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NUTRITION AND HYPERTENSION (T MORI, SECTION EDITOR)

Alcohol and Hypertension—New Insights and Lingering Controversies

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Abstract

Purpose of Review To examine outstanding issues in the relationship of alcohol to hypertension. These include whether the increase in BP with alcohol is causally related, the nature of the relationship in women, the contribution of alcohol-related increases in BP to cardiovascular disease and the aetiology of alcohol-related hypertension.

Recent Findings Intervention studies and Mendelian randomisation analyses confirm the alcohol–BP relationship is causal. The concept that low-level alcohol intake reduces BP in women is increasingly unsustainable. Alcohol-related hypertension is in the causal pathway between alcohol use and increased risk for several cardiovascular outcomes. The aetiology of alcohol-related hypertension is multifactorial with recent data highlighting the effects of alcohol on the vasoconstrictor 20-HETE and oxidative stress.

Summary The high prevalence of both alcohol use and hypertension mandates a careful alcohol history in every patient with elevated BP. Early intervention for excessive alcohol use offers the promise of lower levels of BP and reduced risk of adverse cardiovascular outcomes.

Keywords Alcohol · Blood pressure · Hypertension

Introduction

Alcohol-related hypertension is a well-defined clinical entity with a comprehensive foundation based on a large number of cross-sectional and prospective epidemiological studies. Such studies have evaluated worldwide the relationship between alcohol consumption, blood pressure (BP) and hypertension prevalence and incidence over several decades. They have consistently demonstrated that moderate-to-heavy drinkers have higher BP and a greater risk for hypertension. Alcohol intervention trials and recent Mendelian randomisation studies indicate this relationship is causal.

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Intervention Trials

Intervention trials have provided high-level evidence of a direct causal relationship between alcohol and elevated BP. A meta-analysis of 15 intervention trials ($N = 2234$) showed systolic BP (SBP) and diastolic BP (DBP) lower by 3.3/2.0 mmHg with a reduction in alcohol intake [1]. These falls correlated with the percentage change in alcohol intake suggesting a dose-response relationship. The falls were greater in those with higher baseline BP but unrelated to trial duration. A limitation of this analysis was that trials were largely confined to heavier drinkers (≥ 3 drinks/day) limiting conclusions in relation to light-to-moderate alcohol intake and BP. A recent meta-analysis with 2865 participants in 36 trials of at least 7 days and up to 2-year duration showed no change in BP in those who drank ≤ 2 drinks/day (≤ 24-g alcohol/day) [2•]. However, BP fell 5.5/4.0 mmHg when participants consuming ≥ 6 drinks/day reduced their alcohol intake by 50%. Again, there was a strong dose-response association for initial alcohol consumption independent of the length of each trial.

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Mendelian Randomisation Studies

Mendelian randomisation studies enable further exploration of causal links between alcohol consumption, BP and risk of hypertension. Using indicator variables closely linked to alcohol intake, such studies permit analyses less likely to be confounded by lifestyle or socio-economic factors or differential under-reporting of alcohol intake by hypertensives. The 2 major indicator variables have been the G to A mutation of alcohol dehydrogenase 1 (ADH1) on chromosome 4 (rs1229984) and/or the G to A mutation of aldehyde dehydrogenase 2 (ALDH2) on chromosome 12 (rs671). The rs1229984 variant heightens ADH1 activity leading to more rapid oxidation of alcohol to acetaldehyde and has been more commonly utilised in studies in Caucasian populations. The rs671 variant is widespread in eastern Asian populations and results in reduced activity of ALDH2 and decreased metabolism of acetaldehyde. In either case, higher levels of acetaldehyde after alcohol intake result in flushing and nausea and are associated with either reduced or no alcohol intake.

A large Mendelian randomisation meta-analysis of 56 epidemiological studies with 261,991 participants of European descent used the rs1229984 variant [3•]. Carriers of the A allele consumed 17.2% fewer units of alcohol/week (1 unit = 7.9 g alcohol) than non-carriers and had higher abstention (odds ratio (OR) = 1.27), significantly lower SBP (− 0.88 mmHg) and reduced odds of hypertension (OR = 0.94).

