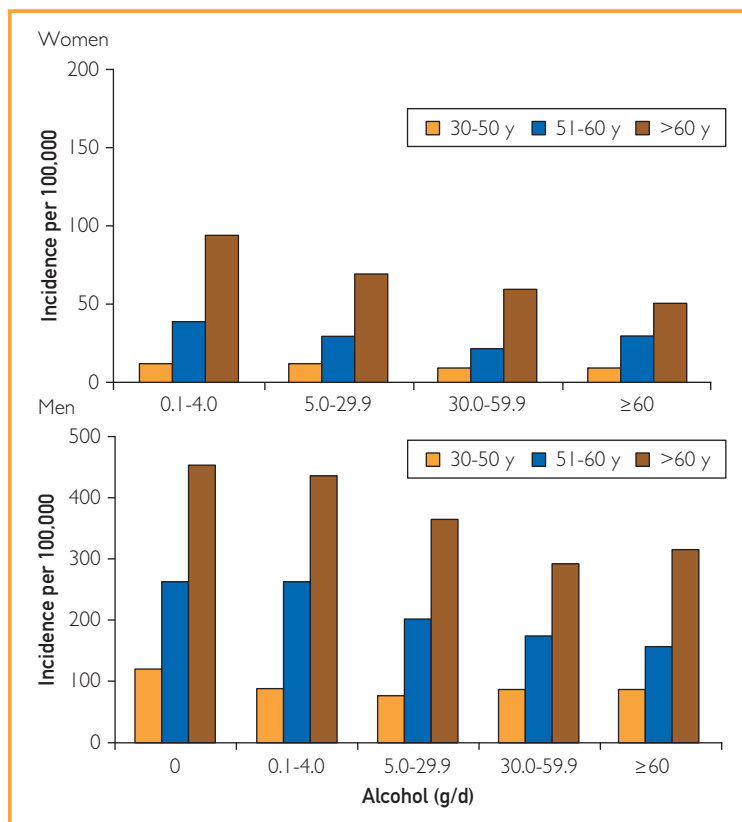


FIGURE 3. Fully adjusted incidence rates of coronary artery disease according to age and alcohol intake. From *Circulation*,¹¹ with permission.

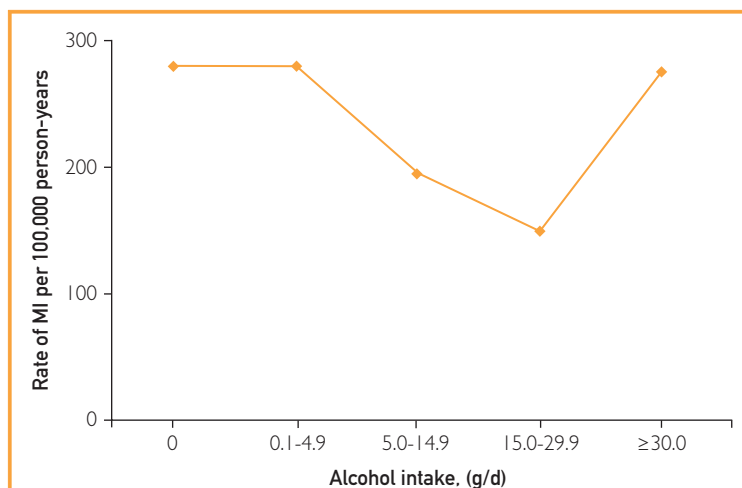


FIGURE 4. Alcohol intake and risk of myocardial infarction in 8867 middle-aged men already following healthy lifestyle recommendations. Adapted from *Archives of Internal Medicine*,¹⁴ with permission.

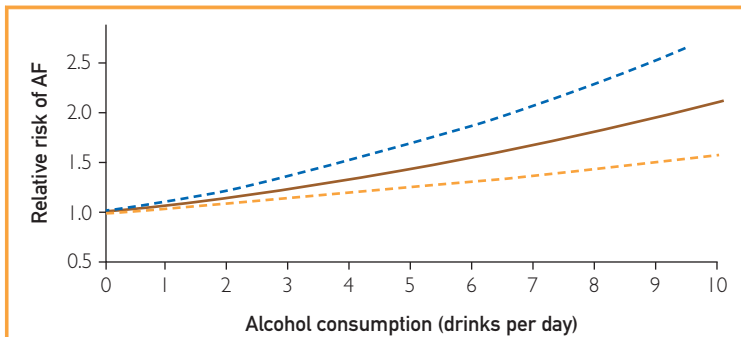


FIGURE 5. Dose-response relationship between alcohol consumption and risk of atrial fibrillation (AF). At 10 drinks/day, the risk of AF is doubled. Confidence interval is marked by dashes. Adapted from *European Journal of Cardiovascular Prevention and Rehabilitation*,²⁷ with permission.

