Light-to-Moderate Alcohol Consumption and Prognosis in Patients With Left Ventricular Systolic Dysfunction

Howard A. Cooper, MD,*† Derek V. Exner, MD, MPH,* Michael J. Domanski, MD, FACC*
Bethesda, Maryland, and Washington, D.C.

OBJECTIVES
The study evaluated the relationship between light-to-moderate alcohol consumption and prognosis in patients with left ventricular (LV) systolic dysfunction.

BACKGROUND
Although chronic consumption of large amounts of alcohol can lead to cardiomyopathy, the effects of light-to-moderate alcohol consumption in patients with LV dysfunction are unknown.

METHODS
The relationship between light-to-moderate alcohol consumption and prognosis was assessed in participants in the Studies of Left Ventricular Dysfunction (SOLVD), all of whom had ejection fraction values \( \leq 0.35 \). Baseline characteristics and event rates of patients who consumed 1 to 14 drinks per week (light-to-moderate drinkers, \( n = 2,594 \)) were compared with those of patients who reported no alcohol consumption (nondrinkers, \( n = 3,719 \)). The association between light-to-moderate alcohol consumption and prognosis was evaluated using Cox proportional hazards analysis, controlling for baseline differences and important covariates.

RESULTS
Mortality rates were lower among light-to-moderate drinkers than among nondrinkers (7.2 vs. 9.4 deaths/100 person-years, \( p < 0.001 \)). Among patients with ischemic LV dysfunction, light-to-moderate alcohol consumption was independently associated with a reduced risk of all-cause mortality (RR [relative risk] 0.85, \( p = 0.03 \)), particularly for death from myocardial infarction (RR 0.55, \( p < 0.001 \)). The risks of cardiovascular death, death from progressive heart failure, arrhythmic death, and hospitalization for heart failure were similar for light-to-moderate drinkers and nondrinkers in this group. Among patients with nonischemic LV dysfunction, light-to-moderate alcohol consumption had no significant effect on mortality (RR 0.93, \( p = 0.5 \)).

CONCLUSIONS
Light-to-moderate alcohol consumption is not associated with an adverse prognosis in patients with LV systolic dysfunction, and it may reduce the risk of fatal myocardial infarction in patients with ischemic LV dysfunction. (J Am Coll Cardiol 2000;35:1753–9) © 2000 by the American College of Cardiology
ejection fraction (EF) ≤0.35 were eligible for enrollment. Those with a recent myocardial infarction (MI), significant valvular heart disease, or other serious comorbid illness were excluded. Patients with chronic alcoholism were excluded only if this was deemed likely to interfere with patient compliance. Patients were required to be clinically stable and to have had no recent changes in their heart failure medications. The specific inclusion and exclusion criteria have been published (9–11). The SOLVD protocols were approved by the local institutional review board at each participating center and by the National Heart, Lung, and Blood Institute. Each participant provided written informed consent.

Collection of data. All SOLVD participants (n = 6,797) underwent a detailed evaluation at entry. Patients were classified as asymptomatic or symptomatic and then enrolled in the Prevention or Treatment trial, respectively. There were 4,228 patients in the Prevention trial, approximately one third of whom had New York Heart Association (NYHA) functional class II symptoms. The Treatment trial included 2,569 patients, the majority of whom had NYHA functional class II and III symptoms.

At baseline, participants were asked the average number of alcoholic drinks they had consumed per week during the previous two years. Our analyses are based on these self-reported figures. Data on alcohol consumption were missing for 91 patients (1.3%), and these patients were excluded from this analysis. In addition, 97 patients (1.4%) who were diagnosed with alcoholic cardiomyopathy were excluded (Fig. 1).

Definition of end points. Follow-up averaged 33.4 ± 14.3 months in the two trials combined. Causes of death were determined by the principal investigator at each clinical site. Deaths from cardiovascular causes were classified by the SOLVD investigators as caused by pump failure; probable arrhythmia with some antecedent worsening of heart failure; probable arrhythmia with no antecedent worsening of heart failure; fatal MI; other cardiac, stroke, or vascular cause; or unknown. In this analysis, all deaths from pump failure and probable arrhythmia with some antecedent worsening of heart failure were classified as deaths caused by progressive heart failure. Arrhythmic deaths were limited to those classified as probable arrhythmia with no antecedent wors-

ning of heart failure. Two predefined indicators of the progression of heart failure were death from progressive heart failure and hospitalization for heart failure. Deaths from noncardiovascular causes were classified as a cancer or a noncancer cause.

