

## Blood Coagulation, Fibrinolysis and Cellular Haemostasis

# Alcohol consumption is associated with a decreased risk of venous thrombosis

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### Summary

Moderate alcohol consumption is associated with lower levels of several coagulation factors. It is an established protective factor for cardiovascular disease; however, the effect on venous thrombosis is unknown. In a large population-based case-control study, we evaluated the association between alcohol consumption and the risk of venous thrombosis. The MEGA study included consecutive patients with a first venous thrombosis between March 1999 and September 2004 from six anticoagulation clinics in the Netherlands. Partners of patients were asked to participate, and additional controls were recruited using a random digit dialling method. All participants completed a standardized questionnaire, and blood samples were collected. A total of 4,423 patients and 5,235 controls were included in the analyses. Alcohol consumption was associated with a reduced risk of venous thrombosis, with 2–4 glasses per day resulting in

the largest beneficial effect (odds ratio [OR] 0.67, 95% confidence interval [CI95] 0.58–0.77) compared to abstainers. The effect was more pronounced in women (OR 0.66, CI95 0.53–0.84) than men (OR 0.82, CI95 0.63–1.07) and also more striking for pulmonary embolism (OR 0.56, CI95 0.46–0.70) than for deep venous thrombosis of the leg (OR 0.74, CI95 0.63–0.88). Compared to abstainers, fibrinogen levels were decreased in individuals who consumed alcohol (maximum decrease: 0.30 g/l). Factor VII and von Willebrand levels were mildly decreased in these individuals but not consistently over the categories of alcohol consumption. In conclusion, alcohol consumption is associated with a reduced risk of venous thrombosis, which may be in part mediated by decreased fibrinogen levels.

### Keywords

Alcohol, case-control study, epidemiology, risk factors, venous thrombosis

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### Introduction

The protective effect of moderate and the harmful effect of heavy alcohol consumption on the risk of arterial disease has been shown in many epidemiological studies (1). Similar effects of alcohol consumption on the risk of venous thrombosis are also not unlikely considering the effect of alcohol consumption on coagulation factors. A systematic review reported an association between moderate alcohol intake and reduced levels of fibrinogen, factor VII and von Willebrand factor, whereas heavy and binge alcohol drinking was associated with increased levels of fibrinogen and factor VII (2).

Few studies have reported on the relationship between alcohol consumption and venous thrombosis. In an Italian cohort

study of elderly individuals, low to moderate alcohol consumption appeared beneficial with relative risks of 0.7 for less than one drink a month, 0.6 for less than one ounce per day and 0.5 for one or more than one ounce per day (3). In contrast, two US cohort studies found no effect of alcohol consumption on the risk of venous thrombosis (4, 5). In these cohort studies alcohol intake was only assessed at baseline and variations of alcohol intake during follow-up may have resulted in misclassification of alcohol levels and spurious estimates. In a French case-control study no effect of alcohol consumption was found (6). In this study, the control group consisted of patients with influenzal or rhinopharyngeal symptoms in whom alcohol consumption may differ from the base population of cases. Alcohol is consumed regularly by two billion people worldwide (7), which makes it impor-

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tant to elucidate the relationship between alcohol consumption and the risk of venous thrombosis. In the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA study), a large population-based case-control study, we investigated alcohol use as a risk factor for venous thrombosis. In addition we analyzed the association of alcohol consumption with fibrinogen, factor VII and von Willebrand factor levels to verify if a protective effect could be explained by changes in these coagulation parameters.

## Methods

### Study design

Details of the MEGA study have been published (8). Between March 1999 and September 2004, consecutive patients with a first deep venous thrombosis (DVT) of the leg or a pulmonary embolism (PE) were included from six anticoagulation clinics. All patients were between the age of 18 and 70. Patients with severe psychiatric problems or those unable to speak Dutch were considered as ineligible. Partners of patients were asked to participate as control subjects. From January 2002 until September 2004, an additional control group was recruited using a random digit dialling method. Phone numbers were dialed at random within the geographical inclusion area of the patients. During the phone call a specific person within a household (e.g. youngest woman between 20 and 50) was asked to participate. The random control subjects were frequency matched to the patients with respect to age and sex. Only control subjects with no recent history of venous thrombosis were included and the same exclusion criteria applied as for the patients.