Paradoxically, long-term mild to moderate alcohol consumption appears to be associated with a significantly reduced risk of HF.³⁵ This decrease in risk of HF is independent of other factors, including CAD, and is seen even among older cohorts and hypertensive patients.^{36,37} In a recent meta-analysis, moderate drinking reduced the risk of HF by as much as 10% to 20%.³⁸

ALCOHOL AND HYPERTENSION

Habitual alcohol consumption raises blood pressure (BP) in a dose-dependent fashion. Long-term heavy drinking is one of the most common reversible causes of hypertension (HTN); excessive alcohol intake is responsible for approximately 16% of cases of HTN worldwide.³⁹ The American Society of Hypertension warns that consuming more than 2 alcoholic drinks per day increases the risk for high BP.⁴⁰ Beyond the first 1 or 2 drinks per day, each additional alcoholic drink will increase BP by approximately 1.5 mm Hg. Within 2 to 4 weeks of abstinence or substantial reduction of intake, the alcohol-induced HTN usually resolves.

A meta-analysis involving studies from the United States, Japan, and Korea reported a linear dose-response relationship between alcohol and BP whereby the relative risk for HTN was 1.7 for 50 g of ethanol per day (about 4 drinks per day) and 2.5 at 100 g/d (8 drinks per day).⁴¹ The consumption of alcohol in amounts above 14 drinks per week is an independent risk factor for HTN, and among the US population, black men appear to be the group at highest risk.⁴² People living in Asia have also been noted to be

particularly prone to BP increases with excessive alcohol intake.⁴¹

A study of 28,848 women from the Women's Health Study and 13,455 men from the Physicians' Health Study followed up for an average of 11 and 22 years, respectively, assessed the associations of incremental doses of alcohol with BP over time.⁴³ In women, a J-shaped association was observed, whereas in men, increasing doses of alcohol were linearly associated with BP. The threshold above which alcohol significantly increased the risk of HTN in women was 4 or more drinks per day, whereas the increased risk of HTN appeared in men even with doses of 1 or more drinks per day.⁴³

In a study of a Mediterranean population, the consumption of beer or spirits, but not wine, was associated with a higher risk of HTN (Figure 6).⁴⁴ Although red wine has been reported to modestly increase brachial BP, it lowers central aortic BP.^{45,46} Furthermore if the wine is consumed with a meal, the increase in BP appears to be largely eliminated.⁴⁶

