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ALCOHOL IS BAD FOR BLOOD PRESSURE

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SUMMARY

1. The regular consumption of alcohol elevates blood pressure, with global estimates that the attributable risk for hypertensive disease from alcohol is 16%.

2. The increase in blood pressure is approximately 1 mmHg for each 10 g alcohol consumed and is largely reversible within 2–4 weeks of abstinence or a substantial reduction in alcohol intake.

3. This increase in blood pressure occurs irrespective of the type of alcoholic beverage. In particular, the postulated effects of vasodilator flavonoid components of red wine to lessen or reverse alcohol-related hypertension have not been borne out in intervention studies.

4. Heavy drinking, especially a binge pattern of drinking, is linked to a higher incidence of cerebral thrombosis, cerebral haemorrhage and coronary artery disease deaths, although a role for alcohol-related hypertension in the causal pathway is not well defined.

5. In contrast, the light to moderate intake of alcohol has been consistently linked to a reduced risk of atherosclerotic vascular disease end-points. Such a protective effect may also extend to hypertensive subjects.

6. However, the magnitude of any protective effect appears to have been exaggerated because of unmeasured confounders, especially diet, lifestyle and patterns of drinking. Furthermore, a decrease in overall mortality with drinking appears confined to older subjects and to populations with a high background cardiovascular risk profile.

7. Any putative cardiovascular benefits from drinking need to be carefully considered against the effects of alcohol to elevate blood pressure, together with many other adverse health consequences from drinking. Maximum cardiovascular benefit occurs at relatively low levels of consumption (i.e. one to two standard drinks a day in men (10–20 g alcohol) and up to one a day in women (10 g alcohol)). In hypertensive subjects, consumption beyond these levels would be unwise.

Key words: alcohol, blood pressure, hypertension, myocardial infarction, stroke.

INTRODUCTION

The well-documented effect of alcohol in increasing levels of blood pressure and the incidence of hypertension has been discounted by some on the basis of the contrasting observation of the favourable effects of alcohol against atherosclerotic cardiovascular disease end-points. Beneficial effects for both ischaemic heart disease and ischaemic stroke have been reported, even in the setting of established hypertension.[1] This has led to an ongoing debate as to the relative risks and benefits of alcohol for hypertensive subjects, a debate further clouded by claims that drinking red wine, in contrast with beer or spirits, will mitigate any blood pressure-raising effect of alcohol,[2] a property attributed to the high content in red wine of anti-oxidant and vasodilator flavonoids. The present review will re-assess the clinical implications of alcohol-related hypertension in the light of these competing claims.

ALCOHOL-RELATED HYPERTENSION

Burger *et al*.[3] conducted a systematic review of all studies from 1988 to 1999 of moderate alcohol consumption (< 40 g/day) in relation to blood pressure and concluded that there were linear blood pressure elevations at drinking levels of > 20 g/day for women and > 30 g/day for men. This dose-related increase in blood pressure, together with the relatively high prevalence of alcohol consumption, translates into a relatively high attributable risk for hypertension. In the WHO Global Burden of Disease Study,[4] 16% of all hypertensive disease was attributed to alcohol. More robust prospective population studies and randomized controlled intervention trials also strongly support the concept that alcohol is a major risk factor for the elevation of blood pressure and the subsequent development of hypertension. In 1999, a meta-analysis of the three prospective studies then available reported a 40% increase in the relative risk of developing hypertension in those drinking more than 25 g alcohol/day and a greater than fourfold increase in risk in those drinking more than 100 g/day.[5] Since then, large-scale prospective studies from Japan[6] and the US[7] have indicated that the risk of hypertension increases twofold with alcohol intake of 30–50 g/day or more. In subjects drinking 30 g/day or more, 20% of the incident cases of hypertension were attributed to alcohol consumption,[7] whereas in middle-aged

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Swedish males with high normal blood pressure, alcohol intake was an independent predictor for subsequent development of hypertension within 6 years.[8] The first intervention trial in community based subjects was conducted in Western Australia,[9] in which normotensive drinkers reduced their alcohol consumption by drinking a low-alcohol beer (0.9% ethanol) for 6 weeks before switching back to their usual alcohol intake, consuming a normal-alcohol beer (5% ethanol) from which the low-alcohol beer had been distilled. Alcohol consumption fell by approximately 80% and was accompanied by a fall in blood pressure of 3.8/1.4 mmHg supine and 4.4/2.5 mmHg standing, the majority of which occurred during the first 2 weeks of switching to the low-alcohol beer. Blood pressure was still declining at 6 weeks, increasing once again when normal intake was resumed. Subsequent trials in both treated[10] and untreated[11] hypertensives have revealed falls of a similar magnitude.

