

Alcohol and coronary artery disease

S Gupta¹, VM Figueredo^{1,2*}

Abstract

Introduction

Multiple diverse epidemiological studies have demonstrated a protective effect of low to moderate alcohol consumption on the risk of coronary heart disease (CHD) events. Moderate alcohol consumption favourably affects lipid profile, platelet aggregation, coagulation and endothelial function, all of which mediate its protective effect on CHD. Alcohol in moderate doses also causes reduction in infarct size similar to that seen with ischemic preconditioning. The benefits of red wine over other forms of alcohol have not been proven clinically. This review discusses current evidence and mechanisms related to the effects of alcohol on coronary artery disease.

Conclusion

Further research is needed to establish safe upper dose limits for the protective effect of alcohol in diverse patient populations. Also, since most epidemiologic studies are over a decade old, it would be worthwhile repeating them in the era of statin therapy.

Introduction

Numerous and diverse epidemiologic studies have shown a protective effect of low to moderate alcohol consumption against the risk of coronary heart disease (CHD) events. Although a J-shaped curve appears to represent the relationship between all-cause mortality and alcohol consumption, most studies suggest a stepwise decline in CHD mortality with increasing alcohol dose, with increasing mortality due to other processes associated with heavy alcohol consumption.

*Corresponding author
Email: FigueredoV@einstein.edu

¹ Einstein Medical Center, Philadelphia, PA, United States

² Jefferson Medical College, Philadelphia, PA, United States

This review explores current evidence and mechanisms behind the protective effect of alcohol specifically on coronary artery disease (CAD).

Discussion

Evidence From Epidemiologic Studies

In a pooled analysis of 8 prospective studies from North America and Europe, including 192,067 women and 74,919 men free of cardiovascular diseases and diabetes, there was an inverse association between alcohol and risk of CHD in all age groups (Figure 1). In the Copenhagen City Heart Study, with a longitudinal follow-up over 16 years, increasing alcohol intake was associated with decreasing risk for myocardial infarction (MI), decreasing low-density lipoprotein cholesterol and fibrinogen, as well as increasing diastolic and systolic blood pressures and high-density lipoprotein cholesterol, and U-shaped relationship with triglycerides (Figure 2). These associations were not modified by alcohol dehydrogenase ADH1B and ADH1C genotypes. In the Physicians' Health Study, moderate alcohol drinkers who were homozygous for the slow metabolizing ADH 3 had higher high density cholesterol (HDL) levels and lower risk for MI. Figure 3 summarizes various pathways by which moderate alcohol consumption affects the risk of CHD.

Influence of Pattern of Alcohol Consumption on Coronary Artery Disease

In the Prospective Epidemiological Study of Myocardial Infarction (PRIME) study conducted in France and Northern Ireland, patterns of alcohol consumption differed significantly despite comparable weekly alcohol intake, with weekend binge drinking more prevalent in Ireland and daily moderate drinking

more prevalent in France. The annual incidence of MI or CHD death (hard coronary events) was nearly double in Ireland versus that in France (5.63 versus 2.78 per 1000 patient years). In a multicenter prospective, inception cohort study involving 1935 patients after the first episode of MI, binge drinkers had a 2-fold higher risk of mortality than drinkers who did not binge, and the increased risk was independent of moderate versus heavy drinking or type of alcoholic beverage consumed. These studies suggest that both quantity and pattern of alcohol consumption may modify or negate the protective effect of alcohol against CHD. Potential mechanisms by which binge drinking increases cardiovascular mortality are summarized in figure 4.

Effect of Alcohol on Lipid Parameters

The protective role of alcohol in CHD is largely attributed to its effects on high density lipoprotein-cholesterol (HDL-C). Alcohol intake increases HDL-C in a dose-dependent fashion up to 18%, associated with, and possibly caused by, an increase in the transportation rates of HDL apolipoproteins apoA-I and A-II. Incremental alcohol intake is associated with significantly elevated levels of HDL-C, phospholipid enrichment of HDL, and a shift from HDL 3 subfraction to HDL 2, all of which may augment the anti-atherogenic effect of HDL-C. Moderate alcohol consumption favourably affects other lipid parameters as well. In the Cardiovascular Health Study, alcohol consumption was associated with less total low density lipoprotein (LDL) cholesterol particles, lower levels of the more atherogenic particles (small LDL, HDL, and very-low-density lipoprotein particles), and higher levels of the less atherogenic particles (large LDL and medium- and large-sized HDL particles), as measured by nuclear magnetic resonance spectroscopy.