A meta-analysis of 8 studies with predominantly Japanese subjects used the rs671 variant of ALDH2 [4]. In males, the GG homozygotes, GA heterozygotes or AA homozygotes had mean alcohol intakes of 20–30 g/day, 10–15 g/day or 0–2 g/day, respectively. BP was 7.44/3.95 mmHg higher in GG vs AA and 4.24/1.58 mmHg higher for GA vs AA, with an estimated increase of 2.4/1.6 mmHg per 10-g alcohol/day. The pooled OR of hypertension for GG vs AA was 2.42 and for GA vs AA, 1.72. In females, alcohol intake was very low with no differences by genotype for alcohol intake or BP. Since this meta-analysis, there have been several large cross-sectional studies from eastern Asia of the rs671 variant of ALDH2 in relation to the level of BP [5–7]. The first found that in South Korean men, the rs671 genotype predicted higher SBP and DBP (1.59/0.85 mmHg per 10-g alcohol/day) and increased risk of hypertension [5]. A study in nearly 5000 southern Chinese men (The Guangzhou Biobank Cohort Study) found that GG homozygotes consumed 10 times as much alcohol (9 g/day) as AA homozygotes [6]. However, at this relatively low alcohol intake, small but significant increases were only seen in DBP (1.15 mmHg per 10 g/day). In a third study from the more northern coastal Chinese province of Jiangsu (3788 male and female diabetic patients and controls), the A allele of rs671 was strongly associated with reduced odds (OR = O.20–0.26) of being an alcohol drinker [7]. Each additional A allele predicted 2.24/1.52 mmHg lower BP in men but not in women where the background prevalence of drinking was very low.

The most recent analysis utilised both the rs1229984 variant of ADH1 and the rs671 variant of ALDH2 [8•]. Participants were from the China Kadoorie Biobank18, a prospective cohort study of half a million adults. This study genotyped a subset of participants (N = 161,498) who were subdivided into one of 9 combinations of the GG, GA and AA polymorphisms of each enzyme. Mean alcohol intake data was estimated for each combination and classified into 6 drinking categories. Among males, SBP increased by 4·8 mmHg (95% CI 4·5–5·1) per 280 g/week genotype-predicted alcohol intake. In the few women who drank alcohol, the genotypes were unrelated to SBP.

In summary, Mendelian randomisation studies consistently support the concept that the relationship between alcohol intake and BP is causal. A lingering concern is that the chosen indicator variables may themselves have a direct influence on BP [9], but such pleiotropic effects were unlikely given similar levels of BP across genotypes in the low- or non-alcohol-consuming females.

Alcohol-Related Hypertension in Women

An important gap in the epidemiological literature relates to the nature of the alcohol–BP relationship in women, with mixed reports. A meta-analysis of 12 cohort studies showed a modest J-shaped relationship in women that was interpreted as evidence of a protective effect of low alcohol intake against hypertension, with a relative risk (RR) of hypertension of 0.82 at quite low intakes (≤ 5 g/day) [10]. At higher intakes, a linear dose-response relationship was found with an increased RR of hypertension of 1.81 at 50 g/day and 2.81 at 100 g/day. In contrast, in men, there was an increased RR of hypertension of 1.57 at 50 g/day and 2.57 at 100 g/day with a linear dose-response relationship. A subsequent meta-analysis of 16 prospective studies (33,904 men and 193,752 women) again suggested protective effects in women consuming < 10 g/day (RR of hypertension = 0.87) but increased risk with a consumption of 31–40 g/day (RR = 1.7) [11]. Once again, there was no significant reduction in risk with low consumption in men but increased risk with a consumption of 31–40 g/day (RR = 1.77). A recent larger systematic review and dose-response sex-specific meta-analysis of 18 prospective studies (125,907 men and 235,347 women) showed no significant change in risk for hypertension in women consuming 12–24 g/day compared with abstainers (RR = 0.94), and a significant increase in risk for those consuming ≥ 36 g/day (RR = 1.42) [12•]. In men, there was a significant and linear increase in the risk of hypertension across all 3 drinking categories (12–24 g/day RR = 1.19, 36–48 g/day RR = 1.51 and ≥ 60 g/day RR = 1.74).

