Review

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Alcohol and cardiovascular diseases: where do we stand today?

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For centuries, multiple medical risks of heavy alcohol drinking have been evident with simultaneous awareness of a less harmful or sensible drinking limit. The increased risks of heavy drinking, defined as three or more standard-sized drinks per day, are both cardiovascular (CV) and non-CV. The CV risks include the following: (i) alcoholic cardiomyopathy (ACM), (ii) systemic hypertension, (iii) atrial arrhythmias, (iv) haemorrhagic stroke and, probably, ischaemic stroke. By contrast, modern epidemiological studies have shown lower morbidity and mortality amongst light–moderate drinkers, due mostly to a reduced risk of coronary artery disease (CAD), with contributions from ischaemic stroke and heart failure (HF). A low level of alcohol drinking has no clear relation to increased risk of any CV condition, except for haemorrhagic stroke. There is good evidence that supports the existence of mechanisms by which alcohol might protect against CAD, but the mechanisms for other alcohol–CV associations remain unclear. Interrelationships amongst the CV conditions affect the individual alcohol–disease relationships; for example, lower CAD risk in light–moderate drinkers is to a large extent responsible for the reduced HF risk. International comparison data plus the presence of proposed beneficial nonalcohol components in wine (particularly in red wine) suggest that this beverage type might afford extra CAD protection. However, the effect of beverage choice is confounded by a healthier drinking pattern and more favourable risk traits in wine drinkers. Debate persists about methodological and public health issues related to the epidemiology of alcohol-related CV disease.

Keywords: alcohol drinking, cardiovascular disease, epidemiology, risk factors.

Introduction

Few topics in epidemiology have generated as much interest, confusion and controversy in recent decades as the roles played by drinking alcoholic beverages in the aetiology and prognosis of cardiovascular (CV) disorders. Interest is generated largely by the long-standing almost universal enjoyment of these beverages in human societies, despite the obvious risk of medical and social harm from overindulgence. Factors contributing to confusion include disparities between the effects of light–moderate and heavy drinking, differences between individuals in the effects of alcohol, and differences in the relationships with specific CV conditions. Since a previous review in this journal [1], the evidence has steadily grown for both harmful and beneficial alcohol–CV disease associations. The apparent beneficial effect of light–moderate drinking and the role of this in the public health arena remain controversial.

Because the characteristics of the alcohol–CV disease associations differ, several conditions will be considered separately, including alcoholic cardiomyopathy (ACM), systemic hypertension (HTN), arrhythmias, stroke, atherothrombotic disease [especially coronary artery disease (CAD)] and heart failure (HF). Complex interactions exist between alcohol and these disorders and between the disorders; attempts will be made to understand these interactions.

Where we stand today evolves from where we stood yesterday, and tomorrow's views will evolve from those of today. Thus, historical aspects that provide relevant insights will be discussed. Importantly, awareness of past errors may avoid their repetition. Largely because of the disparities already mentioned, clinicians and investigators have been misled by attempts to simplify the alcohol–CV disease relationships with resultant slowing of progress. The author has previously

presented some of the historical material in this review in more detail [2, 3].

Moderate and heavy drinking: definitions

Definitions of 'light–moderate' and 'heavy' drinking are arbitrary and varied. In this review, the amount of drinking above which net harm is usually seen in epidemiological studies is used as the operational definition of heavy drinking. Thus, usual ingestion of at least three or less than three standard-sized drinks per day is termed 'heavy' and 'light–moderate' drinking, respectively. Individual traits, such as sex and age, may lower the upper limit of light–moderate drinking for some persons and raise it for others. As some heavy drinkers allege lighter intake, such systematic 'underestimation' (lying) lowers the apparent threshold for harmful alcohol effects in survey data.

Standard-sized portions of wine, liquor or beer contain approximately the same amount of alcohol. This is fortunate, because alcohol consumption is often considered by individuals in terms of 'drinks' rather than millilitres or grams of alcohol. Thus, it seems best to describe relations between drinking and health in terms of drinks per day or week. When talking with clients, health professionals should always keep in mind the importance of defining the size of drinks.

Alcoholic cardiomyopathy

Definition

There have been various definitions of 'cardiomyopathy'; here, cardiomyopathy denotes heart muscle disease from causes other than disorders of the valves, coronary vessels, lungs and pericardium. Even with these exclusions, the cardiomyopathies comprise a heterogeneous group of disorders, one of which is poisoning of the myocardium due to a chronically large alcohol intake [3, 4].

