Alcohol and long-term prognosis after a first acute myocardial infarction: the SHEEP study

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Introduction

Compelling epidemiological evidence suggests that moderate intake of alcoholic beverages is associated with lower risk of coronary heart disease (CHD) morbidity and mortality in the general population.¹⁻⁴ Less data are available, but moderate alcohol intake may also be related to reduced mortality in patients with established CHD,⁵⁻⁸ though studies are mixed in this regard.⁹

Because the alcohol–CHD relationship has never been tested in a randomized trial, enthusiasm is mounting for a randomized trial of alcohol among patients with CHD.¹⁰,¹¹ If such a secondary prevention trial is to occur, however, it is particularly important to confirm that the association of alcohol intake with prognosis after an acute myocardial infarction (AMI) is as consistent as that seen for incident CHD and that its candidate mechanisms are apt to be similar.

Context

Few studies have investigated the relation between alcohol consumption, former drinking, and prognosis after an acute myocardial infarction (AMI), particularly for non-fatal outcomes.

Objective

To investigate the prognostic importance of drinking habits among patients surviving a first AMI.

Design, settings, and patients

A total of 1346 consecutive patients between 45–70 years with a first non-fatal AMI underwent a standardized clinical examination and were followed for over 8 years.

Main outcome measures

Total and cardiac mortality and hospitalization for non-fatal cardiovascular disease in relation to individual alcoholic beverage consumption at the time of AMI and 5 years before inclusion, assessed by a standardized questionnaire administered during hospitalization.

Results

We recorded 267 deaths, and 145 deaths from cardiac causes, during the follow-up period. After adjustment for several potential confounders, hazard ratios for total and cardiac mortality were 0.77 (0.51–1.15) and 0.61 (0.36–1.02) for those drinking >0–<5 g per day, 0.77 (0.50–1.18) and 0.62 (0.36–1.07) for those drinking 5–20 g per day, and 0.89 (0.56–1.40) and 0.69 (0.38–1.25) for those drinking over 20 g per day. Risk of hospitalization for recurrent non-fatal AMI, stroke, or heart failure generally showed a similar pattern to that of total and cardiac mortality. Recent quitters at the time of AMI had a hazard ratio of 4.55 (2.03–10.20) for total mortality. Measures of insulin sensitivity appeared to be the strongest mediators of this association.

Conclusions

Moderate alcohol drinking might have beneficial effects on several aspects of long-term prognosis after an AMI. Our findings also highlight that former drinkers should be examined separately from long-term abstainers. The potential mechanisms that underlie this association still need to be elucidated.

Keywords

Alcohol • Acute myocardial infarction • Prognosis
Three studies have reported on the role of alcohol intake prospectively in survivors of a recent AMI. The Onset study showed that moderate alcohol intake reported at the time of MI was inversely related to mortality, while binge drinking was associated with higher mortality. In the Lyon Diet Heart Study, moderate wine drinking was associated with a more favourable prognosis after an AMI, although only a heterogeneous composite outcome was available. In the Survival And Ventricular Enlargement trial, light-to-moderate drinking was not associated with mortality or with risk of developing heart failure.

Several biological mechanisms have been suggested to mediate the effect between alcohol drinking and CHD risk, including high-density lipoprotein cholesterol (HDL-C). However, corresponding pathways for the potential effects of drinking after AMI have not been explored; limited data from our group suggest they may differ from incident CHD.

It also remains possible that any association between alcohol intake and post-AMI prognosis might be explained by the ‘sick quitter’ hypothesis. According to this hypothesis, abstainers include some former drinkers who stopped drinking due to illness, and their pre-existing disease could explain their higher risk. Former drinkers were not systematically considered in previous reports on drinking and survival after an AMI.

Therefore, we investigated the long-term prospective relationship between drinking habits and total and cardiac mortality in patients surviving their first AMI. Drinking habits both at the time of the event and before AMI were evaluated. We included a variety of non-fatal endpoints, including recurrent AMI, revascularization procedures, hospitalization for heart failure, and stroke. We also examined possible mediators of the effect of alcohol consumption and tested whether variants in the apolipoprotein (apo) E and interleukin (IL) 6 genes, which may modify the association of alcohol intake with incident CHD, also influence the association of alcohol intake with post-AMI prognosis.

