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REVIEW ARTICLE

# THE MEDITERRANEAN DIET, PART II: RED WINE AND CARDIOVASCULAR DISEASE – MORE FACTS, LESS FANCY

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**ABSTRACT**

*The Western-type diet, rich in saturated fats and low in fish and vegetables, has been associated with a high incidence of cardiovascular disease due to its proinflammatory, pro-oxidative and prothrombotic properties. In contrast, a Mediterranean-type diet (less meat, more fish, nuts, fruits, olive oil and red wine) has been linked to a better health status, including a reduced risk for cardiovascular disease. Wine contains many oxidizable phenolic compounds, and in red wine the concentration of these antioxidants is especially high. These compounds may exert anti-inflammatory activity and confer favorable effects on lipoprotein oxidation, platelet aggregation and vasodilatation. Cardioprotective effects have been demonstrated in numerous experimental and human studies, but controversy still exists on the type of alcohol-containing drink and on the specific role of alcohol and wine antioxidants. This review examines the scientific evidence underlying the prevention of cardiovascular disease by red wine.*

## INTRODUCTION

Based on national statistics, Bronte-Stewart (1) observed more than 50 years ago that the prevalence of ischemic heart disease in France was among the lowest in Europe. In 1979, St. Leger et al. (2) reported that in France an inverse relationship existed between coronary heart disease (CHD) mortality and wine consumption. Subsequently, Renaud and de Lorgeril (3) reported in 1992 that the consumption of alcohol (20-30 g/day) in France was associated with a reduction in the risk of CHD of at least 40%. This finding conflicted with the fact that the French diet is well known for its high content in saturated fat, a classical risk factor for CHD.

This phenomenon is now known as "the French paradox", which is usually defined as a lower-than-expected CHD mortality rate in a country or region in which the diet has historically been rich in saturated animal fat (4, 5). Interestingly, recent WHOSIS data providing statistics on the incidence of cardiovascular disease (CVD) still show that France has the lowest percentage of deaths due to cardiovascular disease of all European countries (see, e.g., www.ehnheart.org).

There is epidemiological evidence confirming that mild to moderate intake of alcohol (ethanol) may have a beneficial effect on cardiac health. Regular mild to moderate consumption of alcohol-containing beverages has been associated with a low risk for CVD compared with heavy drinking or abstinence. In particular, this benefit has been associated with the consumption of red wine (3) and the hypothesis is supported by experimental evidence and studies in humans (6). The biochemical actions that may play a role in the protective effect of red wine include antithrombotic, anti-inflammatory and antioxidant mechanisms and changes in lipid profile (7), but lifestyle characteristics, dietary components and general eating culture may contribute to the protection against CHD (4).

The aim of the present paper is to review the epidemiological and experimental studies that have investigated this protective effect of alcohol, especially red wine, on the myocardium and the cardiovascular system.

## HUMAN STUDIES

### Studies on alcohol

An excellent paper by Di Castelnuovo et al. (8) reported on a meta-analysis of 34 prospective studies available through a PubMed search up to December 2005 on alcohol dosing and total mortality. On the basis of a total of 1,015,835 men and women and 94,533 deaths, they found a J-shaped relationship between alcohol consumption and total mortality (see Fig. 1). This important publication mentions that the lowest mortality occurred at 6 g/day alcohol (relative risk [RR]: 0.81; 95% confidence interval [CI]: 0.80-0.83) and that lower mortality was observed at up to 4 drinks/day for men and up to 2 drinks/day for women compared to abstinence. Although not based on randomized, controlled trials, their analyses based on adjusted observational studies and adjusted prospective studies provided evidence for a 15-18% reduced risk. Three important large-

