Alcohol Consumption and Plasma Concentration of C-Reactive Protein

Michelle A. Albert, MD, MPH; Robert J. Glynn, PhD; Paul M Ridker, MD, MPH

Background—Moderate alcohol intake has been associated with lower cardiovascular mortality. However, data evaluating the relationship between C-reactive protein (CRP), a predictor of cardiovascular risk, and alcohol consumption are sparse.

Methods and Results—The relationship between alcohol consumption and CRP was evaluated in a cross-sectional survey and over time among 1732 men and 1101 women participating in the Pravastatin Inflammation/CRP Evaluation Study. CRP levels were lower in those with moderate alcohol intake versus light or occasional intake: in 5 categories of alcohol intake (no alcohol or <1 drink monthly, 1 to 3 drinks monthly, 1 to 4 drinks weekly, 5 to 7 drinks weekly, and ≥2 drinks daily), median CRP levels were 2.60 mg/L (interquartile range (IQR), 1.20 to 5.30 mg/L), 2.20 mg/L (IQR, 1.00 to 4.40 mg/L), 1.70 mg/L (IQR, 0.80 to 3.80 mg/L), 1.60 mg/L (IQR, 0.80 to 3.30 mg/L), and 1.80 mg/L (IQR, 0.80 to 2.90 mg/L), respectively. This relationship was present among men, women not taking hormone replacement therapy, nonsmokers, and those individuals with and without a history of cardiovascular disease (all P<0.001). In multivariate analysis, the relationship between alcohol consumption and CRP remained significant after controlling for multiple traditional cardiovascular risk factors. Alcohol consumption did not significantly affect the change in CRP or lipid levels associated with statin use.

Conclusion—Moderate alcohol consumption was associated with lower CRP concentrations than no or occasional alcohol intake, an effect that was independent of alcohol-related effects on lipids. Alcohol may attenuate cardiovascular mortality in part through an anti-inflammatory mechanism. (Circulation. 2003;107:443-447.)

Key Words: alcohol ■ protein, C-reactive ■ inflammation

Moderate alcohol consumption is associated with decreased all-cause mortality, most of which is a result of a reduction in cardiovascular deaths.1–4 Although several prospective studies have demonstrated either a U- or J-shaped relationship between cardiovascular mortality and alcohol intake,3,5 the mechanisms underlying this association remain uncertain. Potential explanations for the effect of alcohol on vascular events have focused primarily on lipoprotein6,7 and hemostatic factors.8,9 However, alcohol consumption maintains a significant association with cardiovascular risk even after controlling for many of these risk factors. Furthermore, alcohol has an unclear and complex modification of hemostatic parameters,9 suggesting that alcohol may influence cardiovascular risk through alternative pathways. Currently, little data are available about potential relationships between inflammatory markers and alcohol consumption. Recently, Imhof et al10 noted a U-shaped association between alcohol consumption and C-reactive protein (CRP), with a less strong association among women. Experimental evidence indicates that inflammation plays a major role in mediating atherosclerotic plaque stability.11–13 Furthermore, population-based studies have shown that markers of inflammation such as CRP predict future cardiovascular disease risk.14–17 As a result, we sought to confirm and extend these data by evaluating the relationship between CRP and alcohol consumption in individuals with and without a history of vascular disease.

Methods
We obtained self-reported alcohol intake and measured CRP levels among 1732 men and 1101 women participating in the Pravastatin Inflammation/CRP Evaluation (PRINCE) Study,18 a multicenter community-based trial designed to study the effect of pravastatin 40 mg or placebo on CRP levels over 6 months of follow-up. PRINCE consisted of participants from physician community practices across 49 states and the District of Columbia. Participants with known chronic inflammatory conditions, need for anti-inflammatory therapy, use of statin therapy within the 6-month period before enrollment, and contraindications to statin therapy were excluded. At study entry, 1679 participants without a history of myocardial infarction,
stroke, or coronary revascularization (primary prevention cohort) and 1154 participants with a history of cardiovascular disease (secondary prevention cohort) provided a blood sample for CRP and lipid evaluation, as well as data on age, sex, smoking status, diabetes history, and estrogen and aspirin use. In addition, participants were asked to self-report their alcohol intake in 1 of 5 ordinally ranked groups as follows: no alcohol intake or <1 drink monthly (group 1), 1 to 3 drinks per month (group 2), 1 to 4 drinks per week (group 3), 5 to 7 drinks per week (group 4), or ≥2 drinks daily (group 5). Data on weight, height, and blood pressure were measured by the subject’s physician at study entry.

