



EFFECT OF ALCOHOL CONSUMPTION ON CARDIOVASCULAR SYSTEM: A REVIEW

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ABSTRACT

Alcohol intake has consistently shown a J- or U-shaped relationship with several cardiovascular diseases. Light to moderate alcohol intake has been associated with lower risk of coronary artery disease, heart failure (HF), as well as CV mortality. On the other hand, heavy consumption has been associated with deleterious CV outcomes including increased mortality. However, the evidence is based from observational and population-based studies where risk of confounding cannot be excluded even after meticulous methodological approaches. Higher risk of certain CV diseases like HF in former drinkers compared to abstainers. Further, Mendelian randomization studies using genetic polymorphisms in enzymes have recently questioned the beneficial association of low-moderate drinking with CV system. Light to moderate alcohol consumption have beneficial effect on overall cardiovascular profile and mortality. However, there are considerable limitations in the reported literature to determine a strong causality of a protective effect of moderate alcohol consumption by itself.

Keywords: Alcohol, Coronary artery disease, Heart failure, cardiovascular mortality, Cardio protection and Cardiomyopathy.

INTRODUCTION

The moderate alcohol consumption might be associated with overall beneficial health effects, excess and binge drinking is one of the leading causes of mortality worldwide [1]. The same correlation holds true for alcohol and cardiovascular diseases [2]. It is suggested that whereas moderate amount of alcohol is protective against coronary artery disease (CAD), higher cardiovascular morbidity and mortality is observed among abstainers and heavy drinkers [3]. There have been multiple observational studies and meta-analyses demonstrating a J- or U-shaped association between alcohol consumption and all-cause mortality [2]. The purpose of this review is to discuss the effect of alcohol consumption on cardiovascular mortality and coronary artery disease (CAD), the shortcomings of the reported studies, the cardioprotective mechanism of alcohol and the disparities due to age, sex, ethnicity, pattern, and type of beverage consumed.

What Is Light, Moderate, Heavy and Binge Drinking?

As per the Center for Disease Control (CDC), a standard drink contains 0.6 oz (14.0 g or 1.2 tablespoons) of pure alcohol. Generally, this amount of pure alcohol is found in 12-oz of beer (5% alcohol content), 8 oz of malt liquor (7% alcohol content), 5 oz of wine (12% alcohol content), and 1.5 oz of 80 proof (40% alcohol content) distilled spirits or liquor (e.g., gin, rum, vodka, whiskey) [4]. The Dietary Guidelines for Americans define moderate drinking as up to one drink per day for women and up to two drinks per day for men, and light drinking as any amount less than moderate drinking [4]. Heavy drinking is defined as consuming 8 or more drinks per week for women and 15 or more drinks per week for men. Binge drinking, the most common form of excessive drinking, is defined as consuming four or more drinks during a single occasion for women and five or more drinks during a single occasion for men, respectively [4].

Alcohol and Cardiovascular Mortality:

Studies have consistently reported a J-shaped or U-shaped curve to describe the relationship between alcohol use and total cardiovascular (CV) mortality observational and prospective studies showing a lower risk for CV diseases in light to moderate drinkers compared to abstainers, and highest risk among heavy drinkers [5]. One study involving more than one million individuals that reported inverse relationship between mortality and consumption of alcohol, up to four drinks per day in men and two drinks per day in women, was inversely associated with total mortality [5]. The maximum protection was noted at one half to one drink daily for women (18% decreases in total mortality) and one to two drinks daily for men (total mortality decrease of 17%). 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.