Among the 6,055 eligible patients 5,051 participated (83%). Of the 5,051 participating patients, 3,656 had an eligible partner of whom 2,982 participated (82%). Of the 4,346 eligible random control subjects 3,000 participated (69%).

All participants gave written informed consent and the study was approved by the Medical Ethics Committee of the Leiden University Medical Center, Leiden, The Netherlands.

### Data collection

Within a few weeks after diagnosis and registration at the anticoagulation clinics patients received a letter with information about the study and were subsequently contacted by phone. If the patient was willing to participate, a questionnaire was sent. The control subjects received the questionnaires immediately after inclusion by phone. The questionnaire was returned by 4,637 patients (77%), 2,821 partners (77%) and 2,789 random control subjects (64%). The participants who did not return a questionnaire were asked questions by phone. This short interview did not include questions regarding alcohol consumption.

The question referring to alcohol consumption included ten categories of alcohol consumption: none, one glass or less per week, 2–6 glasses per week, one glass per day, 2–4 glasses per day, 5–9 glasses per day, 10–19 glasses per day, 20–29 glasses per day, 30–39 glasses per day and 40 or more glasses per day. Because only 85 individuals filled in an amount in the highest four categories of alcohol consumption these categories were taken together in the analysis. The questionnaire did not ask about kind of alcohol used. Participants who returned the ques-

tionnaire with missing data on alcohol consumption, body weight or height, smoking or pregnancy were excluded from all analyses. The total excluded proportion was the same in patients (4.6%) and control subjects (4.7%). In the analyses only partner controls with a participating patient were included leading to a total of 4,423 patients, 2,576 partner and 2,659 random control subjects for the present analyses.

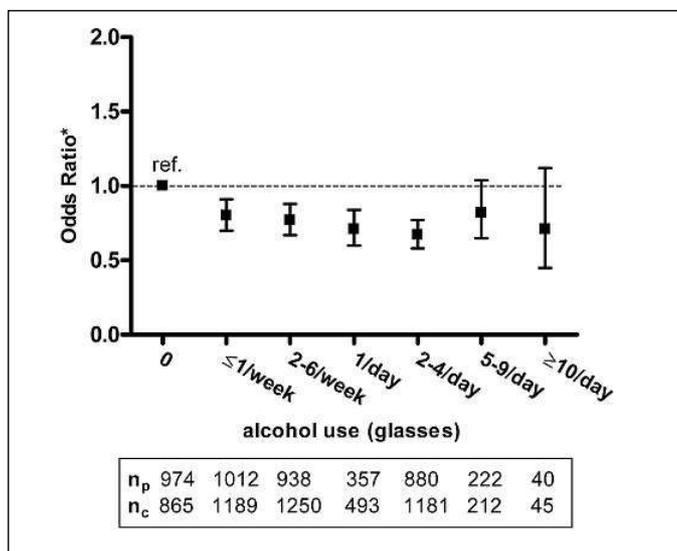
### Blood collection

At least three months after withdrawal of anticoagulation the patients and their partners were asked to visit the anticoagulation clinic after an overnight fast where a blood sample was drawn. Only in case of continuous use for more than one year a blood sample was taken during anticoagulation therapy. From December 1999 onwards, we obtained self-administered buccal swabs by mail when participants were unable or unwilling to come for a blood draw. From June 2002 onwards, blood draws were no longer performed in patients and their partners, and the study was restricted to DNA collection by buccal swabs sent by mail. The random controls were invited for a blood draw within a few weeks after the questionnaire was sent. Within this group buccal swabs were sent when someone refused the blood draw.