A meta-analysis of 15 randomized controlled trials[12] was published in 2001. Seven trials included only hypertensive subjects, six included normotensive subjects and two included either normotensives or hypertensives. The median duration of the interventions was 8 weeks and the median reduction in alcohol consumption was 76% from initial intakes of three to six standard drinks per day. The pooled effect estimates for the fall in systolic and diastolic blood pressure with alcohol restriction were 3.31 and 2.04 mmHg, respectively, and were similar in hypertensives and normotensives, as well as in treated versus untreated hypertensive subjects. A further systematic review was published in 2005[13] that also included studies that directly administered alcohol. The estimates from this analysis for falls in systolic and diastolic blood pressure with alcohol restriction were 2.7 and 1.4 mmHg, respectively. This latter review included several studies that used ambulatory or home blood pressure monitoring and, when a comparison was made to studies using conventional clinic blood pressure measurement, the analysis re-emphasised previous reports of a biphasic effect of alcohol on blood pressure.[14] An early depressor effect of alcohol lasted for several hours and was ascribed to acute vasodilator effects, whereas repeated episodes of drinking led to a sustained increase in blood pressure after 7 days.[14]

In summary, the cross-sectional, longitudinal and intervention trial data all provide overwhelming and consistent support for the concept that the regular consumption of alcohol increases both the level of blood pressure and the subsequent incidence of hypertension.

BEVERAGE PREFERENCE

The so-called 'French paradox', with lower than expected rates of coronary artery disease in the French despite a relatively high intake of saturated fat, has been ascribed, at least in part, to the consumption of significant amounts of red wine. The anti-oxidant, vasodilator and antiplatelet effects of polyphenolic flavonoids present in large concentrations in red wine have been proposed as the pathophysiological basis for this phenomenon. The vasodilator effects of red wine or isolated flavonoids, such as epicatechin and quercetin, or phenolic acids, such as coumaric or caffeic acid,[15] have been well established *in vitro* and also implied from animal studies, in which red wine polyphenolics have resulted in substantial falls in blood pressure.[16] Such effects have been attributed to increased nitric oxide production leading to increased endothelium-dependent relaxation.[17] The epidemiological correlate of such observations has been the finding in some studies that wine drinking is associated with smaller effects on blood pressure than beer or spirits. In the Lipid Clinics Prevalence Study,[18] there were significant positive regression coefficients for beer and spirits drinkers in relation to blood pressure, but no significant relationship seen in wine drinkers. In the Kaiser Permanente study in Californians presenting for routine health examinations, those who preferred wine had the lowest diastolic blood pressure and those who preferred liquor had the highest systolic and diastolic blood pressure.[19] Conversely, a study from western New York[20] found no consistent beverage-specific associations with hypertension risk in North Americans drinking beer, wine or spirits. The PRIME study of men living in France or Northern Ireland found a weaker association for wine and blood pressure compared with beer.[2] However, none of these studies adjusted for the now well-recognized dietary differences between wine, beer and spirits drinkers[21] or important differences in the relative amounts of alcohol and patterns of drinking,[22] which, together, may well account for any differential effects on blood pressure. Furthermore, no support was evident for a vasodilator effect of red wine flavonoids in a recent 4 week cross-over trial from Western Australia that compared effects of wine, de-alcoholized red wine, beer and water on 24 h ambulatory blood pressure in 26 men.[23] In that study, the increases in blood pressure with either red wine or beer were of a similar magnitude, with the effect of both beverages predominantly on awake systolic blood pressure, which increased by 2.9 mmHg for red wine and 1.9 mmHg for beer compared with the ingestion of water as a control.