Baseline variables. Age, blood pressure, and LV EF values were assessed as continuous variables. All remaining variables, including study drug allocation (enalapril/placebo), were assessed as dichotomous variables. The NYHA functional class symptoms were grouped as class I, class II, or class III/IV. The etiology of LV systolic dysfunction was classified as ischemic or other (nonischemic) by the enrolling physician. Data on blood lipids were not collected.

Categorization of alcohol consumption. To provide clinically meaningful information, patients were classified as nondrinkers (average consumption of zero alcoholic drinks per week), light-to-moderate drinkers (between 1 and 14 drinks per week), and heavy drinkers (more than 14 drinks per week).

Statistical analysis. Data from the Prevention and Treatment trials were pooled after no interaction was found between trial assignment and alcohol consumption with regard to mortality. Evidence of statistical interaction between alcohol consumption and the etiology of LV dysfunction was observed (p = 0.05); thus, ischemic and nonischemic patients were separately evaluated. Continuous characteristics are presented as mean ± SD. Pairwise differences were evaluated using a chi-square test or t-test. Death from any cause was used as the primary end point in this analysis, and additional analyses were performed for

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**Abbreviations and Acronyms**

- CI = confidence interval
- EF = ejection fraction
- HDL = high density lipoprotein
- LV = left ventricular
- MI = myocardial infarction
- NYHA = New York Heart Association
- RR = relative risk
- SOLVD = Studies of Left Ventricular Dysfunction

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**Figure 1.** Number of alcoholic drinks consumed per week at baseline for eligible participants in the Studies of Left Ventricular Dysfunction. (Percentages do not equal 100 because of rounding.)
cause-specific mortality end points and hospitalization for heart failure. Incidence rates were calculated as the number of events per 100 person-years of follow-up.

Multivariate Cox proportional hazards models were used to assess the independent relationship between alcohol consumption and mortality. Three multivariate models of increasing complexity were used in an attempt to highlight any confounding influences and to minimize the impact of missing data. The basic model included age, gender, EF, and NYHA class, adjusting for important demographic and prognostic factors. As the SOLVD trials were designed to assess the effect of enalapril, study drug assignment was also included in this model. An intermediate model added race, current smoking status, a history of diabetes and hypertension, as these have also been shown to affect outcome and were likely to differ between drinkers and nondrinkers. Finally, a fully adjusted model, which also included the baseline use of digoxin, diuretics, beta-blockers, antiarrhythmic drugs, aspirin and anticoagulants, was used to assess for the possible confounding impact of baseline medication use. Relative risk (RR) estimates and 95% confidence intervals (CI) were obtained from the Cox models. Two-sided p values <0.05 were considered to be significant. All analyses were performed using Stata: Release 6.0 (College Station, Texas).

RESULTS

Baseline characteristics. The distribution of alcohol consumption at baseline for the 6,609 participants in SOLVD without alcoholic cardiomyopathy is displayed in Figure 1. Alcohol consumption ranged from 0 to 84 alcoholic drinks per week. The majority of participants (55%) were nondrinkers, while a substantial minority were light-to-moderate drinkers (38%) consuming 1 to 14 drinks per week. There were few heavy drinkers (6%) consuming >14 drinks per week. Because the small number of heavy drinkers precluded accurate risk estimates, this group was not analyzed further.

Baseline characteristics of nondrinkers and light-to-moderate drinkers are shown in Table 1. Differences in mean age, the proportion of women and minorities, NYHA class, the prevalence of diabetes and hypertension, and baseline medication use were observed. Mean EF was nearly identical in the two groups, and a similar proportion of both groups had ischemic cardiomyopathy. As anticipated, the proportion of participants who were current smokers was somewhat higher among light-to-moderate drinkers than among nondrinkers.

Causes of death. Table 2 shows the causes of death among nondrinkers and light-to-moderate drinkers. Of the cardiovascular causes, progressive heart failure was the most common cause of death, followed by arrhythmia, MI and other cardiovascular causes. Light-to-moderate drinkers had a lower incidence of each cardiovascular cause of death, except for a slightly higher incidence (not statistically significant) of deaths classified as other cardiovascular deaths. Noncardiovascular deaths were also less common among light-to-moderate drinkers. The incidence of cancer death was similar in the two groups, while noncardiovascular deaths from causes other than cancer occurred less frequently in light-to-moderate drinkers.

