

ORIGINAL ARTICLE

Effects of Wine, Alcohol and Polyphenols on Cardiovascular Disease Risk Factors: Evidences from Human Studies

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Abstract — **Aims:** The aim of this review was to focus on the knowledge of the cardiovascular benefits of moderate alcohol consumption, as well as to analyze the effects of the different types of alcoholic beverages. **Methods:** Systematic revision of human clinical studies and meta-analyses related to moderate alcohol consumption and cardiovascular disease (CVD) from 2000 to 2012. **Results:** Heavy or binge alcohol consumption unquestionably leads to increased morbidity and mortality. Nevertheless, moderate alcohol consumption, especially alcoholic beverages rich in polyphenols, such as wine and beer, seems to confer cardiovascular protective effects in patients with documented CVD and even in healthy subjects. **Conclusions:** In conclusion, wine and beer (but especially red wine) seem to confer greater cardiovascular protection than spirits because of their polyphenolic content. However, caution should be taken when making recommendations related to alcohol consumption.

INTRODUCTION

Cardiovascular disease (CVD) is one of the main causes of death worldwide and is developed by a multifactorial process. Most CVDs are due to atherosclerosis, a degenerative process of the arteries that is induced by oxidative stress and chronic inflammatory status. The risk factors of this disease are smoking, diabetes mellitus, arterial hypertension, abnormalities in serum levels of total cholesterol and its fractions, overweight/obesity, family history of early CVD and physical inactivity, among others.

Although excessive alcohol consumption is unquestionably harmful at several levels, consistent epidemiological evidence has pointed out that moderate alcohol consumption is inversely associated with cardiovascular risk factors and cardiovascular events (Mukamal *et al.*, 2003; Brien *et al.*, 2011; Ronksley *et al.*, 2011). However, after the description of the French Paradox 20 years ago, part of the research was focused on the different effects of wine consumption compared with other alcoholic beverages. The French Paradox reported the low CVD incidence and mortality of the French population despite their high dietary intake of saturated fats. This phenomenon was attributed to wine consumption and not only to alcohol, since plasma HDL-cholesterol (HDLc) concentrations were similar to those reported in other countries with a higher prevalence of CVD (Renaud and de Lorgeril, 1992). Some detractors have observed that rather than by red wine, this paradox could be explained by the lag time between the increase in total serum cholesterol concentration and the full effect of the resulting increase in coronary artery atheroma and risk of death from ischemic heart disease, as the French population had consumed lower animal fats since the last decade prior to the study (Law and Wald, 1999). Other authors believed that not only red wine but also alcohol consumption were responsible for the paradox (Chawla, 2004). Despite this controversy, the French Paradox triggered widespread studies of the effects of red wine components (more concretely polyphenols and

above all, resveratrol) in order to explain this paradox and also led to a distinction of types of alcoholic beverages (with or without phenolic compounds) and opened the debate as to which type of alcoholic beverage is more cardioprotective.

Several *in vitro* and animal models studies have focused on polyphenol cardiovascular actions (Pal *et al.*, 2003; Stocker and O'Halloran, 2004). In this framework, wine and/or beer polyphenols seem to have antioxidant (Vinson *et al.*, 2003), anti-inflammatory (Palmieri *et al.*, 2011), hypotensive (Bhatt *et al.*, 2011) or even anti-platelet aggregation effects (Crescente *et al.*, 2009). Nevertheless, human clinical trials have shown that these potential effects are not always achievable within the context of moderate alcohol consumption as the concentrations of the polyphenolic metabolites that reach the human body are always very low. In addition, caution should be taken when considering epidemiological data, as many potential confounding factors arise and causality cannot be demonstrated, being only achievable with interventional trials. Therefore, the aim of this review was to update the knowledge of the relationship between CVD and moderate consumption of alcoholic beverages with different polyphenol content, through a PUBMED search of human trials on moderate alcohol consumption and CVD from 2000 up to 2012.