Plasma samples obtained at baseline were assayed for CRP by a clinically validated high-sensitivity assay. Lipid levels were determined in a Centers for Disease Control and Prevention standardized laboratory. Because distributions of CRP are skewed, median values are reported for each alcohol intake category. For pravastatin-treated participants, the median change and the median percentage change in CRP and mean change in lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) over 6 months were also calculated for each alcohol category. The ANOVA and χ² statistic were used to compare differences in baseline cardiovascular risk factors among participants according to alcohol intake status. Pearson correlation coefficients were computed to assess the relationship between alcohol intake and CRP, as well as between alcohol intake and baseline clinical variables, using the natural log of baseline CRP levels. The correlation between alcohol intake and end-of-study CRP levels and between alcohol intake and change observed over time for lipid parameters was also assessed.

Multivariate linear models were used to evaluate the association between baseline log-normalized levels of CRP and alcohol intake among various subgroups (smokers, nonsmokers, participants with and without a history of cardiovascular disease, men, and women). Nonsmokers included never and past smokers. In addition, these models also evaluated the relationship between alcohol consumption and CRP levels after adjustment for past and current smoking, systolic blood pressure, diabetic status, body mass index, HDL cholesterol, sex, and aspirin use. Systolic blood pressure and body mass index were modeled as continuous variables. The general model was also adjusted to control for exercise frequency and education status. Finally, we performed analyses to assess any interactions between alcohol intake, pravastatin allocation, and change in CRP or lipids over time. All probability values are 2-tailed.

### Results

Table 1 shows baseline characteristics of PRINCE participants according to category of alcohol intake. The mean ages for men and women participants were 60.9 ± 13.1 and 63.4 ± 12.5 years, respectively. Nondrinkers (group 1) were more likely to be women (49.8% versus 13.1%, P < 0.001) and to have diabetes (23.4% versus 6.9%, P < 0.001), but they were less likely to be smokers (14.2% versus 26.2%, 0.001).
P<0.001) compared with heavier consumers of alcohol (group 5). Heavier alcohol use (group 5) was associated with a lower body mass index (27.8±4.5 versus 29.4±5.9 kg/m², P<0.001) and triglyceride levels (148.5 mg/dL, interquartile range [IQR], 109.0 to 215.0 mg/dL] versus 166.0 mg/dL [IQR, 118.0 to 240.0 mg/dL]; P=0.03) but higher total cholesterol (229.1±37.3 mg/dL versus 221.9±39.9 mg/dL; P=0.29) and HDL cholesterol (44.8±12.5 mg/dL versus 38.1±10.7 mg/dL; P<0.001) levels than no alcohol use (group 1).

As expected, CRP levels were higher among individuals with a history of cardiovascular disease (2.60 mg/L; IQR, 1.20 to 5.30 mg/L) compared with those participants without a history of cardiovascular disease (2.00 mg/L; IQR, 0.90 to 4.20 mg/L) and among women (3.10 mg/L; IQR, 1.40 to 6.00 mg/L) compared with men (1.80 mg/L; IQR, 0.90 to 3.80 mg/L). As previously reported,20 women on hormone replacement therapy (HRT; 3.90 mg/L; IQR, 1.90 to 6.80 mg/L) and among women (3.10 mg/L; IQR, 1.40 to 6.00 mg/L) had higher CRP concentrations than women not on HRT (2.80 mg/L; IQR, 1.20 to 5.40 mg/L) and nonsmokers (2.10 mg/L; IQR, 0.90 to 4.50 mg/L).