History

Alcoholic cardiomyopathy dominated the alcohol–CV disease literature for decades. Distinguished 19th and early 20th century European physicians noted that chronic heavy drinking was related to heart disease [2]. In Germany in 1894, Bollinger described the 'Munchener bierherz' as cardiac dilation and hypertrophy amongst Bavarian heavy drinkers of beer. In the UK, Graham Steell stated in 1893: 'not only do I recognize alcoholism as one of the causes of muscle failure of the heart but I find it a comparatively common one'. In *The Study of the Pulse*, William MacKenzie in 1902 described heart failure from alcohol and used the term 'alcoholic heart disease'. In France in 1911, Vaquez strongly supported the view that heavy alcohol intake could cause heart muscle disease.

Two epidemics of acute cardiomyopathy in heavy beer drinkers confused the issue [2, 3]. The first was caused by accidental arsenic contamination of water used to brew beer in Manchester, UK, in 1900. The second was caused by deliberate introduction of small amounts of cobalt into beer to improve foaming in several sites in North America and Europe in the 1960s. Biochemical mechanisms were never established. Importantly, these episodes strongly suggested a multifactorial aetiology of myocardial damage and, specifically, that alcohol plus small amounts of either arsenic or cobalt was essential. Indeed, other predisposing factors were clearly involved, as heart involvement was not evident in most heavy drinkers of the contaminated beer.

A major diversion from wider acceptance of ACM resulted from recognition in 1929 of cardiovascular beriberi. Aalsmeer and Wenckebach described high-output HF due to decreased peripheral vascular resistance amongst eaters of polished rice in Java [5]. This was later shown to be due to thiamine (cocarboxylase) deficiency. Subsequently, it was logically widely assumed that HF amongst Western heavy drinkers was caused by associated nutritional deficiency states. However, most cases did not fit that hypothesis as they had low-output HF, were well nourished, and responded poorly to thiamine. Blacket and Palmer resolved the situation: 'It [beriberi] responds completely to thiamine, but merges imperceptibly into another disease, called ACM, which doesn't respond to thiamine' [6]. Beriberi is characterized by generalized peripheral arteriolar dilation with a resultant large arteriovenous shunt and high cardiac output at rest. There are a few documented cases of complete recovery within 1–2 weeks after thiamine administration.

Many cases earlier labelled 'cardiovascular beriberi' would now be diagnosed as 'alcoholic heart disease' or ACM. Could chronic deficiency of thiamine have a role in some ACM cases? The answer to this remains unclear.

Current view

For the past 60 years, circumstantial evidence has accumulated supporting the idea that there can be direct toxicity to myocardial cells from alcohol. It can be considered that the ACM concept is established based on the sheer volume of clinical observations of an alcohol association, evidence of impaired myocardial function in a substantial proportion of chronic heavy drinkers and several controlled studies [3, 4]. Measurable abnormalities often precede clinical illness by years. When clinically evident, the entity cannot be distinguished from dilated cardiomyopathy of other or unclear cause. Today, most cases of dilated cardiomyopathy still have an unclear aetiology; postviral autoimmune processes and genetic factors are the leading proposed causes. The lack of diagnostic tests for ACM seriously impairs epidemiological study. In fact, it is unclear whether alcohol can cause the condition in the absence of one or more cofactors or preconditioning traits [4]. The proportion of heavy drinkers developing ACM is not known, but it is believed to be substantially less than the 15–20% that develop liver cirrhosis.

An important Spanish study [7] showed good correlation between lifetime alcohol consumption and structural and functional myocardial and skeletal muscle abnormalities in alcoholic men. A relationship was seen only in those reporting ingestion of the equivalent of 120 g alcohol day^{-1} for 20 years. The same Spanish group later reported data indicating greater susceptibility in women, a strong genetic predilection and equivalent favourable prognosis with reduced alcohol intake and total abstinence. It seems unlikely that this condition could result from light–moderate drinking (see related discussion of heart failure below).

Clinical picture and course

In advanced ACM, the heart is dilated with diminished left ventricular systolic contractility. Symptoms are related to reduced cardiac output. Arrhythmias and HF are common, and mortality is high. With abstinence or a marked reduction in alcohol intake, improvement may occur in many, but not all, cases.

Mechanisms

The mechanisms of ACM development remain unclear [3, 4, 8, 9]. An interesting hypothesis relates to the existence of a nonoxidative metabolic pathway for alcohol related to fatty acid metabolism in the heart, muscle, pancreas and brain [10, 11]. Accumulated fatty acid ethyl esters are toxic to myocardial cells and, in fact, these compounds are used as markers of chronic alcohol abuse. Acetaldehyde, the first metabolite of alcohol and a highly toxic compound, has been implicated in several alcohol-related pathologies. A variety of other possible mechanisms have also been suggested [3, 4], but evidence remains incomplete.