Methods
Subjects and design
We followed individuals enrolled as non-fatal AMI cases in the Stockholm Heart Epidemiology Program (SHEEP), a population-based case-control study of incident AMI. The study base comprised all Swedish citizens living in the Stockholm County, 45–70 years of age, free of previously clinically diagnosed AMI. Male cases were identified during a 2 year period (1992–93) and female cases during 3 years (1992–94). Cases were identified through a special organization at the 10 emergency hospitals in the region. Criteria for AMI included (i) certain symptoms according to case history information, (ii) specified changes in blood levels of the enzymes CK and LD, (iii) specified ECG changes, and (iv) autopsy findings. The diagnosis ‘acute myocardial infarction’ required two of the criteria (i–iii) to be met, or that autopsy findings showed myocardial necrosis of an age compatible with the time of disease onset. Later comparison with a population-based register-based incidence register indicated close to complete ascertainment of all first AMIs. A total of 2,246 cases of MI were identified, of which 1,603 were non-fatal defined as surviving the AMI for at least 28 days. Eighty-four percent or 1,381 of the non-fatal cases participated in the questionnaires handed out a few days after the AMI, and 1,346 provided complete data on alcohol consumption.

A health examination measuring blood pressure, height, and weight with a blood sampling was undertaken at least 3 months after the AMI onset. A total of 1,209 patients with complete alcohol data participated in the health examination, nine patients could not participate because they died between the 28th day and the end of the third month following the AMI.

Alcohol
The questionnaire distributed a few days after AMI onset queried patients about their drinking habits in the last year and during their lifetime since age 15. Consumption of alcoholic beverages in the last year was assessed by using the corresponding items of the Willett food frequency questionnaire. The usual intake of five beverage types—regular beer, strong beer, wine, light spirits (e.g. liqueur, vermouth, and port) and spirits were asked. The estimated alcohol content of these beverages was 3.5, 4.9, 11, 19, and 39%, respectively. Average daily alcohol intake was calculated in grams. We grouped strong beer with regular beer and light spirits with regular spirits in beverage-specific analyses. We refer to these measurements as drinking habits at the time of AMI.

Previous alcohol consumption was reported as an average consumption during 10 year intervals of age prior to inclusion: 15–24, 25–34, 35–44, 45–54, 55–64, and 65–69 years. Previous alcohol intake was defined based on intake in the preceding 5–10 years. If a patient had lived more than 5 years in the current 10 year interval at inclusion, then previous alcohol consumption was defined as the average consumption of this 10 year interval, e.g. if aged 61 at inclusion, then previous alcohol consumption was taken from the average consumption in the 10 year interval between 55–64 years of age. If a patient at inclusion had lived 5 years or less in the current 10 year interval, e.g. aged 58 at inclusion, then previous alcohol consumption was chosen from the previous 10 year interval, e.g. the average consumption during 45–54 years of age. In sensitivity analyses, we also separated long-term abstainers from former drinkers based on whether they consumed alcohol anytime after 35 years of age.

Based on these measurements, we categorized alcohol consumption into five groups. We first distinguished between current abstainers and current drinkers. Current abstainers were then further divided into: (i) longer-term abstainers (i.e. abstainers based on both current and previous drinking questions), and (ii) recent quitters (i.e. abstainers at the time of AMI, but reporting previous alcohol consumption). Current drinkers were categorized as (iii) consumers of alcohol but less than 5 g, (iv) between 5–20 g, (v) over 20 g per day based on the drinking habits at inclusion. Further information on drinking patterns or drinking habits at the time of the health examination was not ascertained.

Covariates
Lipids, coagulation, inflammation
As previously described elsewhere, lipids, coagulation factors, and inflammatory markers were measured from blood samples drawn by venous puncture after overnight fasting at the health examination.

Diabetes
Subjects were classified as diabetics if they had a history of diabetes or insulin or drug treatment for diabetes, or whose fasting blood glucose level exceeded 6.7 mmol/L at the health examination.

Insulin, insulin-like growth factor binding protein-1 (IGFBP-1), insulin resistance
Insulin and IGFBP-1 levels were estimated from fasting blood samples. An estimate of insulin resistance was calculated using the homeostasis
model assessment (HOMA-IR) as follows: insulin resistance = fasting glucose × fasting insulin/22.5.35

**Hypertension**
Hypertension was defined as (i) being on antihypertensive drug therapy, for the reason of hypertension, when included in the study; (ii) a history of regular antihypertensive drug therapy during the last 5 years (or a part of that time), (iii) a systolic blood pressure ≥170 mmHg or a diastolic blood pressure ≥95 mmHg. Blood pressure values were the mean of two measurements in supine position after 5 min rest.

**Obesity**
Patients with a measured BMI-value over 30 kg/m² were classified as being obese.

**Physical inactivity**
Patients who reported inactive leisure time, including occasional walks, during the last 5–10 years were categorized as physically inactive.

**Smoking**
Subjects who had never smoked regularly (i.e. for at least 1 year) were considered as never-smokers. Subjects who smoked when included into the study or had stopped smoking within the last 2 years were classified as smokers. Subjects who had stopped smoking for more than 2 years before inclusion were classified as ex-smokers.