Direct evidence from intervention studies for effects of alcohol on BP in women remains limited. The first meta-analysis of alcohol intervention trials included only one trial in women [1] while the second meta-analysis included data from only 3 trials in women [2]. One of these studies was from our group in which 24 women each undertook 3 consecutive 4-week periods consuming either a low level of alcohol as red wine (42–73 g/week), a higher level of alcohol as red wine (146–218 g/week) or de-alcoholised red wine [13•]. There was no change in BP with lower level intake compared with de-alcoholised red wine, whereas the higher level intake increased 24-h ambulatory BP and HR. This suggests that the previously reported modification of risk for hypertension by gender at low alcohol intake may have been due to unmeasured confounders. In this regard, Roerecke et al. [12•] invoked potential gender differences in pattern of alcohol intake as a possibility, with male drinkers likely consuming more per drinking occasion; however, data on pattern of drinking was not assessed in most prospective studies.

Alcohol-Related Hypertension and Cardiovascular Disease

Although the evidence that alcohol directly elevates BP and increases the risk of hypertension is robust, the implications for cardiovascular disease (CVD) risk remain an area of contention. While alcohol adversely impacts BP, the regular light-to-moderate consumption of alcohol has been associated with possible beneficial outcomes for several other cardiovascular (CV) risk factors such as higher levels of HDL cholesterol (HDL-C), lower fibrinogen and insulin levels, improved glycaemic control and reduced inflammation. Such effects of alcohol have been invoked in the aetiological pathway between light-to-moderate alcohol intake and a reduced incidence of ischaemic heart disease (IHD) and myocardial infarction (MI) [14]. However, the relationship of alcohol use to CV outcomes is quite heterogeneous. This possibly reflects differences in the relative weight of predisposing risk factors on CV endpoints. For example, an alcohol-related increase in HDL-C may outweigh adverse effects of alcohol on BP in relation to IHD while for haemorrhagic stroke, an alcohol-related increase in BP may be more relevant. It also reflects the marked heterogeneity of the effects of alcohol on CV outcomes in relation to the amount of alcohol consumed, with the association often J-shaped or U-shaped, light-to-moderate consumption conferring a decrease in risk and heavier and hazardous consumption either attenuating any decrease or actually increasing risk.

Such heterogeneity was highlighted recently by a study of 1,937,360 patients in the CALIBER (CArdiovascular research using LInked Bespoke studies and Electronic health Records) programme in England which analysed alcohol consumption and initial presentation of 12 CVDs [15•]. The study excluded patients with prior CVD thus addressing one issue consistently raised as a possible reason for J-shaped associations—that of reverse causality—individuals reducing their alcohol intake because of a prior diagnosis of CVD [16]. They found lower risks of unstable angina, MI, unheralded coronary death, heart failure, ischaemic stroke, peripheral arterial disease and abdominal aortic aneurysm with moderate drinking (alcohol intake within UK national guidelines) compared with non-drinkers. Lower risks of stable angina or MI were also observed with heavier drinking (exceeding UK guidelines). However, this heavier drinking was simultaneously related to increased risks of unstable angina, unheralded coronary death, heart failure, ischaemic stroke, peripheral arterial disease and abdominal aortic aneurysm. These associations were largely unchanged after adjustment for SBP but nearly a fifth of the cohort were using antihypertensive drugs.

Further insights into alcohol-related hypertension as a CV risk factor come from a study of CV outcomes in 599,912 current drinkers that characterised the dose-response associations and calculated hazard ratios (HR) per 100 g/week of alcohol (12.5 units/week) across 83 prospective studies from 19 high-income countries [17•]. After adjustment for potential confounders, the amount of alcohol consumed was positively and linearly associated with stroke (HR = 1·14), coronary disease excluding MI (HR = 1·06), heart failure (HR = 1·09), fatal hypertensive disease (HR = 1·24) and fatal aortic aneurysm (HR = 1·15). In contrast, there was an inverse and log-linear association with MI (HR = 0·94). Adjustment for SBP strengthened the inverse association between alcohol consumption and MI, but weakened the positive associations between alcohol consumption and all other CVD outcomes suggesting that elevated SBP could be mediating the positive association of alcohol with stroke, coronary disease excluding MI and heart failure. One point of contention is that non-drinkers and former drinkers were not included. If included, they indicated U-shaped associations between alcohol and CV mortality but were excluded because of notable differences between never drinkers and current drinkers in relation to gender, ethnicity, smoking and diabetes status.

