expression or up-regulation of vascular inducible nitric oxide synthase. However, acute alcohol intake is known to increase heart rate and sympathetic activity. The group of Narkiewicz observed that pressor responses to acute alcohol consumption were potentiated in hypertensive patients compared with normotensive controls.[7] Thus, excessive activation of sympathetic neural mechanisms might contribute to both alcohol-related BP increases and cardiovascular events in hypertensive patients.

The cardiovascular effects of low levels of alcohol consumption are not entirely clear. The purported cardio-protective benefits of low/moderate alcohol consumption is unlikely to be solely related to BP reduction. Alcohol improves lipid profile, decreases the risk of thrombosis, and reduces insulin levels. In one prospective study, low alcohol consumption (150 mL red wine/day) showed a significant decrease in BP only 3–4 h after ingestion. In the same study, those assigned to the wine group who were homozygous for the gene variant encoding fast ethanol metabolism, ADH1B*2 (TT), had a significant decrease in mean 24-h systolic BP and pulse pressure when compared with the non-fast metabolizers.[8]

Abstinence or moderation?

Commandment # 6 of Williams' and Mancia's Ten Commandments of the 2018 ESC/ESH HTN Guidelines on Hypertension in Adults[9] simply states: '*lifestyle interventions such as sodium restriction,* **alcohol moderation**, *healthy eating, regular exercise, weight control, and smoking cessation, all have health benefits beyond their impact on blood pressure*'.

The hypertensive effect of alcohol truly matters for population health, since alcohol-induced hypertension may be one of the most prevalent form of secondary hypertension. But what does this mean for an individual patient with hypertension? A heavy drinker should be strongly encouraged to cut back on his or her alcohol intake in an effort to better control BP, since hypertension associated with alcohol drinking may be reversible with abstinence.

In no uncertain terms did a recent paper in the Lancet state: 'Alcohol use is a leading risk factor for global disease burden and causes substantial health loss. We found that the risk of all-cause mortality, and of cancers specifically, rises with increasing levels of consumption, and the level of consumption that minimizes health loss is zero'.[10] However, the authors documented a clear J-shape curve between alcohol consumption and ischaemic heart disease and ischaemic (but not haemorrhagic) stroke. For ischaemic heart disease the authors found a significant lower relative risk up to three standard drinks per day.

Cardiovascular disease remains the leading cause of death as is noted in the 2006 year-end statement of the American Heart Association: 'In the past 100 years, only during the 1918 flu pandemic cardiovascular disease was not the number-one cause of death'.[11] Admittedly, the ratio between cardiovascular death and cancer death has fallen almost by half, i.e. from 2.9 to 1.6 over a quarter of a century,[12] but ischaemic heart disease and stroke have by no means disappeared and are even growing in developing countries. Why then did the J-curve pattern of these two diseases in the above Lancet study not cause even a minimal dip or flattening in the ascending curve of total mortality with increasing alcohol consumption?

All in all, excessive alcohol consumption is clearly related to high BP. Of note, alcohol is unique among addictive substances in that it has been subject to an eclectic array of quips and wisecracks that are prone to trivialize its use and abuse. However, despite its well documented vasodilatory properties, clinical evidence does not endorse the saying by P. G. Wodehouse of alcohol being 'a misunderstood vitamin'. The data remain muddied regarding low drinking levels; alcohol either reduces BP some or could be an innocent bystander only.

Until, we have better insight the Greek Dictum 'Παν μέτρον άριστον' 'Everything in moderation' with the *sotto voce* amendment of Framingham's William B. Kannel: 'Everything in moderation—even moderation. . .' seems a reasonable compromise.

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References

References are available as supplementary material at *European Heart Journal* online.

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Are the cardiac effects of alcohol good, bad, or neither?

There are consistent observational data to indicate that the association between alcohol use and adverse cardiac outcomes as a whole is U-shaped; that low-moderate amounts of alcohol use (up to one drink or 12.5 g alcohol per day in women and up to two drinks or 25 g per day in men) are associated with a reduced risk of overall cardiovascular events and mortality (*Figure 1*) when compared with abstinence or heavy alcohol use.

However, this generalization masks important nuances that merit closer scrutiny.

Patterns of drinking, the type of alcohol consumed, and factors associated with alcohol consumption, such as socio-economic status, education, and dietary patterns may be important modifiers of the cardiac effects of alcohol. Alcohol use may also have differing effects in healthy hearts, when compared with those with established cardiac disease,

and in particular, left ventricular dysfunction; and alcohol's effects on coronary outcomes may differ from its effects on arrhythmias, on heart failure risk, on atrial fibrillation, and on the risk of ischaemic stroke and intracerebral haemorrhage.