**Socioeconomic position**
As a measure of socioeconomic position, we classified educational attainment as mandatory school only vs. high school, college, or university.

**Genotyping**
Genotyping was performed as described earlier.34 Carriers of ApoE genotype ε4 were defined as participants with the ε3/ε4 or ε4/ε4 genotypes. Three SNPs in the IL-6 promoter region were determined; genotype 1 was 3/3, genotype 2 was 2/2, and genotype 3 was 2/3.35

**Follow-up**
The centralized health care system in Sweden provides virtually complete follow-up information for all patients by matching their unique 10 digit person identification numbers to health care registers. The average follow-up, from the AMI, was 3152 days (SD = 259 days, median = 3159 days, interquartile range = 373 days). All-cause and cardiac mortality was used as a primary end-point as provided by the National Cause-of-death Register. Patients were also followed for non-fatal AMI using the Swedish Myocardial Infarction Register.36 Information on hospitalization for heart failure (ICD-9 and 10 codes were 428, 150, respectively) and stroke (431, 434, I64, I63, I61) was derived from the Swedish Hospital Discharge Register.37–39 Follow-up was closed on 1 December 2001.

**Statistics**
We used sex/age- and multivariable-adjusted Cox proportional hazard models to examine the association between alcohol consumption and all-cause and cardiac mortality. The group of longer-term abstainers was the reference category in these models. We present hazard ratios with their 95% confidence intervals throughout; no adjustment for multiple comparisons was made, as recommended.40 There was no evidence of non-proportionality of hazards when investigated by log–log curves or by formal two-sided test of interaction with time (with a significance level of 0.05). Hazard ratios calculated separately for the first 3 years, 3–6 years, and for the rest of the follow-up period were also similar. Rothman’s synergy index with 95% confidence intervals was used to evaluate interaction between the effect of alcohol and genotypes.41 In beverage type analyses, we examined the association of individual beverages in categories with risk, adjusting simultaneously for intake of other beverage types. To examine potential mediators, we compared the change in regression coefficients from multivariable models for the effect of 5–20 g/day with and without inclusion of specific biomarkers. Statistical analyses were performed using SAS 9 for Windows.

**Results**
Table 1 presents the characteristics of the longer-term abstainers, those drinking between >0−<5 g, 5−20 g, and over 20 g of alcohol per day, and recent quitters at the time of the examination. Longer-term abstainers were the oldest and recent quitters the youngest. The mean age of the whole patient population was 59.4, SD = 7.2 years.

Overall, current drinkers had the most favourable lipid profile, and their levels of fibrinogen, von Willebrand factor, hsCRP, homocysteine, and IGFBP-1 also tended to be lower when compared with longer-term abstainers or recent quitters.

Table 2 presents the hazard ratios for all-cause and cardiac mortality among the five groups relative to long-term abstainers. In age- and sex-adjusted models, drinkers, especially those drinking 5–20 g, had lower all-cause and cardiac mortality than longer-term abstainers, a difference that was somewhat attenuated after adjustment for several potential confounders. Recent quitters consistently had the highest mortality. Though the number of recent quitters was small, grouping longer-term abstainers and recent quitters (i.e. using abstainers at the time of examination as the reference group) substantially inflated the observed protective effect of alcohol. Specifically, the hazard ratios and 95% confidence intervals for cardiac mortality were 0.51 (0.32–0.84), 0.52 (0.31–0.86), and 0.56 (0.32–0.99) when those drinking between >0−<5 g, 5–20 g, and over 20 g of alcohol per day, respectively, were compared with abstainers at the time of examination in the multiadjusted model.

In sensitivity analyses (data not shown), we additionally controlled for left ventricular function among the 85% of the patients with information on this variable as a continuous variable, and found no evidence of substantial confounding. Likewise, adjustment for other measures of infarct severity (Killip class, ventricular tachycardia, and Q-wave MI) had little effect on our estimates of risk. The association between alcohol consumption 5–10 years before AMI—as reported retrospectively after the event—and all-cause and cardiac mortality was largely the same as the association with alcohol consumption at inclusion (data not shown).

