Alcohol and red wine: impact on cardiovascular risk

Michael Böhm¹, Stephan Rosenkranz² and Ulrich Laufs¹

¹Medizinische Universitätsklinik und Poliklinik, Innere Medizin III, Kardiologie/Angiologie, Homburg/Saar and
²Klinik für Innere Medizin III, der Universität zu Köln, Köln, Germany

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Historical background

The potential beneficial effects of wine on health were reported by Paracelsus, Plinius and Galenus. Hippocrates of Kos (459–377 AD) suggested the application of wine as a tranquilizer, analgesic and also used its diuretic properties. In addition, the disinfection of the gastrointestinal mucosa as well as the treatment of wounds are well documented. Caesar also recognized early and were documented by Pharaoh Rameses II, who complained about heavy alcohol consumption in the Egyptian population.

Effects of alcohol and wine on cardiovascular mortality

At present there are numerous epidemiological studies reporting the protective effects of moderate alcohol and wine intake [1–5]. Effects on lipids and haemostasis of different alcoholic beverages have been suggested to play a role [6–9]. A large database has been provided by the Health Professionals Follow-Up Study in 50000 male individuals. The relative risk of developing symptomatic coronary heart disease was reduced by one-quarter following wine alcohol intake of 5–30 g/day [6,10]. ‘The French Paradox’ concerns the phe-
nomenon that coronary mortality is closely correlated with the intake of dairy fat. France and Switzerland fall out of this correlation: they have a rather low coronary mortality, although the dairy fat intake is high (Figure 1) [9,11]. When this association is corrected for the daily wine intake, France and Switzerland significantly approach the regression line of the other countries (Figure 2) [11], suggesting a protective effect.

These observations could be biased by the lifestyle influence that might occur in patients consuming red wine, which is usually more expensive than other beverages. Therefore, wine-consuming individuals might have a better access to medical care and also might have a better management of cardiovascular risk factors.

In the Copenhagen Heart Study examining 6000 male and 7000 female individuals, a 12 year prospective follow-up showed an inverse correlation between the amount of alcohol consumed and coronary risk only for wine drinkers and not for consumers of beer and spirits [12,13]. Similarly, a U-shaped curve for ischaemic stroke was detected. For two drinks a day there was a 40% reduction of the risk for stroke [14]; however, there was an increase in the risk of stroke after heavy alcohol intake [15]. These correlations were challenged by recent observations showing no difference between various types of alcohol with regard to coronary heart disease [16]. Nevertheless, binge drinking appears to increase risk compared with regular moderate consumption of alcoholic beverages [16,17]. In support of the beneficial effects of alcohol are data on genetic variations of alcohol dehydrogenase. In individuals who slowly metabolize alcohol, there was a remarkably reduced risk of myocardial infarction (Figure 3).
was accompanied by significantly increased levels of high-density lipoprotein (HDL) cholesterol in men (Figure 3) [18]. Taken together, epidemiological data support a beneficial effect of alcohol. It is noteworthy that recent studies in patients from France provide evidence that patients with a higher risk of cardiovascular disease benefit more than patients at a low risk [8,9]. In particular, women do not appear to benefit from the consumption of alcohol [2,4,8,12,13,19]. This might be due to the relatively low cardiovascular risk of pre-menopausal women [20], as well as the higher levels of blood alcohol following alcohol consumption [21]. In addition, the threshold for developing alcoholic liver cirrhosis appears to be lower in women [22]. Finally, alcohol consumption correlates with an increased rate of breast cancer [5].

Another problem is the consultation of patients following myocardial infarction concerning the use of alcoholic beverages. Two studies provided evidence that a moderate alcohol intake reduces the rate of coronary complications [7,23]. A relative risk reduction of 0.38 was observed in survivors of myocardial infarction who had an alcohol intake of seven drinks per week. There was no difference between the types of alcoholic beverages consumed.

**Actions of wine and other alcoholic beverages on cardiovascular risk factors**

**Serum lipids**

Regular alcohol intake increases the vasoprotective HDL-fraction [24,25]. Daily intake of 10–20 g alcohol increases HDL levels by ~12% after 4–5 weeks [26]. This effect is brought about by an increase in the transport rate of HDL apolipoprotein Apo-A-I and -II (Figure 4) [24]. On the other hand, excessive alcohol consumption elevates serum triglycerides, thereby potentially increasing vascular risk.