PREVENTIVE EFFECTS OF MODERATE ALCOHOL CONSUMPTION ON THE CARDIOVASCULAR SYSTEM

Based on literature data, several cardiovascular protective effects have been associated with moderate alcohol consumption. Moderate alcohol consumption is differently defined by scientific societies from different countries. Part of this controversy is attributable to the fact that different countries consider that an alcoholic drink contains different amounts of alcohol: between 8 g (10 ml) in the UK to 14 g of ethanol (17.5 ml) in the USA, whereas other countries, such as Australia, France, the Nederland or Spain, consider that a

drink contains 10 g of ethanol (12.5 ml). In this context, the US National Institute on Alcohol Abuse and Alcoholism (NIAAA) considers moderate drinking as the consumption of no >56 g (four drinks) on any single day and no >196 g (14 drinks) per week for men and no >42 g (three drinks) on any single day and no >98 g (seven drinks) per week for women or 28 g (two drinks) or 14 g (one drink) a day for men and women, respectively. Despite the differences between countries, this is the most accepted posture. Accordingly, one drink contains 14 g of pure alcohol. Therefore, 12 ounces (330 ml) of regular beer (5% alcohol, ~50 g/l), 5 ounces (125 ml) of wine (12% alcohol, ~120 g/l) or 1.5 ounces (40 ml) of distilled spirits (40% alcohol, ~400 g/l) are ~1 drink. Nevertheless, over the last decades, the definition of moderate alcohol consumption has changed (tending to decrease the amount of alcohol) making comparison of the different clinical trials difficult.

Oxidative status

Several *in vitro* studies regarding polyphenols from wine, beer and vegetables have shown that these compounds exhibit an antioxidant effect, while alcohol itself is known to induce oxidative stress. Therefore, one may ask whether there is a counteracting effect between polyphenols and alcohol. In a clinical trial in which 30 g of alcohol/day was administered to healthy volunteers during 4 weeks in the form of red wine (a polyphenol-rich alcoholic beverage) or gin (a polyphenol-free alcoholic beverage), plasma malondialdehyde (MDA) and superoxide dismutase activity decreased, and lag phase time of low-density lipoprotein (LDL)-particles oxidation increased after red wine, but not after gin consumption (Estruch *et al.*, 2011). Nevertheless, in the same trial a decrease in the rate of LDL oxidation was observed after both red wine and gin, whereas the decrease in the amount of conjugated dienes formed was significant only after the gin period. In another trial with healthy subjects, ethanol (40 g/day) was administered as beer, wine or spirits at the two main meals for 30 days. Ethanol decreased antioxidant and increased lipoperoxidation serum parameters. However, some of these changes appeared to be attenuated when ethanol was consumed as beer or wine (Addolorato *et al.*, 2008). In a trial in which 400 ml/day of red wine consumption was compared with abstinence in healthy volunteers, red wine consumption increased plasma total antioxidant status and decreased plasma glutathione (GSH) and MDA (Micallef *et al.*, 2007). Likewise, 375 ml red wine daily for 4 weeks in healthy volunteers reduced the maximum concentrations of conjugated dienes and thiobarbituric acid-reactive substances (TBARS) in Cu-oxidized plasma LDL (Tsang *et al.*, 2005). In addition, a postprandial reduction of oxidative stress has also been observed after red wine consumption (Covas *et al.*, 2003). In relation to white wine, a 1-month intervention with 375 ml of white wine in healthy men increased paraoxonase 1 and GSH peroxidase, reduced GSH levels and decreased superoxide dismutase activity, oxidation protein products and TBARS concentrations (Rajdl *et al.*, 2007). However, other authors have reported that red wine does not seem to influence lipid peroxidation (Blackhurst and Marais, 2006). Thus, the effects of wine (or beer) consumption on oxidation parameters remain still open.

