Alcohol Consumption and Hemostatic Factors
Analysis of the Framingham Offspring Cohort

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Background—Moderate alcohol consumers have lower rates of cardiovascular disease than abstainers. One proposed mechanism is a beneficial effect on hemostatic parameters, but previous studies have provided conflicting results.

Methods and Results—We measured levels of fibrinogen, plasma viscosity, von Willebrand factor, factor VII, plasminogen activator inhibitor antigen-1, and tissue plasminogen activator antigen in a cross-sectional analysis of 3223 adults free of cardiovascular disease enrolled in the Framingham Offspring Study. We assessed their alcohol consumption with a standardized questionnaire. Light-to-moderate alcohol consumption was associated with lower levels of fibrinogen, plasma viscosity, von Willebrand factor, and factor VII. This association was most pronounced for consumers of 3 to 7 drinks weekly for viscosity and 7 to 21 drinks weekly for the other hemostatic measures. Alcohol intake of 7 to 21 drinks weekly or more was associated with impaired fibrinolytic potential, reflected by higher levels of plasminogen activator inhibitor antigen-1 and tissue plasminogen activator antigen. Wine drinkers had lower plasminogen activator inhibitor antigen-1 levels than other drinkers, particularly at 3 to 21 drinks weekly, but beverage type did not otherwise consistently affect the results.

Conclusions—Light-to-moderate alcohol consumption is associated with lower levels of coagulatory factors, but higher intake is associated with impaired fibrinolytic potential. These findings are consistent with the hypothesis that a balance between hemostatic and fibrinolytic activity may contribute to the complex relation of alcohol use with coronary heart disease. (Circulation. 2001;104:1367-1373.)

Key Words: alcohol ■ fibrinogen ■ fibrinolysis ■ thrombosis ■ plasminogen activators ■ von Willebrand factor

The association of alcohol consumption and coronary heart disease (CHD) is complex. Relative to abstention, light-to-moderate alcohol consumption is associated with lower risks of myocardial infarction and cardiovascular death.1-2 Heavier alcohol consumption, in contrast, is associated with no change or even an increase in these risks.

The physiological forces that mediate this complex association remain poorly understood. Alcohol consumption increases HDL cholesterol levels, but this effect accounts for only approximately one half of the association between moderate drinking and CHD.3 Alcohol administration also elevates HDL levels in a dose-dependent manner,4 so HDL levels alone cannot explain the plateau or increase in risk of CHD associated with heavier alcohol use.

Hemostatic function may also affect CHD risk. In various studies, measures of hemostatic function and fibrinolytic potential have both been associated with risk of CHD, although not universally so.5-11 Whether these factors mediate a relation of alcohol and coronary heart disease is unclear. For example, some have proposed that moderate alcohol use could prevent CHD through higher tissue plasminogen activator (TPA) antigen levels.12 However, increased TPA antigen levels, which reflect both free and bound TPA, are associated with impaired fibrinolytic potential and an increased risk of CHD.7,9,11 Previous studies of the relation between alcohol consumption and hemostatic function have also been limited by small sample size, restriction to men,

Received April 19, 2001; revision received July 11, 2001; accepted July 11, 2001.
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Presented in part in short abstract form at the 43rd Annual Scientific Session of the American College of Cardiology, March 1994, Atlanta, Ga.
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Circulation is available at http://www.circulationaha.org
failure to distinguish between beverage types, and measurement of few hemostatic parameters. 12–30

We therefore studied the relation between alcohol consumption and hemostatic function in 3223 adults enrolled in the Framingham Offspring Study, a prospective study of cardiovascular disease among the children of the original Framingham Heart Study subjects.31 We studied both women and men, examined a broad range of coagulatory and fibrinolytic parameters, and considered the effects of individual beverage type.

