

Is wine good for your heart? A critical review

N Gall

Vita vinum est—Wine is life
Petronius, *Satyricon*

History

For millennia, physicians used wine for its medicinal qualities.^{1,2} Receipts for wine based medicines dating back 4000 years have been discovered in Egypt and Sumeria. The Greeks used wine extensively. Hippocrates, one of their most respected physicians, in the fifth century BC, used wine for many ailments, diarrhoea, difficult childbirth, and lethargy included. He also used it as a disinfectant, an aid to digestion, a diuretic, and as a carrier for other drugs. He advised white wine for dropsy and red wine for hunger and nourishment. The Romans also recognised wine's qualities. Galen, living around 150 AD, was one of Rome's most famous physicians and the Emperor's wine taster. He used wine as a gladiatorial disinfectant and advised:

"dark and sweet wines produce much blood, while white and light ones produce but little blood, so that the first ones are proper to feed the body and the other ones to get rid of liquid through the urine".

The ancient Jewish book, the Talmud, containing civil and ceremonial law and legend contains this assertion:

"wine is the foremost of all medicines—wherever wine is lacking medicines become necessary".

In the bible wine is also recommended:

"Use a little wine for thy stomach's sake and thine often infirmities." (I Timothy 5.23)

Throughout much of the last two thousand years wine remained an important part of the physician's armamentarium. It was felt to be an important part of a balanced diet, formally documented in the 11th century as the "Salerno regimen". The two disciplines of medicine and oenology became firmly linked with the publication of the first book on wine. It was written in the 14th century by Arnaldus of Villanova, a physician from the University of Montpellier.

During the 19th century, alcohol's toxic and addictive effects became clear and it fell out of favour with the medical profession. More recently, however, there has been a resurgence of interest in wine's potentially favourable effects on the vasculature.³

Epidemiological evidence⁴⁻⁷

It has long been recognised that a nation's fat intake correlates with its coronary mortality.⁸ However France, in particular, does not appear to fit into this pattern, having a lower mortality than expected; the so-called "French paradox".⁹ St Leger *et al*, in their seminal paper,¹⁰ examined countrywide data and showed a strong inverse correlation (particularly marked in France) between alcohol intake, particularly

as wine, and coronary mortality. This was independent of fat intake or other dietary constituents. It has been hypothesised that this might explain, at least in part, the French paradox. Over 60 epidemiological studies have since been published endeavouring to confirm this hypothesis.

ECOLOGICAL STUDIES

Ecological studies, like St Leger's, have examined national statistics, a number confirming his original finding. These studies have also suggested that although alcohol intake correlates inversely with events, wine consumption correlates best. The most significant effect occurs in countries with a high fat intake.⁸

Ecological studies are not without their drawbacks however. The data on alcohol consumption are a population average and therefore do not account for regular as opposed to binge drinking, nor for the proportion of the population drinking. These studies may also be affected by confounders for which it is difficult to control, the major cardiac risk factors, for example. Dietary data does not account for age related variation in intake nor for wastage. Concern has also been expressed about the mortality data used, as there are national variations in death certification.¹¹ In France, for example, deaths from heart failure secondary to, but distant from, a myocardial infarction have been classified as chronic myocarditis in the past. More recently, Law and Wald have proposed an alternative explanation, "the time-lag hypothesis".¹² They propose that cardiovascular mortality more closely relates to past rather than current fat intake and that taking this into account negates alcohol's apparent benefits. They have provoked much debate.¹³⁻¹⁶

Thus, although the ecological data are consistent, due to methodological problems one should exercise caution when making conclusions using these data alone.

CASE-CONTROL STUDIES

Case-control studies examine data retrospectively comparing cases with matched controls. Several have been published examining the association between alcohol and endpoints such as myocardial infarction, coronary death, sudden cardiac death, and angiographically assessed coronary artery atheromatous burden. In general, these studies confirm the inverse association between regular light-to-moderate alcohol intake (one unit weekly to two units daily) and cardiovascular endpoints. There is no definitive evidence from these studies that one beverage is more beneficial.

These studies again have limitations. Participants may not be representative of the general population, in terms of compliance, lifestyle, and frequency and pattern of drinking. Re-

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ported alcohol intake may also be affected by recall bias.