Effect of Alcohol on Atherosclerotic Plaque Development

In a study of rats fed a lipid rich diet and either 3% or 6% ethanol, alcohol prevented the development of the early atherosclerotic lesions (fatty streaks), in a dose-dependent manner. Surprisingly, a reduction in the level of high density lipoprotein cholesterol (HDL-C) was noted in mice with increasing doses of alcohol, suggesting an HDL-C independent atheroprotective effect of alcohol. Alcohol also affects inflammatory pathways of atherosclerosis. In cultured human macrophages, ethanol decreased the production and secretion of interleukin-1 β (IL-1 β), a key cytokine involved in atherosclerotic inflammation of coronary arteries, in a dose-dependent manner. In the Multi-Ethnic Study of Atherosclerosis (MESA), heavy consumption of alcohol was associated with greater coronary artery calcium accumulation, but there was no evidence of a J-shaped association between alcohol and coronary artery calcium over a 2 to 4 year period.

To evaluate the differential effect of alcohol drinking pattern on plasma lipid level and physiological parameters of atherosclerotic plaque development, daily moderate (2 drinks/day, 7 days/week) and weekend binge (7 drinks/day, 2 days/week) patterns of alcohol consumption were studied in a mouse model. While HDL-C levels increased in both binge and moderate groups, LDL-C levels were significantly decreased in the daily moderate drinking mice and significantly elevated in the weekend binge drinking mice. In the former group there was a decrease in atherosclerotic plaque volume, increase in lumen volume and decreased macrophage accumulation, when compared to no alcohol mice. In contrast, after weekend binge alcohol consumption there was an increase in plaque volume, concomitant with a decrease in lumen volume and increased deposition of macrophages.

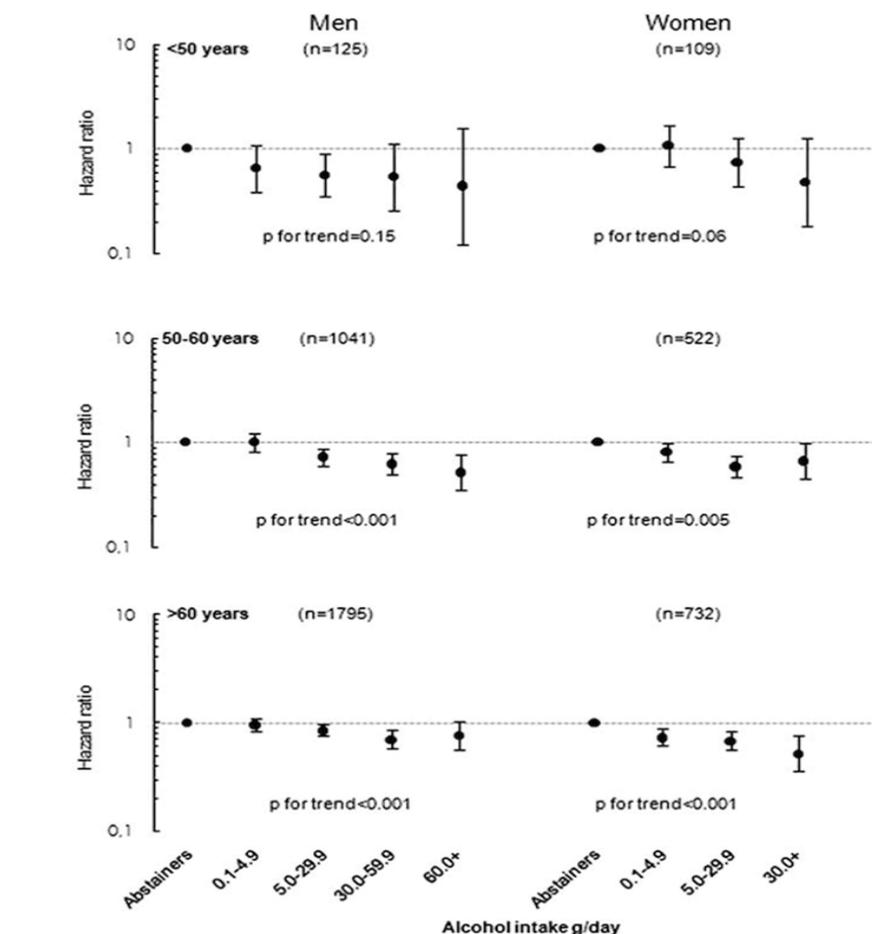


Figure 1: Sex- and age-specific pooled hazard ratios of CHD for categories of daily alcohol intake.

