Should alcohol be considered a minor protective factor for unprovoked venous thromboembolism?

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Drinking alcohol is a very common dietary and recreational habit, with estimated 2 billion consumers worldwide (1). A large variability of alcohol consumption exists, based on geographic, cultural, demographic and socio-economic factors.

The possible harms associated with excessive alcohol consumption are well established, including, among others, cancer (oropharyngeal, esophageal, breast), liver cirrhosis, haemorrhagic stroke, neurological and psychiatric disorders, and accidents (2). "Risky drinking" is tentatively defined as an average of 15 or more standard drinks* per week (8 for women or individuals older than 65 years) or 5 or more on a single occasion (4 or more for women or individuals older than 65 years) (3).

Possible benefits associated with alcohol consumption, besides the pleasure of good quality drinking, have been proposed, but there remains uncertainty on the amount of alcohol that can result beneficial for health (4). There is consistent evidence of a protective role of moderate alcohol consumption in preventing atherosclerotic cardiovascular (CV) diseases (coronary heart disease, ischaemic stroke, peripheral artery disease), but concern still exists on the possibility that even small amounts, in particular in some individuals, may result in harmful effects which might overcome this benefit. The association between alcohol and atherosclerotic CV diseases has been described as J-shaped, with a small increased CV risk among abstainers, lower risk at light to moderate consumption, and continuously increasing risk at higher doses (5). These beneficial effects of moderate dietary alcohol intake on atherothrombosis may be explained through various mechanisms, including decreased platelet aggregation, fibrinogen and plasminogen-activator inhibitor-1 concentrations and increased tissue plasminogen activator concentration (6).

This evidence on the protective effects of moderate quantities of alcohol on CV diseases raised the hypothesis that a similar effect could be exerted also on venous thromboembolism (VTE). This hypothesis was biologically plausible in the light of both the abovementioned effects of alcohol consumption on coagulation and recent epidemiologic evidence that CV disease and VTE share some common risk factors (7, 8). Furthermore, the effects of a diet rich in fruits and vegetables, which is known to reduce CV risk, were also reported on the risk of VTE (9).

A number of recent studies have thus explored the association between alcohol consumption and the risk of VTE, providing conflicting results. Some studies reported a protective role of alcohol on VTE when assumed in moderate quantity (10), whereas other studies failed to find any association (8). However, the definition of "moderate" alcohol intake varied across studies, thus contributing to such inconclusive information. In addition, some types of alcoholic beverages (e.g. liquor) were found to be associated with a higher risk of VTE (11).

In this issue of *Thrombosis and Haemostasis*, Gaborit et al. describe their findings about the association between alcohol and VTE from a large prospective population study, enrolling more than 50,000 people, with a median follow-up of 10 years (the Danish prospective study Diet, Health and Cancer) (12). Of particular interest, the study collected detailed data both on alcohol use (alcohol intake and also drinking pattern and types of alcoholic beverages) and on VTE events (provoked/unprovoked events, isolated pulmonary embolism [PE]).

The lowest incidence rates of VTE (0.82 per 1,000 person-years for women and 1.23 per 1,000 person-years for men) were found in individuals with moderate alcohol intake (defined as 4-13.9 standard drinks per week), whereas the highest incidence rates (1.04 per 1,000 person-years for women and 1.71 per 1,000 person-years for men) were found in individuals with the lowest intake (0.1-3.9 standard drinks per week), followed by those with the highest intake (≥ 21 standard drinks per week). Based on these data, the authors conclude that the association between alcohol intake and VTE tended to be U-shaped, even if this finding resulted statistically significant only for men (12).

Interestingly, the strongest association, and actually the only association that resulted statistically significant, was found between alcohol intake and unprovoked VTE in men, with a protective role provided by moderate alcohol intake (adjusted hazard ratio [HR] 0.59, 95% confidence interval [CI] 0.39-0.90). A similar protection for unprovoked VTE (but not for overall VTE) was also recently shown in another study, with an HR of 0.64 (95% CI 0.4-1.01) (8). With regard to the role of different

* Standard drink is defined as any drink that contains 12-14 g of alcohol. Approximately, this corresponds to 35 cl of 5% alcohol beer, 15 cl of 12% alcohol table wine, 10 cl of 17% alcohol fortified wine, 4.5 cl of 40% alcohol brandy or spirits.
types of alcoholic beverages on VTE, no difference was found between beer-drinkers and wine-drinkers in this study (12).

The results of this and of previous studies seem to show that the protective role provided by moderate intake of alcohol is overall modest and possibly limited to the prevention of unprovoked VTE. However, this effect on unprovoked VTE may be considered relevant, given that up to 40 to 50% of all VTE events are defined unprovoked and are possibly caused by the interplay of a number of minor to moderate risk factors (13, 14). Because potentially mild to moderate protective factors, including weight control and physical activity (15-17) as well as appropriate dietary habits (9) and a moderate alcohol intake, may all result in a reduction of these otherwise non-preventable events by means of their proven effects on coagulation, their role deserves to be further explored since this issue remains controversial. One recent study did not find a relation of ‘heart healthy’ diet to VTE (18).

This being said, caution should be used when advising patients on the optimal alcohol intake. Of course, to date no evidence supports the indication to initiate alcohol drinking as a healthy habit to prevent CV disease or unprovoked VTE, and the negative effects of alcohol consumption need to be carefully considered. However, we would like to conclude by citing an Italian singer and cardiologist who died recently, Enzo Jannacci, with the words of one of his most famous songs: “those who... no liquor, no bread, no wine, no butter, never a breaded cutlet, never a holiday day... those who in fact live sick to die healthy...”.

Conflicts of interest
None declared.

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References