Mendelian randomisation analysis can minimize such confounding from lifestyle or socio-demographic factors in assessing alcohol in relation to CV outcomes. As observed for BP, with both the rs671 variant of ALDH2 and the rs1229984 variant of ADH1 as indicator variables, there was a strong positive association between HDL-C levels and alcohol intake using either conventional epidemiologic or genotypic analysis [8•]. In men, the conventional epidemiological approach of directly measured alcohol intake showed J-shaped relationships with haemorrhagic and ischaemic stroke, acute MI and total coronary artery disease (CAD). However, for haemorrhagic and ischaemic stroke, risk increased progressively across the whole range of genotype-predicted alcohol intake, with no

evidence of a decrease in stroke risk with lighter intake [8•]. The increase in risk was twice that predicted from increase in BP alone, possibly because of adverse effects of alcohol on other unmeasured risk factors. For both acute MI and total CAD, there was no relationship with genotype-predicted mean alcohol intake which was interpreted as possibly indicating that any adverse CAD outcome from alcohol-related increases in BP was offset by the substantial increase in HDL-C [8•]. The stark contrasts between the conventional epidemiological and genetic analyses once again raised the question of unmeasured confounders and/or reverse causation as determinants of the J-shaped relationships observed with conventional epidemiological analyses.

Hypertensive heart failure is another potential adverse outcome from alcohol-related hypertension. A recent meta-analyses of 8 prospective studies (N = 202,378, 6211 cases of heart failure) concluded that light-to-moderate alcohol consumption (< 14 drinks/week) was associated with a reduced risk of heart failure (RR = 0.85) with no reduction in risk above this level [18]. Heart failure risk was increased with heavier alcohol intake in 2 of the studies discussed above [15•, 17•]. In contrast, recent data from the Second Australian National Blood Pressure Study found no evidence in older hypertensive adults of increased risk of incident heart failure after 10.8 years of follow-up in those drinking more than 14 drinks/week when compared with that in never drinkers [19]. However, all participants were commenced on either a diuretic or ACE inhibitor at baseline which could have obscured any potential detrimental effect of alcohol on heart failure.

Reports on possible effects of alcohol-related hypertension on the risk of end-stage renal disease have been varied [20]. In the Australian Diabetes, Obesity and Lifestyle study, moderate-to-heavy versus light alcohol consumption was associated with an elevated risk of albuminuria in both men and women over 5 years but there was a simultaneous and counter-intuitive reduced risk of a lower estimated glomerular filtration rate (eGFR) [21]. More recent meta-analyses including case-control, cross-sectional and prospective population studies have indicated that across the range from low-to-high alcohol intake (60 g/day), drinkers have lower rates of decline in eGFR and proteinuria [22, 23]. Recent US prospective studies, including the Prevention of Renal and Vascular End-Stage Disease study (N = 5476) [24] and the Atherosclerosis Risk in Communities study (N = 12,962) [25], have found that this decreased risk of decline in eGFR persisted after inclusion of SBP in their models with either no change in the estimated reno-protective effect [24] or slight attenuation [25]. It was speculated that this protection might be mediated through decreased renal arteriosclerosis and/or a decreased risk of type II diabetes mellitus [25].

Alcohol and the Metabolic Syndrome

Hypertension often occurs as part of a cluster of CV risk factors—central adiposity, dyslipidaemia with high triglycerides and low HDL-C and insulin resistance—collectively known as the metabolic syndrome. The heterogeneity across the spectrum of alcohol intake, including an adverse effect on BP as opposed to a potentially favourable influence on HDL-C and insulin sensitivity, at least at lower levels of intake, has led to a confusing picture when alcohol consumption has been evaluated against the prevalence and/or incidence of the metabolic syndrome. This may also reflect conflicting findings as to whether alcohol consumption leads to weight gain [26, 27] or central adiposity [28].