Inflammation

In a recent meta-analysis (Brien *et al.*, 2011), the association between alcohol consumption and serum concentration of C-reactive protein (CRP), interleukin 6 (IL-6) and tumor necrosis factor- α (TNF- α) was not significant. However, on considering the type of alcoholic beverage, the results differed. In a randomized, crossover clinical trial, we observed that red wine and gin (30 g/day during 4 weeks) decreased IL-1 α , and red wine but not gin reduced plasma CRP in healthy individuals (Estruch *et al.*, 2004), explaining why CRP is not affected when only alcohol is considered. In addition, in another trial in which 15 g/day of alcohol was administered in the form of red wine during 3 weeks in healthy volunteers (Djurovic *et al.*, 2007), no significant effects were found in plasma IL-6. Furthermore, we have also detected that the effects are not the same in high cardiovascular risk subjects, since alcohol (red wine and gin interventions) increased the anti-inflammatory IL-10 and decreased IL-16, and red wine but not gin decreased IL-6 plasma concentrations in high-risk patients (Chiva-Blanch *et al.*, 2012a). Therefore, it is extremely important to consider the type of alcoholic beverage when analyzing the results as well as the population subset in clinical trials and epidemiological studies.

Atherosclerosis

Atherosclerosis is considered a low-grade inflammatory (and oxidative) disease in which the cell and endothelial expression of adhesion molecules and chemokines participate in the recruitment of circulating leukocytes to the vascular endothelium and further migration into subendothelial spaces. In addition to the antioxidant and anti-inflammatory effects of moderate alcohol (or red wine) consumption, there are specific biomarkers of cell adhesion related to atherosclerosis, which are modulated by moderate alcohol or red wine consumption. In healthy volunteers (Estruch *et al.*, 2004), significant reductions of vascular cellular adhesion molecule-1 (VCAM-1), intercellular CAM-1 (ICAM-1), IL-1 α , and very late antigen-4 (VLA-4) lymphocyte expression and lymphocyte function-associated antigen-1 (LFA-1), macrophage-1 antigen (Mac-1), VLA-4 and monocyte chemoattractant protein-1 (MCP-1) monocyte expression were observed after red wine, but not after gin intake. In another human trial performed by Djurovic *et al.* (2007) in healthy volunteers, no significant changes were observed in VCAM-1 and ICAM-1 plasma concentrations after 15 g/day of alcohol in the form of red wine. Again, the effects in a high cardiovascular risk population were different but protective (Chiva-Blanch *et al.*, 2012a), as red wine polyphenols but not gin decreased serum E-selectin, and ICAM-1, whereas alcohol from red wine and gin decreased the plasma macrophage-derived chemokine concentration. In addition, phenolic compounds of red wine, as well as alcohol, decreased CD40 antigen, CD40 ligand, MCP-1 and VCAM-1. Furthermore, light to moderate alcohol consumption *in vivo* was associated with lower atherosclerotic burden in the proximal aortic arch in a population-based study that included 464 subjects (Kohsaka *et al.*, 2011). On revising these results, it seems plausible to affirm that moderate alcohol consumption has a protective effect on atherosclerosis in many targets, but the mechanism of action is dose-dependent

and differs according to health status and the kind of beverage.

Lipid profile

The most well-described effect of moderate alcohol consumption is the rise in HDLc concentrations, and until recently, this was thought to be the main cardiovascular protector effect of moderate alcohol consumption. It seems unquestionable that moderate alcohol consumption (whatever the alcoholic beverage consumed) elevates HDLc in a dose-dependent manner (Brien *et al.*, 2011), even in the hypertensive population (Park and Kim, 2012). Nevertheless, the current opinion is that HDLc is not one of the most important mechanisms by which ethanol exerts its cardioprotective function (Magnus *et al.*, 2011). Indeed, the effects on triglycerides, LDLc, VLDLc, apolipoproteins (Apo) and lipoprotein(a) are still under debate. There is a limitation in analyzing these effects because the different studies have different lengths and some of the parameters studied have a longer half-life time than that analyzed, especially in cross-sectional studies. In 2014 hypertensive men, a higher consumption of alcohol was associated with a decreased risk of low HDLc and a J-shaped increase in the risk of presenting high triglycerides, with the lowest triglyceride levels being found in moderate alcohol consumers (Park and Kim, 2012). A recent meta-analysis (Brien *et al.*, 2011) concluded that moderate alcohol consumption significantly increases ApoA-I and does not significantly change total cholesterol, LDLc, triglycerides or lipoprotein(a) values.