Univariate analysis. Before adjustment for baseline differences, light-to-moderate alcohol consumption, compared with no alcohol consumption, was associated with a lower risk of death (RR 0.75, 95% CI 0.68–0.84, p < 0.001). Other predictors of a lower risk of death among those patients who were not heavy drinkers included the use of antiplatelet agents (RR 0.66, 95% CI 0.59–0.73, p < 0.001), beta-blockers (RR 0.55, 95% CI 0.47–0.65, p < 0.001) and randomization to the study drug enalapril (RR 0.87, 95% CI 0.78–0.96, p = 0.006). Predictors of a higher risk of death included older age (RR per 10-year increase 1.29, 95% CI 1.22–1.36, p < 0.001), nonwhite race (RR 1.57, 95% CI 1.37–1.81, p < 0.001), lower EF (RR per 10% decrease 1.72, 95% CI 1.59–1.85, p < 0.001), NYHA functional class III/IV (RR 2.82, 95% CI 2.51–3.17, p < 0.001), previous hypertension (RR 1.19, 95% CI 1.07–1.32, p = 0.001), diabetes (RR 1.59, 95% CI 1.42–1.78, p < 0.001).
Multivariate analyses. The results for participants with ischemic LV dysfunction (n = 5,331) and nonischemic LV dysfunction (n = 1,278) are presented in Table 3 and Table 4.

Ischemic LV dysfunction (Table 3). After adjusting for baseline differences in age, gender, EF, NYHA functional class and study drug assignment, light-to-moderate alcohol consumption, compared with no alcohol consumption, was associated with a decreased risk of all-cause mortality (RR 0.78, 95% CI 0.69–0.89, p < 0.001). This association remained significant when race, current smoking status, a history of diabetes mellitus, and a history of hypertension were added (RR 0.82, 95% CI 0.72–0.93, p < 0.001) and antiarrhythmic drugs (RR 1.40, 95% CI 1.24–1.58, p < 0.001).

Nonischemic LV dysfunction (Table 4). Light-to-moderate alcohol consumption, compared with no alcohol consumption, was not significantly associated with the risk of all-cause mortality or cardiovascular mortality in any of the models. The addition of markers of socioeconomic status to the models had little effect on the risk estimates (data not shown). A trend toward an increased risk of hospitalization for heart failure was seen in patients with nonischemic cardiomyopathy (p = 0.1).

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Number of Alcoholic Drinks Consumed per Week</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (n = 3,719)</td>
<td>1–14 (n = 2,594)</td>
<td></td>
</tr>
<tr>
<td>All causes</td>
<td>963 (25.9) Incidence*</td>
<td>531 (20.5) 7.2‡</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>843 (22.7) Incidence*</td>
<td>479 (18.5) 6.5‡</td>
<td></td>
</tr>
<tr>
<td>Progressive heart failure</td>
<td>397 (10.7) Incidence*</td>
<td>225 (8.7) 3.0‡</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>248 (6.7) Incidence*</td>
<td>141 (5.4) 1.9‡</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>140 (3.8) Incidence*</td>
<td>58 (2.2) 0.8‡</td>
<td></td>
</tr>
<tr>
<td>Other cardiovascular†</td>
<td>58 (1.6) Incidence*</td>
<td>55 (2.1) 0.8</td>
<td></td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td>120 (3.2) Incidence*</td>
<td>52 (2.0) 0.7‡</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>50 (1.3) Incidence*</td>
<td>28 (1.1) 0.4</td>
<td></td>
</tr>
<tr>
<td>Noncancer</td>
<td>70 (1.9) Incidence*</td>
<td>24 (0.9) 0.3‡</td>
<td></td>
</tr>
</tbody>
</table>

*Unadjusted incidence is expressed as the rate per 100 person-years of follow-up. †Includes other cardiac, stroke, or other vascular or unknown. 4p < 0.05.
Cause-specific mortality end points (Table 5). Because of the smaller number of cause-specific mortality end points and the additional missing covariate data in the intermediate and fully adjusted statistical models, the relationship between light-to-moderate alcohol consumption and cause-specific mortality end points was analyzed using only the basic multivariate model. Among participants with ischemic LV dysfunction, light-to-moderate alcohol consumption (1 to 14 alcoholic drinks/week) was associated with a reduced risk of fatal MI ($p < 0.001$) and noncardiovascular death ($p < 0.01$). Among participants with nonischemic LV dysfunction, light-to-moderate alcohol consumption was not significantly associated with any of the cause-specific modes of death, although trends toward a reduced risk of arrhythmic death ($p = 0.05$) and an increased risk of other cardiovascular death ($p = 0.06$) were observed. Light-to-moderate alcohol consumption was not associated with an increase in the risk of death from progressive heart failure in either the ischemic or nonischemic group.