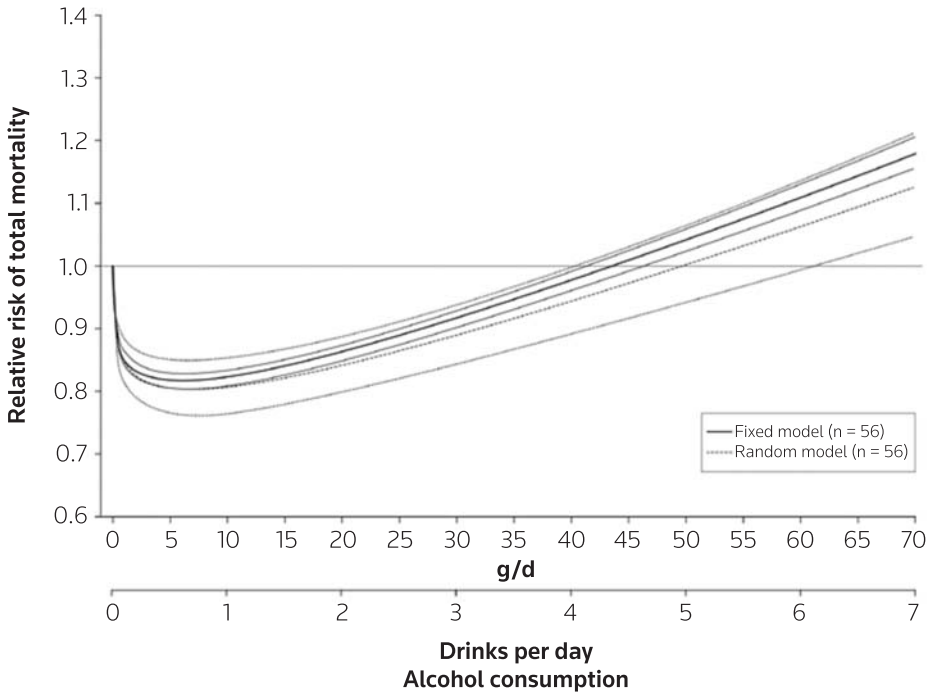



**Figure 1.** Relative risk of total mortality (95% confidence interval) and alcohol intake extracted from 56 curves using fixed- and random-effects models. Published with permission from Di Castelnuovo, A., Costanzo, S., Bagnardi, V., Donati, M.B., Iacoviello, L., de Gaetano, G. *Alcohol dosing and total mortality in men and women: An updated meta-analysis of 34 prospective studies*. Arch Intern Med 2006, 166(22): 2437-45. Copyright © 2006 American Medical Association. All rights reserved.

scale studies used for the above-mentioned meta-analysis will be highlighted below.

Gaziano et al. (9) studied the cause of death in 89,299 reportedly eligible male participants over a period of 5.46 years recruited from the Physician's Health Study. During that period, 3.6% of the participants died, 45.1% (n = 1,450) due to CVD. After adjustment for age, CVD-specific mortality showed a relationship with light to moderate alcohol intake consistent with the L-shaped effect, which was already suggested in a meta-analysis performed in 1993 by Maclure (10). Comparison between drinking and nondrinking participants resulted in a risk reduction in CVD mortality amounting to 32-47%, persisting even in the highest category of more than 2 drinks/day. However, the maximum benefit was reached at 1 drink/day.

Goldberg et al. (11) reported on a prospective study on the health effects of alcohol consumption in middle-aged (n = 2,946; aged 51-64 years) and elderly men (n = 847; aged 65-75 years) free from CHD as part of the Honolulu Heart Program. The study was based on self-reported alcohol consumption determined at baseline and 6 years later, started in 1965 through 1968, and followed the participants until the end of 1988. After adjustment for confounding factors such as smoking, coffee intake and various diseases, an inverse dose–response relationship was observed between alcohol consumption and total mortality in both groups, with a J-shaped pattern. In both age groups there was a trend for lower rates of occurrence of combined fatal and nonfatal CHD events with increasing alcohol consumption. For middle-aged men, it appeared that light drinkers (1-14 mL/day alcohol), modest drinkers (15-39 mL/day alcohol) and heavy drinkers (> 40 mL/day alcohol) had a multivariable-adjusted relative risk for CHD of 0.81, 0.68 and 0.45, respectively, relative to non-drinkers. For elderly men the relative risk was 0.60, 0.28 and 0.72, respectively. This study showed that for men older than roughly 50 years alcohol consumption provided protection against CHD. Importantly, heavy drinkers (> 40 mL/day alcohol) were at increased risk for fatal and nonfatal malignant diseases. The authors concluded that high levels of alcohol consumption appear to be related to an increased risk for diseases of considerable public health importance.

A prospective study by Klatsky et al. (12) on the relationship between alcohol intake and mortality in a large population of 128,934 adults over 7 years demonstrated that light drinkers consuming 1-2 drinks/day have a relative risk for CHD of 0.7 (95% CI: 0.6-0.9) compared with lifelong non-drinkers, independent of the baseline risk. The greatest reduction was observed in drinkers over 50 years of age. In contrast, people under 50 years of age consuming 6 or more drinks/day showed a relative risk for death from all causes of 1.9 (95% CI: 1.2-2.9) compared to lifelong non-drinkers. This increased risk was more pronounced for women than for men.

Cohort studies performed in the past few years have consistently shown that moderate alcohol use is associated with a lower risk for CHD and CVD compared to heavy drinking or abstinence. A PubMed

search over the period January 2007 to April 2009 provided the results of Canadian (13), Australian (14, 15) Japanese (16) and Chinese (17) studies. These recent investigations confirmed that light to moderate alcohol consumption is related to a lower risk for vascular diseases. In contrast, Schooling et al. (18) found that moderate alcohol use had no effect on ischemic heart disease mortality in a population-based case-control study in 54,090 Chinese men and women aged 65 years or over. The authors argued that the lack of replication of the usual protective effect of alcohol may be due to various factors, such as "the wrong type of alcohol" or the fact that "grape wine is rarely drunk".