In the control subjects 2,614 blood samples were obtained (50%). Fibrinogen, von Willebrand factor and factor VII were successfully determined in 2,612 samples. Fibrinogen activity was measured on the STA-R analyzer according to methods of Clauss (9). The intra-assay coefficient of variation (CV) was 1.8, the inter-assay CV was 3.8. Factor VII activity (FVII) was measured with a mechanical clot detection method on the STA-R analyzer following the instructions of the manufacturer (Diagnostica Stago, Asnieres, France). The intra-assay CV was 3.4, the inter-assay CV was 4.0. Von Willebrand factor antigen (vWF) was measured with the immuno-turbidimetric method, using the STA liatest kit (rabbit anti-human vWF antibodies), following the instructions of the manufacturer. For vWF the intra- and inter-assay CV were 3.6 and 2.6.

### Statistical analysis

Odds ratios (OR) were calculated as estimates of the relative risk with 95% confidence intervals (CI95) according to the method of Woolf. Using a multiple logistic regression model ORs were adjusted for age (continuous), sex (categorical), body mass index (BMI=kg/m<sup>2</sup>) (continuous), pregnancy (categorical) and smoking (categorical). Adjustment for age (10 categories) and body mass index (8 categories) as categorical variables resulted in approximately the same risk estimates. Additional adjustment for disease history, including malignancies, did not change the risk estimates. In the analyses with the random control subjects an unmatched analysis including 4,423 patients and 2,659 random control subjects was performed. In the analyses with partners as the control group (2,576 pairs), we performed a matched analysis which adjusts for similar life-style factors between patients and their partners (10). Because the results of the matched and the unmatched analyses showed consistently protective relative risks in all analyses, we calculated pooled risk estimates with a method that combines the matched and unmatched analyses (11). When analyzing the risk in men and women separately it was not possible to perform a matched analysis with the partner controls, there-



**Figure 1: Relative risk of venous thrombosis by level of alcohol consumption.** \*adjusted for age, sex, body mass index, smoking and pregnancy; I, CI95;  $n_p$ , number of patients;  $n_c$ , number of control subjects; ref., reference category.

fore risk estimates were calculated with an unmatched analysis with all patients and the random control subjects.

A Chi<sup>2</sup>-test was used to compare alcohol consumption between patients with DVT of the leg with those in patients with PE.

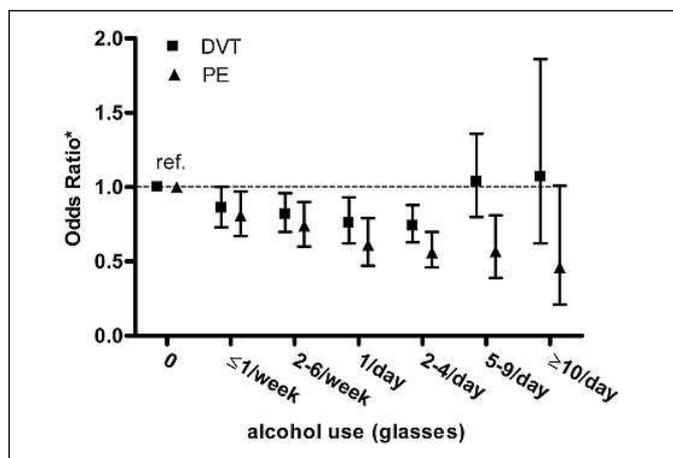
SAS 9.1 (SAS institute Inc, Cary, NC, USA) was used for all statistical analyses.

## Results

In the current analysis 4,423 patients with a first venous thrombosis and 5,235 control subjects were included. Mean age of the patients was 48.5 years (5<sup>th</sup>-95<sup>th</sup> percentiles, 25.8–67.7) and the control subjects were on average 46.8 years (5<sup>th</sup>-95<sup>th</sup> percentiles, 25.4–66.4). In the patient and in the control group 54% were women ( $n_{\text{patient}}=2400$ ,  $n_{\text{control}}=2816$ ). In the patient group 57% ( $n=2528$ ) was diagnosed with DVT of the leg, nearly a third ( $n=1340$ ) with PE and 13% ( $n=555$ ) with the combined diagnosis of DVT and PE.