Supraventricular arrhythmias

Popularly known as the 'holiday heart phenomenon', there is an association of alcohol consumption, especially binge drinking, with supraventricular arrhythmias, especially paroxysmal atrial fibrillation [12–14]. Typically, the arrhythmia resolves with abstinence and, with sustained abstinence, does not recur. Atrial fibrillation is most common, but atrial flutter or supraventricular tachycardia may occur. In a comparison of incident atrial arrhythmias in 1322 subjects reporting six or more drinks per day to that in 2644 lighter drinkers (<3 drinks per day), we showed a twofold higher risk in the heavier drinkers for atrial fibrillation, atrial flutter, supraventricular tachycardia and premature atrial contractions [15]. Prospective analyses have shown increased atrial fibrillation risk amongst heavy but not light–moderate drinkers [13, 14]. Patients with these rhythm disturbances are usually healthy and do not have a personal or family history of heart disease. Mechanisms of these disorders remain unresolved, but suggested possibilities include cardiac conduction interference, refractory period shortening and increased sympathetic activity [16]. It is unlikely that light–moderate alcohol intake increases the risk of rhythm disturbances.

Systemic HTN

An important association between heavy drinking and prevalence of HTN was first reported in middle-aged French servicemen in 1915 [17], but then received no further attention for more than half a century. Rediscovered in the late 1970s, this relationship became firmly established by a large number of cross-sectional and prospective epidemiological studies with confirmation from clinical studies [18–20]. The results showed an alcohol–HTN link in both sexes, and in various ethnic groups in several continents, independent from

several potential confounders including adiposity, sodium intake, smoking and socio-economic status [18–20].

Findings differed with respect to the presence of higher blood pressure amongst light–moderate drinkers compared to abstainers, with several studies showing lower pressures in lighter drinkers, especially amongst women [18–22]. Figure 1 presents these associations from a cross-sectional analysis by our group in 1977 of men and women of three racial groups [21]. Subsequently, we showed that blood pressures were similar in former drinkers compared to lifelong abstainers and that abstinence resulted in regression of blood pressure elevations within a week [22]. The pressure elevations translated into approximately a twofold higher HTN prevalence amongst persons reporting six or more drinks per day versus abstainers or light drinkers.

Experimental data in humans and animals demonstrate no acute (minutes to hours) blood pressure rise after alcohol exposure [18–20]. Substantial mealtime drinking in the evening appears to depress pressure during the night for up to 8 h, followed by pressure increases the next morning [18]. A more sustained alcohol–HTN association develops in days to weeks, which could be characterized as a 'subacute' response. This response to heavy drinking was first experimentally demonstrated in hospitalized hypertensive men who drank 4 pints of beer (1 pint = 568 mL) [23]. The authors reported that increases and decreases in pressure with drinking and abstinence, respectively, occurred in 3–4 days. The phenomenon was later observed in nonhospitalized normotensive and hypertensive individuals [24, 25]. Experiments have shown that substantial alcohol intake may negate the effects of HTN medications [24]. Furthermore, reducing intake of alcohol may not only enhance the blood pressure lowering effect of weight loss, exercise or salt restriction, but may, in some instances, have a greater effect than these other measures [26, 27]. The incidence of CV sequelae of HTN is similar in abstainers, light drinkers and heavy drinkers [28].

As discussed in a recent review [20], solid evidence regarding the biological mechanisms of the alcohol–HTN association remains elusive. Data are inconsistent with respect to several potential neuroendocrine mechanisms [18–20]. In Asians, the alcohol–HTN association seems to be independent from alcohol-induced flushing, a phenomenon that is due to elevated blood acetaldehyde levels produced by a common genetic polymorphism in this racial group [18]. Heightened sympathetic nervous system responsiveness is widely considered to have a role in this relationship [18–20]. Sympathetic overactivity occurs during withdrawal from very heavy drinking, but was not seen in the above-mentioned studies [23–27]. In the absence of long-term randomized controlled trials, we cannot rule out all possible indirect explanations, perhaps especially psychosocial stress. Short-term intervention studies