**Studies on wine**

In an effort to throw light on the French paradox de Lorgeril et al. (4) argued that CHD mortality is about 50% higher in the French Alsace, a typical white wine-drinking region, than in the typical red wine-drinking Mediterranean area. These authors did not pursue the many differences between these two regions in culinary habits and lifestyle, which makes the comparison debatable. However, various prospective studies led to the hypothesis that there is a greater beneficial effect for wine than for beer and spirits on the incidence of ischemic heart disease (19).

A Danish study by Grønbaek et al. (20) in 6,051 men and 7,234 women with 10-12 years of follow-up provided evidence that the risk of cause-specific deaths from cardiovascular and cerebrovascular disease decreases with increasing intake of wine. Relative to the risk of 1.00 for subjects who never drank wine, those who drank 3-5 glasses of wine/day showed a risk of death of 0.51 (95% CI: 0.32-0.81). A similar intake of spirits implied an increased risk, while beer drinking did not affect mortality.

A study published in 2000 by the same group (21) involving pooled cohort studies reinforced the previous findings. This investigation comprised 13,064 men and 11,459 women 20-98 years of age, and a follow-up of 257,859 person-years was achieved. A total of 13,613 participants drank alcohol, of whom 12,846 (64%) included wine in their intake. A J-shaped relationship was found between both total alcohol intake and wine intake at various levels and death of all causes. Compared with non-drinkers, non-wine-drinkers had a relative risk of death of all causes of 0.66 (95% CI: 0.55-0.77). With regard to CHD, wine drinkers had a significantly lower mortality ($P$ = 0.007). The lowest risk of death was observed for those participants who consumed 8-21 drinks/week (RR: 0.64; 95% CI: 0.48-0.84).

Renaud et al. (22) reported on a French prospective cohort study in which 36,583 middle-aged men from Nancy, France, participated. The subjects had normal electrocardiographic tests and were not taking drugs for CVD risk factors. Mortality from all causes and specific causes was recorded over a period of 13-21 years. After adjustment for confounding factors, it was found that moderate wine drinkers consuming < 60 g/day alcohol (4 drinks) had a lower risk for all-cause mortality, including cardiovascular mortality. For these moderate drinkers, the risk for CVD mortality was 0.76 (95% CI: 0.59-0.97) compared to non-drinkers. By contrast, for non-wine-drinkers the relative risk was 0.85 (95% CI: 0.63-1.15). A lower risk of death from all causes of up to 37% was also recorded for those who drank 2-4 glasses of wine/day.

Another prospective cohort study in 56,926 men and 72,008 women from Northern California undergoing regular health evaluations was performed from 1978 to 1998 (23). The adjusted relative risk of death from all causes compared to non-drinkers was the lowest for those who drank exclusively wine (RR: 0.8; $P < 0.001$), whereas the risk was 1.0 for those who drank exclusively spirits and 1.2 for those who drank exclusively beer. These numbers applied for the category who drank 1-2 drinks/day. Surprisingly, those who drank exclusively wine, but more than 6 glasses/day, showed a relative risk as low as 0.5. The adjusted risk of death from CAD was the lowest (RR: 0.4, $P <$ 0.001) for those who drank exclusively wine, either red or white, in the category of 1-2 glasses/day. At 3-5 glasses/day the relative risk was 0.9 and at 6 or more drinks/day this risk amounted to 0.7. For all drinking categories these numbers were higher for beer and the highest for spirits, up to 1.6 for 6 or more drinks/day.

An interesting Finnish study (24) published in 2007 comprised 2,468 businessmen and executives aged 40-55 years in 1974. Quality of life at old age was assessed in survivors in the year 2000. The researchers were able to track the alcoholic beverage preference during the follow-up of this male cohort from the highest social class. In 2000, those preferring wine had the highest quality of life score. Moreover, wine drinkers had a 34% lower total mortality due to lower cardiovascular mortality (RR: 0.66; 95% CI: 0.45-0.98). The relative risk for those preferring beer was 0.91 (95% CI: 0.68-1.14). The authors mention that they were not able to adjust for personal characteristics or early life differences.

Additional evidence that wine has qualities that improve cardiovascular health comes from human studies with de-alcoholized red wine. A Greek study in 15 male patients with angiographically documented CAD investigated flow-mediated dilatation after consumption of 250 mL of either red wine or de-alcoholized red wine on 2 different days. It was shown that the acute ingestion of de-alcoholized red wine led to greater dilatation than regular red wine of the same type ($P < 0.05$), which was attributed to red wine constituents other than alcohol (25). Interestingly, the positive flow response increased following the ingestion of de-alcoholized red wine, while it decreased after the consumption of regular red wine ($P = 0.006$).

This study confirmed findings by Swedish investigators (26) who measured blood flow and arterial brachial artery dilatation in 12 healthy subjects less than 40 years of age without known cardiovascular risk factors. Flow-mediated dilatation of the brachial artery was considerably higher ($P < 0.05$) after drinking 250 mL of de-alcoholized red wine than after drinking regular red wine or before drinking.