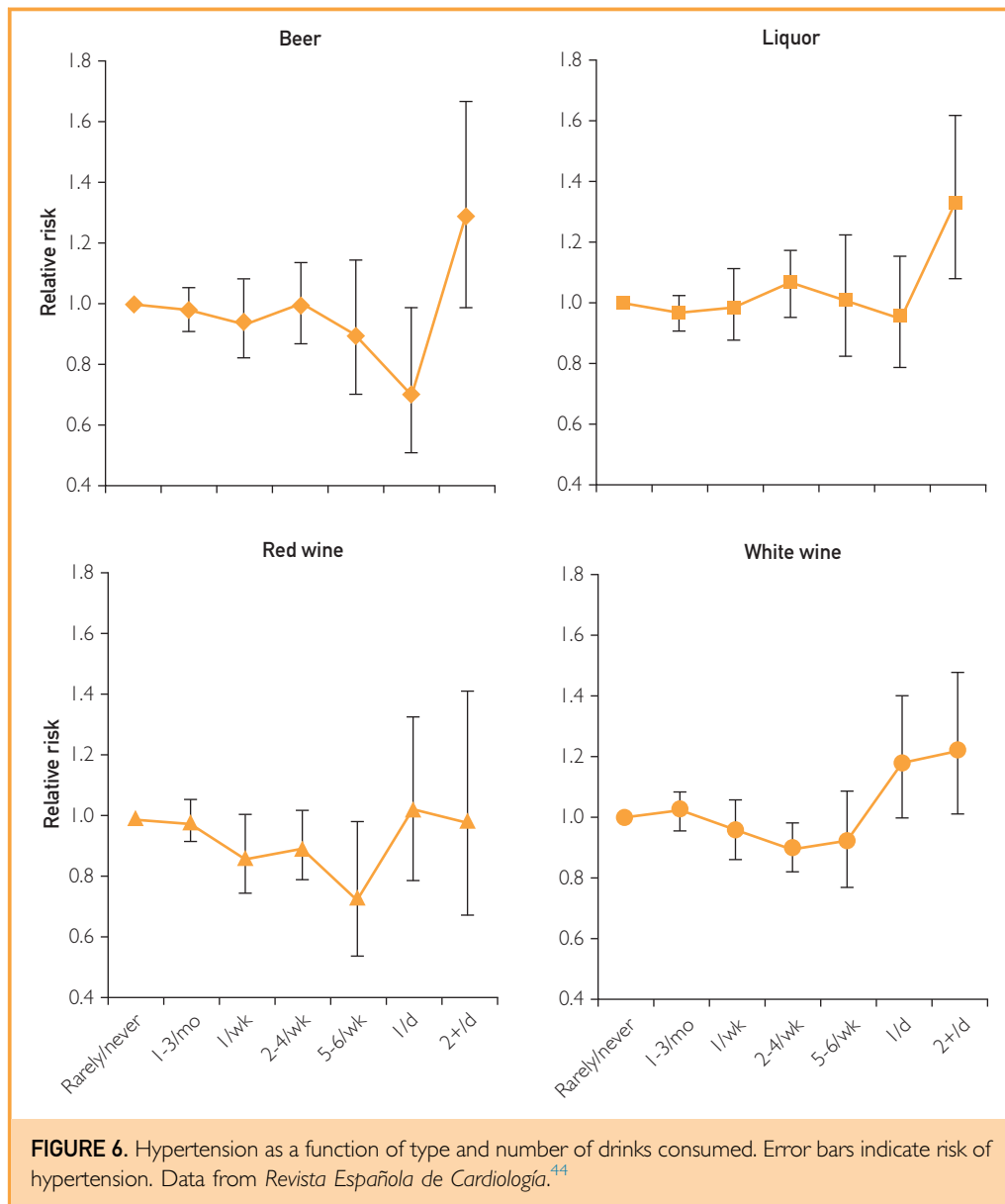
ALCOHOL AND STROKE

Heavy drinking and chronic alcoholism are strong independent risk factors for stroke.⁴⁷⁻⁴⁹ Even so, most studies reveal a J-shaped association between alcohol and ischemic stroke, with a protective effect from light to moderate drinking and an elevated risk of stroke with heavy drinking⁵⁰⁻⁵² (Figure 7). A recent study of 47,000 Japanese women followed for an average of 17 years found that ethanol consumption of 300 g/wk or more (21 or more drinks per week) increased total stroke by approximately 2-fold.⁵³

The American Stroke Association guidelines recommend that heavy drinkers with ischemic stroke or transient ischemic attack should eliminate or reduce their alcohol consumption. They also defined "reasonable" alcohol consumption as no more than 2 drinks per day for men and 1 drink per day for women.⁵⁴

ALCOHOL AND DM

Consistent data indicate that regular light to moderate drinking is associated with substantial reductions in type 2 DM of 30% to 40%, irrespective of the alcoholic beverage consumed.⁵⁵⁻⁵⁷ In the Physicians' Health Study, light to moderate alcohol consumption was associated with a decreased risk of type 2 DM during 12 years of follow-up.⁵⁸ However, the protection that



moderate drinking provides against new-onset diabetes is attenuated or abolished with higher doses (more than 4 drinks per day)⁵⁹ (Figure 8). As in the general population, moderate alcohol intake seems to protect against CAD in diabetic individuals.⁶⁰

This J-shaped relationship is also apparent for risk of metabolic syndrome,⁶¹ whereby a lower prevalence of metabolic syndrome is seen in people who regularly consume light to moderate amounts of alcohol.⁶² These results were replicated in an elderly Italian population⁶³ and were confirmed by a meta-analysis

that reported favorable metabolic effects in women consuming less than 20 g/d and men with less than 40-g/d intake.⁶⁴ The American Diabetes Association suggests limits of not more than 2 drinks per day for diabetic men and not more than 1 drink per day for diabetic women.⁶⁵