PROSPECTIVE COHORT STUDIES

Most of the data on alcohol's effects come from prospective studies in which a population, with preassessed risk factors, is followed up. End-points are then related to risks. Studies have been performed on almost every continent and among specific populations, including doctors and nurses. They show an association between regular, light-to-moderate alcohol intake and a reduction in coronary death, sudden cardiac death, myocardial infarction, angina, and ischaemic stroke. The relative risk of coronary death is reduced by around 30%, a level which produces significant benefits in absolute terms.⁵ This association appears to be consistent across sexes, races, and particularly in high risk groups.¹⁷

The data are in general consistent, allowing for publication bias. However, many are open to criticism.¹⁸⁻²⁰ The earlier studies did not adequately control for potential confounders including diet, hypertension, lipid concentrations, the presence of diabetes, social class, aspirin use, stress levels, and exercise. Some of these confounders are, however, positively associated with alcohol intake and accounting for them reduces alcohol's apparent benefit. They also did not differentiate lifelong teetotallers from former drinkers who had given up through ill health, possibly relating to their alcohol intake: the "sick-quitter hypothesis"; sick-quitters having greater risk of ischaemic heart disease.¹⁸

Alcohol intake is assessed only on entry to the trial. Self reported intake is often an underestimate and may vary over time, possibly affecting the overall conclusions. There is also variability in the definition of one unit of alcohol between countries which will make comparisons between studies and conclusions therefrom difficult. It is also difficult to account for potentially important differences in drinking patterns. Commentators have drawn attention to the fact that the benefits of alcohol appear to accrue from as little as one unit per week a level at which one might question the biological plausibility.

Later studies have accounted for many of these criticisms and using lifelong teetotallers as the comparison group have reached a similar conclusion. Many lifestyle related criticisms have been refuted in studies using socially uniform populations, for example, doctors.^{21 22}

Several studies have attempted to define whether certain beverages hold particular advantage,²³ data recently meta-analysed by Rimm *et al.*²⁴ In many studies one beverage does better but overall there are as many studies favouring wine, red and white, as there are beer and spirits. In many societies, those who drink wine tend to be better educated, smoke less, take more exercise, have better diets²⁵ and are less likely to binge, potentially biasing the conclusions. Studies showing the superiority of one beverage, in general, were performed in countries where that form of alcohol is drunk regularly, in moderation, with meals by the

majority. In addition, only half of people express a preference for one particular beverage.⁵ Other confounders include the natural variation in beverage; wine for instance will vary with grape variety, terroir, fermentation, blend, and aging.

Overall, even the most vociferous of critics agree that alcohol taken in light-to-moderate quantities, preferably regularly and with meals, appears to favourably affect ischaemic heart disease.²⁰ There is little epidemiological evidence to confirm the original hypothesis that wine is more beneficial.

Potential biological explanations⁷

The pathological basis of ischaemic heart disease is the atherosclerotic plaque.^{26 27} This is a collection of intimal macrophages (foam cells) uncontrollably ingesting oxidised low density lipoprotein (LDL) surrounded by proliferating smooth muscle cells and extracellular matrix. The overlying endothelium is dysfunctional, reducing its ability to produce vasodilatory, antithrombotic molecules such as nitric oxide. It appears that this process starts very early on in life and takes decades to become of clinical significance; the plaque may grow or rupture exposing the highly thrombogenic plaque contents causing distal tissue ischaemia.

Plausible biological mechanisms have been sought, with over 75 studies published so far, again meta-analysed by Rimm *et al.*²⁸ Some investigators have also looked at the effects of wine's non-alcoholic components because of some of the epidemiological data. Interest has centred specifically on flavonoids and resveratrol.

Flavonoids are polyphenolic antioxidants found in many plants and are especially abundant in grape skins.¹ There are many different forms but quercetin is the one most frequently studied. Resveratrol, a tri-hydroxy stilbene, not only has antioxidant actions but also functions as an antifungal agent.¹ In some regions fungal infection, particularly with *Botrytis cinerea*, is cultivated by the vigneron as it increases the grape's sugar levels facilitating the production of the world's greatest sweet wines, for example, Chateau d'Yquem. The vine, however, is not so enamoured by this micro-organism and resveratrol is produced, initially in the leaves. It tracks to the grape skins where it acts. Red wines, which gain their colour from juice skin contact during fermentation, contain by far the largest quantities of these molecules, although champagne and beer contain smaller quantities of flavonoids.

LIPID EFFECTS (FOR A REVIEW SEE FROHLICH²⁹)

Cholesterol is the *sine qua non* of atherogenesis. It is transported to areas of need as LDL. This lipoprotein diffuses into the arterial wall where it may become oxidised eventually leading to foam cell formation. Over recent years the proatherogenic effects of triglycerides and lipoprotein (a) have also become clear. High density lipoprotein (HDL), plasma concentrations of which show an inverse correlation with coronary endpoints, is involved in cholesterol

excretion and therefore has antiatherogenic actions. Alcoholic beverages appear to influence many of these lipoproteins.