The influence of regular red wine and de-alcoholized red wine on endothelial dysfunction induced by cigarette smoking was evaluated in a double-blind, crossover study in 20 healthy volunteers. It was found that the dysfunction was counterbalanced by simultaneous consumption of either type of wine (27). These results are in line with those obtained in a similar experimental set-up in which both regular red wine and de-alcoholized red wine reduced the rise in systolic blood pressure caused by smoking a cigarette (28).

The human studies mentioned above mostly argue the benefits of red wine beyond the aforementioned benefits of alcohol. The French paradox stems from the use of red wine and not white wine. However, a large prospective cohort study by Klatsky et al. (23) suggested that

there is no difference between red and white wine in this respect. They found almost identical reductions in the risk of death due to cardiovascular diseases, including CAD, in those drinking either red or white wine or "other wines". Also, Mukamal et al. (29) could not detect any influence of the type of wine in their study group of 38,077 male health professionals during 12 years of follow-up. Moreover, these authors state that "uncontrolled confounding may explain the greater benefits attributed to red wine in some studies".

### Wine versus beer or spirits

A literature search on epidemiological data that would establish a clear-cut benefit of wine versus beer or spirits led to no definite conclusion. The study by Mukamal et al. (29) demonstrated that no single type of beverage conferred additional benefit, nor did consumption with or without meals. Likewise, the Leisure World Cohort Study that followed 8,877 women and 5,101 men over a period of 23 years found that those who drank 2 or more drinks/day had a 15% lower risk of death from all causes, which was not limited to any type of alcoholic beverage (30). A Spanish population-based case-control study comprising 244 participants and 1,270 controls showed that drinking up to 20 g of alcohol as wine, beer or spirits significantly reduced the adjusted risk of myocardial infarction (31). In contrast, the aforementioned Finnish study (24) determined a relative risk for cardiovascular death for wine drinkers of 0.66 and for beer drinkers of 0.91. It is also noteworthy that Criqui and Ringel (31) found the strongest and most consistent inverse association of wine ethanol with CHD.

## THE RED WINE HYPOTHESIS

Among others, Flesch et al. (32), Perez-Vizcaino et al. (33) and Booyse et al. (34) emphasize that red wine contains a variety of polyphenols, including resveratrol, which have anti-inflammatory, antioxidant and antiatherogenic actions. To the best of our knowledge, however, no large-scale human studies (notably prospective, double-blind, placebo-controlled studies) have been carried out to evaluate their possible cardioprotective properties. Rather, the beneficial effects "beyond alcohol" rely on results obtained from laboratory experiments, animal studies and small-scale short-term human studies.

### Antioxidant actions

Among the phenolic compounds in red wine, resveratrol (3,4,5-trihydroxystilbene) has been studied extensively for a number of health benefits, including cardioprotection and protection against neurodegeneration, viral infection and cancer development, all attributed to its potent antioxidant properties (35-37).

Ou et al. (38) studied the antioxidant effect of resveratrol using human umbilical vein endothelial cell (HUVEC) cultures. They treated these cells with oxidized low-density lipoprotein (LDL) and measured parameters of endothelial injury such as cytotoxicity, apoptosis, generation of reactive oxygen species (ROS) and cytosolic calcium accumulation. Resveratrol attenuated the harmful effects leading to endothelial dysfunction. Other in vitro experiments by Zhao et al. (39) demonstrated that resveratrol increased viability, attenuated apoptosis and decreased the production of ROS and $Ca^{2+}$ overload. In a mouse model of arsenic trioxide-induced cardiomyopathy it was found that resveratrol significantly attenuated the induced Q-T interval prolongation and cardiomyocyte injury, as measured by apoptotic insult, myofibrillar loss and vacuolization (39). Li et al. (40) undertook a study to determine whether resveratrol could upregulate endogenous antioxidant and phase 2 enzymes. They used cultures of aortic smooth cells and cardiomyocytes and found that resveratrol induced these protective molecules, conferring increased resistance to oxidative and electrophilic cellular stress.

There is overwhelming evidence that the risk of CHD increases with higher levels of oxidized LDL. This proatherogenic lipoprotein is formed by enhanced oxidative stress, whereas in a vicious circle oxidized LDL itself stimulates the formation of vascular oxygen radicals. Different short-term experiments in humans have shown that red wine intake decreases LDL oxidation in vivo (42-44).

A study by Pignatelli et al. (45) assessed the antioxidant activity of red and white wine in 20 healthy subjects randomly allocated to drink 300 mL of red or white wine. Ten other healthy subjects refrained from consuming any alcoholic beverage and served as controls. The researchers determined urinary $PGF_{2\alpha III}$ (a marker for oxidative stress) and plasma levels of polyphenols. A significant decrease in the urinary marker was observed in participants drinking red wine relative to those drinking white wine ($P < 0.001$). Moreover, the subjects on red wine had higher plasma polyphenols than those on white wine ($P < 0.001$) and plasma polyphenols were inversely correlated with $PGF_{2\alpha III}$ ($r = 0.77$; $P < 0.001$). This was interpreted as convincing evidence that red wine has more antioxidant activity than white wine.