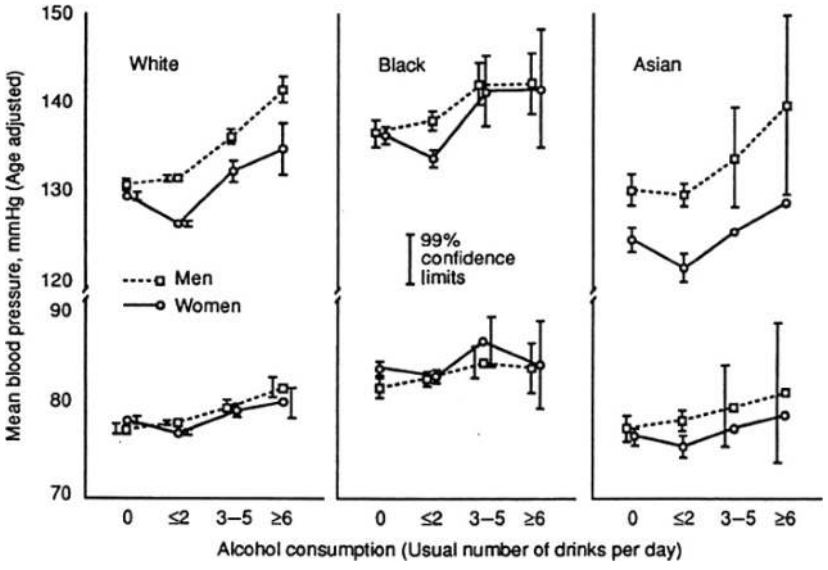

Fig. 1 *Mean systolic (top) and diastolic (bottom) blood pressures amongst white, black and Asian men and women with known drinking habits. Adapted from Klatsky* et al. *[21].*

provide evidence against the involvement of many confounders [23–27]. The weak effect of beverage type (wine, liquor or beer) strengthens the likelihood that ethyl alcohol has the most important role [29].

Relevant to the issue of alcohol threshold is the suggestion that heavy alcohol intake may be underreported [30], thus possibly invalidating the apparent increased HTN risk of lighter drinkers. Underreporting of alcohol intake places some heavier drinkers in lighter categories, a misclassification that lowers the threshold of apparent harm.

Based on these findings, it seems that heavier drinking is causally related to HTN in some persons and that alcohol-associated HTN is a common reversible form of elevated blood pressure. Estimates of the proportion of HTN attributable to alcohol vary according to the proportion of heavy drinkers in the group under consideration [31]. However, even using the lowest attributable risk estimates of 5–7% [31], the proportion translates into millions of individuals with alcohol-associated HTN in western countries.

Atherosclerotic CAD

Epidemiology

Because it is by far the commonest CV condition, CAD dominates mortality and morbidity statistics for all CV disorders. Although combined CV disease data are often presented, the disparities with respect to the effects of alcohol dispute the value of the practice. Even more problematic is the use of CV disease and CAD as synonyms.

Age, gender and ethnicity are important with regard to CAD risk. Established environmental risk factors include smoking, HTN, diabetes mellitus, elevated blood levels of LDL cholesterol and triglycerides, reduced HDL cholesterol and several pro-thrombotic traits.

The common clinical expressions of CAD are stable and unstable angina, myocardial infarction and sudden death from cardiac arrest. Relief of symptoms by alcohol was noted by Heberden in 1786 in his classic description of angina [32]. This led to a probably incorrect assumption that alcohol dilates the coronary vessels. It is more likely that the apparent benefit of alcohol with regard to angina is explained by an anaesthetic effect [33]. As the subjective CAD symptom angina pectoris is difficult to quantify, it is little used in epidemiological studies.

Virtually all observational epidemiological studies show reduced risk of acute myocardial infarction and CAD death in moderate drinkers compared to abstainers [34–37]. Many analyses have shown a *U*-curve or *J*-curve association between increasing alcohol intake and CAD, with lifelong abstainers as the referent. Figure 2 presents an example of one meta-analysis. In the absence of long-term randomized controlled trials including CAD event outcomes, observational studies provide the best available data. Other evidence supporting a benefit of alcohol in CAD includes international comparisons, case–control studies, prospective short-term studies of CAD risk traits and analyses of coronary arteriograms. In most studies, the alcohol–CAD relation is nonlinear with increased risk in heavier versus lighter drinkers. Possible explanations for the nonlinearity include more binging by heavier drinkers, more individuals with HTN amongst heavy drinkers, elevated triglyceride levels in some heavy drinkers, and misdiagnosis of cardiomyopathy as CAD.

Some have questioned the observational data showing an alcohol–CAD association on methodological grounds. The issues most often raised are that several analyses grouped together lifelong abstainers and ex-drinkers and that some studies inadequately controlled for baseline CAD. A false