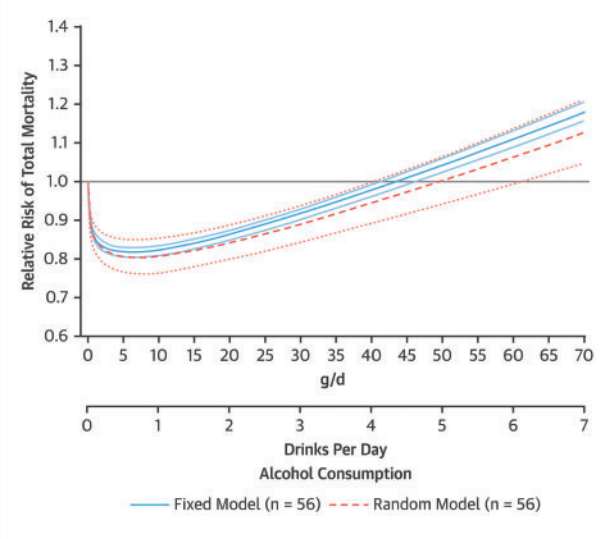

Figure 1 The U-shaped relationship between alcohol use and all-cause mortality. Reproduced with permission from Ref.[1]

It is important to acknowledge that even if there is a beneficial cardiac effect of a modest level of alcohol intake, the net health consequences may still be negative when we consider the risk of cancer, injury and cirrhosis associated with alcohol use.

Finally, the observational data that have given rise to the popular tenet that modest amounts of alcohol may have beneficial cardiac effects are subject to the same limitations and potential for bias and confounding as any other observational data. We have repeatedly seen positive, biologically plausible associations that have been proven non-causal by subsequent randomized trials (e.g. vitamin D and cancer prevention; hormone replacement therapy and cardiovascular disease prevention).

While tempting to point to the large number of individuals on whom the U-shaped relationship is based as evidence for the robustness of the association between low-moderate alcohol use and favourable cardiac outcomes, these large numbers may simply serve to make a biased or confounded relationship more precisely biased or confounded.

For these reasons, restraint should be shown before endorsing the use of alcohol to reduce cardiovascular risk.

Pattern of drinking

An average of up to one drink per day in women and up to two drinks per day in men is considered moderate alcohol consumption, and this pattern is associated with lower cardiovascular outcome rates. If, however, this weekly quantity is consumed during a single day, the reverse