**Methods**

Since 1971, a total of 5124 subjects have been interviewed and examined 6 times. For this cross-sectional analysis, we used data collected from the 3798 subjects examined between April 1, 1991, and March 1, 1994, during the fifth examination cycle. Because they may have changed their alcohol consumption in response to illness, we excluded individuals with prevalent cardiovascular disease (myocardial infarction, angina pectoris, congestive heart failure, or stroke; BMI, kg/m²

<p>| TABLE 1. Demographic Characteristics and Unadjusted Hemostatic Parameters According to Usual Weekly Consumption of Alcohol in Women |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Number of Drinks</th>
<th>Median No. of drinks</th>
<th>Age, y</th>
<th>Smoker, %</th>
<th>BMI, kg/m²</th>
<th>Diabetes, %</th>
<th>Hypertension, %</th>
<th>Total cholesterol (mmol/L)</th>
<th>HDL cholesterol (mg/dL)</th>
<th>Triglycerides (mg/dL)</th>
<th>Fibrinogen (µmol/L)</th>
<th>PAI-1, ng/mL</th>
<th>TPA, ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (n=618)</td>
<td>0</td>
<td>55.3±10.0</td>
<td>19.1</td>
<td>27.9±5.8</td>
<td>6.8</td>
<td>30.8</td>
<td>5.39±0.98</td>
<td>208.0±37.9</td>
<td>1.34±0.35</td>
<td>9.54±1.81</td>
<td>21.8±16.4</td>
<td>8.5±3.7</td>
</tr>
<tr>
<td>1–&lt;3 (n=497)</td>
<td>1</td>
<td>53.8±9.6</td>
<td>16.1</td>
<td>26.8±5.8</td>
<td>2.6</td>
<td>24.9</td>
<td>5.28±0.92</td>
<td>203.9±35.6</td>
<td>1.42±0.37</td>
<td>9.08±1.58</td>
<td>19.8±16.0</td>
<td>7.8±4.5</td>
</tr>
<tr>
<td>3–&lt;7 (n=315)</td>
<td>4</td>
<td>53.2±10.3</td>
<td>17.8</td>
<td>25.9±5.2</td>
<td>3.2</td>
<td>20.3</td>
<td>5.41±1.02</td>
<td>208.8±39.5</td>
<td>1.50±0.37</td>
<td>8.88±1.52</td>
<td>18.7±14.3</td>
<td>8.4±4.3</td>
</tr>
<tr>
<td>7–&lt;21 (n=335)</td>
<td>10</td>
<td>54.2±9.6</td>
<td>25.2</td>
<td>25.1±4.3</td>
<td>3.3</td>
<td>15.8</td>
<td>5.40±1.02</td>
<td>208.4±39.5</td>
<td>1.69±0.44</td>
<td>8.51±1.72</td>
<td>21.7±17.6</td>
<td>8.7±4.7</td>
</tr>
</tbody>
</table>

*Values are mean±SD or percent. BMI indicates body mass index; HDL, high-density lipoprotein; vWf, von Willebrand factor antigen; PAI-1, plasminogen-activator inhibitor antigen-1; and TPA, tissue plasminogen activator antigen.*

Blood samples were collected from the antecubital vein between 8 AM and 9 AM in the supine position after an overnight fast. For determination of plasma fibrinogen, viscosity, factor VII, plasminogen activator inhibitor antigen-1 (PAI-1), and TPA antigen, blood was anticoagulated with 3.8% trisodium citrate (9:1 vol/vol) and cooled on ice until centrifugation. For determination of von Willebrand factor (vWF) antigen and lipids, blood was collected in a
TABLE 2. Demographic Characteristics and Unadjusted Hemostatic Parameters According to Usual Weekly Consumption of Alcohol in Men