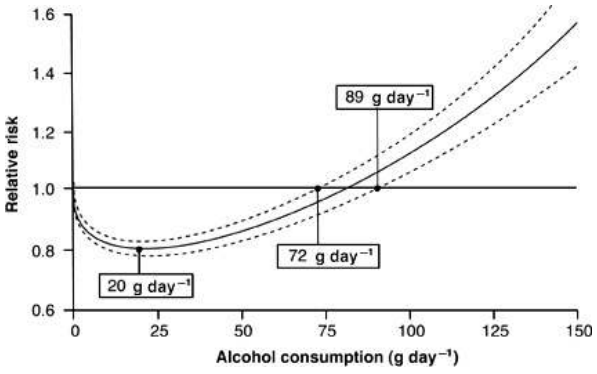

Fig. 2 *The relationship between average alcohol consumption and coronary heart disease, as expressed by a J-shaped curve. The solid line represents the results of a meta-analysis, and the dashed lines represent the lower and upper confidence intervals. The nadir of the curve, at 20 g per day, is the equivalent of two small drinks. From Corrao* et al. *[35].*

impression of benefit from light–moderate drinking might ensue if the nondrinking referent group included 'sick quitters' with increased CAD risk. These issues are refuted by the findings from cohort studies with separate categories for ex-drinkers and lifelong abstainers as well as by analyses controlling for baseline CAD [34–37].

Mechanisms to explain the lower CAD risk in drinkers

Reviews of the multiple plausible mechanisms for CAD protection have been published [38–43] (see Table 1). A link via HDL cholesterol is well established. Except in individuals with severe liver disease, alcohol ingestion raises HDL levels by poorly understood mechanisms. Inverse relationships between HDL level and CAD risk probably result from removal of lipid deposits in large arteries plus assisting the prevention of tissue oxidation of LDL cholesterol. Findings suggest that approximately half of the lower CAD risk in drinkers is mediated by higher HDL levels [38, 43] and that major HDL subfractions, known as HDL_2 and HDL_3, are involved [44]. The failure of HDL-raising medications to have a beneficial effect [45] and more sophisticated characterization of HDL subfractions [46] have raised questions about the likelihood of a simplistic interpretation [47]. Nevertheless, the HDL link remains the best established mechanism to explain the beneficial effect of alcohol on CAD.

Triglycerides are now believed to play an independent role in the risk of CAD. The alcohol association via triglycerides is likely to be unfavourable because some heavy drinkers have substantially increased blood triglyceride levels. However, light–moderate drinking seldom causes increased triglyceride levels.

Alcohol has several antithrombotic actions. These include inhibition of platelet stickiness and lowered fibrinogen levels. As thrombosis in atherosclerotic arteries plays a key role in major CAD events, these effects may be important factors in the protective effect of alcohol.

Both overeating and physical inactivity are important underlying factors in the current worldwide epidemic of obesity and diabetes mellitus. Whereas heavy alcohol drinking has been linked to higher blood glucose levels and reduced compliance to diabetes management [48, 49], light–moderate drinking is associated with lower diabetes risk and favourable effects on insulin–glucose metabolism [50]. A meta-analysis of 15 prospective cohort studies [50] demonstrated a *U*-shaped curve for the association between amount of alcohol consumed and type 2 diabetes risk. The nadir of the curve was at 1–2 drinks per day, with a 30–40% reduction in risk compared with abstainers. In one study, alcoholic beverage type was reported to have little influence, but drinking pattern was important:

Table 1 *Possible mechanisms for coronary artery disease (CAD) protection by alcohol*

Mechanism of alcohol effect	Action and comment	Strength of evidence[a]
Raises HDL cholesterol	'Reverse' LDL cholesterol transport from blood vessel wall; a long-term effect; also a possible antioxidant	Good; ~50% of alcohol effect
Lowers fibrinogen, thromboxane A and platelet stickiness; increases prostacyclin and endogenous tissue plasminogen activator	Decreased clot formation in atherosclerotic blood vessels (a key factor in CAD events); a short-term action	Good
Lowers risk of type II diabetes mellitus	Possibly by reducing insulin resistance; diabetes is a major CAD risk trait	Good
Reduces LDL oxidation in blood vessel walls	Hypothetical effect of antioxidants, plentiful in red wine and abundant in dark beer, would presumably be a nonalcohol action	Weak to moderate
Increases preconditioning of cardiac myocytes	Resistance to damage by oxygen deprivation	Weak
Decreases psychosocial stress	Stress is a possible CAD risk factor	Weak

[a]Author's judgement.

light–moderate daily or almost daily intake was the most favourable pattern [50]. As glucose intolerance and reduced insulin sensitivity are major CHD risk factors, these effects are likely to play a role in the protection by alcohol against CAD.

It has been suggested [42] that the presence of alcohol might enhance a protective mechanism known as postischaemic preconditioning, which is characterized by reduced myocardial damage in tissues previously exposed to intermittent ischaemia. Evidence for the role of alcohol is sparse, making this protective mechanism speculative.