CARDIOPROTECTIVE MECHANISMS OF ACTION

The main active ingredient of any alcoholic beverage is ethanol, and most evidence indicates that this compound, rather than any other

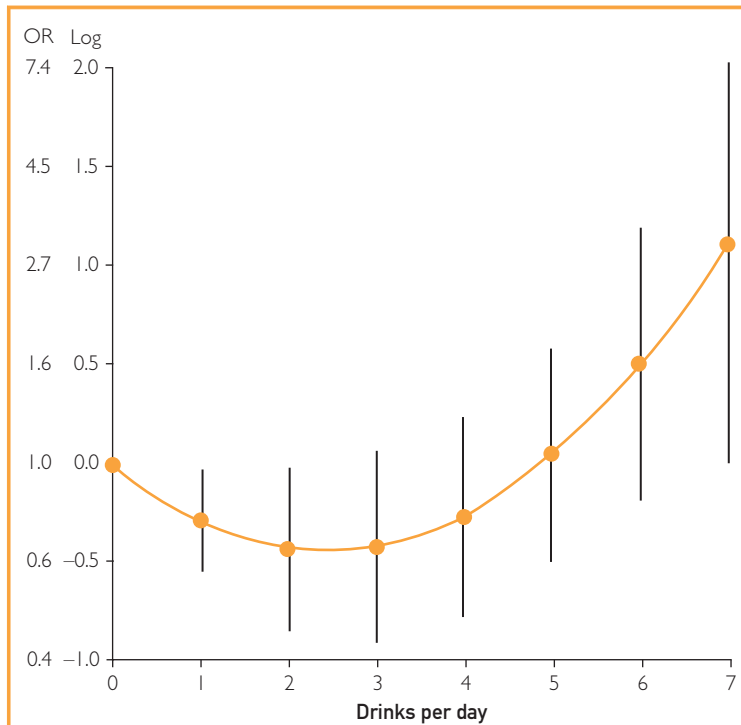


FIGURE 7. Fully adjusted statistical association between daily alcohol intake and ischemic stroke. OR = odds ratio. From *JAMA*,⁵⁰ with permission.

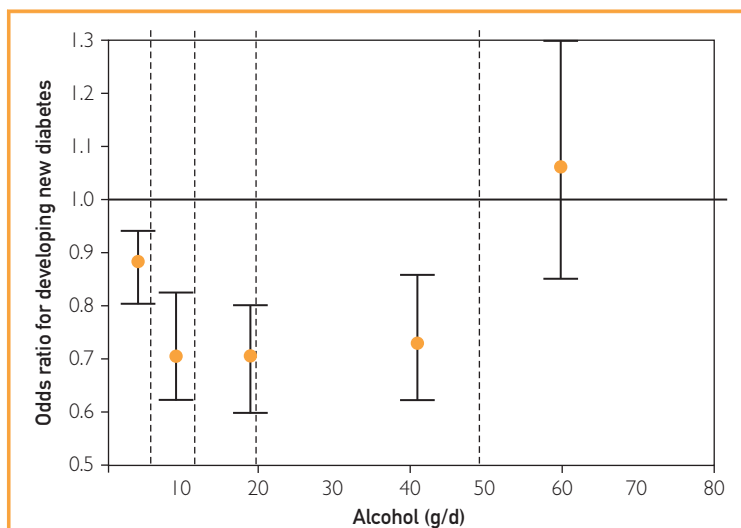


FIGURE 8. Alcohol intake and incidence of new-onset type 2 diabetes mellitus. Error bars indicate 95% CI. From *Journal of the American College of Cardiology*.⁵

specific component of a drink, is the primary factor for both conferring health benefits and causing toxicity, depending on the pattern of consumption and dosing.^{66,67} Accumulating scientific evidence suggests that light to moderate alcohol intake may enhance insulin sensitivity, elevate high-density lipoprotein (HDL) cholesterol, reduce inflammation, increase adiponectin, and improve endothelial function (Figure 9).⁶⁷⁻⁶⁹ In a linear dose-dependent fashion, alcohol intake increases HDL cholesterol (especially the cardioprotective HDL₂ subfraction) and apolipoprotein A-I.⁷⁰ Alcohol intake is also linearly associated with lipoprotein particle size (higher ethanol consumption is linked to larger low-density lipoprotein and HDL particles); however, a U-shaped association is seen with particle number, whereby consumers of 7 to 13 drinks per week had fewer particles than abstainers or heavy drinkers.⁷¹