<table>
<thead>
<tr>
<th>Number of Drinks</th>
<th>0 (n=350)</th>
<th>1–3 (n=225)</th>
<th>3–7 (n=288)</th>
<th>7–21 (n=429)</th>
<th>≥21 (n=164)</th>
<th>P (Linear)</th>
<th>P (Quadratic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median No. of drinks</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>11</td>
<td>27</td>
<td>0.22</td>
<td>0.002</td>
</tr>
<tr>
<td>Age, y</td>
<td>55.6 ± 10.1</td>
<td>53.8 ± 9.6</td>
<td>52.7 ± 9.3</td>
<td>54.4 ± 10.3</td>
<td>54.7 ± 8.9</td>
<td>0.22</td>
<td>0.002</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>20.6</td>
<td>16.4</td>
<td>12.9</td>
<td>18.9</td>
<td>33.5</td>
<td>0.04</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.3 ± 4.5</td>
<td>28.7 ± 4.6</td>
<td>28.3 ± 4.3</td>
<td>27.9 ± 3.9</td>
<td>28.0 ± 4.0</td>
<td>0.09</td>
<td>0.43</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>12.3</td>
<td>8.9</td>
<td>3.8</td>
<td>4.4</td>
<td>7.3</td>
<td>&lt;0.001</td>
<td>0.008</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>9.6</td>
<td>5.2</td>
<td>4.2</td>
<td>5.2</td>
<td>7.6</td>
<td>0.09</td>
<td>1.24</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>6</td>
<td>10</td>
<td>6</td>
<td>10.1</td>
<td>6</td>
<td>9.6</td>
<td>52.7</td>
</tr>
<tr>
<td>mmol/L</td>
<td>5.07 ± 0.88</td>
<td>5.19 ± 0.97</td>
<td>5.16 ± 0.90</td>
<td>5.30 ± 0.88</td>
<td>5.49 ± 0.93</td>
<td>&lt;0.001</td>
<td>0.15</td>
</tr>
<tr>
<td>mg/dL</td>
<td>195.8 ± 34.0</td>
<td>200.4 ± 37.5</td>
<td>199.2 ± 34.8</td>
<td>204.6 ± 33.8</td>
<td>212.0 ± 35.8</td>
<td>0.09</td>
<td>0.43</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>6</td>
<td>10</td>
<td>6</td>
<td>10.1</td>
<td>6</td>
<td>9.6</td>
<td>52.7</td>
</tr>
<tr>
<td>mmol/L</td>
<td>1.02 ± 0.25</td>
<td>1.04 ± 0.22</td>
<td>1.12 ± 0.27</td>
<td>1.20 ± 0.31</td>
<td>1.28 ± 0.36</td>
<td>&lt;0.001</td>
<td>0.10</td>
</tr>
<tr>
<td>mg/dL</td>
<td>39.2 ± 9.7</td>
<td>40.1 ± 8.6</td>
<td>43.4 ± 10.4</td>
<td>46.3 ± 12.1</td>
<td>49.5 ± 13.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>6</td>
<td>10</td>
<td>6</td>
<td>10.1</td>
<td>6</td>
<td>9.6</td>
<td>52.7</td>
</tr>
<tr>
<td>mmol/L</td>
<td>1.84 ± 1.19</td>
<td>1.87 ± 1.62</td>
<td>1.71 ± 1.20</td>
<td>1.75 ± 1.28</td>
<td>1.96 ± 1.66</td>
<td>0.86</td>
<td>0.09</td>
</tr>
<tr>
<td>mg/dL</td>
<td>163.2 ± 105.5</td>
<td>165.5 ± 143.1</td>
<td>151.4 ± 106.0</td>
<td>155.3 ± 113.3</td>
<td>173.4 ± 146.7</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>6</td>
<td>10</td>
<td>6</td>
<td>10.1</td>
<td>6</td>
<td>9.6</td>
<td>52.7</td>
</tr>
<tr>
<td>μmol/L</td>
<td>9.17 ± 1.78</td>
<td>8.91 ± 1.60</td>
<td>8.65 ± 1.56</td>
<td>8.76 ± 1.76</td>
<td>8.84 ± 1.83</td>
<td>0.002</td>
<td>0.008</td>
</tr>
<tr>
<td>mg/dL</td>
<td>311.8 ± 60.4</td>
<td>303.0 ± 54.5</td>
<td>294.1 ± 52.9</td>
<td>297.8 ± 59.9</td>
<td>300.8 ± 62.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma viscosity, centipoise</td>
<td>6</td>
<td>10</td>
<td>6</td>
<td>10.1</td>
<td>6</td>
<td>9.6</td>
<td>52.7</td>
</tr>
<tr>
<td>Factor VII, %</td>
<td>1.24 ± 0.09</td>
<td>1.25 ± 0.11</td>
<td>1.22 ± 0.09</td>
<td>1.24 ± 0.09</td>
<td>1.24 ± 0.09</td>
<td>0.21</td>
<td>0.10</td>
</tr>
<tr>
<td>vWF, %</td>
<td>99.1 ± 15.6</td>
<td>98.9 ± 14.9</td>
<td>98.5 ± 16.6</td>
<td>96.4 ± 15.5</td>
<td>94.3 ± 13.9</td>
<td>&lt;0.001</td>
<td>0.12</td>
</tr>
<tr>
<td>PAI-1, ng/mL</td>
<td>136.0 ± 47.6</td>
<td>128.1 ± 45.7</td>
<td>126.7 ± 46.2</td>
<td>121.3 ± 46.2</td>
<td>123.3 ± 45.3</td>
<td>&lt;0.001</td>
<td>0.16</td>
</tr>
<tr>
<td>TPA, mg/mL</td>
<td>23.9 ± 16.0</td>
<td>24.2 ± 16.6</td>
<td>22.8 ± 15.6</td>
<td>24.9 ± 18.4</td>
<td>29.0 ± 16.8</td>
<td>0.02</td>
<td>0.006</td>
</tr>
</tbody>
</table>
| Values are mean ± SD or percent. Abbreviations as in Table 1.