A recent cross-sectional study examined *a priori* the associations between alcohol intake and isolated systolic, combined systolic and diastolic and isolated diastolic hypertension in 5317 Chinese men.[24] That study found that, in those subjects who predominantly consumed liquor, there was a significantly higher odds ratio for the presence of isolated systolic hypertension, whereas combined systolic–diastolic hypertension and isolated diastolic hypertension did not differ according to type of alcoholic beverage. However, in that study, liquor drinkers generally drank more alcohol. A similar result was seen in a study of 4335 Japanese male workers,[25] who were grouped into those who predominantly consumed beer, sake, shochu (a traditional Japanese spirit), whiskey or wine. Again, blood pressure was highest with the consumption of liquor, but this finding for the shochu group disappeared after a further analysis that adjusted for their increased alcohol consumption.

In conclusion, the amount of alcohol consumed, not beverage preference, appears to be the more important determinant of the alcohol–blood pressure relationship.

ALCOHOL AND ATHEROSCLEROTIC VASCULAR DISEASE

The mean 4/2 mmHg fall in systolic and diastolic blood pressure predicted from a reduction in alcohol intake in the meta-analysis of Xin *et al*.[12] should translate into an 18% decrease in the incidence of death from stroke and a 12% decrease in the incidence of death from coronary heart disease. However, alcohol has complex interrelationships with multiple cardiovascular risk factors and, although increasing blood pressure at relatively low levels of consumption, simultaneously acts to favourably increase high-density lipoprotein–cholesterol levels,[26] decrease fibrinogen[27] and reduce platelet activation and aggregation.[28] However, at high levels of consumption, higher triglyceride levels,[29] increased plasma homocysteine[30] and increased risk of type 2 diabetes mellitus[31] are seen. Given these

contrasting consequences of drinking for cardiovascular risk factors, it is not surprising that the inter-relationships of alcohol with stroke and coronary heart disease outcomes are equally complex.

The relationship between alcohol and stroke, for example, was recently described as an epidemiological labyrinth,[32] the complicated findings due to contrasting effects of light versus heavy alcohol consumption on haemorrhagic versus ischaemic stroke. For haemorrhagic stroke, a systematic review revealed that, with increasing consumption, there was a progressive increase in risk.[33] It is tempting to propose that this reflects an effect of alcohol-related hypertension in combination with the aforementioned influence of alcohol to inhibit platelet aggregation and decrease levels of fibrinogen. For ischaemic stroke, the same systematic review[33] suggested that there was a J-shaped relationship, but with the evidence for a decrease in risk with low-level alcohol intake considered inconsistent. In contrast, heavy alcohol intake led to an increase in risk, a finding that was much more robust and linked especially to recent heavy consumption and binge drinking.[34] The evidence that alcohol-related hypertension is the mediator of this increased risk of ischaemic stroke is not strong, the increase in risk remaining in several studies even after adjustment for level of blood pressure. Alternative pathogenic pathways include cardioembolic stroke in the setting of alcohol-related arrhythmia, dehydration and hypotension after an acute alcoholic binge or, possibly, an acute impairment of fibrinolytic capacity.[35]

A meta-analysis of the risks for coronary artery disease with increasing alcohol consumption suggested that, similar to ischaemic stroke, there is a J-shaped relationship. The maximum decrease in risk was 20% and was seen at an intake of 20 g alcohol/day.[36] Increasing consumption beyond this level saw attenuation of any beneficial effect, so that by 72 g/day any protective effect was lost and beyond consumption of 89 g alcohol/day a 5% increase in relative coronary risk was seen. Similar to stroke, the relative roles of alcohol-related hypertension and/or alcohol-related cardiac arrhythmia in dictating the attenuation and reversal of any protective benefit are unknown.