Figure 1 shows the relationship between alcohol consumption and the risk of venous thrombosis. Moderate alcohol consumption was associated with a decreased risk of venous thrombosis, with two to four glasses per day resulting in the strongest effect on the risk of venous thrombosis (OR<sub>2-4/day</sub> 0.67, CI95 0.58–0.77) compared to abstainers. Even drinking more than four glasses per day appeared to be still somewhat protective (OR<sub>5-9/day</sub> 0.82, CI95 0.65–1.04, OR<sub>≥10/day</sub> 0.71, CI95 0.45–1.12). Moderate alcohol consumption was associated with a somewhat more decreased risk for women (OR<sub>2-4/day</sub> 0.66, CI95 0.53–0.84) than men (OR<sub>2-4/day</sub> 0.82, CI95 0.63–1.07).

The associations of alcohol consumption with the risk of DVT and PE separately are presented in Figure 2. The protective effect of alcohol consumption appeared to be more pronounced



**Figure 2: Relative risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) by level of alcohol consumption.** \*adjusted for age, sex, body mass index, smoking and pregnancy; I, CI95; ref., reference category.

for the diagnosis of PE (OR<sub>2-4/day</sub> 0.56, CI95 0.46–0.70) than for DVT (OR<sub>2-4/day</sub> 0.74, CI95 0.63–0.88). Drinking two glasses per week or more clearly protected more against PE than against DVT ( $p=0.02$ ).

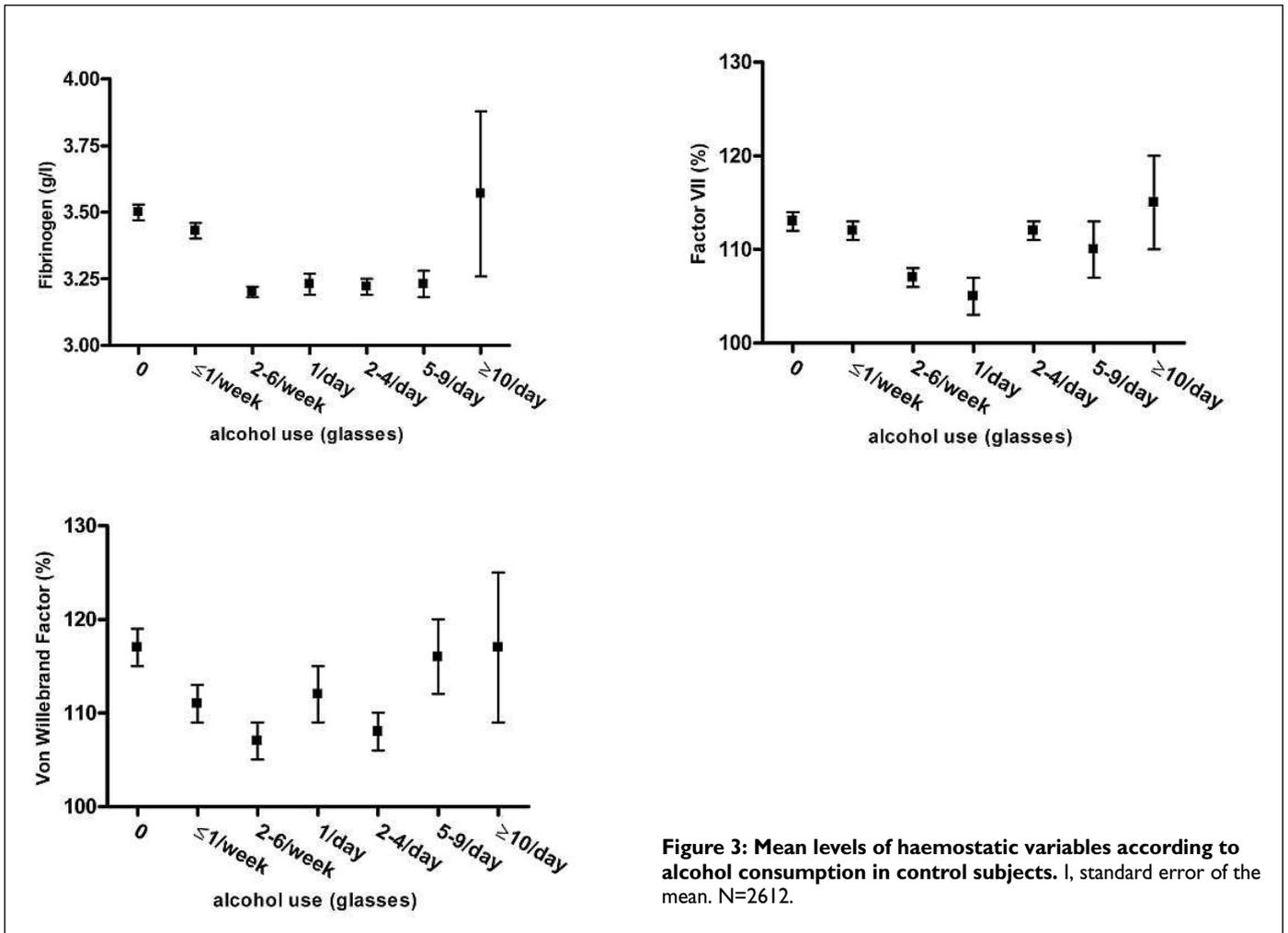
In Figure 3 mean fibrinogen, factor VII and von Willebrand factor levels are presented for different categories of alcohol consumption in control subjects. Alcohol consumption categories which were associated with the most pronounced reduction in venous thrombotic risk were also associated with reduced levels of fibrinogen. Factor VII levels and von Willebrand factor levels were also lower in drinkers than non-drinkers, but there were no consistent patterns over the categories of alcohol consumption.