If the differential effects of different kinds of beverages are pinpointed, ethanol itself seems to decrease plasma ApoB, whereas red wine (but not gin) increases ApoA-I and II in healthy volunteers (Avellone *et al.*, 2006; Estruch *et al.*, 2011). In a high cardiovascular risk population, ethanol itself seems to increase HDLc as well as ApoA-I and II (Chiva-Blanch *et al.*, 2012b). Regarding lipoprotein(a), few studies have been carried out and the results are inconclusive, requiring further research. No changes in lipoprotein(a) were observed in a study using red wine for 4 weeks in healthy subjects (Avellone *et al.*, 2006), whereas in two 4-week clinical intervention trials performed in healthy men (Estruch *et al.*, 2011) and in a high-risk population (Chiva-Blanch *et al.*, 2012b), red wine but not gin was associated with reduced lipoprotein(a). Similarly, in another study lipoprotein(a) decreased after 10 days of red but not white wine intervention (Sharpe *et al.*, 1995).

Glucose metabolism

Two meta-analyses of 20 and 15 cohort studies, respectively (Koppes *et al.*, 2005; Baliunas *et al.*, 2009), pointed out that alcohol intake is protective against type-2 diabetes (T2D) when consumed in moderate amounts compared with lifetime abstainers or excessive consumers (>60 g/day in men and >50 g/day in women), showing a U-shaped relationship. This beneficial effect has been associated with improved insulin sensitivity (IS) and decreased serum insulin concentrations. Along this line, in the Nurses' Health Study, higher alcohol intake (≥ 15 g/day) was shown to attenuate the positive association between glycemic load and the incidence of T2D (Mekary *et al.*, 2011).

Otherwise, the results of the few prior clinical studies examining the effects of moderate alcohol consumption on IS have been inconsistent. Two studies performed in healthy men reported no significant improvement in IS after 17 days of whisky (Sierksma *et al.*, 2004) or 4 weeks of red wine or dealcoholized red wine (Beulens *et al.*, 2006). Similarly, short-term consumption of red wine in post-menopausal women (Naissides *et al.*, 2006) had no benefit on IS. In contrast, a study that compared the effects of red wine and vodka for 8 weeks in 20 insulin-resistant individuals found little improvement of IS with any beverage (Kim *et al.*, 2009). Napoli *et al.*, 2005 also reported a 43% improvement in IS after 2 weeks of red wine intake in 9 diabetic men. In another trial in 51 post-menopausal women (Davies *et al.*, 2002), consumption of 30 g/day alcohol (ethanol in orange juice) was associated with a 7.2% improvement in IS compared with 0 g/day, while 15 g/day had no effect. Finally, in a recent randomized clinical trial performed in high-risk men, moderate dealcoholized red wine and red wine, but not gin consumption, improved IS (Chiva-Blanch *et al.*, 2012b). Thus, although not all, several randomized clinical trials have observed a significant protective effect of moderate alcohol intake, mainly in the form of red wine, against insulin resistance.