As shown in the Figure, overall there was a progressive decline in CRP levels with increased alcohol intake, with a threshold effect at the highest level of alcohol consumption. Specifically, the lowest baseline CRP levels were observed among participants who reported moderate alcohol use (group 4: 5 to 7 drinks weekly; CRP, 1.60 mg/L; IQR, 0.80 to 3.30 mg/L). Furthermore, in multivariate analysis, the relationship between log-normalized levels of CRP and alcohol intake remained significant after controlling for past and current smoking, systolic blood pressure, diabetes, body mass index, HDL cholesterol, age, sex, and aspirin use (Table 2; P<0.001 for trend). This linear relationship was present among those in the primary and secondary prevention cohorts, men, women taking HRT, women not taking HRT, and nonsmokers (all P<0.01). Among smokers (P=0.032), there was an inverse relationship between category of alcohol intake and CRP concentrations. Among women taking HRT, this effect was less striking, and no statistically significant association between alcohol consumption and CRP levels was observed (P=0.51).

To assess the association between alcohol intake and baseline clinical variables, Pearson correlations were computed. The magnitude of correlation between categories of alcohol intake and baseline CRP level, although small (r = –0.14), was similar to that observed between alcohol and baseline HDL cholesterol (r = 0.13), alcohol and past smoking (r = 0.10), and alcohol and diabetes (r = –0.14; all P<0.05). For pravastatin-treated participants, the correlation between alcohol categories and change in CRP levels at 6 months was not significant (r = 0.01, P = 0.52).

Table 3 shows absolute and percent changes in CRP and lipid levels at 6 months in pravastatin-treated participants according to category of alcohol intake. As shown, the magnitude of LDL decrease and HDL increase with statin therapy was generally similar across alcohol groups. In

### TABLE 2. Regression Coefficients and Their Associated Standard Errors for Log-CRP According to Alcohol Categories

<table>
<thead>
<tr>
<th></th>
<th>Group 2: 1–3 Drinks/Month</th>
<th>Group 3: 1–4 Drinks/Week</th>
<th>Group 4: 5–7 Drinks/Week</th>
<th>Group 5: &gt;2 Drinks/Day</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>Crude model</td>
<td>−0.18±0.06</td>
<td>−0.32±0.06</td>
<td>−0.44±0.08</td>
<td>−0.48±0.10</td>
</tr>
<tr>
<td></td>
<td>Adjusted model</td>
<td>−0.06±0.06</td>
<td>−0.15±0.06</td>
<td>−0.18±0.08</td>
<td>−0.24±0.10</td>
</tr>
<tr>
<td>Men</td>
<td>Crude model</td>
<td>−0.14±0.08</td>
<td>−0.25±0.08</td>
<td>−0.28±0.09</td>
<td>−0.34±0.12</td>
</tr>
<tr>
<td></td>
<td>Adjusted model</td>
<td>−0.10±0.07</td>
<td>−0.19±0.07</td>
<td>−0.16±0.09</td>
<td>−0.22±0.11</td>
</tr>
<tr>
<td>Women with no HRT</td>
<td>Crude model</td>
<td>−0.25±0.12</td>
<td>−0.17±0.17</td>
<td>−0.88±0.25</td>
<td>−0.40±0.39</td>
</tr>
<tr>
<td></td>
<td>Adjusted model</td>
<td>−0.04±0.11</td>
<td>−0.009±0.15</td>
<td>−0.46±0.23</td>
<td>−0.15±0.37</td>
</tr>
<tr>
<td>Women with HRT</td>
<td>Crude model</td>
<td>0.03±0.15</td>
<td>−0.07±0.19</td>
<td>0.04±0.29</td>
<td>−0.45±0.39</td>
</tr>
<tr>
<td></td>
<td>Adjusted model</td>
<td>0.07±0.14</td>
<td>0±0.18</td>
<td>0.18±0.27</td>
<td>−0.29±0.37</td>
</tr>
</tbody>
</table>

