1.1.1 ***Alcohol***

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1.1.1.1 Summary

A large number of epidemiological data—both on apparently healthy people and on patients with a history of cardiovascular events—indicate a consistent reduction in the risk for cardiovascular events or for all-cause mortality among moderate alcohol drinkers, but, on the other hand, the harm of excess and irregular drinking.

A J-shaped relationship between cardiovascular and total mortality and increasing amounts of alcohol consumed was consistently observed in several meta-analyses, showing that low to moderate consumption of alcohol (no more than one drink daily in women and two drinks in men) significantly reduces total mortality, while higher doses increase it. Definitions of standard drinks vary between countries, but in this paper a standard drink is considered to contain 10 g of alcohol (ethanol), which is equivalent to 250 ml (half a pint) of beer, a small glass of wine or a 40 ml measure of spirits.

There is no reason to discourage adults who are already regular light-moderate alcohol consumers from continuing. Although low-moderate, non-binging alcohol consumption—in the absence of contraindications and in the context of healthy eating and a healthy lifestyle—reduces the risk of coronary heart disease, it is not recommended that adult abstainers begin drinking. This is because even moderate alcohol intake is also associated with increased risk of other harm and there is a risk that some of those who start to drink will consume more than the low-risk drinking limits. For these reasons it is not recommended that anyone be advised to drink more frequently on health grounds.

The hazards of excess or binge drinking should be always highlighted and heavy or binge drinkers urged to cut their consumption.

Regarding cardiovascular patients, if not contraindicated, regular alcohol consumers should not exceed one drink/day for women (10 g) or up to two drinks/day (20 g) for men as a component of a balanced cardio-protective dietary pattern, with appropriate energy intake levels. At present, a cardiovascular patient who is teetotal should neither be recommended, nor "prescribed" to start drinking for health gain.

The protective effect of regular and moderate alcohol consumption in coronary heart disease and ischaemic stroke has been consistently shown in many epidemiological

studies.[1,2,3,4] The association between alcohol consumption and CHD mortality is described through a J-shape relationship, where teetotallers and heavy drinkers are at the highest risk whereas light-moderate drinkers are at the lowest risk. However, if low alcohol intake is inversely related to CHD, the other side of the coin shows an increased risk for certain cancers, cirrhosis and death from accidents mainly associated with increasing alcohol consumption. [5,6,7] Total mortality was also reduced in moderate drinkers; however, excess drinking is definitely harmful.[6]

The absence and the unfeasibility for ethical considerations of randomised controlled trials leave room for residual uncertainty about cardiovascular protection by alcohol consumption and consequently there has been a point-counterpoint debate on this topic in scientific literature.[8,9,10]

In the last decade, several open questions have been addressed: the confounding factors and the weakness of study design (choice of reference category), the role of different alcoholic beverages, the effects of alcohol in women and men or in unhealthy individuals (i.e. cardiovascular patients), the harm of irregular (binge) drinking.

1.1.1.2 The role of confounding and study design

A weakness of several studies on alcohol consumption is the heterogeneity of the reference groups, which sometimes have included lifelong teetotallers, former drinkers and/or occasional drinkers.[11] However, the lower risk associated with moderate alcohol consumption does not appear substantially related to the inclusion of the above mentioned categories in the reference groups.[6,11]

It has been suspected that the protective effect of moderate alcohol consumption on cardiovascular disease might be due to a favourable risk profile in moderate drinkers, but a higher prevalence of cardiovascular risk factors in abstainers.[6,11,10,12,13] Unmeasured factors that might differ between drinkers and abstainers might contribute to the apparently lower risk among drinkers (the so-called uncontrolled or residual confounding). It has been argued that drinkers have many healthier characteristics than non-drinkers and thus show lower ischaemic heart disease risk. However, when all the possible confounding factors are taken into consideration to assess whether other factors might account for these mortality differences, a large meta-analysis found there was still more than a 10% lower total mortality rate in the light to moderate drinkers.[6]