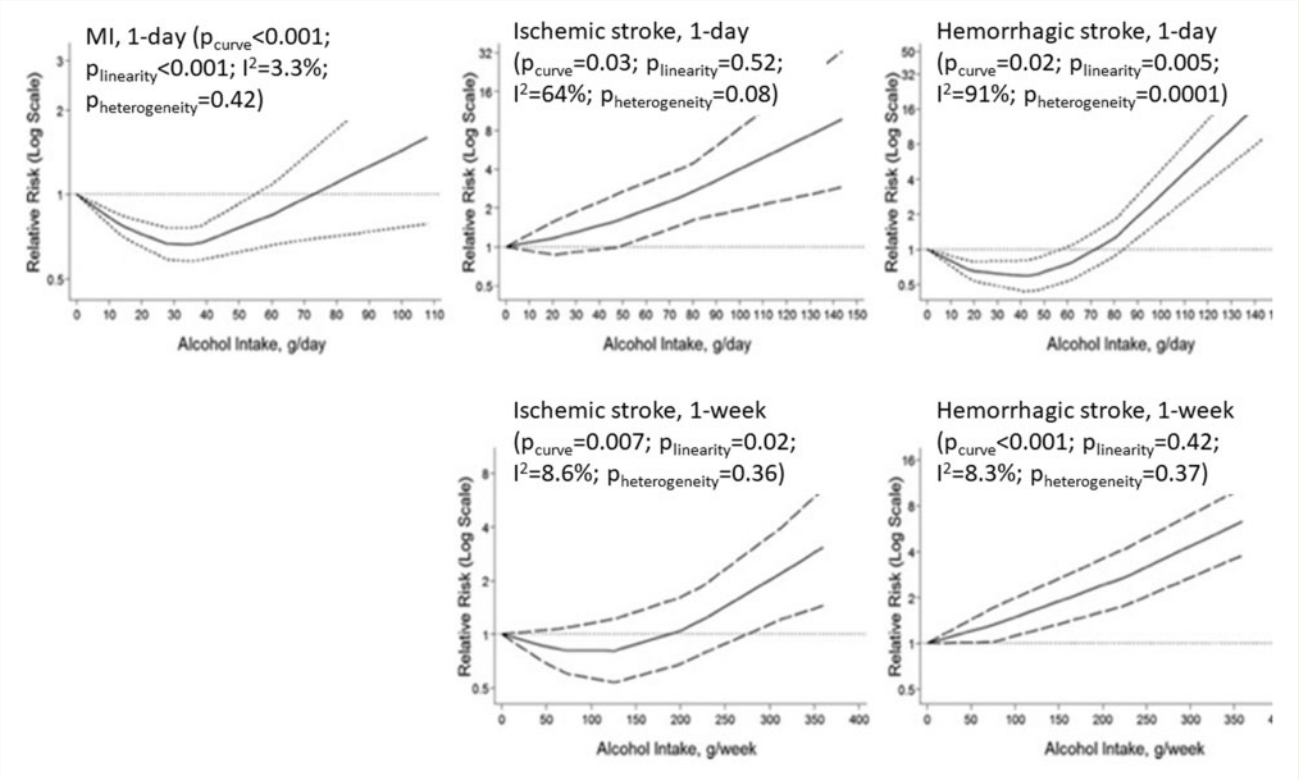

Figure 2 The relationship between acute alcohol use and the risk of cardiovascular events. A heavy episode of alcohol consumption is associated with an increased acute risk of harmful cardiovascular events. Reproduced with permission from Ref.[2]

is observed. Binge, or heavy episodic alcohol use, typically defined as the consumption of ≥5 drinks during any one day, is associated with an increased risk of adverse cardiovascular events (*Figure 2*) and all-cause mortality. Furthermore, heavy acute alcohol use may be a trigger that acutely precipitates myocardial infarction. Therefore, heavy episodes of alcohol use should be discouraged.

Type of alcohol use

There remains uncertainty whether some types of alcohol are harmful (e.g. beer or spirits) and others protective (e.g. wine). Types of alcohol consumed are highly likely to be associated with potentially confounding factors, such as socio-economic status and pattern of drinking.

Alcohol use in established left ventricular dysfunction

In vitro, alcohol has demonstrated toxic effects on cardiomyocytes. In the CARDIA study, alcohol intake was associated with adverse cardiac remodelling during 20 years' follow-up. Heavy alcohol use may be associated with the development of alcoholic cardiomyopathy. As the causal factor in this condition, abstinence should intuitively be recommended in those with non-ischaemic cardiomyopathy where alcohol use may play a causal role.

It appears paradoxical that observational data on alcohol use in other populations with systolic left ventricular dysfunction (e.g. analyses from SOLVD) suggest that low-moderate alcohol consumption in these groups is associated with better cardiovascular outcomes than abstinence or heavy consumption. While this apparent paradox may be due to differences in the quantities of alcohol consumed between those who develop alcoholic cardiomyopathy and those with heart failure who have a better outcome at low-moderate consumption levels, it seems counter-intuitive to advocate the use of a potential myocardial toxin in those who exhibit significant myocardial injury.

Non-cardiovascular effects of alcohol

The relationship between alcohol use and cardiovascular outcomes does not appear homogeneous. Alcohol use has been associated with an increased risk of intracerebral haemorrhage, even at low-moderate levels of consumption. Also, there appears to be a continuous positive association between alcohol use and the risk of cancer. Consideration of non-cardiovascular effects must be made when evaluating the potential risks and benefits of alcohol use.

Mendelian randomization studies

Adequate randomized, controlled trials of alcohol use are lacking. Mendelian randomization is a genetic epidemiologic approach that leverages the assumed random assortment of genetic variants to evaluate the causal relationship between a risk/protective factor and clinical events. A major advantage of Mendelian randomization approaches are that genetics are not susceptible to reverse causation, unlike behavioural exposures. The available Mendelian randomization data are not consistent with a beneficial cardiovascular effect of alcohol. This new line of research adds to the uncertainty about the causal nature of the relationship between alcohol use and cardiovascular outcomes.

Conclusion

The answer to the question, 'Are the cardiac effects of alcohol good, bad, or neither?' remains elusive because our best scientific tool to address this question—the randomized, controlled trial—has not been successfully implemented. While some cite ethical reasons for the paucity of randomized data, a larger barrier to the conduct of a trial randomizing adults to low-moderate alcohol use vs. abstinence is one of practicality. Funding such a trial would be challenging, a potentially prohibitively large sample size would be required, especially given anticipated cross-over rates, and masking is likely to be imperfect in the absence of a suitable placebo.

Faced with the reality that we may never be able to answer the question posed in the title, a prudent approach would be to accept a low-moderate level of alcohol use in those without significant cardiomyopathy or cirrhosis.

No matter how voluminous and consistent the observational evidence, it is not sufficient to justify recommending alcohol use for the prevention of adverse cardiovascular events.

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References

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