**Haemostasis**

Antithrombotic actions of wine and alcohol intake reduce ADP-stimulated and collagen-stimulated aggregation of platelets, as shown in the Caerphilly Prospective Heart Disease Study in 1600 males aged 49–66 years [8,9]. In vitro studies have provided evidence that the phenolic red wine ingredients trans-resveratrol and quercetin directly inhibit platelet aggregation [27]. In addition, juice from grapes, but not from oranges or grapefruits, can inhibit platelet aggregation [28]. These effects correlate with the concentration of polyphenols in the juices. A reduction of fibrinogen concentrations was reported for regular, moderate alcohol intake [29,30]. Finally, the concentration of tissue plasminogen activator has been observed to closely correlate with the frequency of alcohol intake [31].

**Antioxidative effects of red wine**

Endothelial function can be impaired by increased oxygen radical load. A crucial role to induce this alteration plays the damage imposed on the endothelial layer by oxidized low-density lipoprotein (LDL) [32]. In 10 individuals following a meal enriched by dairy fats, there was a significant increase of oxidative capacity. However, when the meal was taken with red Bordeaux wine, there was a significant increase of plasma antioxidative capacity (Figure 5) [31,33]. It was speculated...
that the concomitant intake of red wine reduces oxidation of LDL, which is well recognized to be crucial in the development of atherosclerosis [32]. Finally, the effects of red wine phenolics are more efficacious than the effect of \( \alpha \)-tocopherol (Figure 6) [33].

Effects on C-reactive protein (CRP)

It is well known that atherosclerosis is accompanied by inflammation. Increased levels of CRP are able to predict complications of cardiovascular disease [34]. In a cross-sectional survey in 1732 men and 1101 women participating in the Pravastatin Inflammation/CRP Evaluation Study, there was a dose-dependent decrease of CRP concentrations by alcohol. This effect was independent of alcohol-related effects on lipids, e.g. HDL increase [35]. The authors of the study concluded that alcohol may attenuate cardiovascular mortality, at least in part, through anti-inflammatory mechanisms [35,36].

Direct effects on vascular function

Endothelium-derived nitric oxide (NO) is an important regulator of vascular tone [36]. Endothelial dysfunction has been suggested to be an early stage of arteriosclerosis [37]. In vitro studies show that wine harvested ‘en barrique’ increases the release of NO in isolated coronary rings of human explanted hearts in vitro [38]. This effect was inhibited by the NO synthase inhibitor L-NMMA. Such effects were not produced by light white or red wines, suggesting that compounds from the oak barrels or phenolic compounds of red wine induce NO-releasing effects. Consistent with these observations, the application of red wine, but not of vodka, produced an increase of coronary endothelial-mediated flow reserve in patients undergoing coronary arterio-
The effects of wine ingredients via endothelial release of NO.

**Antiproliferative effects of wine and alcohol**

‘En barrique’ harvested wines, like Barolo or Chateauneuf du Pape, were able to inhibit platelet-derived growth factor (PDGF) and angiotensin II receptor-mediated growth of isolated cultivated vascular smooth muscle cells (Figure 7) [42]. These effects were shared by tannin acid and quercetin, also occurring at high concentration in red wine. PDGF plays a crucial role in the development of atherosclerosis by stimulating growth and migration of vascular smooth muscle cells [37]. These effects are mediated by transmembranous signalling of receptor tyrosine kinases of the α- or β-PDGF-receptor subtypes [43]. Inhibition of PDGF receptor leads to antiatherosclerotic properties in apo-E-deficient transgenic mice and inhibits neointimal formation in primates [43,44]. Recent experimental data suggest that red wine, but not white wine, is able to inhibit PDGF-receptor signalling [45]. Further studies revealed that flavonoids of the catechin family, which accumulate in red wine during mash fermentation, inhibited β-PDGF receptor phosphorylation and produced a complete inhibition of PDGF-mediated signal transduction events [45]. Of the various ingredients of red wines, catechins were the most potent compounds to induce these potentially physiologically important effects [45].

**Conclusion**

There is evidence that compounds specific for red wine reduce cardiovascular risk in addition to the beneficial effects of ethanol alone. Red wine has been shown to improve surrogate markers of cardiovascular disease, such as NO release in the vessel wall, anti-inflammatory actions, antioxidative effects and inhibitory effects on β-PDGF-receptor phosphorylation. Therefore, the potential beneficial effects of red wine on cardiovascular risk have to be recognized. However, they have to be well balanced against the risk of excessive alcohol consumption to produce liver cirrhosis and neoplastic disease.

Conflict of interest statement. None declared.

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