Light to moderate alcohol intake does not appear to protect against coronary artery calcium (CAC) accumulation, and although heavy consumption of hard liquor or beer was reportedly associated with greater CAC accumulation, wine intake was neutral for CAC.⁷² In the Cardiovascular Risk Survey, a multiethnic, community-based, cross-sectional study of 14,618 people, consumption of less than 60 g/d was linked to less peripheral atherosclerosis, whereas consumption of 60 g/d or more was associated with more atherosclerosis.⁷³

In the Pravastatin Inflammation/CRP Evaluation Study, C-reactive protein levels were lower in those with moderate alcohol intake vs no or minimal alcohol intake. This anti-inflammatory effect persisted after adjustment for multiple traditional CV risk factors, suggesting that moderate drinking may confer cardioprotection in part by acting as an anti-inflammatory agent.⁷⁴

Importantly, moderate alcohol consumption (1 or 2 drinks) increases insulin sensitivity and glucose metabolism for the ensuing 12 to 24 hours.⁷⁵ The biological mechanism whereby alcohol improves insulin sensitivity appears to involve suppression of fatty acid release from adipose tissue and elevation of adiponectin levels.^{76,77} This reduction in fatty acids decreases substrate competition in the Krebs cycle of skeletal muscles, thereby facilitating glucose metabolism.⁷⁸ One or 2 drinks per day will reduce triglycerides modestly (7%-10%) and decrease abdominal obesity.⁷⁹ Thereafter,

abdominal obesity and triglycerides increase in direct proportion to the amount of alcohol consumed.^{78,80}

Red wine is rich in polyphenols, which possess antioxidant, anti-inflammatory, and antiplatelet activities.⁸¹ Indeed, multiple small, randomized controlled trials have found that red wine stimulated superior improvements in insulin resistance, lipid profiles, and endothelial function compared with other alcoholic beverages.⁸¹ In a recent study, daily ingestion of 275 mL/d of dealcoholized red wine decreased systolic and diastolic BP by increasing nitric oxide levels in the vasculature.⁸² Another recent study compared the effects of 3 alcoholic beverages—red wine, beer, and vodka—on oxidative stress.⁸³ Only red wine shielded the vasculature against hyperoxia-induced oxidative stress and transient increase in arterial stiffness.

INCONSISTENCY OF CARDIOPROTECTION AMONG VARIOUS ETHNICITIES

The cardioprotective effect of light to moderate drinking has not been consistently replicated among all the ethnicities and nations that have been studied.^{44,84,85} The INTERHEART study,⁸⁶ a landmark 27,000-patient international epidemiological study, found that regular alcohol intake was associated with a decrease in the risk of MI in both sexes and all adult age groups. Individuals from 50 different nations were included in the INTERHEART study, which found that regular alcohol intake reduced the risk of MI by 14%; however, this cardioprotection was not apparent among the cohort from India.⁸⁶ These results were replicated in a study conducted in India involving 4465 participants, in which the cohort of current and/or past alcohol users had a higher risk of CAD compared with alcohol abstainers.⁸⁵ Similarly, light to moderate drinking has not been consistently associated with cardioprotection in Chinese populations.^{87,88}

IDEAL DRINKING PATTERNS, DOSES, AND BEVERAGES

The standard definition of light to moderate alcohol intake is up to 1 drink per day for women and up to 2 drinks per day for men. Among the various alcoholic beverages, red wine, likely owing to its unique array of nonalcoholic components, is generally associated with the best health outcomes, especially for