Gaziano et al. examined the relationship between light-to moderate alcohol consumption and cause-specific mortality in a prospective cohort of 89,299 US men from the Physicians' Health Study enrollment cohort who were free of known myocardial infarction (MI), stroke, cancer, or liver disease at baseline [6]. The authors reported a U-shaped relationship between light-to-moderate alcohol intake and risk of total mortality. A decreased total mortality risk of up to 26% was seen among those who consumed 1 to less than 14 drinks per week. The relationship between stable alcohol intake and total mortality in a longitudinal study of 6644

men and 8010 women, age 25 to 98 years, who had attended at least two health surveys with a 5-year interval between them [7]. Stable drinkers demonstrated U-shaped all-cause mortality, with relative risks of 1.29 for nondrinkers (< 1 drinker week) and 1.32 for heavy drinkers (> 13 drinks per week) compared with light drinkers (1 to 6 drinks per week). The stable abstainers had a relative risk of 1.32 for developing coronary artery disease as compared with stable light drinkers. Cancer mortality was also increased in all groups of heavy drinkers [7]. The overall cardiovascular mortality was lower among men and women who reported consuming at least one drink daily than among non-drinkers. The all-cause mortality increased as the level of alcohol consumption increased with the highest mortality among heavy drinkers, particularly among adults less than 60 years of age. In the middle-aged and elderly population, moderate alcohol consumption slightly reduced overall mortality which was offset by smoking which approximately doubled this risk.

The effects of alcohol consumption in middle-aged (aged 51 to 64 years) and elderly men (aged 65 to 75 years) of Japanese-American origin who were participating in the Honolulu Heart Program and were free from coronary heart disease, cerebrovascular disease, and cancer at baseline examination and at subsequent re-examination 6 years later [8]. The authors found that even after adjusting for several potential confounding factors, overall mortality exhibited a J shaped pattern with the alcohol consumption. In another 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 mortality compared with either heavy users (> 7 drinks per week in women or > 14 drinks per week in men) or lifetime abstainers [9].

Alcohol and Coronary Artery Disease:

Alcohol has been shown to have a favorable effect on the development of CAD. Studies have reported that moderate alcohol use is linked with a decreased atherosclerotic burdens assessed by coronary angiography [10], computerized tomography-detected coronary calcium [11], and carotid ultrasound [12]. Several observational studies have shown reduced risk of acute MI and CAD death in moderate drinkers compared to abstainers [13]. Similar to mortality, Meta analyses have also shown a U-curve or J-curve association between increasing alcohol intake and CAD, with lifelong abstainers as the referent. The regular alcohol consumption was associated with a reduced incidence of MI in all adult age groups and in both genders. Light to moderate drinking was associated with improved CV health in higher-risk individuals, such as those with known CAD and/or diabetes, but it also reduced CV risk in lower-risk individuals. One study showing that consuming 15.0 to 29.9 g/day of alcohol (i.e., 2 drinks per day) were associated with the lowest risk for MI, with higher intake associated with intermediate risk [14]. Several other epidemiological studies have also shown that light to moderate drinkers as compared to non-drinkers or heavy drinkers have lower rates of nonfatal acute MI and coronary deaths [9].

The light to moderate alcohol intake has also been shown to improve outcomes in patients with established CV disease. In a prospective cohort study of 1913 adults hospitalized with AMI, all-cause mortality was compared by self-reported average weekly consumption of alcohol in the year before the acute coronary

event, over a median follow-up of 3.8 years looking. The authors concluded that moderate alcohol consumption during the prior year, as measured at the time of index AMI, was associated with lower subsequent mortality following AMI. In another prospective study, 1351 patients with established CAD who had undergone coronary artery bypass surgery were followed for 4.3 years. The authors found that the patients who had a moderate amount of alcohol consumption, i.e., between 7 and 13 drinks per week had a 30% reduction in clinical events as compared with abstainers or patients who consumed small amount [15]. Other studies evaluating alcohol's effects on patients who have had a MI also report the typical J-shaped relationship between drinking and adverse events or total mortality [16].

Age, Sex, Ethnicity, and Type of Beverage Consumed:

Age: The cardioprotective benefit of moderate alcohol intake appears to be more favorable for middle-aged and older people compared with younger individuals. In a pooled analysis of eight prospective studies including 192,067 women and 74,919 men, an inverse association was found between alcohol intake and risk of CAD events. However, the absolute reductions in CAD were not clinically significant for people younger than 50 years of age [17]. One study show the relationship between alcohol use and coronary heart disease in 4410 adults aged > 65 years and free of cardiovascular disease at baseline [18]. Intriguingly, consumption of 14 or more drinks per week was associated with the lowest risk of coronary heart disease there by supporting that alcohol intake is beneficial even in an older population group. Younger individuals are at a much lower risk for CAD but are more likely to engage in excessive and/or binge drinking and are therefore at higher risk of alcohol-related accidents, violence, and overdoses [19]. Thus, the risks of regular drinking especially heavy drinking may outweigh the cardiovascular benefits for younger population.