## Discussion

In this large case-control study moderate alcohol consumption was associated with a decreased risk of venous thrombosis. This potential beneficial effect of moderate alcohol consumption appeared to be more pronounced in women than men and for PE than for DVT of the leg.

Very little is known about the mechanisms by which alcohol may exert antithrombotic effects. Some studies have shown that moderate alcohol consumption is associated with a more favorable coagulation profile, indicated by lower levels of fibrinogen, factor VII and von Willebrand factor (12, 13). In accordance with these studies we found reduced levels of fibrinogen, factor VII and von Willebrand factor in moderate alcohol drinkers. Reduced levels were most striking for fibrinogen, where levels were even decreased up to high levels of alcohol consumption (5–9 glasses per day).

The difference between men and women in the alcohol-related risk of venous thrombosis may be explained by the differential effects of wine and beer (14), the latter of which is consumed more by men than women. Unfortunately, in our study we had no information about the kind of alcoholic drinks the partici-



**Figure 3: Mean levels of haemostatic variables according to alcohol consumption in control subjects.** I, standard error of the mean. N=2612.

pants consumed. A question about type of alcoholic drinks could have provided important additional information. A recent study however, showed that wine, beer and spirits were to the same extent protective for myocardial infarction, suggesting that type of alcohol drink did not influence the effect (15).

It was striking that the protective effect of drinking two or more glasses of alcohol per week was higher for PE than for DVT of the leg. We do not have an explanation for these findings.

A limitation of our study is that alcohol consumption was self-reported. Although it is possible that individuals under-report alcohol consumption, this is mainly a problem when there is a difference between patients and control subjects in reporting behavior. If patients and controls both had underreported, the protective effect we observed was underestimated. If patients underreported more than controls, the true effect would have been less pronounced. The proportion of individuals who failed to report their alcohol consumption was the same in patients (0.71%) and controls (0.66%), which suggests that the two groups behaved similarly in answering this question.

In conclusion, in this large population-based case-control study alcohol consumption is associated with a decreased risk of venous thrombosis, with two to four glasses per day resulting in

the largest effect. This effect may be mediated by a decrease in coagulation factors, especially fibrinogen.

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