Endothelial function and blood pressure

Although it is well documented that heavy alcohol consumption is associated with hypertension, moderate alcohol consumption seems to exert the opposite effect, similar to the pattern observed for CVD (Bau *et al.*, 2007). However, the effects of moderate alcohol consumption on endothelial function remain controversial. Moderate alcohol consumption increases the release of nitric oxide from the endothelium, while heavy or chronic alcohol intake decreases the bioavailability of nitric oxide (Toda and Ayajiki, 2010). In a multi-ethnic cross-sectional study, those who drank between >1 drink/month and 2 drinks/day were more likely to have a higher flow-mediated dilation (FMD) than non-drinkers and those who drank >2 drinks/day (Suzuki *et al.*, 2009), independently of the type of alcoholic beverage consumed. In a randomized trial, healthy young individuals received 30 g of alcohol as red wine, white wine, beer, whisky or water. Red wine showed a significant beneficial effect on endothelial function 1–4 h after ingestion, while beer and white wine had a borderline effect on vascular endothelium 1 h after-intake, and whisky exerted no effects (Tousoulis *et al.*, 2008). In a crossover clinical trial of patients with coronary artery disease, 4 ml/kg body weight of either red and white wine increased FMD at 360 min post-intake (Whelan *et al.*, 2004). Finally, in 22 healthy young males, red wine and dealcoholized red wine with ethanol were administered, but only the red wine intervention increased the coronary flow velocity reserve (CFR) in response to adenosine, which is reduced in early stages of atherosclerosis (Kiviniemi *et al.*, 2007). Other ethanol-containing beverages including vodka and white wine showed no such effect. These authors also observed that acute and high consumption of either red wine or dealcoholized red wine decreased plasma endothelin-1 concentration (Kiviniemi *et al.*, 2010). Therefore, it seems that the beneficial effects of moderate alcohol consumption on endothelial function do not persist >4–6 h.

Regarding blood pressure (BP), the results of a recent meta-analysis have pointed out that alcohol consumption increases the risk of hypertension in a dose-dependant manner (Taylor *et al.*, 2009). In addition, a reduction of alcohol consumption in heavy drinkers leads to a decrease in BP in a dose–response relationship (Xin *et al.*, 2001). Furthermore, drinking outside meals seems to increase the risk of hypertension independently of the amount of alcohol consumed (Stranges *et al.*, 2004). However, moderate doses of alcohol seem to not affect or reduce BP. In fact, a J-shaped association between alcohol consumption and BP changes in a normotensive population has been found, with a threshold effect at 18 ml of daily ethanol consumption (Okubo *et al.*, 2001). Possibly, the explanation for the different effects of alcoholic beverages on BP may be the difference in their polyphenol content. Thus, in a recent study in high cardiovascular risk subjects, moderate alcohol consumption, in the form of gin or red wine, did not affect BP, whereas dealcoholized red wine (mainly polyphenols) decreased BP (Chiva-Blanch *et al.*, 2012c). Therefore, it seems that moderate alcohol consumption does not affect BP, as shown by the results of clinical trials and meta-analyses in which no consistent association between beer, wine or liquor consumption with the risk of hypertension was observed (Stranges *et al.*, 2004; Frisoli *et al.*, 2011).

Thrombosis/fibrinolysis system

As a constant bilateral pattern of the effects of alcohol consumption on CVD, there is consistent association between heavy alcohol consumption and a lower fibrinolytic capacity, a more procoagulant state and a higher blood viscosity (Toth *et al.*, 2012), whereas moderate alcohol consumption is consistently associated with a decreased procoagulant state (by lowering several coagulation factors) and blood viscosity, as well as with a higher fibrinolytic capacity. In healthy individuals, the plasminogen activator inhibitor-1/plasminogen activator (PAI-1/tPA) ratio remained unaffected after acute red wine consumption, being increased after beer intake. Acute alcohol consumption increased the PAI-1/tPA ratio, an effect not observed after red wine, suggesting that substances other than alcohol contained in red wine, but not in beer, may depress the effect of acute alcohol consumption on the overall fibrinolytic activity in these subjects (Tousoulis *et al.*, 2008). In another randomized clinical trial, also performed in healthy individuals, plasma fibrinogen levels decreased after red wine and gin consumption, suggesting that this effect is due to ethanol contained in alcoholic beverages (Estruch *et al.*, 2011). In a large-population case-control study in patients with a first venous thrombosis (Pomp *et al.*, 2008) compared with abstainers, alcohol consumption (2–4 drinks/day) was associated with a reduced risk of venous thrombosis and lower fibrinogen levels. Therefore, the anticoagulant effect of moderate alcohol consumption seems to be exerted in healthy individuals as well as in patients with a pro-coagulation profile.