Sex: Given differences in volume of distribution, first-pass metabolism, and overall body size between the two genders, women experience toxic effects of alcohol at approximately half the daily dose of men [20]. However, the beneficial cardiovascular effects of moderate alcohol consumption in women are similar to those seen in men [21]. In the study of 87,526 female nurses aged 34 to 59 years, moderate alcohol consumption decreased the risks of CAD and ischemic stroke during 334,382 person-years of follow-up, compared with nondrinkers. The study among 10,576 black and 105,610 white postmenopausal women are from the Women's Health Initiative (WHI), without a history of cancer or cardiovascular disease. During a mean 8-year follow-up period, moderate drinking was associated with a lower risk of total mortality among Caucasian women regardless of hypertensive status, and hypertensive but not no hypertensive African-American women [22]. One Observational Study of 3198 postmenopausal women, both frequency and quantity of alcohol intake were inversely associated with the risk of developing CAD, irrespective of the beverage type [23].

Ethnicity: The cardioprotective effect of moderate alcohol consumption might not be universal and vary according to different ethnicities. Most of the reported literature on the beneficial effects of alcohol has been studied in western world. In the study of acute MI patients, alcohol consumption in South Asians was not protective against CAD as was observed in other countries. There was an inverse association suggesting possible harm of alcohol for coronary risk in Indian men.

Type of Alcohol Consumed (the French Paradox):

The red wine has been shown to have higher levels of bioflavonoid which have antioxidant, anti-endothelin-1, and antiplatelet effects compared with white wine and other forms of alcohol, the ethanol itself rather than a specific type (wine, beer, liquor) appears to be the major factor in conferring the health benefits [24]. Most of the observational and prospective studies have shown equal protection from all types of alcohol suggesting that the specific alcoholic beverage is less important than the quantity and pattern of the alcohol intake [25]. A differential cardioprotective effect of wine is probably confounded by the fact that wine drinkers have more favorable CAD risk profile and also as compared to beer or liquor, wine is more often used in moderation.

Controversies Regarding the Cardioprotective Effect of Alcohol:

Most of the studies that evaluated the relationship between alcohol consumption and CAD have used current abstainers and did not differentiate between lifetime abstainers and sick quitters, i.e., the former drinkers who gave up drinking due to health reasons [26]. Including sick quitters into control group might confound the results by falsely indicating a protective effect of light or moderate drinking. However, in few studies where the comparisons were made with lifetime abstainers only, the protective effect of moderate alcohol consumption persisted [27]. But it should be taken in to account that these lifetime abstainers are people in high-income societies and often differs from the general population in socioeconomic status, drinking and nutritional habits, and therefore, these results should be interpreted with caution. Moreover, alcohol might have different influence on CV risk acutely as compared to long-term period. The rate alcohol consumption was associated with an immediate elevated CV risk while a benefit against MI and stroke was confirmed after 24 h [28]. Further, a “healthy drinker” hypothesis suggests that people who drink alcohol in moderation usually have healthier life style as compared to heavy and binge drinkers. Heavy and binge drinkers are likely to smoke more, do less exercise and follow worse diets as compared to their counterparts which might explain higher cardiovascular mortality. Although there are numerous modifiable risk factors identified for ischemic heart disease, smoking is one of the most important risk factors and several studies have proven its influence on alcohol and CAD relationship.