Vacutainer containing EDTA. We separated plasma by centrifugation at 2500g for 20 minutes at 4°C and stored aliquots at −70°C.

We used the Clauss method to determine plasma fibrinogen. Plasma viscosity was measured with the Brookfield Viscometer, Model DV-II (cone/plate method). We used ELISA assays to measure vWF and factor VII antigen concentrations. For PAI-1 and TPA antigens, we used sandwich ELISA assays (TintElize PAI-1 and TintElize TPA, Biopool AB). The intra-assay coefficients of variation were 2.6% for fibrinogen, 2.0% for plasma viscosity, 3.0% for factor VII antigen, 8.8% for vWF antigen, 8.1% for PAI-1 antigen, and 5.5% for TPA antigen.

All statistical analyses were performed on men and women separately. We first used simple linear and logistic regression (ie, no adjustment for covariates) to assess the effect of alcohol consumption on continuous and binary variables, respectively. We further modeled the effect of alcohol consumption on hemostatic parameters by using ANCOVA to control for confounding factors. In these models, we assigned indicator variables to individual categories of alcohol consumption to minimize constraints on the shapes of the relations. In all analyses, we controlled for age, smoking, diabetes, hypertension, physical activity, body mass index, and fasting triglycerides, HDL, and total cholesterol. We retained diabetes and HDL as covariates, though they may be both confounders and causal intermediates, to provide maximal control of possible confounding, resulting in conservative estimates of the associations reported. We performed log transformations of PAI-1 and TPA antigen levels to maximize normality and equality of the variances of the conditional outcome variables. We did not adjust for triglyceride levels in the beverage-specific models to provide more stable estimates; models from the complete sample gave essentially identical results when triglyceride levels were excluded. A 2-tailed probability value of <0.05 was considered statistically significant.

Results

The characteristics of this population are presented in Tables 1 and 2. In both sexes, alcohol consumption was positively associated with HDL level and associated with age, smoking, diabetes, hypertension, and triglyceride level in nonlinear relations.

Hemostatic Measures

Tables 1 and 2 show unadjusted relations between alcohol consumption and coagulatory parameters. Except for the relation between plasma viscosity and alcohol use among men, alcohol consumption was statistically significantly associated with all 5 measures in both sexes, whether in linear or U-shaped relations.

Figure 1 demonstrates these relations after adjustment for confounding factors. Fibrinogen and vWF levels were lowest among men and women who consumed ≥7 drinks weekly. Plasma viscosity demonstrated a U-shaped relation with alcohol use in both sexes. Factor VII concentrations were generally lowest among men and women reporting the heaviest alcohol consumption.
Fibrinolytic Measures
The unadjusted association of fibrinolytic parameters and alcohol consumption was similar and U-shaped in women and men (Tables 1 and 2). Figure 2 illustrates how alcohol consumption relates to fibrinolytic parameters after adjustment. Among both women and men, PAI-1 and TPA antigen levels were substantially higher with alcohol consumption >7 drinks weekly, with inconsistent differences below this level of consumption.