On the other hand, a meta-analysis of 122 studies observed that consumption of less than 12 g/day (<1 drink/day) in comparison with abstainers was significantly associated with a decreased relative risk of total stroke. This meta-analysis also observed a J-shaped association between the risk of ischemic stroke and alcohol consumption (with

the lower risk again at 12 g alcohol/day) as well as a linear relationship between increased alcohol consumption and the risk of hemorrhagic stroke (Reynolds *et al.*, 2003).

Secondary prevention of cardiovascular disease

As explained in the previous sections, moderate alcohol consumption confers cardioprotective effects in healthy subjects and in high cardiovascular-risk patients. However, one question arises from this assertion: are these beneficial effects also applicable to patients with a previous cardiovascular event? Except in individual situations in which alcohol could interfere with multiple-drug therapy and should, therefore, be avoided, some studies have also reported beneficial effects of moderate alcohol consumption in this population. In a clinical trial in patients hospitalized following a cardiovascular event, moderate red wine consumption showed some benefits on various blood parameters of lipid and oxidative status, decreasing plasma total and LDLc concentrations and increasing erythrocyte membrane fluidity (Rifler *et al.*, 2011). A meta-analysis of the effects of alcohol consumption in patients with a documented cardiovascular event concluded that light to moderate alcohol consumption (5–25 g/day) was significantly associated with a lower incidence of secondary cardiovascular and all-cause mortality, but an association was found between long-term moderate alcohol consumption and the development of atrial fibrillation, and therefore, subjects with atrial fibrillation should avoid alcohol consumption (Costanzo *et al.*, 2010).

Gender-related differences

When advising the general population about moderate alcohol consumption, the differences in gender-related alcohol metabolism must be taken into account. The general consensus is that moderate alcohol consumption is less than 30 g alcohol/day (two drinks) and 15 g alcohol/day (one drink) for men and women, respectively. These differences have been highlighted in clinical trials and meta-analyses, in which the protective effects observed were higher in men than in women (Di Castelnuovo *et al.*, 2002; Taylor *et al.*, 2009), and these protective effects disappeared at lower doses in women than in men (Di Castelnuovo *et al.*, 2006) except in the case of the risk of venous thrombosis, in which women seem to benefit more from moderate alcohol consumption (Pomp *et al.*, 2008). In parallel, a recent cross-sectional study observed a negative association between alcohol consumption and LDL concentration in young women but a positive association in older men (Whitfield *et al.*, 2012). Nevertheless, other studies have shown similar beneficial effects of moderate drinking in both genders (Mukamal *et al.*, 2005).

In addition to the differences in the effects between genders, ethnic differences in alcohol metabolism should also be taken into account, thereby modifying the beneficial effects derived from moderate alcohol consumption (Bau *et al.*, 2007).

Furthermore, the effects of alcohol at different ages are also different, as seen in the case of LDL. It seems that post-menopausal women and adult men have the greatest cardiovascular protection from moderate alcohol consumption. Pre-menopausal women have a lower incidence of CVD, and therefore, the effects of moderate alcohol consumption might

be lower (Di Castelnuovo *et al.*, 2006). In addition, teenagers and young adults tend to have unhealthier drinking patterns such as binge drinking (defined as 3–5 drinks within 2 h), which is unquestionably harmful (Di Minno *et al.*, 2011).

WINE, BEER AND CVD

The effects of moderate consumption of different alcoholic beverages on the cardiovascular system are still controversial and are summarized in Table 1. Most of the epidemiological studies correlating moderate alcohol consumption with cardioprotector effects do not take into account the type of beverage consumed. Furthermore, the scientific evidence of these studies is lower than that of interventional trials. Although interventional clinical trials regarding alcohol consumption must contemplate several ethical considerations and the length of these studies is limited because of the personal difficulties to accomplish the interventions, well-designed randomized clinical trials are required to assess the differences in effects of the different alcoholic beverages on the cardiovascular system, always within the context of moderate consumption.