Crude model is unadjusted. Adjusted model includes body mass index, systolic blood pressure, HDL cholesterol, aspirin use, diabetic status, and past and current smoking.
TABLE 3. Absolute Change and Percent Change in CRP and Lipid Levels at 24 Weeks in Pravastatin-Treated Participants According to Category of Alcohol Intake

<table>
<thead>
<tr>
<th>Category of Alcohol Intake</th>
<th>Group 1: No Alcohol Intake/≤1 Drinks/Month</th>
<th>Group 2: 3 Drinks/Month</th>
<th>Group 3: 1-4 Drinks/Week</th>
<th>Group 4: 5-7 Drinks/Week</th>
<th>Group 5: &gt;2 Drinks/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP, mg/L</td>
<td>(n=436)</td>
<td>(n=168)</td>
<td>(n=147)</td>
<td>(n=62)</td>
<td>(n=41)</td>
</tr>
<tr>
<td>Primary prevention</td>
<td>−0.27 (−17.0)</td>
<td>−0.14 (−6.6)</td>
<td>−0.19 (−15.5)</td>
<td>−0.10 (−4.9)</td>
<td>−0.10 (−13.8)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>−39.6 (−16.5)</td>
<td>−38.3 (−16.1)</td>
<td>−37.5 (−15.9)</td>
<td>−29.9 (−12.8)</td>
<td>−40.2 (−16.6)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>−32.7 (−21.9)</td>
<td>−31.9 (−21.4)</td>
<td>−31.0 (−21.2)</td>
<td>−27.2 (−18.7)</td>
<td>−32.8 (−22.1)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>2.3 (6.8)</td>
<td>2.4 (7.0)</td>
<td>2.1 (5.9)</td>
<td>1.5 (4.4)</td>
<td>2.3 (6.9)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>−21.5 (−14.3)</td>
<td>−12.0 (−9.8)</td>
<td>−16.0 (−11.6)</td>
<td>−13.5 (−8.3)</td>
<td>−36.0 (−25.6)</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>(n=720)</td>
<td>(n=160)</td>
<td>(n=132)</td>
<td>(n=92)</td>
<td>(n=50)</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>−2.8 (−13.0)</td>
<td>−2.6 (−13.4)</td>
<td>−2.4 (−7.0)</td>
<td>−1.7 (−10.2)</td>
<td>−2.2 (−21.1)</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>−40.0 (−18.4)</td>
<td>−40.6 (−18.8)</td>
<td>−39.5 (17.8)</td>
<td>−32.0 (−15.2)</td>
<td>−40.6 (−18.2)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>−32.2 (−24.5)</td>
<td>−32.3 (−24.4)</td>
<td>−33.5 (−24.7)</td>
<td>−26.2 (−20.5)</td>
<td>−30.3 (−23.5)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>2.0 (6.6)</td>
<td>1.7 (5.7)</td>
<td>2.2 (7.4)</td>
<td>0.4 (3.7)</td>
<td>3.2 (8.2)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>−26.0 (−17.6)</td>
<td>−35.5 (−23.7)</td>
<td>−21.0 (−13.7)</td>
<td>−19.5 (−13.1)</td>
<td>−40.0 (−28.7)</td>
</tr>
</tbody>
</table>

Values are mean (%) or median (%).
P<0.05 for all categories.

Discussion

These cross-sectional data demonstrate that moderate alcohol consumption (5 to 7 drinks weekly) was associated with lower CRP levels than no or occasional alcohol use. Heavier consumers of alcohol had CRP levels comparable to moderate drinkers. This observation was present in almost all subgroups assessed and remained significant after adjustment for past and current smoking, systolic blood pressure, diabetes, body mass index, HDL cholesterol, sex, and aspirin use (P<0.001 for trend). Additional adjustment for exercise frequency and education status also did not significantly change this relationship (P<0.001).