More recently, Mendelian randomization studies have looked at the association between alcohol and cardiovascular disease [29]. These studies are centered on the fact that genetic variants affecting alcohol metabolism are allocated randomly which theoretically comprises a form of “natural” randomized controlled trial. Some evidence has suggested that individuals with an alcohol dehydrogenase polymorphism (ADH1C) resulting in “slow metabolism” of alcohol May obtain more cardiovascular benefit [30], thus supporting a causal relationship between the protective effect of light-moderate drinking on CAD. In contrast, a recent meta-analysis of 56 studies showed that individuals with the ADH1B polymorphism who were more likely to be abstainers had decreased CV risk and thus reduction of alcohol consumption might be beneficial for CV health even in light and moderate drinker’s alcohol.

Mechanism of Cardioprotective Action of Alcohol:

There are several mechanisms that have been proposed to explain the beneficial effects of moderate alcohol consumption on CV diseases which include an increase in high-density lipoprotein (HDL) cholesterol, increased insulin sensitivity, favorable effects mediated by alterations in protein kinase C (PKC), anti-inflammatory effect, increase adiponectin, increase fibrinolysis, decrease in platelet aggregation, and coagulation and improved endothelial function [31]. As these mechanisms are interconnected through complex metabolic pathways, the exact contribution of an individual component is difficult to assess. HDL cholesterol is an important factor for maintaining appropriate concentrations of low density lipoprotein (LDL) cholesterol in vascular and other cells throughout the body. Additionally, HDL reduces expression of adhesion molecules and inhibits oxidation of LDL, migration of inflammatory cells into endothelium, and thus thrombosis. Moderate alcohol intake is associated with an increase in HDL and apolipoprotein (Apo) A1, the major HDL carrier protein in a dose-dependent fashion [32]. Epidemiological studies support that a significant decrease in CAD risk in alcohol drinkers is mediated by higher HDL levels [33].

Moderate alcohol consumption is also associated with increase in insulin sensitivity and glucose metabolism by suppression of fatty acid release from adipose tissue and elevation of adiponectin levels [34]. This reduction in fatty acids decreases substrate competition in the Krebs cycle of skeletal muscles, thereby facilitating glucose metabolism [35]. One or two drinks per day reduce triglycerides modestly (7–10%), decrease abdominal obesity and improve the overall CV risk profile which is of significance in patients with metabolic syndrome [36]. Therefore, an inverse relationship is seen in heavy drinkers, which lead to worsening of metabolic syndrome and raised homocysteine levels, and ultimately increased CV mortality [37].

Moderate alcohol consumption mimics classic cardiac preconditioning and protects against ischemia reperfusion injury, as evidenced by reduced infarct size and decreased hypoxia induced cell death. The mechanism of benefit involves the PKC family of isoforms which are activated by myocardial ischemia. Alcohol shares many of the same signal transduction pathways and effectors molecules that have been implicated in conventional and/or pharmacologic preconditioning [38]. Alcohol is also believed to have anti-inflammatory properties that are likely mediated through changes in cytokine profiles and cell signaling pathways. Recent data have shown that acute alcohol consumption may exert beneficial effects on the vascular system by suppressing production of proinflammatory cytokines such as tumor necrosis factor- α , interleukin-1 receptor antagonist, interleukin-5, interleukin-6, and C-reactive protein [39]. Moreover, alcohol has shown to have several antithrombotic effects including inhibition of platelet adhesion and lowered fibrinogen levels. As thrombosis in atherosclerotic arteries plays a key role in major CAD events, these effects may be important factors in the protective effect of alcohol however no human studies have confirmed a causal relationship.

Alcohol and Blood Pressure:

The effects of alcohol consumption on blood pressure (BP) are less certain. Although low to moderate alcohol intake has no immediate effect on BP response, binge drinking has been shown to cause acute rise in systolic BP by mean of 4–6 mm Hg [40]. Moreover, different studies conflict in regard to association between

long-term impact of light-moderate and heavy alcohol consumption and hypertension (HTN) incidence. In the CARDIA study, stratification of patients based on different levels of alcohol intake did not reveal an association with increase in incident HTN over a period of 20 years even after adjusting for several potential confounders [41]. In contrast, two meta-analyses studying effect of different doses of alcohol intake demonstrated differential association with risk of HTN in men and women [[42, 43]. While, a J-shaped curve was observed in women with reduced risk of HTN for <10 g intake and increasing risk for > 20 g intake/day, men had a more linear increase in BP response with intake > 30 g/day. Endothelial cellular dysfunction, oxidative stress, and imbalances in neurohormonal pathways are the most plausible pathways involved in ethanol-induced HTN. To consolidate these findings, both men and women have increased risk of HTN with alcohol intake greater than moderate levels.