Angiographic studies have also shown reduced progression of atherosclerosis in subjects with known CAD consuming alcohol. In the Stockholm Female Coronary Risk Angiographic Study, women < 65 years hospitalized with acute MI or unstable angina underwent serial quantitative coronary angiography 3–6 months following their index event and repeated 2 to 5 years later. In this group, moderate alcohol consumption (over 5 g/day) was protective of coronary atherosclerosis progression (Figure 5).

Effects of Alcohol on Hemostatic Function

In an analysis of the Framingham Offspring Study, light to moderate alcohol consumption was associated with lower levels of fibrinogen, plasma viscosity, factor VII, and von-Willebrand factor. However, fibrinolytic potential decreased with

increasing alcohol consumption, most dramatically at approximately seven drinks weekly. Wine drinkers generally had the lowest plasminogen activator inhibitor antigen-1 (PAI-1) levels at moderate levels of consumption, but the remaining parameters were not significantly different among beverage types.

In a study of platelet activation in response to ADP and platelet aggregability in response to ADP, epinephrine, and collagen among 2,013 participants, alcohol consumption was inversely associated with platelet aggregation induced by ADP among both women and men and by epinephrine among men. A dose-dependent effect of alcohol on decreased platelet aggregation was also seen in the Caerphilly Prospective Heart Disease Study. In vitro, alcohol blocks stimulation of platelet phospholipase A2 induced by agonists

Competing interests: None declared. Conflict of interests: None declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

such as collagen and thrombin, and thereby prevents mobilization of arachidonate required for the generation of thromboxane A₂ (TxA₂)¹⁸. Alcohol has also been shown to potentiate the effect of aspirin, which blocks the conversion of released arachidonate to TxA₂.

In addition, polyphenols present in red wine, namely trans-resveratrol and quercetin, demonstrated a dose dependent inhibition of both thrombin-induced and ADP-induced platelet aggregation, whereas ethanol inhibited only thrombin-induced aggregation in in-vitro experiments.

Effects of Alcohol on Endothelial Function

Low concentrations of alcohol induce increased release of nitric oxide NO, a vasodilator, from the endothelium due to activation and expression of nitric oxide synthase. In contrast, administration of high concentrations of alcohol impairs endothelial function in association with reduced nitric oxide bioavailability.

Effects of Alcohol on Vasculature

Ethanol in moderate doses has been shown to directly promote vasculogenesis and improve microvascular function, thus improving myocardial perfusion in the setting of chronic ischemia. In a swine model of chronic myocardial ischemia, animals were supplemented with either moderate doses of ethanol or sucrose of equal caloric value, serving as controls.

At 7 weeks, arteriolar density, myocardial perfusion and microvascular reactivity were significantly increased in ethanol-treated animals compared with controls in the at-risk myocardium. Analysis of vascular endothelial growth factor (VEGF) and NOTCH pathway signalling (markers of neovascularization) suggested proneovascular and proliferative activity in the ischemic area.

In vitro ethanol at concentrations similar to those of moderate alcohol consumption was shown to dilate