1.1.1.3 Is wine better than beer?

Many epidemiologic studies have explored the hypothesis that consuming alcohol in the form of wine (or beer) might confer a protection against cardiovascular disease above that expected from its alcohol content.[14] Wine and beer might indeed conceivably show additional non-ethanol related beneficial effects. In fact, while the potential mechanisms

underlying the effects of alcohol have essentially been limited to lipid metabolism and the haemostatic system, those related to wine or beer consumption have been extended to specific antioxidant and vaso-relaxant properties of their different polyphenolic and phenolic constituents.[14,9, 15]

In spite of a large number of experimental studies suggesting a protective role of wine-derived polyphenols on ischaemic CVD risk, epidemiological evidence of a greater effect of wine versus beer has not been established (see also Section 1.3.10.2 on polyphenols). A meta-analysis conducted on studies that investigated the relation between fatal or not fatal vascular events and specific alcoholic beverages (wine and beer), whatever the amount consumed, showed an overall relative risk (RR) of wine drinkers in respect to non-drinkers of 0.68 (95% CI: 0.59-0.77), whereas the protection associated with beer drinking showed an overall RR of 0.78 (95% CI: 0.70-0.86).[14] However, after the exclusion of the studies that did not simultaneously adjust for different types of alcoholic beverages (the most unbiased method to control for confounding), no meaningful difference in the RRs of vascular risk between wine and beer drinkers as compared with abstainers were apparent (0.75 vs 0.77).[14] The difference between wine and beer consumption was also investigated considering the amount of alcohol intake.[14] In contrast with wine, for which a clear inverse dose-effect curve was found, the fitted models failed to show any significant relationship between different amounts of beer intake and vascular risk.

Using ecological studies, which are not well controlled for confounding, international comparisons showed lower coronary artery disease mortality in wine-drinking countries (e.g. France) than in countries where beer or distilled spirits are the preponderant alcoholic beverages.[16] Several studies suggest that alcohol consumption at mealtimes is more favourable for CHD, and wine is more often drunk with meals than beer or liquor.[16]

Whether wine is better than beer or spirits remains therefore to be elucidated, but it seems likely that the ethanol component of different beverages is a major factor that reduces the cardiovascular risk.[10]

1.1.1.4 Is the effect of alcohol different in men and women?

There is controversial evidence that alcohol consumption may have a different protective role in men and women.

In a meta-analysis of studies on alcohol consumption and stroke,[17] a greater protection in women than in men was apparent. In another meta-analysis of studies reporting trend (dose–response) effect of alcohol intake on vascular risk separately for men and women, the predicted dose–response models were very similar for both sexes.[18] At 12 grams of alcohol per day the relative risk was 0.83 (95% CI: 0.69–0.99) in men and 0.72 (95% CI: 0.54–0.96) in women. A maximum reduction (RR = 0.80; 95% CI: 0.57–1.12

in men and RR = 0.66; 95% CI: 0.39–1.12 in women) was predicted in both groups at 18–24 grams of alcohol per day, but statistical significance was only reached up to the amount of 12 grams of alcohol per day.

On the contrary, an earlier meta-analysis[19] had found a lower protective effect of alcohol consumption against coronary artery disease risk in women.

Thus, a possible sex difference in the protective effect of alcohol on vascular risk might exist and explain some seemingly controversial results in different epidemiological studies.[20]

Finally, in a meta-analysis on alcohol and total mortality[6] the dose-response curves are similar for both sexes at low alcohol intake (up to 10 grams per day), but they differ with increasing intake; in fact, the protection in women disappears at a dose consistently lower than in men (18 vs 38 grams of alcohol per day, in men and women, respectively).

Additional studies are needed to test whether women benefit more from alcohol than men or whether they, in practice, drink lower amounts on average, thereby maximising the benefit.

1.1.1.5 Alcohol consumption and cardiovascular secondary prevention

Promoting the secondary prevention of cardiovascular events in survivors of primary vascular events, as well as in hypertensive or diabetic patients, is important.[21,22] Among factors implicated in secondary prevention, a substantial benefit can come from more physical activity and a better diet.