Beverage-Specific Analyses
Of the 1456 men studied, 223 consumed beer exclusively, 88 wine exclusively, and 92 liquor exclusively. In contrast, of the 1767 women studied, 46 consumed beer exclusively, 425 wine exclusively, and 159 liquor exclusively. In analyses restricted to these individuals, we found no consistent differences between beer, wine, and liquor drinkers in levels of coagulatory factors among either men or women.

In contrast, Figure 3 shows the relation of fibrinolytic factors to alcohol consumption among individuals who consumed a single beverage type. Overall, wine drinkers had lower concentrations of PAI-1 than did liquor drinkers, even after controlling for demographic and clinical factors and usual alcohol consumption ($P=0.03$ among women, $P=0.001$ among men). Among men, wine drinkers also tended to have lower overall PAI-1 concentrations than beer drinkers did, although this difference was not statistically significant ($P=0.10$). The lower PAI-1 levels among wine drinkers were most marked among individuals in the 3 to <7 and 7 to <21 drinks per week categories. We found no overall differences among beer, wine, and liquor drinkers in TPA antigen levels.

Discussion
In this analysis of the Framingham Offspring Study, we found that alcohol consumption has complex associations with hemostatic parameters. Light-to-moderate alcohol use was associated with lower levels of fibrinogen, plasma viscosity, factor VII, and vWf. On the other hand, fibrinolytic potential was lower with increasing alcohol consumption, most dramatically at ≥7 drinks weekly. We found similar findings for beer, wine, and liquor drinkers, although wine drinkers generally had the lowest PAI-1 levels at moderate levels of consumption.

We cannot establish causation in this observational study, but our results are consistent with the hypothesis that changes in thrombotic tendency contribute to the complex relation between alcohol consumption and CHD, both positively and negatively. With light alcohol consumption, the lower levels of coagulatory factors may predominate, without significant increase in risk from changes in fibrinolytic parameters. This combination would be expected to reduce the risk of myocardial infarction. At higher levels of consumption, the lower levels of plasma viscosity and fibrinogen appear to plateau or reverse, and fibrinolytic potential declines more substantially. These latter changes could increase the risk of CHD events, as evidenced in cohort studies.

Extensive evidence implicates impaired hemostasis in the pathogenesis of acute coronary syndromes, including the
prospective association of measures of hemostatic function and fibrinolytic potential with risk of CHD, although a causal role has not been proven. Also, these associations have not been universally confirmed in all studies, even for fibrinogen levels. Although some of these hemostatic variables may prove not to be independent risk factors for CHD, we found consistent associations of alcohol consumption with all 4 hemostatic measures and both measures of fibrinolytic potential. The magnitude of the differences in hemostatic factor levels that we found was also similar to the magnitude of differences seen in prospective studies of these factors. For example, in the ECAT Study, the mean differences between groups with and without coronary events were 28 mg/dL of fibrinogen, 12.9 percentage points in vWF antigen, and 11.9 ng/mL of TPA antigen, all similar to the differences we found across the range of alcohol consumption.

The specific mechanisms by which alcohol may alter hemostatic parameters remain uncertain. Some investigators have speculated that alcohol could change hemostatic factor levels though changes in lipid metabolism, although we controlled for lipid levels in this study. Alcohol appears to increase endothelial cell production of TPA antigen directly via upregulation of gene expression. Alcohol could also lower fibrinolytic potential through activation of the renin-angiotensin system, either by volume depletion caused by inhibition of vasopressin release or a direct effect of acetaldehyde. Finally, heavy alcohol consumption affects coagulation by damaging the synthetic capacity of hepatocytes, both directly and through metabolites, but it is uncertain whether moderate alcohol intake acts similarly.

**Previous Studies of Alcohol and Hemostatic Factors**

Most investigators have found lower plasma fibrinogen concentrations among drinkers than abstainers, although a few have found them equal. Beverage type does not appear to influence the effect of alcohol on fibrinogen. The association of alcohol use with plasma viscosity has not been extensively studied in epidemiological studies. Experimental studies show that alcohol in large doses increases plasma viscosity.