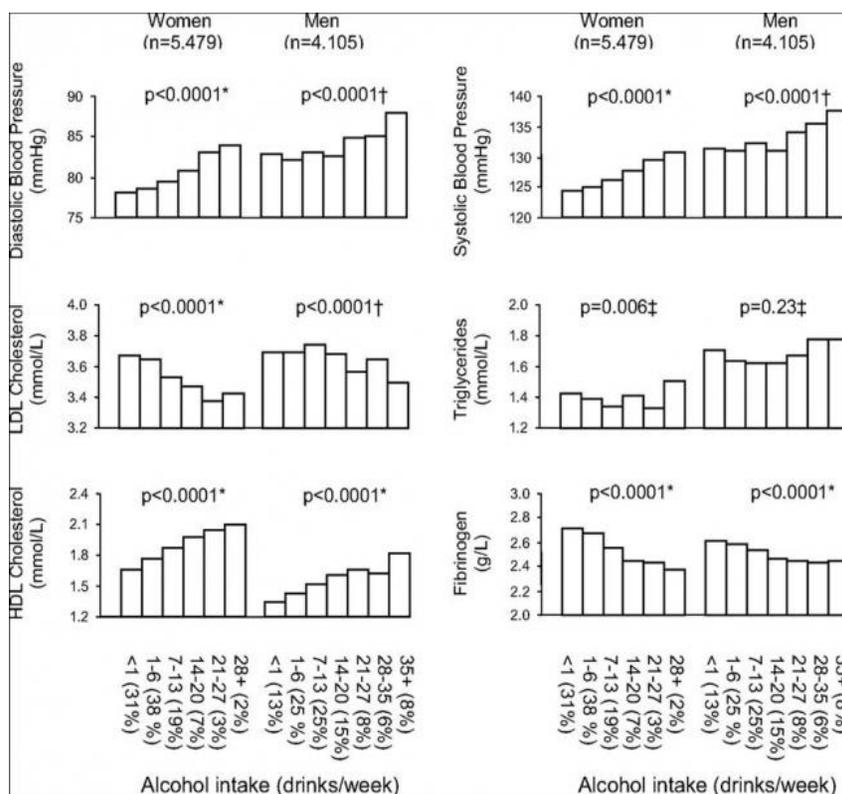


Figure 2: Average levels of diastolic blood pressure, systolic blood pressure, LDL cholesterol, triglycerides, HDL cholesterol, and fibrinogen according to alcohol intake. The percent of all women and men in each alcohol drinking category is shown in parenthesis after the amount of drinks per week. *Probability value for linear trend. †Probability value for trend for alcohol intake more than 21 drinks per week for men. ‡Probability value for U-shape.

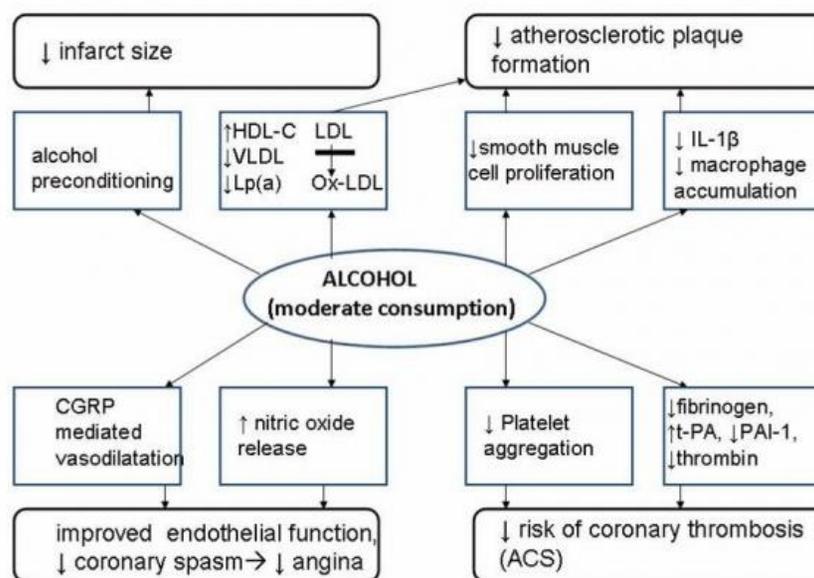


Figure 3: Effects of moderate consumption of alcohol on coronary artery disease.

isolated porcine coronary arteries and increase coronary blood flow in isolated perfused guinea pig hearts.

Ethanol induces the release of calcitonin related gene peptide (CGRP) which mediates the vasodilatory effect.

Competing interests: None declared. Conflict of interests: None declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

In human beings, CGRP dilates coronary arteries at the site of atheromatous stenoses, delays the onset of myocardial ischemia and increases work tolerance during treadmill exercise in patients with stable angina.

Effects of Alcohol on Revascularized CAD

Alcohol may affect restenosis after angioplasty. Local delivery of ethanol to pig coronaries immediately after inducing balloon injury was shown to reduce intimal hyperplasia after several weeks. In a retrospective study of 225 patients who had undergone angioplasty with stenting, those who consumed > 50 g alcohol a week had a lower mean late loss of the luminal diameter, a lower rate of coronary restenosis within the stented segment, and a lower rate of repeat angioplasty.