The positive relationship between alcohol use and HDL-C levels would suggest that this might contribute to a reduced incidence of the metabolic syndrome while the opposite would be anticipated for BP. Such a divergent outcome, dependent on level of intake, was found in a meta-analysis of 6 prospective studies where there was a J-shaped relationship between alcohol and the metabolic syndrome with a reduction in light drinkers (up to 5 g/day) (RR = 0.86) but an increase in those drinking > 35 g/day (RR = 1.84) [29]. Recent studies have reported an increased association of the metabolic syndrome with heavier drinking [30–32], a lower prevalence with lighter drinking [33, 34] or both [35]. Interestingly, several reports have shown an association between increased prevalence of the metabolic syndrome and binge drinking [30–32], this being sometimes greater in occasional heavy drinkers than in regular heavy drinking [30]. In the Brazilian Longitudinal Study of Adult Health, the type of alcoholic beverage and consumption of alcohol with meals were also identified as potential predictors [36].

Alcohol-Related Hypertension and Type II Diabetes Mellitus

Type II diabetes mellitus is associated with an increased risk of hypertension, features of the metabolic syndrome, a pro-inflammatory state, increased oxidative stress and a prothrombotic state with haemostatic and fibrinolytic abnormalities. The reduction in risk seen for IHD with light-to-moderate alcohol intake extends to patients with type II diabetes mellitus [37], raising the question of the overall balance of risks of drinking alcohol in this setting. Gaining a better understanding of the effects of alcohol on BP versus other CV risk factors in type II diabetes mellitus has therefore been a recent research priority.

The CASCADE (CArdiovaSCulAr Diabetes and Ethanol) trial uniquely recruited 224 participants with type II diabetes mellitus who drank less than 1 alcoholic drink/week and randomly assigned them to consume 150 ml of red wine, white wine or mineral water with dinner for 2 years [38].

Improvements in glycaemic control were only seen with white wine. HDL-C levels increased only with red wine and in a subsequent report, this increase appeared to be largely confined to females [39]. Red wine improved the total number of components of the metabolic syndrome, but had no effects on visceral adiposity or abdominal fat distribution [40]. After 2 years, there were no significant differences in BP across the 3 groups. However, in a sub-study measuring 24-h ambulatory BP, there was a transient decrease in BP overnight after 6 months of red wine versus mineral water [41]. These divergent results for red and white wine do not provide a firm basis for optimal advice on instituting alcohol use in non-drinkers with type 2 diabetes.

A second trial addressed the balance of effects on BP, diabetic control and CV risk factors in participants with type II diabetes [42•]. They entered a three-period cross-over study where for each 4-week period, they consumed either red wine (women drinking 24 g and men drinking 31 g alcohol/day), equivalent volumes of dealcoholized red wine or water alone. There was no effect of alcohol on HDL-C or fibrinogen levels and glycaemic control and insulin sensitivity were unaffected, despite a higher daily alcohol intake than in the CASCADE trial. There were no improvements in inflammatory markers, mediators of inflammation resolution or markers of oxidative stress [43]. There were, however, biphasic effects of alcohol on 24-h ambulatory BP with higher awake SBP and DBP and a fall in asleep DBP while both awake and asleep heart rate increased. Such biphasic effects of alcohol are well described and may relate to initial vasodilation after alcohol ingestion followed by a later pressor effect. The unfavourable effects on awake BP and HR highlight the desirability of longer term trials with hard CV endpoints to inform recommendations on optimal alcohol use in type II diabetes mellitus; however, such trials may be hard to implement.

Aetiology of Alcohol-Related Hypertension

The potential aetiology of alcohol-related hypertension has been previously reviewed [44, 45]. Much of the research in this area has been in animal models which have largely substantiated that alcohol raises BP [45]. Animal studies cannot account for additional modifiers such as the pattern of drinking, chronicity of alcohol use, type of alcoholic beverage, other risk factors and predisposing genetic traits. Overall, the evidence suggests that alcohol-related hypertension is multifactorial in nature, including effects on the autonomic nervous system, the renin-angiotensin axis, baroreceptor sensitivity and enhanced calcium flux into vascular smooth muscle cells increasing vascular reactivity [44]. The search for gene-environment interactions in the context of alcohol–BP inter-relationships also continues. The largest study to date was a genome-wide association study in which gene–alcohol interactions with BP were explored in a meta-analysis across 570,000 individuals [46•]. A large number of potential genes or single nucleotide polymorphisms were identified, many of which were novel, and several related to both BP and alcohol metabolism or dependence.