### Antithrombotic properties

Coronary artery disease has been associated with platelet aggregation and it has been postulated that red wine polyphenols reduce thrombus formation. Vitseva et al. (46) took a basic approach and coincubated human platelets with seed or skin extracts of purple grapes. This led to marked inhibition of platelet aggregation at pharmacologically relevant concentrations, suggesting a platelet-dependent antithrombotic effect, believed to be protective against cardiovascular events. This supported the earlier findings by De Lange et al. (47), who added unfractionated red wine, a red wine polyphenol extract and alcohol in different concentrations to a standardized quantity of blood platelets 2 min before aggregation was induced by different concentrations of adenosine diphosphate. Their results indicated that alcohol in concentrations of up to 24% did not inhibit platelet aggregation. In contrast, the polyphenolic extract significantly and concentration-dependently inhibited platelet aggregation from concentrations of 45 mg/L or more. Only at very high concentrations was red wine inhibitory, which makes it unlikely that consumption of red wine in moderate amounts would be of clinical relevance. Further research by the same group (48) revealed that concentration-dependent inhibition of platelet aggregation was accompanied by activation of PECAM-1 (platelet endothelial cell adhesion molecule) through the effects of an alcohol-free polyphenolic grape extract.

Animal studies also support the hypothesis that red wine components inhibit platelet aggregation (49-51). One study by De Curtis et al. (52) used normolipidemic rats and rats on a cholesterol-rich diet.

The thrombotic tendency was measured as the occlusion time of an artificial prosthesis inserted in the abdominal aorta. The cholesterol-fed rats had a severalfold increase in lipids and factor VII clotting activity and showed an increased thrombotic tendency and platelet adhesion. Alcohol-free red wine almost completely reversed the prothrombotic effect of the cholesterol-rich diet. The authors concluded that regular consumption of red wine, rather than alcohol, can prevent arterial thrombosis associated with diet-induced hypercholesterolemia, an effect mediated by downregulation of platelet function.

In a similar study, Soulat et al. (53) evaluated, among other things, whether alcohol alone or red wine extract would attenuate the thrombotic response at the site of advanced atherosclerotic lesions in *Apoe*-deficient mice and in wild-type counterparts. They measured blood thrombotic reactivity in a cylindrical perfusion chamber model of experimental thrombosis in which the surface of the ex vivo thrombus could be assessed. Alcohol alone or red wine extract was added to the drinking water of both types of mice for 12 weeks. In the wild-type mice the red wine extract tended to reduce thrombogenicity relative to alcohol, which was on the whole less marked than in the *Apoe*-deficient mice ($P < 0.05$).

### Antiatherosclerotic properties

One of the first studies addressing the effect of red wine on the progression of atherosclerosis was published in 1997 by Hayek et al. (54). For their investigations they used atherosclerotic *Apoe*-deficient mice and divided them into 4 groups of 10 animals each. For a period of 6 weeks the groups received placebo (1.1 % alcohol), catechin or quercetin (see Table I) (50 µg/day/mouse) or red wine (0.5 mL/day/mouse) in the drinking water. None of the additives had an effect on plasma LDL or high-density lipoprotein (HDL) levels. After 6 weeks, atherosclerotic lesions were reduced by 39%, 46% and 48%, respectively, in mice treated with catechin, quercetin and red wine in comparison with placebo-treated mice. In addition, it was found that LDL had a reduced susceptibility to oxidation. Already after 2 weeks of consumption of additives, LDL isolated from the treated groups was found to be 39%, 48% and 44% less oxidized, respectively, in comparison to the placebo group.

A similar study in a hypercholesterolemic rabbit model on dietary cholesterol challenge (55) found that de-alcoholized red wine, regular red wine or resveratrol added to the drinking water for 12 weeks caused a significant reduction in size, density and mean area of atherosclerotic plaques relative to animals on control diet. The lipid levels were not affected. These findings provided evidence that resveratrol, red wine or de-alcoholized red wine improves endothelial function in these hypercholesterolemic animals; plasma levels of endothelin-1 (ET-1) decreased significantly, in parallel with a significant elevation in nitric oxide (NO) levels, compared to rabbits on a control diet (56).

Lefèvre et al. (57) studied the effect of red wine on blood flow recovery in hindleg ischemia in hypercholesterolemic *Apoe*-deficient mice. They showed that the consumption of red wine (mimicking 2 glasses/day in humans) improved blood flow recovery by 32%. The intake of red wine also reduced oxidative stress and increased the capillary density by 46%. The ischemia-induced neovascularization coincided with an increase of 60% in endothelial progenitor cells. It is noteworthy that these experiments were carried out using a cabernet sauvignon from the French Languedoc-Roussillon area, a wine that contains a relatively high concentration (4-6 mg/L) of resveratrol, the average concentration being 1.6 mg/L, which equals about 0.2 mg/glass.