In a study of patients with previous coronary artery bypass grafting (CABG) and patent grafts, there was a trend towards roughly 30% lower risk among moderate drinkers with respect to clinical events and graft progression, though these associations were not statistically significant for either endpoint. Approximately one-third of the trend toward less angiographic progression among moderate drinkers appeared to be related to higher HDL-C levels.

Alcohol Preconditioning

In a rat model, chronic and low dose ethanol drinking resulted in a significant reduction of infarct, a protective effect similar to that observed with ischemic preconditioning (IPC) independent of the effects of alcohol on lipids and coagulation factors. This effect was postulated to be mediated through protein kinase C (PKC) as both ethanol and IPC cause its activation. PKC isozymes phosphorylate protein substrates (ATP sensitive potassium channels and heat shock proteins etc.) which may ultimately mediate cardioprotection against ischemia-reperfusion injury.

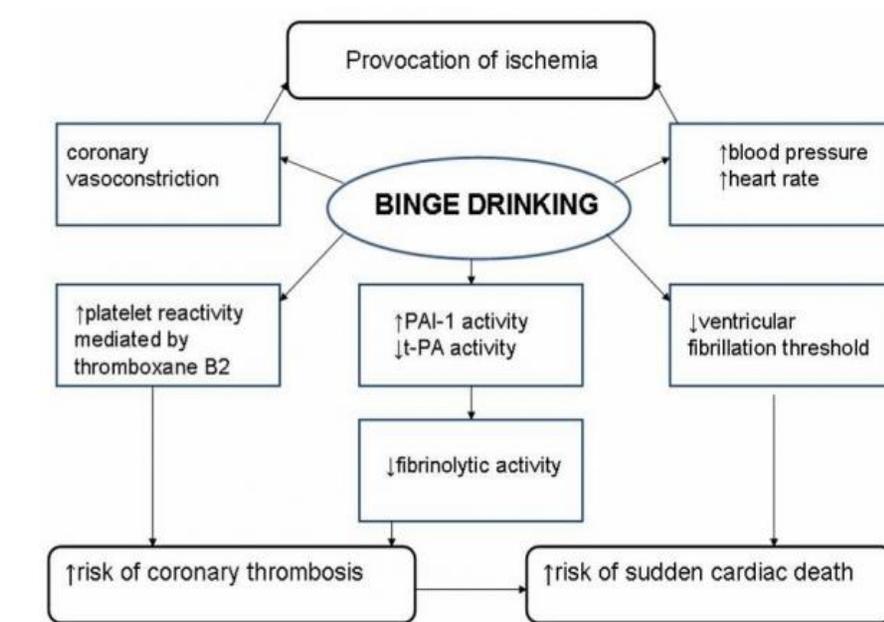


Figure 4: Effects of binge drinking on increasing cardiovascular mortality.

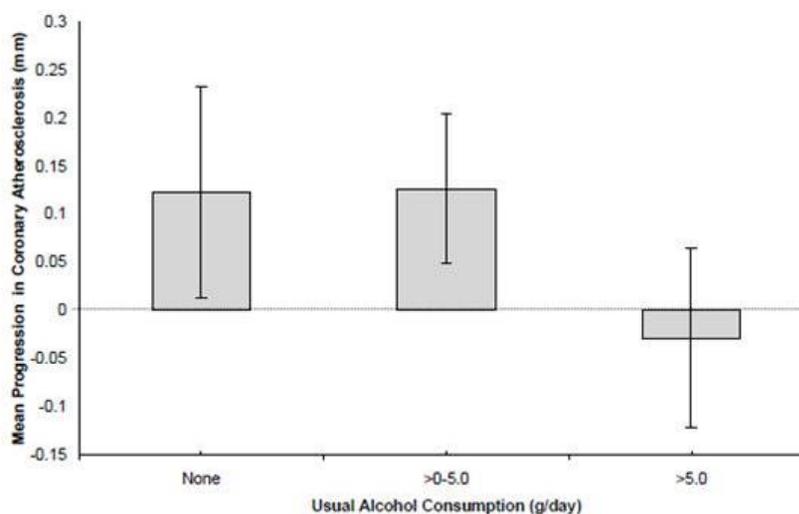


Figure 5: Mean progression of coronary artery narrowing in 93 women with acute coronary syndromes according to daily alcohol use. Results are adjusted for age, index event, smoking (never/former vs. current), educational status, diabetes mellitus, sedentary lifestyle, body-mass index (in quartiles), history of hyperlipidemia, and menopausal status (in three categories).