High density lipoprotein

Prospective epidemiological studies have suggested that alcohol, in all of its forms, increases plasma HDL. Controlling for concentrations of HDL in mortality studies has suggested that 50% of alcohol's apparently favourable effect resides in its ability to increase HDL³⁰ and specifically the more antiatherogenic subform, HDL₂ and its major apolipoprotein, Apo A1. These studies, however, suffer from confounding by various factors including the limited assessment of alcohol intake, social and dietary factors.

To clarify the issue, acute intervention studies have been performed in primates³¹ and in healthy humans.³² The latter studies are affected by the beverage used, the pattern of intake, the subject's body habitus, and fitness. Liver function and genotypic differences also add complication. Despite these drawbacks the studies have supported the epidemiological data, in that HDL increases within days of starting alcohol intake. Regular, moderate intake is far more effective than binge drinking and no beverage holds an advantage. HDL rises more if the baseline level is lower and the subject is less physically fit.

Rimm has calculated that for every gram of ethanol drunk per day HDL increases by 0.133 mg/dl. The mechanisms underlying this are unclear.

Low density lipoprotein oxidation

It is LDL's oxidation that initiates the process of atherogenesis. Alcohol's involvement in affecting plasma oxidative susceptibility and LDL oxidisability has therefore been examined.

In vitro experiments have shown that while ethanol is a pro-oxidant, alcoholic beverages including red and white wine, beer, and some spirits reduce LDL's oxidisability.³³⁻³⁶ Flavonoids and resveratrol also work. In vivo, however, the pro-oxidant effects of ethanol dominate, both in human and animal experiments. It is perhaps only red wines that contain enough antioxidants to negate this effect.

Many different methods have been used to assess LDL or plasma oxidisability.³⁷ No study has shown that plasma oxidisability relates to cardiovascular endpoints and the use of other antioxidants appear not to afford benefit.³⁸ It is therefore impossible to say whether red wine's in vivo antioxidant action is important.

Lp (a)

A small number of cohort studies and intervention studies on this lipoprotein have been published. Some have found significant decreases,³⁹ although in Rimm's meta-analysis the trend was non-significant. Interestingly many of these studies did not show a reduction in HDL as would be expected, calling into question their validity. It therefore remains to be established whether alcohol acts through this mechanism.

Other lipoproteins⁴⁰

Most studies have shown that alcohol causes a small increase in triglyceride levels but that this is unlikely to negate the other benefits. A reduction in LDL has been noted by some but the importance of this is uncertain.

HAEMATOLOGICAL EFFECTS

A significant proportion of coronary morbidity and mortality occurs through plaque thrombosis. It has been estimated that up to 50% of alcohol's benefits lie in affecting thrombogenesis.

Platelet aggregation (for a review see Renaud and Ruf⁴¹)

Platelet aggregation is pivotal in the pathogenesis of acute coronary syndromes. It is possible to assess platelet aggregation using mediators such as ADP, thrombin, and collagen. Alcohol's effect on these processes has been examined in vitro and in vivo.

In vitro experiments have shown that ethanol inhibits many platelet aggregants, although there is little consistency in which mediators are inhibited. Resveratrol and quercetin share this effect.⁴² In vivo, the effects are more complex. There is an immediate reduction in aggregation to most mediators. It is speculated that this may be due to an increase in platelet membrane fluidity and reduced procoagulant prostanoid production. Interestingly, membrane fluidity is reduced by a diet rich in saturated fat. Soon after there may be a proaggregatory effect, particularly marked in alcoholics and binge drinkers, which may explain some of the increase in acute coronary events after a binge. This rebound phenomenon, which may be related to an increase in plasma lipid peroxides, may not occur in those drinking red wine because of its antioxidant action. Unfortunately comparison of much of the platelet data is impossible because of experimental variation. In addition, all of the data come from short experiments. There is uncertainty therefore as to how long the effects persist. It is also unclear whether the results are applicable to the patient population as human experiments have been performed in young, fit adults in general.

The Lyon Diet Heart Study is a randomised secondary prevention trial performed in patients postmyocardial infarction.⁴³ Subjects were randomised, in addition to usual care, to either a Western or a Mediterranean diet. A dramatic reduction in cardiac events was found. A substudy examined platelet aggregation in the two groups, with no difference found.⁴⁴ No correlation was found between alcohol intake and aggregation in the Mediterranean group. However, in the Western group alcohol intake mirrored improvements in platelet aggregation. It is hypothesised that while the Mediterranean diet, being low in saturated fat, does not promote platelet aggregation, a Western diet does. Alcohol intake may, however, normalise this effect. Experimental data add to this view.⁴⁵

It seems likely therefore that alcohol exerts some of its favourable actions, especially in

those with a poor diet, by this route but it is as yet unproved.