Genetic variants: conflicting data

Genetic variants affecting alcohol metabolism theoretically comprise a form of 'natural' randomized controlled trial. Evidence suggested that individuals with an alcohol dehydrogenase polymorphism (*ADH1C*) resulting in 'slow metabolism' of alcohol may obtain more CAD benefit [51], thus supporting a causal relationship for the protective effect of light–moderate drinking on CAD. However, subsequent Mendelian randomization analyses have yielded conflicting conclusions. For example, a Danish study showed that increasing alcohol intake was associated with decreasing risk of myocardial infarction, but the association was not modified by *ADH1B* and *ADH1C* genotypes [52]. A recently reported meta-analysis involved 56 studies with data for the *ADH1B* polymorphism. Individuals with the polymorphism were more likely to be abstainers and less likely to be heavy drinkers, yet had a more favourable CAD risk factor profile and fewer CAD events [53]. The authors interpreted the data as indicating that reduction of alcohol intake even by light drinkers might reduce CAD risk [53], but others [54] pointed out that the results might be due to uncertain assumptions about the distribution and effects of the polymorphism and/or reduction of intake in some subjects to levels affording optimal benefit. It is also possible that a genetic variant influencing drinking behaviour might have other actions affecting CAD, such as an influence upon another CAD risk factor or a direct effect upon CAD risk. At present, ongoing genetic studies can be considered to have an important role, but the outcome details remain unclear.

Drinking pattern and beverage choice: is only red wine important?

Drinking pattern is a factor of importance for diabetes [55], CAD [56–60], total mortality [61, 62] and HTN [63]. The most favourable drinking pattern is regular daily or almost daily light drinking, with avoidance of clearly harmful binge drinking. Drinking variability over time is another potential factor of interest. Drinking with meals and high overall frequency (daily or almost daily) are apparently more favourable with respect to both CAD and HTN.

International comparison data showing lower CAD mortality in red wine-drinking countries (vs. beer- or liquor-drinking countries) [64] led to the hypothesis that CAD benefit is specific for red wine. The 'French paradox' refers to the fact that France does not conform to the same linear relationship between mean dietary fat intake and CAD mortality as other countries, until the analysis is adjusted for wine intake. The hypothesis that red wine has protective benefit additional to that of alcohol is indirectly supported by the presence of nonalcoholic phenolic compounds with antioxidant and antithrombotic properties in wine, especially red wine [34, 40, 65–68]. Several classes of these compounds in grapes and other fruits and vegetables might have effects that promote endothelial health. The compounds include catechins, quercetin and resveratrol, all of which are active *in vitro* and in animal studies to produce beneficial effects on established biological markers of vascular disease. Effects in humans *in vivo* are less well established. There are issues related to bioavailability because of limited absorption from the gastrointestinal tract. Resveratrol, in particular, is poorly absorbed, so huge doses would be required for human effects comparable to those reported in other species, which is incompatible with levels obtainable from moderate drinking.

Epidemiological data in prospective studies suggest that white wine, red wine and beer may all be effective in reducing CAD risk [67–70]. Especially convincing in discrediting the belief that CAD benefit is due exclusively to nonalcohol ingredients in red wine are reports of equivalent benefit in beer-drinking populations [71–73]. The issue of beverage choice is complicated by probable confounding by the fact that wine drinkers have the most favourable CAD risk profile [74]. It is likely that the usual pattern of wine drinking may also be important. Compared to beer or liquor, wine is more often sipped slowly with meals.

Thus, antioxidation is unlikely to be the primary mechanism involved in protection by alcoholic beverages against CAD. Whilst the French paradox

has received considerable attention, the beverage choice issue remains unresolved at this time. Ethyl alcohol is probably the major factor with respect to lower CAD risk.

Alcohol and CAD: is the relationship causal?

Few epidemiological associations have been examined as critically as the inverse alcohol–CAD relationship. No randomized controlled trials with CAD outcome data have been conducted; therefore, confounding cannot be completely ruled out and some uncertainty remains about the causal nature of the association. Sceptics have emphasized the possible methodological flaws that might produce a spurious apparent benefit of moderate drinking. As already mentioned, some studies failed to separate lifelong abstainers from ex-drinkers, thus increasing risk in the nondrinker referent group by inclusion of sick quitters. Possible confounding by healthy lifestyle habits of moderate drinkers has also been postulated and could be termed 'the healthy drinker hypothesis'. There has been less attention to biases that might reduce apparent benefit, but confounding probably acts both ways. For example, smoking and drinking are correlated. Thus, residual confounding by incomplete control for smoking could reduce the apparent benefit of alcohol drinking. Underreporting by heavy drinkers is another source of bias against apparent CAD protection by moderate alcohol intake. By including some heavy drinkers in lighter drinking categories, underreporting distorts many alcohol–health associations. In the case of CAD, underreporting would lessen the apparent benefit of light drinking.