Table 3 shows several models where we additionally adjusted for potential mediators of the effect of alcohol and how adjustment modified the strength of the association between alcohol intake and prognosis. We compared base models with models that additionally adjusted for each individual biomarker, restricting both models to those who had non-missing values for the
Table 1  Characteristics of the SHEEP patients according to their alcohol consumption

<table>
<thead>
<tr>
<th>Daily alcohol consumption (g/day)</th>
<th>Longer-term abstainers</th>
<th>&gt;0–&lt;5.0 g</th>
<th>5.0–20 g</th>
<th>&gt;20 g</th>
<th>Recent quitters</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>140</td>
<td>437</td>
<td>447</td>
<td>308</td>
<td>14</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>61.7 (6.7)</td>
<td>60.9 (6.9)</td>
<td>58.9 (7.1)</td>
<td>57.0 (7.1)</td>
<td>56.8 (7.1)</td>
</tr>
<tr>
<td>Peak CK (ng/mL), mean (SD)</td>
<td>28.2 (27.7)</td>
<td>25.9 (28.8)</td>
<td>28.1 (25.0)</td>
<td>27.6 (24.3)</td>
<td>27.0 (34.1)</td>
</tr>
</tbody>
</table>

Serum levels of (mean (SD))

<table>
<thead>
<tr>
<th></th>
<th>Longer-term abstainers</th>
<th>&gt;0–&lt;5.0 g</th>
<th>5.0–20 g</th>
<th>&gt;20 g</th>
<th>Recent quitters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>6.24 (1.22)</td>
<td>6.20 (1.19)</td>
<td>6.23 (1.16)</td>
<td>6.10 (1.11)</td>
<td>6.52 (1.58)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.29 (1.86)</td>
<td>1.99 (1.36)</td>
<td>1.97 (1.34)</td>
<td>2.12 (1.56)</td>
<td>1.99 (0.96)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.06 (0.28)</td>
<td>1.06 (0.29)</td>
<td>1.10 (0.35)</td>
<td>1.08 (0.28)</td>
<td>1.15 (0.38)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>4.19 (1.02)</td>
<td>4.28 (1.03)</td>
<td>4.28 (0.99)</td>
<td>4.09 (0.95)</td>
<td>4.47 (1.33)</td>
</tr>
<tr>
<td>Lipoprotein(a) (g/L)</td>
<td>0.29 (0.39)</td>
<td>0.33 (0.39)</td>
<td>0.29 (0.33)</td>
<td>0.27 (0.33)</td>
<td>0.26 (0.43)</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>3.99 (1.02)</td>
<td>3.81 (0.96)</td>
<td>3.66 (0.82)</td>
<td>3.68 (0.97)</td>
<td>4.11 (1.02)</td>
</tr>
<tr>
<td>PAI-1 (IU/mL)</td>
<td>17.8 (13.4)</td>
<td>19.4 (17.0)</td>
<td>18.8 (17.1)</td>
<td>24.6 (24.4)</td>
<td>20.4 (14.8)</td>
</tr>
<tr>
<td>tPA/PAI-1 complex (μg/L)</td>
<td>6.18 (2.51)</td>
<td>6.53 (3.42)</td>
<td>6.72 (3.35)</td>
<td>8.10 (4.02)</td>
<td>6.32 (2.91)</td>
</tr>
<tr>
<td>von Willebrand factor (IU/ml)</td>
<td>1.62 (0.57)</td>
<td>1.66 (0.67)</td>
<td>1.47 (0.47)</td>
<td>1.52 (0.54)</td>
<td>1.56 (0.29)</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>5.34 (9.81)</td>
<td>4.13 (7.15)</td>
<td>3.26 (4.73)</td>
<td>4.29 (6.81)</td>
<td>5.29 (5.80)</td>
</tr>
<tr>
<td>IL-6 (ng/L)</td>
<td>9.58 (31.36)</td>
<td>9.00 (33.23)</td>
<td>7.91 (26.64)</td>
<td>8.10 (4.02)</td>
<td>7.97 (3.92)</td>
</tr>
<tr>
<td>Homocysteine (μmol/L)</td>
<td>13.4 (5.0)</td>
<td>12.6 (4.4)</td>
<td>12.8 (5.3)</td>
<td>12.4 (3.8)</td>
<td>15.8 (8.9)</td>
</tr>
<tr>
<td>Insulin (mU/mL)</td>
<td>41.8 (4.18)</td>
<td>38.9 (4.19)</td>
<td>36.1 (5.74)</td>
<td>36.4 (3.93)</td>
<td>27.2 (1.37)</td>
</tr>
</tbody>
</table>

Male sex, n (%)  
Hypertension, n (%)  
Diabetes mellitus, n (%)  
Obesity (BMI > 30 kg/m²), n (%)  
Sedentary lifestyle, n (%)  
Current smokers, n (%)  
High school/college or university, n (%)  
Index hospitalization, n (%)  
Q-wave infarction  
Tachycardia  
Killip classification  
1  
2+  
Thrombolysis  
Beta-blockers  
Aspirin  
Nitrites  
Ca antagonist  
Diuretics  
Digitalis  
ACE-inhibitors  
Average use of (g/day)  
Beer  
Wine  
Spirits

Blood pressure, height, and weight with a blood sampling was undertaken at least 3 months after the AMI onset. All other information was obtained a few days after the event.