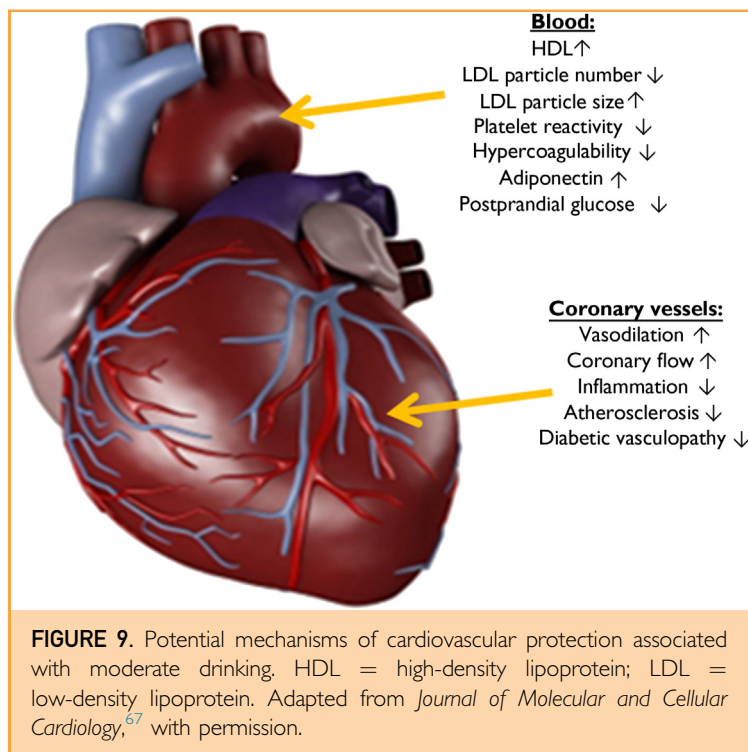


FIGURE 9. Potential mechanisms of cardiovascular protection associated with moderate drinking. HDL = high-density lipoprotein; LDL = low-density lipoprotein. Adapted from *Journal of Molecular and Cellular Cardiology*,⁶⁷ with permission.

CV issues.^{17,82,83,89,90} Binge drinking, usually defined as episodic excessive alcohol intake (≥ 5 drinks within a few hours) often with intent to become intoxicated, is associated with 2-fold higher risk of mortality.^{91,92} Even occasional binges attenuate the protection offered by otherwise light to moderate consumption. Cultures, such as those following the traditional Mediterranean diet, in which alcohol is consumed before or during the largest daily meal seem to have the most benefit from habitual light to moderate drinking.^{15,93} The advantages of this pattern of drinking at dinnertime may be due to the effectiveness of low- to moderate-dose alcohol in blunting postprandial glucose spikes and subsequent inflammation⁹⁴ or may possibly be related to enhanced social bonding with an emphasis on moderation generally espoused by this tradition.¹⁵ Finally, the health benefits of drinking, like those bestowed by exercise,⁹⁵ are best attained when done daily and in moderation.^{5,95} This is likely due to the fact that many of the benefits of light to moderate drinking are transient, generally dissipating within 24 hours.⁵

WARNINGS AND PRECAUTIONS

The Atherosclerosis Risk in Communities (ARIC) study found that among individuals deemed to be

at low risk for addiction, moderate alcohol consumption was safe and did not lead to adverse outcomes related to problem drinking.⁹⁶ However, other studies indicate that among nondrinkers, it is not possible to reliably predict who might be at increased risk for falling into a pattern of dangerously high alcohol intake once they begin drinking.^{3,5} Indeed, habitual alcohol intake appears to be a “slippery slope” that many individuals cannot safely navigate; thus, the American Heart Association cautions people not to start drinking if they do not already consume alcohol.⁹⁷ Furthermore, among the 16 million Americans who meet the diagnostic criteria for alcohol abuse or dependence, only 1.5 million seek and receive formal treatment, usually with discouragingly low rates of long-term abstinence.⁸⁸ Heavy long-term alcohol use increases the risks for many malignancies, particularly cancers of the gastrointestinal tract and liver.⁹⁸ Additionally, for women, even light to moderate alcohol intake is associated with increased risk for breast cancer.⁹⁹ Until we have more randomized outcome data and tools for predicting susceptibility to problem drinking, it would seem prudent to encourage physicians and patients to focus on more innocuous interventions to prevent CV disease.

ACKNOWLEDGMENTS

We thank Darwish Najj, MD (Saint Luke’s Mid America Heart Institute and University of Missouri-Kansas City) for assistance with data discovery and analysis.

Abbreviations and Acronyms: **AF** = atrial fibrillation; **BP** = blood pressure; **CAC** = coronary artery calcium; **CAD** = coronary artery disease; **CV** = cardiovascular; **DM** = diabetes mellitus; **HDL** = high-density lipoprotein; **HF** = heart failure; **HTN** = hypertension; **MI** = myocardial infarction

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