We found dose-dependent differences in how alcohol consumption relates to plasma viscosity and fibrinogen (a major determinant of plasma viscosity) that echo this experimental finding. Although fibrinogen concentrations plateau at the highest levels of alcohol intake, plasma viscosity increases when consumption exceeds 7 drinks weekly. This may suggest that light alcohol consumption lowers plasma viscosity through hemostatic factors such as fibrinogen, whereas greater alcohol consumption increases viscosity directly, with potentially concerning consequences.

The associations between alcohol consumption and vWF and factor VII levels are not straightforward. Previous epidemiological and experimental studies differ on how alcohol consumption affects vWF concentrations, and alcohol consumption does not consistently lower factor VIII levels (which are highly correlated with vWF). Previous epidemiological studies and experimental trials have...
also reported inconsistent results regarding the association between alcohol use and factor VII levels.

Although drinkers were first reported to have greater overall fibrinolytic activity than nondrinkers in 1979, alcohol administered with dinner decreases TPA activity for the ensuing 5 hours. Crossover trials of alcohol administration have variously reported dose-dependent decreases or no change in TPA activity. Most, but not all, studies indicate that alcohol increases TPA antigen concentrations, consistent with lower TPA activity. Likewise, PAI-1 levels generally rise with alcohol consumption in a variety of settings, with rare exceptions.

Our results cannot be interpreted without limitation. In any observational study, unmeasured confounding factors can contribute to the associations found. For example, moderate alcohol consumption is associated with several behavioral, medical, and lifestyle factors, including greater cigarette smoking, less concurrent illness, and higher socioeconomic status. We controlled for important factors that correlate with lifestyle characteristics, including body mass index, smoking, and physical activity, and our results were generally similar before and after adjustment for these and other factors. Our patient population also includes children of a single suburban community, attenuating their variability in lifestyle features. Most importantly, randomized trials of alcohol administration, which minimize confounding, have demonstrated results similar to ours, particularly for fibrinogen and TPA antigen levels. Only large, long-term, randomized trials of alcohol consumption could answer these concerns definitively, but they remain unlikely to occur.

We did not collect information on red and white wine separately and cannot determine whether red wine differs from other alcoholic beverages in its effect on hemostatic factors. Our patient population also includes children of residents of a single suburban community, attenuating their variability in lifestyle features. Most importantly, randomized trials of alcohol administration, which minimize confounding, have demonstrated results similar to ours, particularly for fibrinogen and TPA antigen levels. Only large, long-term, randomized trials of alcohol consumption could answer these concerns definitively, but they remain unlikely to occur.

We relied on self-reported alcohol consumption, which is prone to misclassification. Although heavy drinkers may have deliberately underreported their consumption, such individuals generally have low participation rates in prospective studies, and any resulting misclassification should lead to false findings of no association. We also have no specific information on drinking pattern, which could modify how alcohol consumption relates to hemostatic factors, although it may not influence the relation of alcohol consumption and fibrinogen level.

Although we excluded individuals with known cardiovascular disease, some abstainers may be former drinkers who stopped because of clinical or subclinical illness. However, former drinkers and long-term abstainers have similar risks of heart disease, as do abstainers and very light drinkers. This same concern may also apply to light-to-moderate drinkers, many of whom were formerly heavy drinkers. Exclusion of the individuals in the lightest drinking category in this study, which include abstainers and rare drinkers, would not appreciably change the patterns of effect. However, we cannot generalize our findings to patients with known cardiovascular disease.

In conclusion, we found that alcohol consumption has complex associations with hemostatic parameters in both men and women. Moderate drinkers had lower fibrinogen, plasma viscosity, factor VII antigen, and vWF antigen levels than abstainers, with no substantial change in fibrinolytic measures. Heavier drinkers had higher TPA antigen and PAI-1 levels than moderate drinkers or abstainers and higher plasma viscosity than moderate drinkers. These relations are consistent with the hypothesis that the balance between hemostatic and fibrinolytic function may contribute to the very different risks of CHD carried by moderate and heavy drinkers.

Acknowledgments
This work was supported by grants K23-AA00299 from the National Institute on Alcohol Abuse and Alcoholism and R01-HL-48157 from the National Heart, Lung, and Blood Institute.

References


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_Circulation_. 2001;104:1367-1373
doi: 10.1161/hc3701.096067
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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