The beneficial effects of red wine on the cardiovascular system are summarized in Fig. 1, and seem to be greater than other alcoholic beverages, probably because of its high phenolic content. A meta-analysis analyzing 23 studies of the cardiovascular effects of wine and 22 studies of the cardiovascular effects of beer (Di Castelnuovo *et al.*, 2002) observed an inverse association between moderate wine consumption and vascular risk. This meta-analysis indicated an

Table 1. Effects of different types of alcoholic beverages on the cardiovascular system

	Alcoholic beverage		
	Red wine	Beer	Liquors
Endpoints			
Cardiovascular mortality	++	+	+
All-cases mortality	++	+	+
Cardiovascular events	+	+	+
Risk factors			
Diabetes mellitus			
Insulin sensitivity	++	+	+
Blood pressure			
Anti-hypertensive effect	±	±	±
Lipid profile			
HDL—cholesterol	++	++	++
Apolipoprotein-AI	++	±	±
LDL-cholesterol	±	±	±
Apolipoprotein-B	+	+	+
Triglycerides	±	±	±
Lipoprotein(a)	+	±	±
Hemostasis			
Platelet aggregation	+	+	+
Coagulation	+	+	+
Endothelial function			
Nitric oxide	+	+	+
FMD dilation	++	+	+
Mechanisms			
Oxidative stress	++	+	±
Inflammation	++	+	+

++: higher protective effect; +: protective effect; -: negative effect and ±: not clear or no effect.

average significant reduction of 32% of overall vascular risk associated with wine drinking. Wine drinkers show a reduced cardiovascular mortality and a lower incidence of non-fatal vascular end points. Beer drinking was also associated with a reduced risk of vascular events, although to a lesser extent than that observed with wine. A significant inverse association was still apparent when only CHD was considered but, unlike with wine, it did not reach statistical significance when CVD events or cardiovascular mortality were evaluated separately, likely due to the small number of studies available. Furthermore, studies comparing red and white wine highlight the greater effects of red wine on cardiovascular protection. Nevertheless, when analyzing the cardiovascular effects of the different alcoholic beverages, most of the studies have been focused on red wine and, to a much lesser extent, on white wine or beer, or even different spirits (as the composition of whisky is different from that of vodka, for example), as shown in a meta-analysis (Costanzo *et al.*, 2011) analyzing the effects of wine, beer and spirits consumption on the incidence of cardiovascular events. They compared 11 studies investigating the effects of wine, beer and spirits, two studies of the effects of wine and beer, four studies of only the effects of wine and one study of only the effects of beer. They found a similar J-shaped relationship between wine and beer consumption and the incidence of fatal and non-fatal cardiovascular events (with a maximum protection at 25 g alcohol/day). However, this association was not observed when considering liquors or spirits, although this population subset may have drinking patterns different from those observed for wine and beers consumers. Since large well-performed cohort studies such as the Copenhagen City Heart Study found a J-shaped relation between total alcohol intake and all-cause mortality, even in beer and spirit drinkers (Grønbaek *et al.*, 2000), more studies comparing the different cardioprotective effects or intensities derived from the different types of alcoholic beverages are needed.

In summary, ethanol and polyphenolic compounds have protective effects on different targets and, although they do not seem to act synergistically, the sum of the effects of alcohol and polyphenols is greater than the effects of alcohol alone. Therefore, it seems plausible that wine (especially red wine) and possibly beer confer greater cardiovascular benefits than spirits.