A focus on the endothelium has attempted to understand the balance of effects of alcohol on the release and sensitivity to the vasodilator nitric oxide versus vasoconstrictors such as endothelin and angiotensin II, with the hypothesis that alcohol-induced endothelial dysfunction, especially in combination with alcohol-related oxidative stress and inflammation, may be a precursor to hypertension and atherosclerotic vascular disease [45]. A cross-sectional Japanese study of 404 men used flow-mediated dilatation (FMD) to measure endothelial dysfunction and showed increased odds of impaired function in heavy drinkers (> 46 g/day) even after adjustment for SBP (OR = 2.39) [47]. A case-control study in Chinese alcoholics found a similar decrease in FMD as well as a decrease in nitrate-mediated dilatation in the heaviest drinkers, implying additional underlying vascular smooth muscle damage [48]. In a larger Japanese study ($N = 2734$), a linear and inverse relationship was seen between FMD and alcohol consumption [49]. Both SBP and prevalence of hypertension increased with increasing alcohol intake. BP was negatively correlated with FMD but the reduced FMD with drinking remained after adjusting for BP. We were unable to demonstrate any change in FMD during an alcohol intervention in moderate-to-heavy drinkers [50] suggesting impaired endothelial function might be irreversible with high alcohol consumption [49].

Our group has examined whether arachidonic acid metabolites mediate alcohol-related hypertension. Arachidonic acid is metabolised by cytochrome P450 4A and 4F isoforms into 20-hydroxyeicosatetraenoic acid (20-HETE), a potent vasoconstrictor. In a cross-sectional study of treated hypertensive subjects, we reported a significant correlation between usual alcohol intake and 24-h urinary 20-HETE excretion [51]. We have since demonstrated a relative increase in plasma 20-HETE over 24 h following acute ingestion of alcohol in association with a biphasic effect of alcohol to lower BP acutely but to increase BP the following day [52]. We subsequently showed in healthy males that ~ 60 g/day reduction in alcohol intake for 4 weeks reduced 24-h urinary 20-HETE [53]. Reduced 20-HETE levels after alcohol reduction were associated with a decrease in F_2-isoprostanes—markers of in vivo lipid peroxidative damage formed via non-enzymatic free radical attack on arachidonic acid [53]. This raises the question whether, apart from its possible impact on BP, an increase in 20-HETE levels could also be relevant to any effects of alcohol on chronic oxidative stress and vascular inflammation. 20-HETE activates nF-κB and the MAPK/ERK signalling pathways in human endothelial cells inducing the expression of pro-inflammatory cytokines and transforming endothelium to an inflammatory phenotype [54, 55].

We recently examined the balance of these effects of alcohol on 24-h ambulatory BP, 20-HETE, oxidative stress (F_2-isoprostanes), markers of both inflammation (high-sensitivity C-reactive protein (hs-CRP)) and specialized pro-resolving mediators of inflammation (SPMs) in men regularly drinking between 40 and 100 g alcohol/day [56•]. They consumed either red wine (41 g alcohol) or the equivalent volume of dealcoholized red wine or water with their evening meal during 3 study periods, each of 4-week duration. Drinking alcohol increased 20-HETE and oxidative stress which may have contributed to the increases in ambulatory SBP and DBP. There was a coincident increase in the SPMs, resolvin D1 and 17R-resolvin D1, but no change in hs-CRP, so the increase in resolvins could be interpreted as a homeostatic response ameliorating any acute inflammatory response to alcohol.

A mechanism for increased 20-HETE with alcohol has not been established but we suggested that stimulation of the sympathetic nervous system may be relevant [52]. More speculatively, we raised the possibility that because both alcohol and 20-HETE are substrates for alcohol dehydrogenase (ADH) [57], any increase could reflect inhibition by alcohol of the oxidation of 20-HETE [52]. Others have suggested that up-regulation of expression of both ADH and CYP4A isoforms in glomerular podocytes by low-to-moderate alcohol intake can increase the synthesis of 20-HETE [58].

