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,2,3,5 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) Study18 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,
...also calculated for each alcohol category. The ANOVA and 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%, respectively).
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 240.0 mg/dL]; P<0.001) 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 5.40 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
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suggested that markers of systemic inflammation, including no alcohol intake.1
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consumers of alcohol had CRP levels comparable to moder-
lower CRP levels than no or occasional alcohol use. Heavier
consumption (5 to 7 drinks weekly) was associated with
These cross-sectional data demonstrate that moderate alcohol
the level of alcohol consumption modified the effect of statin
additional regression analyses, there was little evidence that
the level of alcohol consumption modified the effect of statin
treatment on CRP.

**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, diabe-
tes, body mass index, HDL cholesterol, sex, and aspirin use
\((P<0.001)\). 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 relation-
ship 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 demonstra-
ted 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 cardiovas-
cular 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 ath-
erosclerosis formation. Moderate alcohol consumption may
also impair interleukin-6 production, a major regulator of
CRP,25 and result in higher plasminogen activator-inhibitor-1
levels8,9 and increases in tissue plasminogen antigen produc-
tion 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 drink-
ers.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.

### 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 Drink/Month</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>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prevention</td>
<td>((n=436))</td>
<td>((n=168))</td>
<td>((n=147))</td>
<td>((n=62))</td>
<td>((n=41))</td>
</tr>
<tr>
<td>CRP,* mg/L</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 (-18.4))</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.
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.

Acknowledgments

Dr Albert is supported by an award from the Robert Wood Johnson Foundation. The PRINCE trial was investigator initiated, coordinated, and performed centrally within the Center for Cardiovascular Disease Prevention, Brigham and Women’s Hospital, Harvard Medical School, and was run with full independence. The research group wrote all the protocols and manuals, holds all the primary data forms, and performed all the analyses. In addition to funding, the study sponsor, Bristol Myers Squibb, also provided the study drug.

References

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Circulation. 2003;107:443-447; originally published online January 6, 2003;
doi: 10.1161/01.CIR.0000045669.16499.EC
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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