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; PAI-1, plasminogen activator inhibitor 1; tPA, tissue plasminogen activator; TNF, tumor necrosis factor; IGFBP-1, insulin-like growth factor binding protein-1; HOMA, homeostasis model assessment; fasting glucose x fasting insulin/22.5.
Alcohol consumption and prognosis after AMI

value towards the null value.

valid value on HDL, to the model where base model adjustment was expanded with an adjustment for HDL. The change is a positive number when adjustment changes the beta adjusted model. For example in case of the HDL, its mediation was investigated as the change in the beta coefficient from the base model including 1170 cases, i.e. those who had (longer-term abstainers are the reference group)

Adjustments for LDL, LpA, apoA, or apoB showed essentially similar results to the adjustments with total cholesterol (coefficient changes all below 1%).

Table 2 Total- and cardiac-mortality of the SHEEP patients according to their alcohol consumption

<table>
<thead>
<tr>
<th>Total mortality</th>
<th>Number of deaths/person-years of follow-up</th>
<th>Event rate (95% CI) per 100 patient-years</th>
<th>Age and sex adjusted</th>
<th>Base model(^{a}) adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longer-term abstainers</td>
<td>35/1041</td>
<td>3.36 (2.25–4.48)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Recent quitters</td>
<td>8/79</td>
<td>10.13 (3.11–17.14)</td>
<td>4.29 (1.95–9.44)</td>
<td>4.55 (2.03–10.20)</td>
</tr>
<tr>
<td>0–5 g</td>
<td>84/3495</td>
<td>2.40 (1.89–2.92)</td>
<td>0.74 (0.50–1.09)</td>
<td>0.77 (0.51–1.15)</td>
</tr>
<tr>
<td>5–20 g</td>
<td>80/3549</td>
<td>2.25 (1.76–2.75)</td>
<td>0.72 (0.48–1.09)</td>
<td>0.77 (0.50–1.18)</td>
</tr>
<tr>
<td>over 20 g</td>
<td>60/2424</td>
<td>2.48 (1.85–3.10)</td>
<td>0.87 (0.56–1.35)</td>
<td>0.89 (0.56–1.40)</td>
</tr>
</tbody>
</table>

Cardiac mortality

| Longer-term abstainers                  | 23/1041                                    | 2.21 (1.31–3.11)                          | 1                    | 1                           |
| Recent quitters                         | 5/79                                       | 6.33 (0.78–11.88)                         | 3.55 (1.32–9.58)     | 4.47 (1.60–12.47)           |
| 0–5 g                                   | 44/3495                                    | 1.26 (0.89–1.63)                          | 0.58 (0.35–0.96)     | 0.61 (0.36–1.02)            |
| 5–20 g                                  | 42/3549                                    | 1.18 (0.83–1.54)                          | 0.56 (0.34–0.95)     | 0.62 (0.36–1.07)            |
| over 20 g                               | 31/2424                                    | 1.28 (0.83–1.73)                          | 0.65 (0.37–1.15)     | 0.69 (0.38–1.25)            |

\(^{a}\)Base model includes age (as indicators), sex, smoking, obesity (BMI > 30 kg/m\(^2\)), self-reported physical activity, history of diabetes mellitus, and education.

Table 3 Estimated regression coefficients with 95% confidence intervals for total mortality among drinkers >0–20 g (longer-term abstainers are the reference group)