The current data support findings from Imhof et al10 that suggested that markers of systemic inflammation, including CRP, α-globulins, and leukocyte count have a J-shaped relationship with alcohol intake. That study showed a strong relationship between CRP and alcohol intake in both sexes but a weaker association among women. Thus, our data confirm and extend these observations by noting this relationship in patients with and without a history of vascular disease, as well as noting a clearer effect of alcohol on CRP levels among women not on HRT. Among women not taking HRT, the effect of moderate alcohol intake on CRP was robust, whereas the apparent lack of effect among HRT users may reflect, in part, a “first-pass” effect of HRT on CRP.21

That levels of inflammation are lower in moderate drinkers than nondrinkers also supports data from several prospective studies that show that light to moderate alcohol intake is associated with lower cardiovascular mortality than heavy or no alcohol intake.1-5 For example, data from the Physicians’ Health Study demonstrated a U-shaped relationship between alcohol and cardiovascular mortality among light to moderate drinkers.2 A similar observation was noted among middle-aged British men who were new regular alcohol drinkers22 and among women participating in the Nurses’ Health Study.3 Because several epidemiological studies have also demonstrated that CRP predicts future vascular risk,14-17 it is plausible that, at least in part, an inflammatory process mediates the effect of moderate alcohol intake on cardiovascular mortality. Although the mechanism of the latter process is uncertain, a leading hypothesis has been the effect of alcohol on increasing HDL cholesterol levels.6,7 However, in our data, the effect of alcohol on CRP remained significant after adjustment for HDL cholesterol levels.

From an inflammatory standpoint, moderate alcohol use has been reported to have antioxidant properties through alcohol’s polyphenolic content.23 For example, Iijima et al24 demonstrated that red wine polyphenols inhibited vascular smooth muscle cell migration, a critical component of atherosclerosis formation. Moderate alcohol consumption may also impair interleukin-6 production, a major regulator of CRP,25 and result in higher plasminogen activator inhibitor-I levels8,9 and increases in tissue plasminogen antigen production through gene activation.9

In the present study, we observed that moderate alcohol drinkers had higher baseline HDL and lower triglyceride levels, were less likely to be diabetic, and had lower body mass indexes than nondrinkers; these are all clinical variables that are associated with decreased cardiovascular risk. The relationship between higher HDL cholesterol and lower triglyceride levels with increased alcohol intake has been previously well described. Less described and probably more specific to our population is the observation of decreased body mass index and fewer diabetics among moderate drinkers.26 For example, because participants were all under the care of a physician, they were probably more likely to comply with cardiovascular risk factor modification strategies.
Some limitations of our study deserve mention. First, the cross-sectional nature of our study does not enable determination of causality. Second, self-report of alcohol intake by participants may underestimate the true consumption rate. Third, lack of information about the type of alcoholic beverages consumed is a theoretical limitation because some authors have suggested that beverage type may be associated with reduced atherosclerotic burden in experimental animals and improved lipid parameters. Fourth, a reliable distinction between CRP levels among moderate alcohol and heavier alcohol consumers is difficult, particularly among women, because of the small sample size in the heavy alcohol intake group. Also, the relationship between binge drinking and CRP is unclear and may have a different association with CRP than regular “heavy” drinking. Fifth, because former drinkers could not be separated from abstainers, the finding that alcohol had a similar effect on CRP levels in those individuals with and without a history of cardiovascular disease is reassuring. This suggests that the development of cardiovascular disease was likely not a major factor in the cessation of alcohol consumption by former drinkers.

In summary, in this cross-sectional survey, CRP levels were lower with increasing alcohol intake. However, there was not a significant difference in CRP levels between moderate and heavier consumers of alcohol, a finding that may be limited by sample size in the noted groups and confounding by smoking. This observation parallels the demonstration of a J- or U-shaped relationship between alcohol intake and cardiovascular mortality, thus supporting the hypothesis that, in part, the effect of alcohol on cardiovascular mortality may have links to inflammation. Further, because it seems that CRP levels were similar among moderate and heavier alcohol consumers and considering the high morbidity and mortality associated with the latter, we think that moderate alcohol use (5 to 7 drinks weekly) may have benefits on cardiovascular mortality. However, from a public health standpoint, caution must be exercised with regard to the support of moderate alcohol use because of the medical and societal problems associated with consumption.

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References
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