Effects on thrombolytic balance

Other investigators have examined other aspects of the clotting pathways, including the balance between tissue plasminogen activator and its inhibitor, plasminogen activator inhibitor-1. There is some suggestion that alcoholic beverages may tip the balance towards plasmin generation and thrombus dissolution, although this appears short lived. Rimm's meta-analysis demonstrated only a non-significant trend in this regard. Variations in beverage and experimental technique, however, make firm conclusions difficult.

Fibrinogen

Plasma fibrinogen concentrations correlate well with cardiovascular mortality and it appears that alcohol may reduce fibrinogen.⁴⁶

Other effects

It has become clear that nitric oxide plays a pivotal part in normal vessel function, controlling vascular tone on a second-by-second basis with additional antiadhesive and antithrombotic actions. It may therefore be antiatherogenic.²⁷ Many cardiac risk factors adversely affect endothelial nitric oxide production.

In vitro experiments have shown that red wine and its components, including resveratrol, quercetin, and tannin cause endothelial nitric oxide release.^{47, 48} Ethanol and white wine may not however. These results have been reproduced in vivo in humans with purple grape juice.⁴⁹ The clinical relevance of these findings is as yet uncertain.

Alcohol may also inhibit smooth muscle proliferation, a process important in plaque formation.⁵⁰ There are also preliminary data to suggest that insulin resistance, which is a risk factor for ischaemic heart disease, is improved by alcohol.²⁹ Hypertension, though a consequence of alcoholism and binge drinking, does not occur with regular moderate intake.⁵¹

Animal models

In diverse animal models of atherogenesis including the Apo E deficient mouse⁵² and the cholesterol fed rabbit,⁵³ red wine has been shown to reduce the percentage area of aortic surface affected by atheroma and the intima/media ratio, measures of plaque burden and size. Alcohol ingestion may also inhibit neointimal accumulation and cellular concentrations of inflammatory mediators in a rabbit postangioplasty restenosis model.⁵⁴ Whether plaque rupture is affected remains unproved.

Conclusion

There is compelling epidemiological evidence suggesting that regular light-to-moderate alcohol intake is associated with reduced atherosclerotic morbidity and mortality. It is interesting to note that while atherogenesis takes many decades, the beneficial effects of alcohol accrue only in later life. The reasons for this are uncertain but the effects may be a combination of plaque stabilisation, analogous to the effects

of some cholesterol lowering drugs which affect coronary endpoints relatively quickly,⁵⁵ and an antithrombotic effect.

To prove causation requires the correct temporal sequence, an ability to control for confounders, plausible biological explanations, and a consistent and specific effect (ischaemic heart disease appears to be one of the few diseases alcohol benefits).⁵⁶ It is only the relatively small apparent benefit that precludes definitive statements on causation; it is possible that an as yet unrecognised confounding variable could explain the findings. In addition, over 30 years of research has not revealed a definite alternative explanation.

Alcohol, especially in excess, does have detrimental effects, which in many groups outweigh its benefits. Indeed, other interventions, including dietary modification, are far more effective at reducing cardiovascular endpoints. The vast majority of those who abstain do so for a reason, which would preclude advising them to take up alcohol, for example, dislike of the taste/effects, past/family history of alcohol abuse, medical contraindication, or moral/ethical/religious objections. However, one can reassure our patients that regular light-to-moderate alcohol intake, especially in those at risk, whose diet is steadfastly Western will, at the very least, do no harm and almost certainly lead to benefit.

Is there evidence to enable us to advise what to drink? Although the epidemiological evidence suggests not, there are at least theoretical reasons why red wines rich in flavonoids and resveratrol may hold extra benefit.

Flavonoids, being found particularly in grape skins, occur in the highest concentrations in grape varieties with thick skins grown in hot climates.⁵⁷ Cabernet sauvignon based wines from Australia, South America, and the southern Mediterranean are particularly rich sources. Syrah (shiraz) and merlot are good too.

Fungal vine infection is more common in cooler, damper regions and occurs in significant quantities in pinot noir.⁵⁸ Wines from this grape form Burgundy, Sancerre, New Zealand, and the north west United States are particularly rich in resveratrol. Merlot, gamay, syrah, zinfandel, and pinotage wines may also be too.

May I advise: Nuits-St-Georges Premier Cru, Clos des Porrets, 1997, one nocte.

As the French say, *Salut*.

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