Other factors favouring a causal hypothesis are consistency in studies, plausible biological explanations, relative specificity of benefit for atherothrombotic vascular disease, and the temporal sequence in prospective studies. The absence of a linear relation is not a major issue because alcohol–health associations are usually nonlinear. A causal, protective effect of moderate alcohol intake is the simplest and probably correct explanation for the alcohol–CAD association. The following recent statement by Roerecke and Rehm, who have long been sceptical about this relationship, is pertinent: 'For drinkers having one or two drinks per day without episodic heavy drinking, there is substantial and consistent evidence from epidemiological and short-term experimental studies for a beneficial association with ischaemic heart disease risk when compared to lifelong abstainers. The alcohol relationship fulfils all criteria for a causal association proposed by Hill' [75].

Cerebrovascular disease

Complex interrelationships between stroke and other alcohol-related CV conditions make assessment of alcohol drinking and stroke risk an epidemiological challenge [75–77]. Increased risk in heavy drinkers of atrial fibrillation and cardiomyopathy would be expected to contribute to increased risk of cardioembolic stroke, whereas lower risk of CAD in light–moderate drinkers would be expected to result in lower risk of such events. Because it is a major risk trait for every stroke type, systemic HTN is a likely mechanism relating heavy alcohol drinking and stroke. The antithrombotic effects of alcohol probably increase the risk of haemorrhagic stroke whilst lowering ischaemic stroke risk. Independent of CAD effects, the blood lipid effects of alcohol could have a favourable effect on ischaemic stroke risk.

An early Nurses' Health Study analysis [78] found that drinkers were at higher risk of subarachnoid haemorrhage, but lower risk of occlusive stroke [78]. A later analysis from this large cohort [79] showed *U*-curve alcohol relationships with both ischaemic and haemorrhagic stroke. Our previous data showed that heavy but not light–moderate drinkers had an increased risk of haemorrhagic stroke [80] with increased blood pressure in heavier drinkers appearing to be a partial mediator. A recent study in a large Japanese cohort showed similar data [81]. Furthermore, we showed that alcohol drinking was related to lower rates of ischaemic stroke in both sexes, in whites and blacks, and in individuals with extracranial and intracerebral lesions [82].

Recent reviewers have concluded that there is probably a *J*-curve relationship between alcohol consumption and the risk of stroke [75, 83]. At present, the relations between alcohol drinking and specific stroke types remain unclear.

Heart failure

Heart failure is a not an aetiological diagnosis but a common nonspecific syndrome. As it generally occurs in the later stages of underlying CV conditions, improved survival of patients with heart disease and increased general population longevity

have resulted in a substantially increased HF incidence. In most patients with the syndrome, HF is associated with several risk factors, often including both CV and non-CV components [84]. In developed countries, CAD is a factor in a majority of cases. Frequently occurring underlying CV conditions include HTN, valvular disease, cardiomyopathies (including alcoholic) and rhythm disturbances. Common non-CV factors include anaemia, infection, neoplasms, diabetes and obesity.

Alcoholic cardiomyopathy was considered to have the most important role in the relationship between alcohol and HF. By the mid-20th century, this led to the widespread belief that alcohol should be avoided by all patients with heart disease. The disparate relationships between alcohol and CV conditions uncovered more recently have invalidated this belief. Several studies of alcohol and HF risk have consistently shown that light–moderate drinkers are less likely than abstainers to develop the syndrome [37, 85–91]. In the Framingham Heart Study [86], moderate alcohol intake was associated with reduced HF risk and even heavier intake was not associated with increased risk.

The associations between alcohol drinking and risk of cardiomyopathy, HTN, arrhythmias and CAD confound the study of HF risk. We performed separate analyses for HF associated with CAD and HF not associated with CAD [87]. For CAD-associated HF, there was an inverse relation with both moderate and heavy drinking; for non-CAD-associated HF, only heavy drinkers had an increased risk of disease.

Thus, views have 'come full circle' with respect to the alcohol–HF relationship. All available data at this time suggest that there is no reason to prohibit light–moderate alcohol drinking in most individuals with heart disease or at HF risk.

Alcohol-related disease research issues

Alcohol–CV disease associations have played a key role in the understanding of the epidemiology of alcohol-related diseases, for example:

1 Generally, alcohol–health relationships are nonlinear. This is true for all of the alcohol–CV disease associations. It follows that alcohol should always be studied categorically to avoid masking threshold relationships (including *U*-curves and *J*-curves).

2 Available population studies of chronic CV disease end-points are all observational; thus, residual confounding is a possibility. With respect to light–moderate drinkers, favourable lifestyle traits might falsely decrease their apparent risk, whereas associated smoking and underreporting might increase their apparent risk.