A possible association between alcohol consumption and secondary events (cardiovascular and all-cause mortality) in patients with cardiovascular disease has been recently investigated.[23,24] A meta-analysis relating to cardiovascular mortality showed a J-shaped pooled curve with a significant maximal protection (average 22%) by alcohol at about 26 grams/day. Similarly, a meta-analysis on mortality from any cause, also showed a J-shaped pooled curve (average maximal protection 18% at 7 grams/day).[9] So in patients with cardiovascular disease, light to moderate alcohol consumption (5-25 grams/day) was significantly associated with a lower incidence of both recurrent cardiovascular events and all-cause mortality.

Guidelines for the management of hypertension[25] recommend avoiding binge drinking, and suggest regular alcohol consumption limited to no more than 2-3 drinks/day for men and 1-2 drinks/day for women, if not total abstention. A recent analysis investigating whether reducing alcohol consumption lowered blood pressure without losing the cardiovascular benefits of drinking in moderation,[26] concluded that “the hypertensive patient over the age of 60 who drinks over 16 drinks per week should be advised to reduce his or her alcohol intake, but a daily drink may be advisable and the patient

should not stop drinking entirely; it is not suggested that the non-drinker should start drinking".

Diabetic patients have a CHD risk two to four times higher than non-diabetics. A meta-analysis of 15 prospective cohort studies showed a J-shaped relation between alcohol consumption and risk of developing diabetes, with a 30% lower risk in moderate alcohol consumers (1-2 drinks/day).[27] Moreover, moderate alcohol consumption was associated with a lower incidence of heart disease or total mortality in patients with type 2 diabetes.[28,29] Obviously, the decrease in cardiovascular disease risk associated with moderate alcohol consumption in hypertensive or diabetic subjects does not reduce the importance of controlling blood pressure or blood glucose, regardless of drinking habits.

1.1.1.6 Detrimental effects of alcohol consumption: abuse and binge drinking

Abuse of alcohol, binge drinking, and drinking outside meals have all been associated with detrimental effects including foetal alcohol syndrome, liver cirrhosis, pancreatitis, certain cancers, cardiomyopathy, hypertriglyceridaemia, hypertension, haemorrhagic stroke, overweight, alcohol intoxication and addiction.[30,31]

Excess alcohol intake and binge drinking must be avoided by everybody, but in patients with CVD, it can have more serious unhealthy consequences, such as exacerbation of existing pathological conditions. Alcohol abuse or binge drinking are major causes of hyperlipidaemia, vasoconstriction, increased clotting activity and a lower threshold for ventricular fibrillation.[16,10]

A recent meta-analysis found that both binge and heavy drinking are associated with excess CHD risk.[32] Compared with regular drinking, binge drinking (defined in this meta-analysis as the consumption of three or more drinks within one to two hours) doubles total and cardiovascular mortality risk in cardiovascular patients.[24]

Episodic heavy alcohol drinking is reportedly associated with risk of atrial fibrillation (AF). However, recent studies failed to obtain evidence that chronic alcohol intake (especially moderate consumption) was an important factor in the development of AF; moreover, no association of alcohol consumption with risk of death was found among subjects with AF.[14,33]

Few studies have investigated whether drinking with or without meals modifies the negative association between moderate alcohol consumption and CVD or total mortality. Drinking out of mealtimes is considered to be associated with increased CHD and hypertension risk, independently of the amounts drunk.[24, 34]

Moderate regular drinking, possibly during meals, appears as the ideal behavior to get the optimal cardiovascular benefit of alcohol, while excess or binge drinking is to be absolutely avoided.

1.1.1.7 The influence of age

A small number of prospective studies explored the influence of age on the relationship between alcohol consumption and mortality. In the majority of these studies, the J-shaped curve was confirmed in elderly cohorts, while a positive relation was found for women up to 44 years and for men up to 35 years. In young men the curve was steeper than in young women, and the reduction in mortality in the lightest drinkers was larger and was maintained up to higher levels of consumption than for women.[35] As causes of death have different incidence throughout the age categories, the effect of alcohol on health and disease may differ in different life periods.[36] The reduced mortality risk in light/ moderate drinkers is substantially due to reduced coronary heart disease. However, in the young cohorts cardiovascular events or deaths are relatively low while car accidents or violence are prevalent, so a possible alcohol protection is quite difficult to detect in the general population under 40.