The importance of wine polyphenols was also studied by Auger et al. (58), who evaluated the prevention of early atherosclerosis in hamsters fed an atherogenic diet for 12 weeks. They found a reduction of 89% in aorta fatty streaks in animals taking red wine in comparison with controls. Also, 12% alcohol decreased the fatty streak area, although to a lesser degree (58%).

## ASPECTS OF MECHANISTIC ACTIONS OF RED WINE

Polyphenols are known to modulate the nuclear factor NF-kappa-B (NF-κB) pathway. One strategy to prevent and treat inflammatory diseases is to inhibit this pathway, and dietary polyphenols may act at multiple steps of the signal transduction process (59). Opie and Lecour (6) indicated that resveratrol is the most extensively studied polyphenolic constituent of red wine and has major beneficial actions on LDL oxidation, thrombogenicity, ischemia and vascular tone. Also, resveratrol reduces proinflammatory cytokine expression by inhibition of TNF-α-activated NF-κB signaling. This leads to reduced biosynthesis of prostaglandins and reduced activity of cyclooxygenase-2 (COX-2) (60). Not surprisingly, the antioxidant activity of resveratrol increases the oxy resistance of LDL (61, 62).

Recent research has revealed part of the mechanism by which resveratrol attenuates platelet aggregation. Yang et al. (63) found that this polyphenol interferes with surface platelet P-selectin expression induced by the thromboxane antagonist U-46619 in a concentration-dependent manner through a reduction in the activity of phospholipase C β (PLCβ) of platelets. Protein kinase C (PKC) family members are activated through the same signal transduction pathway as PLC. Indeed, in a different experiment the same research group discovered that resveratrol inhibits the activity of PKC in the membrane fraction of platelets, suggesting that this biochemical pathway may decrease thrombus formation (64).

In a human study, Gresele et al. (65) assessed the effect of resveratrol at concentrations attainable after moderate wine intake during 15 days by 20 healthy volunteers (300 mL/day). After wine consumption, the concentration of plasma resveratrol and platelet NO production increased significantly. Subsequent in vitro experiments with resveratrol (at similar concentrations detected in plasma after wine intake) incubated with washed activated platelets revealed a beneficial effect on the stimulation of vasodilatation by, among other things, enhanced activity of platelet NO synthase (NOS) and endothelial NOS, reduced production of ROS and a blunted proinflammatory pathway linked to p38 mitogen-activated protein kinase (MAP kinase p38). These phenomena are in favor of endothelium-dependent vasodilatation, the degree of vascular function being a predictor of cardiovascular health (66).

In a clinically relevant setting of rats exposed to cigarette smoke and smoke extracts, Csiszar et al. (67) were able to attenuate the increased production of ROS in arteries with resveratrol. Smoking-induced upregulation of inflammatory markers such as ICAM-1, inducible NOS, IL-6 and TNF-α in rat arteries was abrogated by resveratrol treatment. In addition, it was observed that resveratrol

treatment protected aortic endothelial cells against apoptosis induced by cigarette smoke. This effect was in line with previous findings which demonstrated that resveratrol exerts vasoprotective effects by protecting cultured aortic segments and/or endothelial cells against increases in $H_2O_2$ levels and $H_2O_2$-mediated apoptotic cell death (68).

Further evidence for the action of resveratrol on the vascular system emerged from experiments by Inanaga et al. (69). They hypothesized that this molecule may attenuate the vascular inflammatory response induced by agiotensin II. Their study in mice showed that resveratrol significantly attenuated IL-6 mRNA expression induced by angiotensin II. Also, IL-6 protein in the supernatant of vascular smooth muscle cells was attenuated, coinciding with suppressed IL-6 gene promoter activity. Furthermore, resveratrol may inhibit the renin–angiotensin system and suppress the expression of the angiotensin type II type receptor in the mouse aorta, blunting angiotensin II-induced hypertension (70). Interestingly, resveratrol is known to activate the sirtuin (*SIRT1*) gene linked to longevity. Exposure of embryonic rat heart-derived cells to hypoxia induced apoptotic cell death, whereas resveratrol decreased this apoptotic process. This effect can be reversed by *SIRT1* inhibition, which suggests that resveratrol may have the potential to prolong the life of myocytes (71).

## OTHER CARDIOPROTECTIVE AGENTS IN RED WINE

In addition to resveratrol, red wine contains other potentially active ingredients (Table I), including the flavonoids quercetin and catechin, although resveratrol (a nonflavonoid) remains the best studied. In this context, an interesting article by Corder et al. (72) mentioned a polyphenol subgroup that may improve vasodilatory reactivity. They observed that in areas in France where people lived relatively long, local wines (such as the Maderan wine) contained higher amounts of procyanidins and proanthocyanidins. The authors showed that these oligomeric compounds reduce the production of the vasoconstrictor endothelin. However, red wine is a complex fluid in which more than 500 compounds have been found, only a few of which have been explored (73, 74).