3 The best choice of referent group is debatable; none is ideal. However, there is consensus that ex-drinkers should be excluded from a nondrinking reference group because some quit alcohol as a result of symptoms or illness. The increased risk of these sick quitters raises the risk in the total nondrinking category. It is unclear whether the best referent group should be lifelong abstainers, infrequent drinkers, light drinkers or some combination of these.

4 Whist the role of choice of wine, liquor or beer has been of great interest, confounding has been a major problem when interpreting the data.

5 The available chronic disease end-points are not ideal in many observational studies. The usual use of hospitalization and/or death limits analyses to severe cases. It is possible that results differ for milder clinical scenarios.

6 Apparent benefit from light–moderate drinking has created debate about public health and personal advice. Relationships between drinking and CV disease risk depend on personal susceptibilities, amount of alcohol consumption, drinking pattern and the end-point under consideration. All persons should avoid heavy drinking, and many should avoid all alcohol [92, 93]. No change in habit is required for most established light–moderate drinkers. It seems clear that (i) individualized advice is best and that (ii) objectivity plus common sense is essential.

Future directions: where are we headed?

Observational cohort studies are yielding diminishing returns, and future research should move in other directions. Attempts to perform randomized trials of the effect of alcohol on disease outcomes would certainly be of interest, but logistical difficulties seem almost prohibitive and firm conclusions are unlikely to follow. From a more practical viewpoint, the following research areas may be more productive.

1 *Genetic research*. As it matures, this growing area of research will explain much in all areas of medicine. With respect to alcohol–CV disease relationships, genetic factors related to ACM, HTN, arrhythmias, HF and CAD are all of potential importance in explaining differences in disease susceptibility between individuals and between populations.

2 *Study of beverage choice disparities*. Such studies are always of interest to the public, and reports probably influence drinking behaviour. From a scientific viewpoint, the importance of these differences is related to the mechanisms underlying the alcohol–CV disease association, including the extent to which observed effects are due to ethyl alcohol. Well-designed randomized studies should be performed amongst established light–moderate drinkers with CAD risk traits as end-points. Blinding of most subjects will probably not be possible.

3 *Study of alcohol–medication interactions*. Most patients with CV disease take multiple medications, and a large proportion of medications for CV disorders have potential interactions with alcohol. There are limited data available about this important practical area. Randomized trials should be feasible.

4 *Alcoholism research*. Both public health and individual advice regarding light–moderate drinking are reasonably dominated by concerns about uncontrolled drinking. More reliable predictors of risk of progression to heavy drinking are greatly needed.

Conclusion

Table 2 shows a summary of the current status of alcohol–CV disease associations. Empiric associations between heavy alcohol intake and increased risk of cardiomyopathy, systemic HTN, atrial arrhythmias and haemorrhagic stroke are established. It is clear that light–moderate drinkers have a lower risk of CAD, ischaemic stroke and heart failure, but possibly an increased risk of haemorrhagic stroke. Plausible mechanisms underlying the protective effect of light–moderate alcohol drinking for CAD have emerged. However, relationships between heavy drinking and both ischaemic stroke and CAD are unclear. Finally, advice to concerned individuals needs to be personalized.

Table 2 *Relationships between alcohol and cardiovascular conditions*

	Probable relationship with alcohol		Potential epidemiological
Condition	Lighter drinking[a]	Heavier drinking[b]	consequences
Dilated cardiomyopathy	Unrelated	One (of several) causes; ? requires cofactors	↑ risk of HF, AF, cardioembolic stroke and HS if on ACs
Systemic HTN	Little or none	Probably causal in susceptible persons	↑ risk of HF, AF, IS and HS
CAD	Protective	? less protective or ↑ risk	↓ risk of HF, cardioembolic stroke and AF; ↑ risk of HS if on ACs
Supraventricular arrhythmia	Little or none	Probably a causal factor, especially with binges	↑ risk of cardioembolic stroke, and HS if on ACs
HS	? unrelated or slight ↑ risk	↑ risk	Disability and ↑ risk of VTE
IS	Protective	Probable ↑ risk; varies with subtype	Disability and ↑ risk of VTE
Heart failure	Indirectly protective	Varies with underlying CV condition	Disability and ↑ risk of VTE

[a]Less than three standard-sized drinks per day; [b]three or more standard-sized drinks per day.
AC, anticoagulant; AF, atrial fibrillation; HS, haemorrhagic stroke; IS, ischaemic stroke; HTN, hypertension; CAD, coronary artery disease; VTE, venous thromboembolism; CV, cardiovascular; ↑, increase; ↓, decrease; ?, possibly.

Conflict of interest statement

No conflicts of interest to declare.

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