Any protective effects for coronary artery disease and ischaemic stroke appear largely confined to men 40 years and older and women 50 years and older.[37] They are also more evident in those at higher absolute risk of atherosclerotic vascular disease, such as smokers,[38] those with high low-density lipoprotein–cholesterol,[39] diabetes mellitus,[40] pre-existing vascular disease[41,42] or with specific genetic predisposition, such as the apoE4 polymorphism[43] or the alcohol dehydrogenase 1C polymorphism.[44] The corollary of these observations is that any benefits of alcohol for protection against ischaemic heart disease and ischaemic stroke will be outweighed by the potential for alcohol-related harm in younger populations or in populations where the background cardiovascular risk is low. This has been most clearly delineated by the Global Burden of Disease Study,[4] in which the protective effects of alcohol only outweighed harmful effects in countries with established market economies and in individuals over 70 years of age. When a global analysis was undertaken, alcohol caused approximately 750 000 more deaths worldwide than it averted through any protective effects against atherosclerotic vascular disease, with more than 80% of these deaths in developing countries. In this regard, questions have been repeatedly raised as to the validity of using non-drinkers as a comparison group. In the recent Behavioural Risk Factor Surveillance System Survey, a telephone survey of over 200 000 adults in the US,[45] 27 of 30 cardiovascular-associated risk factors were significantly more prevalent in non-drinkers than in light to moderate drinkers. The authors concluded that confounding from unmeasured effect modifiers very likely explains a considerable proportion of any of the observed cardiovascular protective effects of alcohol. The issue is further complicated by the phenomenon of reverse causality, where illness leads to the cessation of drinking.[46] The inclusion of such ex-drinkers in the non-drinking category inflates estimates of the protective effect of alcohol, but their exclusion from any analysis is equally problematic, as demonstrated by a 23 year follow up of 12 000 male British doctors.[47] When recent ex-drinkers were included with current drinkers in that study, the relative risks from alcohol for cancer and all-cause mortality were increased, diminishing the overall risk to benefit ratio. Another confounding factor relates to the measurement of alcohol intake on a single occasion at baseline, which excludes the potential influence of changes in alcohol intake during follow up. When account was taken of such variation, such as in the British Regional Heart Study, where alcohol intake was measured regularly throughout a 20 year period of follow up,[48] heavy drinkers had a 74% higher risk of a major coronary event and a 133% higher risk of a stroke than did occasional drinkers, compared with an estimate of only an 8 and 54% higher risk, respectively, when the analysis was based on baseline assessment of alcohol alone. Finally, pattern of drinking is a serious confounder. In an Australian case-control comparison from Newcastle, participants were asked to report how many drinks they usually consumed on a day when they drank alcohol.[49] There was a 25–64% reduced risk of a major coronary event in men who drank one to four drinks per day on 5–6 days/week and a 31–61% decrease in risk in women who drank one to two drinks per day on 3–4 days/week. However, in men who drank nine or more drinks per day on 1–2 days/week there was a 2.4-fold increase in risk and, in women who drank five or more drinks per day, there was a 2.8-fold increase in risk. More recently, in the Onset Study from North America, in subjects prospectively evaluated following a myocardial infarction, binge drinking (defined as consumption of three or more drinks within 2–3 h) completely attenuated the decrease in mortality seen with lighter drinking, resulting instead in a twofold higher mortality during follow up over a median 3.8 years.[50]

With these caveats in mind, in relation to a probable overestimate in most studies of any potential cardiovascular benefit, much of the literature to date also indicates that any protective effects of alcohol will also extend to hypertensive subjects. This was first reported for myocardial infarction in a Scottish study in 1979 in 1305 hypertensive men attending the Glascow Blood Pressure Clinic[51] and subsequently confirmed for both ischaemic heart disease and stroke in a larger British study of 10 000 participants in the Department of Health Hypertension Care Computing Project.[1] The latter study found a 40% decrease in relative risk of stroke in drinkers, with the lowest risk of stroke mortality at intakes of 8–80 g alcohol/week. A decrease in risk of ischaemic heart disease mortality was confined to males only. The beneficial effects of alcohol were offset at intakes > 21 units/week by an increasing incidence of non-circulatory causes of death. In the Scottish study, the protective effect was only significant in those aged 50–59 years and a recent review has once again emphasised that any advice to hypertensive subjects about drinking and cardioprotection should only apply to older subjects.[52] Results from the Physicians' Health Study cohort[53] also suggest that light to moderate alcohol consumption is associated with a reduction in risk of cardiovascular disease mortality in hypertensive men but,