Nutritional flavonoids are found in fruits, vegetables and berries, and a Finnish study by Knekt et al. (75) comprising 5,133 men and women aged 30-69 years determined that participants with low intakes of these ingredients had a higher risk of coronary disease. A subsequent study on the total dietary intakes of 10,054 men and women for 1 year revealed that persons with higher quercetin intakes had lower mortality from ischemic heart disease (76). Likewise, an analysis on flavonoid intake in 4,807 subjects (the "Rotterdam Study") demonstrated that increased intake of flavonoids contributes to the primary prevention of ischemic heart disease (77). More recently, flavonoid intake and cardiovascular disease mortality were investigated in a prospective manner in postmenopausal women. The study comprised 34,489 women and the intake of total flavonoids was registered and 7 subclasses were categorized into quintiles. After 16 years of follow-up, it was found that flavonoid-rich foods (apples, pears, or both, and red wine) reduced the risk of death due to CHD and CVD (78).

Corroborating animal studies have shown that in *APOE*-deficient mice grape powder polyphenols attenuated the development of atherosclerosis by reducing LDL oxidation and cellular uptake of oxidized LDL (79). This and other evidence (45, 80, 81) indicates that, although resveratrol may be an important agent responsible for the cardioprotective effects associated with red wine, it may well be that only a mixture of polyphenols can exert the complete effect.

***Table I.*** *Phenolic substances in wine.*

| |
|---|
| *Nonflavonoids* |
| Hydroxycinnamic acids (e.g., caffeic acids) |
| Benzoic acids (e.g., gallic acids) |
| Stilbenes (e.g., resveratrol) |
| |
| *Flavonoids* |
| Flavan-3-ols (e.g., catechin) |
| Flavonols (e.g., quercetin) |
| Anthocyanins (e.g., malvidin) |

For overview, see, e.g., Ref. 102.