However, acute exposure to ethanol may actually abolish IPC. In a rabbit model, ethanol exposure in situ shortly before ischemia did not reduce infarct size. Moreover, ethanol abolished protection from IPC. When ethanol was administered for 5 minutes and allowed to washout, it did reduce infarct size, suggesting that continued presence of alcohol during ischemia may negate the effects of alcohol on IPC.

Effect of Alcohol Beverage Type

Red wine contains abundant polyphenolic compounds (notably resveratrol and anthocyanins) in addition to alcohol, which may have additional cardioprotective effects beyond the effects of alcohol against CAD. These polyphenols have been shown to reduce oxidative stress (decrease lipid peroxidation), decrease LDL oxidation, improve endothelial function and favourably influence

Competing interests: None declared. Conflict of interests: None declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

cholesterol efflux, though the exact contribution of polyphenols to decreasing the risk of CAD remains unclear.

Conclusion

Despite robust evidence of a protective effect of alcohol on several aspects of CAD, the significant abuse potential and detrimental effect of alcohol on other organs precludes any recommendation to consume alcohol for cardioprotection. However, it is now clear that patients who consume alcohol in moderation (1-2 glasses per day) should be allowed to continue drinking, even after an acute coronary event. There is no established benefit of consuming red wine over any other form of alcohol. Further research is needed to establish safe upper dose limits for the protective effect of alcohol in diverse patient populations.

Also, since most epidemiologic studies are over a decade old, it would be worthwhile repeating them in the era of statin therapy.

References

- Rimm EB, Giovannucci EL, Willett WC, Colditz GA, et al. Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet*. 1991;338(8765):464-468.
- Corrao G, Rubbiati L, Bagnardi V, Zambon A, et al. Alcohol and coronary heart disease: a meta-analysis. *Addiction*. 2000;95(10):1505-1523.
- Hvidtfeldt UA, Tolstrup JS, Jakobsen MU, Heitmann BL, et al. Alcohol intake and risk of coronary heart disease in younger, middle-aged, and older adults. *Circulation*. 2010;121(14):1589-1597.
- Tolstrup JS, Grønbaek M, Nordestgaard BG. Alcohol intake, myocardial infarction, biochemical risk factors, and alcohol dehydrogenase genotypes. *Circ Cardiovasc Genet*. 2009;2(5):507-514.
- Hines LM, Stampfer MJ, Ma J, Gaziano JM, et al. Genetic variation in alcohol dehydrogenase and the beneficial effect of moderate alcohol consumption on myocardial infarction. *N Engl J Med*. 2001;344(8):549-555.
- Ruidavets JB, Ducimetière P, Evans A, Montaye M, et al. Patterns of alcohol consumption and ischaemic heart disease in culturally divergent countries: the Prospective Epidemiological Study of Myocardial Infarction (PRIME). *BMJ*. 2010;341:c6077.
- Mukamal KJ, Maclure M, Muller JE, Mittleman MA. Binge drinking and mortality after acute myocardial infarction. *Circulation*. 2005;112(25):3839-3845.
- De Oliveira E Silva ER, Foster D, McGee Harper M, Seidman CE, et al. Alcohol consumption raises HDL cholesterol levels by increasing the transport rate of apolipoproteins A-I and A-II. *Circulation*. 2000;102(19):2347-2352.
- Schäfer C, Parlesak A, Eckoldt J, Bode C, et al. Beyond HDL-cholesterol increase: phospholipid enrichment and shift from HDL3 to HDL2 in alcohol consumers. *J Lipid Res*. 2007;48(7):1550-1558.
- Mukamal KJ, Mackey RH, Kuller LH, Tracy RP, et al. Alcohol consumption and lipoprotein subclasses in older adults. *J Clin Endocrinol Metab*. 2007;92(7):2559-2566.
- Emeson EE, Manaves V, Singer T, et al. Chronic alcohol feeding inhibits atherosclerosis in C57BL/6 hyperlipidemic mice. *Am J Pathol*. 1995;147(6):1749-1758.
- Nurmi K, Virkanen J, Rajamäki K, et al. Ethanol inhibits activation of NLRP3 and AIM2 inflammasomes in human macrophages--a novel anti-inflammatory action of alcohol. *PLoS One*. 2013;8(11):e78537.
- McClelland RL, Bild DE, Burke GL, et al. Alcohol and coronary artery calcium prevalence, incidence, and progression: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Clin Nutr*. 2008;88(6):1593-1601.
- Liu W, Redmond EM, Morrow D, Cullen JP. Differential effects of daily-moderate versus weekend-binge alcohol consumption on atherosclerotic plaque development in mice. *Atherosclerosis*. 2011;219(2):448-454.
- Janszky I, Mukamal KJ, Orth-Gomér K, Romelsjö A, et al. Alcohol consumption and coronary atherosclerosis progression--the Stockholm Female Coronary Risk Angiographic Study. *Atherosclerosis*. 2004;176(2):311-319.
- Mukamal KJ, Jadhav PP, D'Agostino RB, et al. Alcohol consumption and hemostatic factors: analysis of the Framingham Offspring cohort. *Circulation*. 2001;104(12):1367-1373.
- Mukamal KJ, Massaro JM, Ault KA, et al. Alcohol consumption and platelet activation and aggregation among women and men: the Framingham Offspring Study. *Alcohol Clin Exp Res*. 2005;29(10):1906-1912.
- Renaud SC, Beswick AD, Fehily AM, et al. Alcohol and platelet aggregation: the Caerphilly Prospective Heart Disease Study. *Am J Clin Nutr*. 1992;55(5):1012-1017.
- Pace-Asciak CR, Hahn S, Diamandis EP, et al. The red wine phenolics trans-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis: Implications for protection against coronary heart disease. *Clin Chim Acta*. 1995;235(2):207-219.
- Puddey IB, Zilkens RR, Croft KD, et al. Alcohol and endothelial function: a brief review. *Clin Exp Pharmacol Physiol*. 2001;28(12):1020-1024.
- Niccoli G, Altamura L, Fabretti A, et al. Ethanol abolishes ischemic preconditioning in humans. *J Am Coll Cardiol*. 2008;51(3):271-275.
- Gazzieri D, Trevisani M, Tarantini F, et al. Ethanol dilates coronary arteries and increases coronary flow via transient receptor potential vanilloid 1 and calcitonin gene-related peptide. *Cardiovasc Res*. 2006;70(3):589-599.
- Uren NG, Marraccini P, Gistri R, et al. Altered coronary vasodilator reserve and metabolism in myocardium subtended by normal arteries in patients with coronary artery disease. *J Am Coll Cardiol*. 1993;22:650-658.
- Liu MW, Anderson PG, Luo JF, et al. Local delivery of ethanol inhibits intimal hyperplasia in pig coronary arteries after balloon injury. *Circulation*. 1997;96(7):2295-2301.