Alcohol and Cardiomyopathy:

Alcohol consumption may have a bimodal response with heavy intake leading to both increased risk of developing heart failure (HF) as well as progression of established HF. A metaanalysis eight studies assessing the dose-response relationship between alcohol consumption and HF showed a decreased risk of HF in patients with light to moderate (3-10drinks/week) alcohol intake as compared to abstainers [44]. In another study, elderly patients > 65 years age had a U shaped response with light (1-6 drinks/week) and moderate(7-13 drinks/week) alcohol consumptions associated with a lower risk of HF as compared to abstainers [15]. However, former drinkers had a higher risk of HF compared to abstainers raising questions about protective effects of alcohol on HF. Further, higher risk of HF has been observed in men with heavy intake (> 28 drinks/week) and in lifetime abstainers Compared to light drinkers [45].

Alcohol cardiomyopathy (ACM) is a type of dilated cardiomyopathy with reduced ejection fraction (EF) associated with long-term heavy alcohol consumption. The exact burden of ACM remains unknown but has been reported to account for 23-40% of cases with cardiomyopathy [46]. As seen with relationship of alcohol and other CV diseases, ACM might develop early and at a lower consumption in women as compared to men [47]. Potential mechanisms of ACM include free radical generation and oxidative stress, apoptosis, protein breakdown, and alterations of fatty acid metabolism. Thus, while light to moderate alcohol consumption might confer some benefit from HF risk in early to middle life, heavy drinkers especially elderly patients have much higher risk of developing HF.

Alcohol and Diabetes Mellitus:

Light to moderate alcohol consumption appears to protect against development of CAD and the risk of coronary death in diabetic men and women [48, 49]. In addition, moderate alcohol consumption may lower the risk of developing type-2 diabetes [50] and the metabolic syndrome which are both strong risk factors for coronary disease. The finding of a U-shaped relationship between alcohol consumption and type 2 diabetes risks is similar with the previously demonstrated relationship with cardiovascular diseases and may partly share underlying mechanisms.

CONCLUSION

There is substantial and consistent evidence from observational and short-term experimental studies that having one to two drinks per day without episodic heavy drinking have a beneficial effect on the development of coronary artery disease as compared to lifetime abstainers. However, these studies suffer from either methodological issue, confounding biases, misclassification of alcohol consumption, excluding drinking patterns, the inclusion of sick quitters in reference group's and ethnicity differences. Therefore, it is impossible to determine causality of a protective effect of moderate alcohol consumption on ischemic heart disease by itself. The patients that low to moderate alcohol consumption (one drink/day for women or two drinks/day for men) should not be dangerous to their health. However, life-long abstaining individuals should not be encouraged to start drinking; owing to the fact that scenario has not been assessed even in observational studies and there is no way to predict if a person would consume only in moderation after starting drinking. Heavy or binge drinking can have adverse health outcomes and should be strongly discouraged. The physician should be aware that regular, moderate alcohol consumption, in the context of a healthy lifestyle, good dietary habits, and adequate drug therapy would substantially lower their cardiovascular or mortality risk than either abstainer's or heavy/binge drinkers. The cardiovascular benefit of moderate alcohol intake must be balanced in the individual against the adverse effects of alcohol. Furthermore, the net risk-benefit balance associated with moderate alcohol consumption differs in various age groups and populations. The American Heart Association (AHA) actually recommends against advising people who do not currently drink to initiate light alcohols use.

Abbreviations:

CHD: Coronary heart disease.

HF: Heart failure.

CV: Cardiovascular.

DM: Diabetes mellitus.

AHA: American heart Association.

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