<table>
<thead>
<tr>
<th>Base model(^{a}) adjusted (n = 1320)</th>
<th>Coefficient (95% CI)</th>
<th>Change(%)(^{b})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base model + hypertension adjusted (n = 1316)</td>
<td>-0.24 (0.67–0.31)</td>
<td>10.2</td>
</tr>
<tr>
<td>Base model + HDL adjusted (n = 1170)</td>
<td>-0.37 (0.72–0.18)</td>
<td>-4.5</td>
</tr>
<tr>
<td>Base model + apoA adjustment (n = 1183)</td>
<td>-0.24 (0.68–0.21)</td>
<td>5.7</td>
</tr>
<tr>
<td>Base model + total cholesterol adjusted (n = 1184)</td>
<td>-0.25 (0.69–0.19)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Base model + triglycerides adjusted (n = 1186)</td>
<td>-0.24 (0.67–0.21)</td>
<td>7.2</td>
</tr>
<tr>
<td>Base model + fibrinogen adjusted (n = 1111)</td>
<td>-0.22 (0.70–0.24)</td>
<td>18.4</td>
</tr>
<tr>
<td>Base model + PAI adjusted (n = 1127)</td>
<td>-0.22 (0.70–0.25)</td>
<td>-4.0</td>
</tr>
<tr>
<td>Base model + tPA/PAI complex adjusted (n = 871)</td>
<td>-0.20 (0.72–0.31)</td>
<td>-23.3</td>
</tr>
<tr>
<td>Base model + von Willebrand factor adjusted (n = 876)</td>
<td>-0.16 (0.67–0.35)</td>
<td>7.6</td>
</tr>
<tr>
<td>Base model + CRP adjusted (n = 869)</td>
<td>-0.17 (0.66–0.36)</td>
<td>4.6</td>
</tr>
<tr>
<td>Base model + TNFxf adjusted (n = 804)</td>
<td>-0.21 (0.74–0.31)</td>
<td>4.9</td>
</tr>
<tr>
<td>Base model + IL-6 adjusted (n = 770)</td>
<td>-0.34 (0.89–0.15)</td>
<td>10.6</td>
</tr>
<tr>
<td>Base model + homocysteine adjusted (n = 869)</td>
<td>-0.14 (0.65–0.38)</td>
<td>23.9</td>
</tr>
<tr>
<td>Base model + insulin adjusted (n = 798)</td>
<td>-0.05 (0.62–0.52)</td>
<td>32.8</td>
</tr>
<tr>
<td>Base model + IGFBP-1 adjusted (n = 798)</td>
<td>-0.05 (0.63–0.52)</td>
<td>30.0</td>
</tr>
<tr>
<td>Base model + HOMA adjusted (n = 798)</td>
<td>-0.08 (0.65–0.49)</td>
<td>-5.8</td>
</tr>
</tbody>
</table>

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ApoA, apolipoprotein A; ApoB, apolipoprotein B; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; PAI-1, plasminogen activator inhibitor 1; tPA, tissue plasminogen activator; TNF, tumor necrosis factor; IGFBP-1, insulin-like growth factor binding protein-1; HOMA, homeostatis model assessment, fasting glucose x fasting insulin/22.5.

\(^{b}\)CHANGE, change in the beta coefficient of the base model for those who have a valid value for a given variable, but that variable is not adjusted for vs. base model + given variable adjusted model. For example in case of the HDL, its mediation was investigated as the change in the beta coefficient from the base model including 1170 cases, i.e. those who had valid value on HDL, to the model where base model adjustment was expanded with an adjustment for HDL. The change is a positive number when adjustment changes the beta value towards the null value.

\(^{a}\)Base model includes age (as indicators), sex, smoking, obesity (BMI > 30 kg/m\(^2\)), self-reported physical activity, history of diabetes mellitus, and education.

\(^{b}\)Adjustments for LDL, LpA, apoA, or apoB showed essentially similar results to the adjustments with total cholesterol (coefficient changes all below 1%).
respective biomarker. Adjustment for insulin, IGFBP-1, homocysteine, and fibrinogen levels resulted in the largest decrease in the coefficients for the association between drinking and total mortality. Including tPA/PAI complex in multivariable models increased the drinking-mortality association, consistent with the hypothesis that overall effect of alcohol intake includes an adverse effect on tPA/PAI levels. Adjustment for hypertension, lipids, other coagulation factors, inflammatory markers and insulin resistance did not influence the association considerably.

In stratified analyses, we found roughly similar associations between alcohol consumption and mortality among men and women, in six age categories (45–50, 51–55, 56–60, 61–65, >65 years), among individuals with a BMI value over and below 30 kg/m², among physically active and inactive subjects, never-, current-, and former smokers, and among patients having high school/college degree and lower education.

Given the relatively strong association of prognosis with intake of >0–<5 g/day, we also performed analyses where consumption of >0–<5 g of alcohol was further divided into >0–<1.5 g, 1.5–>3 g, and 3–>5 g per day to test the dose–response relationship. We found that mortality decreased in these groups in a dose-dependent manner. The hazard ratios for total mortality were 0.92 (0.59–1.42), 0.70 (0.41–1.19), 0.46 (0.25–0.85) in these groups when compared with longer-term abstainers, respectively.

Table 4 shows the base model adjusted hazard ratios for cardiovascular events alone and in combination with cardiac mortality. Generally, risk for these events showed a similar pattern to that of total and cardiac mortality. Risk of revascularization tended to parallel that of recurrent MI, much as the association of alcohol intake with risk of ischaemic stroke did with risk of total stroke (data not shown).