TOXIC EFFECTS OF ALCOHOLIC BEVERAGES

Although daily low to moderate alcohol intake is inversely related to CVD, the hormetic behavior of alcohol consumption shows an increased risk of certain cancers, cirrhosis and death from accidents with increasing alcohol consumption (Di Castelnuovo *et al.*, 2010). Three or more drinks per day may increase the risk of heart disease, hypertension, stroke, obesity, hypertriglyceridemia, breast cancer, neurodegeneration, depressive disorders, weakening of bones, suicide and injuries (Saremi and Arora, 2008). Binge drinking, defined by the NIAAA as drinking so much within ~2 h that blood alcohol concentration levels reach 0.08 g/dL (approximately four drinks for women and five for men), and heavy irregular drinking seem to counteract the protector cardiovascular effects of moderate alcohol consumption (Bagnardi *et al.*,

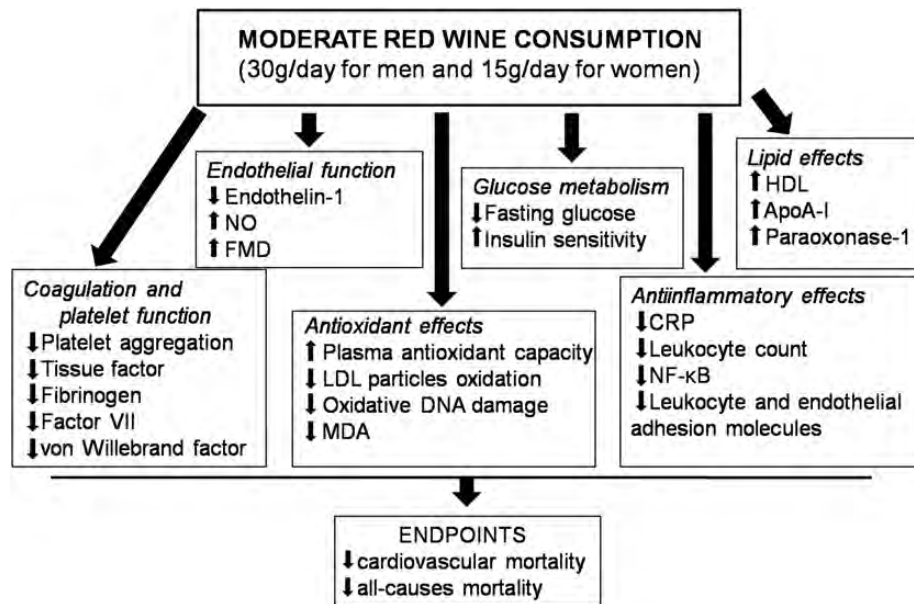


Fig. 1. Cardiovascular effects of moderate red wine consumption. Apo A-1: Apolipoprotein-1; CRP: C-reactive protein; FMD: flow-mediated dilation; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MDA: malon-dialdehyde; NF- κ B: nuclear factor- κ B; NO: nitric oxide; SOD: superoxide dismutase.

2008) by increasing the risk of stroke (Reynolds *et al.*, 2003) and overall mortality (Romelsjö *et al.*, 2012). Wine (or any alcoholic beverage) consumption in any amount is contraindicated for pregnant women, children, patients with liver disease and in combination with certain medications. In addition, regular wine consumption should be used with caution in individuals predisposed to alcoholism, organic diseases, cirrhosis, migraine headaches and allergies.

Finally, there are many reports of contaminants in wines that pose potential health risks, including pesticide and fungicide residues, acetic acid, bacteria, lead, fungi and mycotoxins such as ochratoxin A (Guilford and Pezzuto, 2011), that may also be present in beer (Medina *et al.*, 2005). It is also known that alcoholic beverages may be adulterated or contaminated with methanol (Zhang *et al.*, 2012), a potent neurotoxic.

CONCLUSIONS

Although it is undeniable that heavy or binge alcohol consumption leads to an increase in the risk of all-causes death and makes up an enormous social and economic problem that must be addressed, moderate alcohol consumption, especially in the form of wine and beer, has cardioprotective effects through different mechanisms. Nevertheless, although they are hard to carry out and need careful ethical considerations, more long-term clinical trials are needed to elucidate whether other mechanisms may be involved in these protective effects and which type of alcoholic beverage is more cardioprotective.

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