1.1.1.8 What is the optimal amount of alcohol intake?

A J-shaped relationship between total mortality and increasing amounts of alcohol consumed was observed in several meta-analyses, including altogether more than one million people and hundred of thousands fatal events, showing that low to moderate consumption of alcohol (no more than one drink/day in women and two drinks/day in men) significantly reduces total mortality, while higher doses increase it.

Official definitions of standard "drinks" or "units" vary between countries (see Table 10, below). The most commonly favoured definition—also used by WHO—is 10 g of alcohol (ethanol) per drink, but definitions vary from 8 to 14 grams of pure ethanol in a standard drink.[37] A 250 ml glass (half a pint) of beer (5% alcohol by volume), a 100 ml glass of wine (12% ABV) or a 30 ml measure of spirits (40% ABV) contains 10 g of alcohol. Larger measures or stronger drinks clearly contain more alcohol—a large glass (175 ml) of 14% wine, for example, contains almost 20 g of alcohol.

Table 1 Official definitions of standard drinks or units

Standard drink (g ethanol)	Country
8 (expressed as "units" rather than drinks)	United Kingdom
9.9	Netherlands
10	Australia, France, Hungary, Ireland, New Zealand, Poland, Spain
11	Finland
12	Denmark, Italy, South Africa
14	United States

Source: International Center for Alcohol Policies. ICAP http://www.icap.org/PolicyIssues/DrinkingGuidelines/StandardDrinks/tabid/126/Default.aspx

1.1.1.9 Conclusions

The rates of fatal and non-fatal cardiovascular events are significantly lower for people who drink low to moderate amounts of alcohol than for people who do not drink at all or drink heavily.

Available epidemiologic data—derived at present from a large number of prospective observational studies—confirm the hazards of excess drinking, but also indicate the existence of potential windows of alcohol intake which may confer a net beneficial effect of drinking, in terms of survival, both in men and in women. Moderate alcohol consumption is a traditional component of the Mediterranean diet, and largely contributes to the "adherence to Mediterranean diet scores" frequently used as predictors of lower mortality.

The main message for an adult general population can be summarised as follows: Heavy or binge drinkers should be urged to cut and modify their consumption. There is no reason to discourage people who already regularly consume small to moderate amounts of alcohol—no more than one drink (10 g) per day for women or two drinks per day (20 g of alcohol) for men—from continuing. A similar message can be addressed to patients who already suffered a cardiovascular event.

Although low-moderate, non-binging alcohol consumption—in the absence of contraindications and in the context of healthy eating and a healthy lifestyle—reduces the risk of coronary heart disease, it is not recommended that adult abstainers begin drinking. This is because even moderate alcohol intake is also associated with increased risk of other harm (including breast cancer, violence, accidental death or injury and road traffic accidents). Furthermore, there is a risk that some of those who start to drink will be drawn into consuming more than the very limited amounts of alcohol associated with decreased cardiovascular risk. For these reasons it is not recommended that anyone be advised to drink more frequently on health grounds.

The overall evidence also suggests a reduced risk of ischaemic stroke in light-moderate drinkers, but little or no protection against haemorrhagic stroke. Cerebrovascular events substantially increase in heavy alcohol and binge consumers: moreover, heavy alcohol consumption is a risk factor for both haemorrhagic and ischaemic stroke in young adults.[38,39]

The overall message is that, if alcohol is consumed at all, it should be limited to not more than two drinks a day (20 g) in men and not more than one drink (10 g) per day in women.

Randomised controlled trials are considered to offer a more solid answer than observational studies to many questions in medicine, but intervention trials on diet in general and on alcohol in particular, are difficult, mainly because of selection, blinding or compliance problems and ethically questionable to perform.479-481[40] Ideally, a large randomised controlled trial on alcohol, comparing a reference group of long-term abstainers, excluding former or occasional drinkers and a comparable "intervention" group of light to moderate no-binging drinkers, with appropriate follow-up, collecting not only vascular but total mortality data too, would help in establishing the effect of alcohol on health. Randomised controlled trials on intermediate or surrogate endpoints could represent a more feasible and likely alternative.

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