In the SOLVD studies, only 22 deaths (1.5% of all deaths) were from violent causes. Eighteen patients died as a result of trauma, and four patients died as a result of suicide. The proportion of deaths from violent causes was similar between light-to-moderate drinkers (1.3%) and nondrinkers (1.5%).

**DISCUSSION**

To our knowledge, this is the first analysis of the association between alcohol consumption and prognosis in a large cohort of patients with preexisting LV systolic dysfunction. Our data indicate that in patients with ischemic LV dysfunction, light-to-moderate alcohol consumption (1 to 14 alcoholic drinks/week) was associated with a modest reduction in the risk of death when compared with no alcohol consumption. Furthermore, light-to-moderate alcohol consumption was associated with a substantially reduced risk of fatal MI in this cohort. Heart failure progression, as indicated by either death from progressive heart failure or hospitalization for heart failure, was not associated with light-to-moderate alcohol consumption in patients with ischemic LV dysfunction. Among patients with nonischemic LV dysfunction, light-to-moderate alcohol consumption was not associated with an altered risk of all-cause mortality or death from any specific cause, including death from progressive heart failure. However, a trend toward an increased risk of hospitalization for heart failure was observed in this group.

**Alcohol and coronary heart disease.** Most observational studies have demonstrated that light-to-moderate alcohol consumption is associated with a reduced risk of coronary heart disease (4–7). Coronary heart disease is the leading cause of systolic heart failure in the U.S., and it is an important cause of death and disease progression in this population (8). Thus, it is plausible that light-to-moderate alcohol consumption might have beneficial effects in patients with ischemic LV dysfunction. In SOLVD participants with ischemic LV dysfunction, light-to-moderate alcohol consumption was associated with a small but statistically significant reduction in all-cause mortality and a prominent reduction in the risk of fatal MI. A neutral association between light-to-moderate alcohol consumption and mortality was observed in patients with nonischemic LV dysfunction.

### Table 4. Nonischemic Left Ventricular Dysfunction (n = 1,278): Relationship Between Light-to-Moderate Alcohol Consumption and Outcome*

<table>
<thead>
<tr>
<th>Covariates</th>
<th>All-Cause Mortality</th>
<th>Cardiovascular Mortality</th>
<th>Hospitalization for Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, gender, EF, NYHA class, enalapril</td>
<td>0.89 (0.72–1.10)</td>
<td>0.88 (0.70–1.11)</td>
<td>1.13 (0.91–1.40)</td>
</tr>
<tr>
<td>Add: race, smoking, diabetes, hypertension</td>
<td>0.90 (0.73–1.12)</td>
<td>0.89 (0.70–1.12)</td>
<td>1.20 (0.96–1.50)</td>
</tr>
<tr>
<td>Add: digoxin, beta-blockers, diuretics, antiarrhythmics, aspirin, anticoagulants</td>
<td>0.93 (0.74–1.16)</td>
<td>0.92 (0.72–1.18)</td>
<td>1.21 (0.97–1.52)</td>
</tr>
</tbody>
</table>

*EF = ejection fraction; NYHA = New York Heart Association.

### Table 5. Relationship Between Light-to-Moderate Alcohol Consumption and Cause-Specific Mortality*

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Ischemic LV Dysfunction (n = 5,331)</th>
<th>Nonischemic LV Dysfunction (n = 1,278)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive heart failure</td>
<td>0.86 (0.71–1.05)</td>
<td>0.89 (0.66–1.20)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>0.84 (0.67–1.06)</td>
<td>0.62 (0.38–1.00)</td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>0.55 (0.40–0.76)†</td>
<td>1.07 (0.46–2.50)</td>
</tr>
<tr>
<td>Other cardiovascular</td>
<td>1.28 (0.82–2.00)</td>
<td>2.06 (0.98–4.33)</td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td>0.54 (0.37–0.81)†</td>
<td>0.97 (0.52–1.80)</td>
</tr>
</tbody>
</table>