Due to missing values in previous drinking habits, we may not have identified all recent quitters in our analyses. As a sensitivity analysis, we excluded those 22 (16%) abstainers who had a missing value for previous drinking, with essentially the same results in these restricted analyses. We also repeated our analyses, redefining the 154 current abstainers based on their consumption from age 35 forward into long-term abstainers (n = 92) and former drinkers (n = 62). Compared with long-term abstainers using this expanded definition, the adjusted hazard ratios for total mortality among former drinkers and consumers of >0–<5 g, 5–20 g, and over 20 g per day were 0.89 (0.47–1.68), 0.62 (0.39–0.97), 0.61 (0.38–0.98), and 0.69 (0.42–1.15), respectively, suggesting that the lower risk associated with alcohol consumption was not related to inclusion of even distantly former drinkers. The corresponding hazard ratios for cardiac mortality were 0.86 (0.38–1.90), 0.48 (0.27–0.86), 0.48 (0.26–0.89), and 0.53 (0.27–1.02).

Our analyses did not reveal that any single beverage had a clearly stronger relationship with mortality than other beverage types (data not shown). However, heavier consumption of beer was uniquely associated with higher mortality relative to abstention, with a hazard ratio for total mortality among those who consumed over 20 g of beer per day of 1.50 (0.87–2.57) when compared with beer abstainers.

We also examined if the effect of alcohol is modified by ApoE or IL-6 promoter genotype. These genotypes were all in HWE (P = 0.42 for ApoE, and P = 0.14, 0.18, 0.92 for −598, −573, and −174 IL-6 promoter genotypes, respectively). The effect of alcohol was slightly stronger on cardiac mortality among e4 carriers when compared with non-carriers [HR for drinking, with longer-term abstainers as the reference group, was 0.49 (0.20–1.21) among carriers and 0.76 (0.36–1.57) among non-carriers]. Rothman’s synergy index was 0.59 (0.32–1.08) for this interaction, suggesting that the two separate exposures to ApoE and alcohol do not add to each other in the case of combined exposure. We found no evidence for an interaction with alcohol drinking concerning ApoE genotype and total mortality, or for any of the IL-6 promoter gene variants.

Discussion

In this follow-up study of survivors of a first AMI, we found that current drinkers tended to have lower risk of mortality and non-fatal cardiovascular events than longer-term abstainers, even accounting for the higher risk among former drinkers.
An abundance of epidemiological studies of both community,\textsuperscript{1–3} and clinical samples have associated moderate alcohol consumption with decreased risks for subsequent cardiovascular morbidity and mortality.\textsuperscript{5–8} However, only the Onset,\textsuperscript{12,13} the Lyon Diet Heart Study,\textsuperscript{14} and Survival And Ventricular Enlargement trial\textsuperscript{15} have directly compared prospective mortality across alcohol consumption categories in survivors of a recent AMI.

The present study is distinguished from these previous works in several ways. Neither the Onset Study,\textsuperscript{12,13} the Lyon Diet Heart Study,\textsuperscript{14} nor the Survival And Ventricular Enlargement trial\textsuperscript{15} considered former drinking habits systematically. Our results highlight the importance of investigating long-term drinking habits and not classifying former drinkers as abstainers, which would falsely increase the observed positive effect of alcohol drinking. On the other hand, our analyses revealed that the drinking habits 5–10 years prior to AMI had a rather similar association with mortality as drinking habits ascertained at the time of hospitalization. This concurs with previous findings suggesting that drinking habits are generally stable over time, even when ascertained post MI.\textsuperscript{5,42}

This study also included extensive information on other cardiovascular endpoints than death, including non-fatal AMI, revascularization procedures, hospitalization for heart failure, and stroke. In general, the relation of these events to alcohol consumption showed a similar pattern to that of total and cardiac mortality. In case of PTCA and stroke, the effect size of the protective effect of alcohol was comparable with that of cardiac mortality. Among the previous studies on alcohol drinking and AMI prognosis, the Onset Study used only all-cause and cardiovascular mortality as end-points.\textsuperscript{12,13} In the Lyon Diet Heart Study, due to power considerations, all cardiovascular outcomes were grouped together.\textsuperscript{14} The Survival And Ventricular Enlargement trial investigated incident heart failure and recurrent AMI as separate outcomes, but found no evidence for a more favourable prognosis for moderate drinkers.\textsuperscript{15}

The biological mechanisms by which alcohol may influence the prognosis after an AMI are not yet understood, and previous studies have not reported on possible explanatory mechanisms. Studies on alcohol consumption and CHD risk indicate that HDL-C levels mediate approximately half of the relationship.\textsuperscript{16} Our findings suggest that HDL-C is not the major mediator for the association between alcohol and post-AMI prognosis, similar to our previous findings in a separate study of Swedish women.\textsuperscript{26} These findings raise questions about whether a randomized trial among post-AMI patients would represent an appropriate test of the alcohol–incident-CHD relationship, as the mechanisms do not appear to be the same.