Implications for Hypertension Prevention, Diagnosis and Management

The high rate globally of alcohol consumption led to the recent suggestion that alcohol-induced hypertension may be one of the most prevalent forms of secondary hypertension [59]. Although somewhat tongue-in-cheek, this statement highlights that no matter the setting in which an increase in BP is found, physicians should always take a careful alcohol history.

The necessity for an alcohol history should extend to the setting of pre-hypertension (BP > 130/80 mmHg but < 140/90 mmHg). In a Japanese population, alcohol drinking independently predicted a 1.45-fold increase in the odds of pre-hypertension in males but not in females [60]; however, alcohol drinking in women was very low. Another Japanese cross-sectional study of 22,602 men showed a dose-response relationship between alcohol intake and the prevalence of pre-hypertension with 1.35-, 1.75- and 2.35-fold increases in the odds of being light, heavy or very heavy drinkers vs non-drinkers [61]. Data from 11,194 participants in the US National Health and Nutrition Examination Survey (NHANES) identified ~ 30% as pre-hypertensive, and they had a 12% reduction in the odds of being non-drinkers or moderate drinkers compared with being heavy or binge drinkers [62]. Alcohol consumption also predicts hypertension in individuals initially characterised as pre-hypertensive. In a Swedish birth cohort of 628 men, alcohol consumption at age 40 years was associated with progression to hypertension at 43 years, with BMI, weight change and alcohol intake the most important determinants of progression from pre-hypertension to hypertension over a 6-year period [63].

Three recent studies have raised a possible role for binge drinking in the genesis of an increase in SBP in adolescents and young adults [64, 65•, 66•]. In a prospective study from Canada, 756 males were followed up at 20 and 24 years of age in relation to their pattern of drinking and SBP [64]. Weekly or monthly binge drinking at 20 years predicted SBP at 24 years that was 2.9 and 3.6 mmHg higher than in non-binge drinkers, respectively. More weekly and monthly binge drinkers than non-binge drinkers met the criterion for a diagnosis of pre-hypertension. In the US NHANES, men 18–45 years who binge drank either 1–12 times or > 12 times in the past year had higher SBP (121.8 and 119 mmHg, respectively) compared with non-binge drinkers (117.5 mmHg) [65•]. The National Longitudinal Study of Adolescent to Adult Health determined if binge drinking in adolescence (12–18 years) and early adulthood (24–32 years) were associated with high BP [66•]. In adolescence, the risk of BP > 130/80 mmHg was high with infrequent binge drinking (OR = 1.23). The risk of BP > 140/90 mmHg was even higher with frequent binge drinking (OR = 1.64). Frequent binge drinking in both adolescence and early adulthood was associated with an OR = 2.43 for BP > 140/90 mmHg. Collectively, these data emphasise the need for widespread alcohol screening and counselling in young people if later onset of hypertension and CV disease are to be prevented.

Another increasingly recognised presentation for alcohol-related hypertension is that of masked hypertension (MH), defined as normal clinic BP in the face of elevated BP when measured with either 24-h ambulatory or home BP monitoring. Increased alcohol consumption was first reported in 2000 as a predictor of MH in a cohort of otherwise healthy participants [67] and has consistently associated with MH in cross-sectional studies since [68–71]. A recent cross-sectional study from Turkey indicated that alcohol consumption was more common in participants with MH than in participants with true pre-hypertension (RR = 2.7) [72]. A recent prospective study from Canada of 1836 initially normotensive participants, followed on average for 2.9 years, indicated that consuming ≥ 6 drinks/week was associated with an increased RR of MH of 1.65 [73]. Appreciating that excessive alcohol intake is a predictor of MH may be clinically important, especially if the patient has other CV risk factors or evidence of hypertensive target organ disease.

Heavy alcohol intake has been shown to exaggerate the early morning surge in BP characteristic of the normal BP diurnal rhythm. This has been observed in a population-based sample [74] and in untreated hypertensives [75]. In untreated hypertensives, heavy alcohol intake (≥ 46 g/day)

was estimated to increase by 2.7-fold the risk for an exaggerated early morning surge in BP [75], which may be relevant to increased risk of stroke in heavy drinkers.