again, this was a report in men whose mean age at baseline was 60 years. In those with a systolic blood pressure of 140 mmHg or higher or a diastolic blood pressure of 90 mmHg or higher, the multivariate adjusted relative risks for cardiovascular disease mortality were 0.82, 0.64 and 0.56 in those who reported monthly, weekly and daily alcohol consumption, respectively, compared with individuals who rarely or never drank alcoholic beverages. However, the observation that the consumption of as little as a single alcoholic drink monthly could reduce overall cardiovascular risk by 18% begs credulity in terms of the known time-course and dose–response of any of the favourable effects of alcohol on cardiovascular risk factor pathways, increasing the likelihood that an unmeasured confounder is the explanation, at least in part, for such findings.

Such an unidentified effect modifier is a likely explanation for the results from a prospective cohort study of French middle-aged men who attended the Center for Preventive Medicine.[54] In that study, in moderate wine drinkers (defined as those who consumed < 60 g alcohol/day and no beer) there was a decreased risk of cardiovascular death by 24% compared with abstainers, but this was not observed in heavier wine drinkers or drinkers of beer and spirits. These observations were also extended to moderate wine drinkers who were hypertensive when the cohort was broken down by quartiles of systolic blood pressure. However, the study did not consider the major dietary and drinking pattern differences that have been consistently reported in relation to predominant beverage choice, with wine drinkers less likely to binge drink, more likely to drink with meals and more likely to make healthier diet choices.[21,55] The most recent report of cardiovascular outcomes in abstinent versus drinking hypertensives was from a post hoc analysis of the LIFE study,[56] in which hypertensives with documented left ventricular hypertrophy were treated with either losartan or atenolol. Overall composite cardiovascular outcomes were less for those on losartan compared with those on atenolol. However, in those drinking more than eight drinks per week, there was no decrease in composite cardiovascular risk while being treated with losartan because a decrease in the incidence of myocardial infarction was offset by an increase in the risk of stroke. Such an increase in risk of stroke has been highlighted previously in the Hisayama Study from Japan, in which hypertension and heavy drinking acted synergistically to increase the risk of both cerebral haemorrhage and infarction two- and threefold, respectively.[57]

The above studies highlight the caution necessary in determining the balance of cardiovascular risks and benefits of alcohol consumption. The absence of any prospective randomized trials of alcohol in relation to myocardial infarction and stroke provide further caution concerning any ultimate conclusions on the overall beneficial or deleterious effects of alcohol consumption for cardiovascular events in both normotensive and hypertensive subjects.

CONCLUSION

It is somewhat paradoxical and, indeed, counterintuitive that alcohol can simultaneously confer increased risk for hypertension but diminish risks for atherosclerotic vascular disease in hypertensive subjects. Given that alcohol-related hypertension is a distinct clinical entity with pathological consequences, it is necessary to err on the side of caution before embracing uncritically the concept that for hypertensive subjects alcohol might be ‘good for you’. Alcohol is not only bad for blood pressure, but chronic heavy consumption and binge drinking at least are also unequivocally bad for ischaemic and haemorrhagic stroke and coronary artery disease outcomes. In addition, heavy drinking increases the risk for left ventricular hypertrophy[58] and increased arterial stiffness,[59] increases the risk of heart failure both with and without associated coronary artery disease,[60] increases the risk of atrial fibrillation[61] and increases the risk for central adiposity,[62] type 2 diabetes mellitus[63] and the metabolic syndrome.[29] Although hypertensive subjects may anticipate a decrease in risk with light drinking, any benefits have probably been overestimated because of unmeasured confounders, reverse causation and failure to account for pattern of drinking or variation in alcohol intake over time. In older hypertensive subjects in developed countries, an intake averaging approximately one to two standard drinks a day in men (10–20 g alcohol) and up to one a day in women (10 g alcohol) would appear to offer the optimal level of consumption in terms of relative benefits and risks. Globally, however, the risks for hypertensive disease, let alone alcohol-related harm more broadly, will be reduced significantly by either abstinence or a substantial reduction in alcohol intake.

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