Competing interests: None declared. Conflict of interests: None declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

25. Niroomand F, Hauer O, Tiefenbacher CP, et al. Influence of alcohol consumption on restenosis rate after percutaneous transluminal coronary angioplasty and stent implantation. *Heart*. 2004;90(10):1189-1193.
26. Mukamal KJ, Girotra S, Mittleman MA. Alcohol consumption, atherosclerotic progression, and prognosis among patients with coronary artery bypass grafts. *Am Heart J*. 2006;151(2):368-372.
27. Miyamae M, Diamond I, Weiner MW, Camacho SA, Figueredo VM. Regular alcohol consumption mimics cardiac preconditioning by protecting against ischemia-reperfusion injury. *Proc Natl Acad Sci U S A*. 1997;94(7):3235-3239.
28. Miyamae M, Kaneda K, Domae N, Figueredo VM. Cardioprotection by regular ethanol consumption: potential mechanisms and clinical application. *Curr Drug Abuse Rev*. 2010;3(1):39-48.
29. Miyamae M, Rodriguez MM, Camacho SA, Diamond I, Mochly-Rosen D, Figueredo VM. Activation of epsilon protein kinase C correlates with a cardioprotective effect of regular ethanol consumption. *Proc Natl Acad Sci U S A*. 1998;95(14):8262-8267.
30. Krenz M, Baines CP, Yang XM, et al. Acute ethanol exposure fails to elicit preconditioning-like protection in situ rabbit hearts because of its continued presence during ischemia. *J Am Coll Cardiol*. 2001;37:601-607.
31. Constant J. Alcohol, ischemic heart disease, and the French paradox. *Coron Artery Dis*. 1997;8(10):645-649.

Competing interests: None declared. Conflict of interests: None declared.
 All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
 All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.