A surprising outcome of recent population-based studies has been that a diagnosis of hypertension has not led to changes in drinking behaviour. In a prospective Australian study, the 45 and Up Study, odds ratios of quitting drinking in relation to 32 newly acquired health conditions were evaluated; quitting drinking was significantly associated with 24 of these during a median 5.3-year of follow-up. This included heart disease and stroke but there was no change in the odds of drinking cessation in the nearly 10,000 participants diagnosed with hypertension [76]. Similarly, data from the US NHANES showed awareness of hypertension status did not associate with different levels of alcohol consumption when compared with those unaware [77]. In both groups, excessive consumption (defined as > 1 drink/day for women and > 2 drinks/day for men) was high (24.7% and 32.2%, respectively).

These observations may have their genesis in the low rate of screening or brief interventions for hazardous or harmful alcohol consumption by primary care physicians in the management of hypertension [78•, 79]. In 4000 hypertensive patients from the US NHANES, only 25.5% reported being told to reduce alcohol use for hypertension control [80]. An internet-based survey of over 300 physicians from Europe reported in hypertensive patients only one-third of general practitioners sufficiently screen for alcohol intake and only one in 5 delivers brief interventions to reduce hazardous intake [78•]. Only 28.6% and 14.5% of physicians attending cardiovascular or internal medicine scientific meetings, respectively, reported screening alcohol consumption in patients with newly detected or treatment-resistant hypertension [79].

These findings may in part result from a failure to mention alcohol-related hypertension in some national hypertension management guidelines [81]. In addition, in undergraduate and/or post-graduate clinical training, there may be an insufficient emphasis on both screening for alcohol as a major contributing factor to the prevalence of hypertension, as well as education in brief intervention techniques [78•]. Modelling of the potential benefits of rigorous screening and intervention for hypertensive patients with excessive alcohol consumption suggests there would be a marked increase in the proportion of the general population with a BP < 140/90 mmHg [81]. However, evidence from randomised controlled trials in the primary care setting of improved BP outcomes in hypertensive patients after screening and brief intervention for at-risk drinking still remains mixed [82, 83]. This may reflect ineffectiveness of the brief interventions [84] or targeting for intervention only those with established hypertension rather than all those with at-risk drinking habits [85]. Telehealth brief interventions in the primary care setting in the management of alcohol misuse in hypertensive patients have been comprehensively canvassed [86]. The utilisation and evaluation of effective brief interventions for hazardous drinking remain a priority for future research in hypertensive drinkers, especially if linked to any influence on CV morbidity.

A final word of caution relates to the finding of treatment-resistant hypertension, defined as taking 3 or more antihypertensive medication classes with uncontrolled BP. Given the established effects of alcohol to increase BP in treated hypertensives [87], an alcohol history in this setting is now standard advice in most guidelines and should be viewed as routine before ascribing poor BP control to treatment resistance alone. Alcohol misuse has been directly linked to reduced compliance with antihypertensive medication [88]. Recently published evidence in 3640 participants in the Health Survey of England 2014 indicated inadequate hypertension control in treated hypertensives consuming > 60 g alcohol/day [89]. However, population-based studies of lifestyle factors in association with treatment-resistant hypertension are yet to definitively associate excessive alcohol intake with this phenotype [90].

Conclusions

1. Intervention studies where regular drinkers have altered their intake, together with Mendelian randomisation studies, where polymorphisms of enzymes critical for alcohol metabolism have been utilised as indicator variables, have provided high-level evidence for a causal basis between regular alcohol use and an increase in BP.
2. This increase is seen in both men and women. The concept that low-level alcohol intake reduces BP in women is not supported by intervention studies or a recent large meta-analysis of prospective population studies.
3. Increases in BP may contribute to increased risk for CV outcomes with heavier drinking such as ischaemic and haemorrhagic stroke, heart failure, some CAD outcomes, peripheral arterial disease and abdominal aortic aneurysm.
4. Alcohol-related increases in BP need to be considered by every physician after finding either high-normal or elevated BP and also where hypertension is masked, labile or resistant to treatment.
5. A careful alcohol history and early initiation of intervention strategies for excessive alcohol use offer the promise of reversal of increased levels of BP and reduced risk of adverse CV outcomes together with the wider health benefits of drinking within established safe guidelines.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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