Alcohol consumption has beneficial effects on glucose metabolism.\textsuperscript{19,25} We found that adjustment for insulin and IGFBP-1 levels attenuated the association between alcohol and mortality, and thus that the effect of alcohol may be partly mediated by its effects on glucose metabolism. Although the mechanism for this effect is uncertain, alcohol consumption raises adiponectin levels in feeding studies.\textsuperscript{13} Fibrinogen is another candidate biomarker decreased by alcohol consumption. Our results suggest that fibrinogen might play some role in explaining the prognostic effects of alcohol after AMI. Interestingly, the association of alcohol with improved prognosis would apparently be even stronger if alcohol did not have an adverse PAI-1/tPA raising effect, which has been observed in other cohorts.\textsuperscript{17} Other proposed mechanisms for cardiovascular effects of alcohol that we could not study include decreased platelet activity,\textsuperscript{44} lower levels of inflammation,\textsuperscript{18} better endothelial function,\textsuperscript{20} reduced endothelin-1 synthesis,\textsuperscript{21} reduced LDL oxidation,\textsuperscript{22} and smooth muscle proliferation.\textsuperscript{24}

Our findings suggest that the prognostic importance of consumption of wine, beer, or spirits is roughly similar. This finding concurs with two meta-analyses that found no consistent differences between beer, wine, and spirits in their associations with CHD in community samples, suggesting that the substantial portion of the apparent benefit is from ethanol rather than other components of the alcoholic beverages.\textsuperscript{45,46} The Onset Study reached a similar conclusion, i.e. no beverage type appeared to confer particular benefit.\textsuperscript{12} The Survival And Ventricular Enlargement trial\textsuperscript{15} had no beverage specific data, and the Lyon Diet Heart Study\textsuperscript{14} reported only on the effect of wine.

In this study, we found a relatively strong effect of intake <5 g/day, as has been observed in other cohorts with CHD. This may reflect some under-estimation of alcohol intake expected from self-report. Although the lower risk associated with light drinking could reflect uncontrolled confounding by unmeasured elements of lifestyle or clinical history, we did find a graded dose–response relationship within the >0–<5 g/day category, with essentially identical risk among longer-term abstainers and the lightest drinkers, arguing against uncontrolled confounding alone as an explanation for our findings.

Limitations of this study must be considered. Observational studies inherently limit causal inference. Though, we adjusted for several potential confounders in our multivariable analyses, we cannot exclude the possibility of uncontrolled confounding. However, any remaining confounder potentially able to influence our results considerably would need to be strongly associated with both alcohol use and prognosis of AMI and generally unrelated to the factors included in our models.

As in other studies, alcohol intake was self-reported. We relied on a standardized questionnaire,\textsuperscript{22} which is widely used and which has shown an excellent correlation to alcohol consumption as measured by diet records in a Swedish cohort.\textsuperscript{45}

We cannot draw conclusion on alcohol drinking and mortality within 28 days, as those who died in the early post-MI period were not included in the analyses. Limited data suggest that alcohol consumption may favourably influence AMI case-fatality.\textsuperscript{48} Drinking habits were measured a few days after hospitalization for AMI, and we had no information on possible changes during follow-up. However, earlier studies suggested that drinking habits are generally stable over time, even when ascertained post MI.\textsuperscript{5,42}

We had no information on the pattern of drinking and therefore could not examine the potential effects of binge drinking. Due to the low number of heavy drinkers, we also cannot draw firm conclusions about this category. Among the 308 patients reporting over 20 g of alcohol per day, only 58 consumed over 70 g per day and consequently could be considered as heavy drinker.

There were a relatively high number of missing values for several possible mediating factors, especially homocysteine, insulin, IGFBP-1, inflammatory, and some coagulatory factors. This was
attributable to a freezer breakdown and limited our power to examine their respective roles, but the relationship of alcohol intake with better prognosis was consistent even in the smaller subgroups with available information. Moreover, because the serum biomarkers were assessed a few months after alcohol use was ascertained, they may not accurately reflect alcohol use at the time they were measured.

We relied on national Swedish registries to document non-fatal events, and hence these relied on discharge diagnosis codes that have been validated but are nonetheless prone to misclassification. This is especially true for stroke, where detailed re-review of clinical information with which to distinguish stroke subtypes (which are likely to have different relationships with alcohol intake) was not available, although results were similar for total and ischaemic stroke based solely on discharge diagnoses codes.

Conclusions

Alcohol drinking habits were associated with all-cause and cardiac mortality and other adverse cardiovascular endpoints in patients surviving their first AMI. Recent quitters had the worst prognosis, followed by longer-term abstainers. Moderate alcohol drinking may have beneficial effects on both fatal and non-fatal outcomes after AMI; at the same time, our findings provided further support that former drinkers should be examined separately from long-term abstainers in cohort studies. Better understanding of the mechanisms that underlie this association is still needed.

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