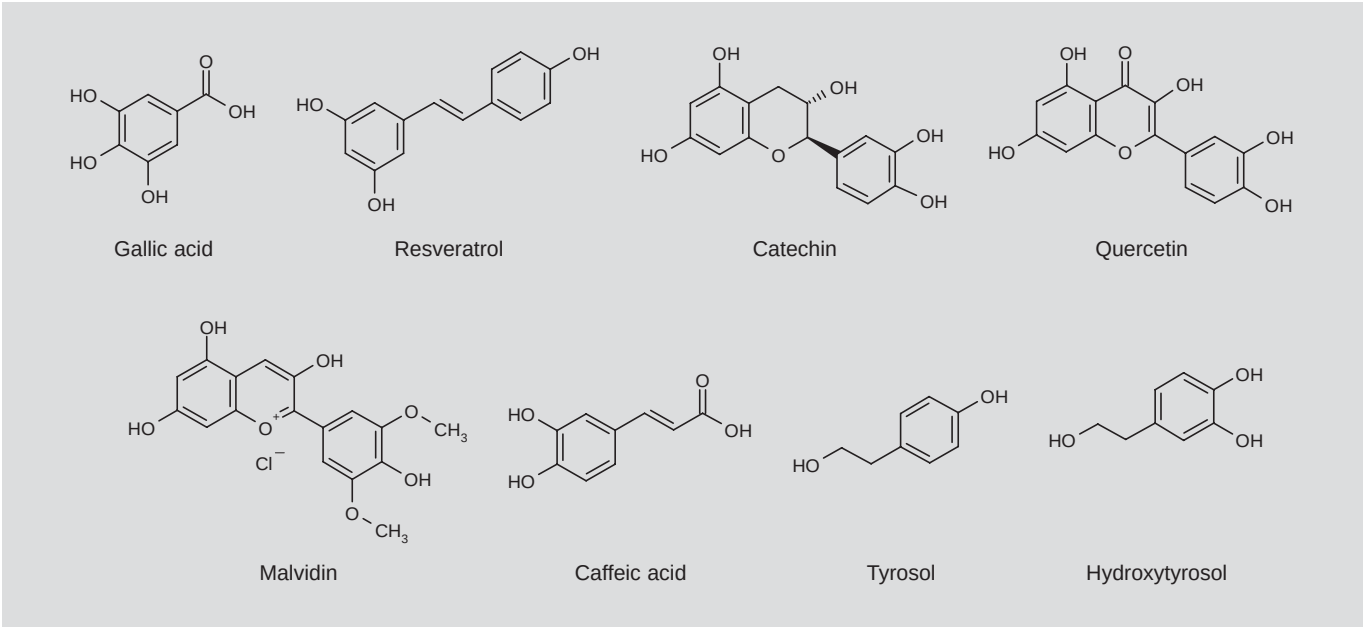
## DISCUSSION AND COMMENTS

The Mediterranean diet is rich in (poly)phenolic compounds present in plants and red wine. Many reports highlight their beneficial effects in various acute and chronic diseases (76, 82). In fact, it has been suggested that the polyphenols found in red wine, especially resveratrol, reduce cardiovascular morbidity and mortality by approximately 30% (83-85). Recently, Klatsky (86) pointed out that light to moderate drinking at a threshold as low as 1-2 drinks/day is inversely related to CAD, ischemic stroke and CAD-related heart failure. This author hypothesized that red wine provides an effect "beyond alcohol", attributable mainly to resveratrol-related antithrombotic and anti-inflammatory actions. It is noteworthy, however, that white wine also contains antioxidants such as caffeic acid, tyrosol and hydroxytyrosol (which are also found in olive oil). These compounds are believed to modulate oxidative stress and inflammatory responses by cytokines such as Il-1$\beta$, IL-6 and TNF-$\alpha$ (87, 88). In fact, rodent experiments reveal that white wine offers similar cardioprotective properties if it is rich in these antioxidants (89).

The impact of light to moderate drinking of red wine in patients with established CVD has also been documented. The Lyon Diet Heart Study (N = 437 male patients) (90), a randomized secondary prevention trial, provided evidence that survivors of recent myocardial infarction had a 59% reduced risk of cardiovascular complications by taking 2 drinks/day. Those who took 4 drinks/day had a 52% reduced risk relative to those who drank no red wine at all. The authors emphasize that despite the small sample size and lack of information on previous drinking habits, these results were obtained in a very homogeneous population.

The same group of authors has recently shown that moderate wine drinking in patients with CHD was associated with higher marine omega-3 plasma concentrations during a high-$\alpha$-linolenic acid (ALA) diet compared to those on a low-ALA diet (91). (Recent experiments in a well-controlled rat model demonstrated that moderate ethanol drinking resulted in a higher omega-3 fatty acid concentration in plasma cells and cell membranes [92], which suggests that this alcohol may also take part in a cardioprotective mechanism.)

To our knowledge, no other studies have been published on the effect of wine drinking in patients suffering from cardiovascular dis-




ease. However, some data are available on the use of (unspecified) alcohol and a very recent publication by Brügger-Andersen et al. (93) reported on the OPTIMAAL trial comprising 5,477 patients with complicated acute myocardial infarction from 7 Western European countries. They stratified their patients according to the frequency of alcohol use. After a follow-up period of 2-7 years, they found a strong positive correlation between moderate alcohol consumption (1-7 drinks/week) and survival, with a 26% lower risk of cardiovascular death relative to non-drinkers ($P < 0.001$).

There has been and still is much debate on the question of whether factors other than wine phenolics contribute to better cardiovascular health among wine drinkers. It seems that wine drinkers have a healthier lifestyle than beer, spirit or mixed drinkers (94). Wine drinkers are more likely to adhere to the Mediterranean diet, are less likely to smoke and likely to have a lower body mass index (95). Moreover, wine drinkers usually have a higher education level and a higher household income, which underlines the socioeconomic aspect of health-related behavior and circumstances (96). In contrast, recent results from the Spanish SUN cohort study suggest that positive cardiovascular effects reported for wine should not be attributed to an overall healthier dietary pattern (97, 98). The participants in this study were graduates from the University of Navarra, which has the advantage of a fairly homogeneous study population but the disadvantage of a less representative sample from a regional area.

Finally, it should be emphasized that the formation of atherosclerotic plaques in humans takes decades, starting from early adulthood on. No study on the effect of red wine on atherogenic disease has been able to follow a cohort in which the starting point is around that age. Another complicating factor is that the alcohol/wine effect cannot be studied in a prospective, double-blind, placebo-controlled manner for obvious reasons. Thus, essential data are still lacking.

There is certainly a causal relationship between the development of atherosclerosis and acute cardiac ischemic disease. However, as the former is a long-term process and the latter a short-term process, these results should be interpreted with caution. Nevertheless, there are solid data for reduced platelet aggregation and the prevention of thrombus formation, which does allow an extrapolation of benefits for red wine on acute vascular disease.

In conclusion, the bulk of published experimental and human studies illustrate the beneficial "beyond alcohol" effect of light to moderate intake of red wine on the risk of CHD and CVD. It would be unrealistic to ignore the well-documented evidence available. Red wine may well modify a risk factor, but is not an approach for treatment. Therefore, it seems safe and most likely beneficial to recommend regular intake of 1-2 glasses of (red) wine in a Mediterranean diet consisting of nuts, fruits, legumes, vegetables, cereal fibers, fish, chicken, goat cheese, olives and olive oil, and to live according to a healthy lifestyle (99-101).

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## DISCLOSURE

The authors state no conflicts of interest.

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