*Other covariates included in the model were age, sex, ejection fraction, NYHA class, and randomization to enalapril. †p < 0.05.
Alcohol and LV performance. Previous research has demonstrated that heavy alcohol consumption is related to the development of cardiomyopathy. In animal models, chronic alcohol consumption leads to interstitial fibrosis and reduced myocardial contractility (1,12). In humans, chronic alcoholism is associated with a high prevalence of subclinical LV systolic dysfunction and histologic changes of cardiomyopathy (2). Despite this, there is no experimental evidence that light-to-moderate alcohol has a deleterious effect on LV performance. Indeed, invasive hemodynamic studies have generally demonstrated either no acute effect or a transient increase in LV contractility after the administration of a moderate amount of alcohol to patients with LV systolic dysfunction (13,14) or hypertrophic cardiomyopathy (15), or to normal volunteers (16,17). In the current analysis, no association between light-to-moderate alcohol consumption and the risk of heart failure progression (death from progressive heart failure or hospitalization for heart failure) was present in patients with ischemic LV dysfunction. Among those with nonischemic LV dysfunction, although a modest trend toward an increased risk of hospitalization for heart failure was seen, there was no increase in the risk of death from progressive heart failure. Taken together, these results suggest that light-to-moderate alcohol consumption does not significantly worsen preexisting LV dysfunction over the intermediate term.

Comparison to previous studies. Our results agree closely with previous research. In a substudy of the Physicians’ Health Study, which examined the relationship between alcohol consumption and mortality in men following a first MI, consumption of one drink per day was associated with a RR reduction of 21% for all-cause mortality and 17% for cardiovascular mortality (18). These figures are similar to the RR reductions of 15% and 10% found in the current analysis for light-to-moderate drinkers with ischemic LV dysfunction.

Light-to-moderate alcohol consumption was associated with a prominent (45%) reduction in the risk of fatal MI in SOLVD participants with ischemic LV dysfunction. This reduction is similar in magnitude to that observed in the complete Physicians’ Health Study cohort, in which consumption of one drink per day was associated with a 35% RR reduction for a first MI (7). A case control study of a cohort of Kaiser Permanente patients found a RR reduction of 30% for MI in those who consumed ≤2 drinks daily when compared with nondrinkers. A smaller but still statistically significant risk reduction was seen even in the category of patients who consumed alcohol only infrequently (>1 drink per month but <1 drink per day) (19).

The lack of association between light-to-moderate alcohol consumption and fatal myocardial infarction among SOLVD participants with nonischemic LV dysfunction is not surprising considering the rarity of this event.

Heavy alcohol consumption has been linked to cardiac arrhythmias, particularly atrial fibrillation but also ventricular arrhythmias (1,20). However, in our analysis, light-to-moderate alcohol consumption was associated with trends toward reductions in the risk of arrhythmic death among patients with either ischemic LV dysfunction or nonischemic LV dysfunction. These findings agree closely with previous studies. In the Kaiser Permanente study cohort, a comparable level of alcohol consumption was associated with a 20% reduction in the risk of sudden cardiac death (21), and in a population-based study from Washington State, the risk for primary cardiac arrest was 30% lower in light drinkers (>1 drink per month and <1 drink per day) compared with nondrinkers (22).

In the present analysis, light-to-moderate alcohol consumption was associated with a prominent reduction in the risk of noncardiovascular death among SOLVD participants with ischemic LV dysfunction. However, because the number of noncardiovascular deaths were few, these results should be interpreted with caution. Nonetheless, our findings are similar to those from the cohort of patients in the Physicians’ Health Study following a first MI, in whom one drink per day was associated with a 34% relative reduction in the risk of noncardiovascular death (18). Other studies have described a similar relationship (19,23,24). It has been postulated that noncardiovascular mortality may be lower because cardiovascular comorbidity is reduced in light-to-moderate drinkers (23,24). Further research is required to clarify this issue.

Study limitations. Our analysis has several limitations. First, the relationship between alcohol consumption and prognosis may have been confounded by factors other than those for which we adjusted. This issue might be of particular importance in the analyses of cause-specific mortality end points, for which only the basic model was used. However, the detailed characterization of the SOLVD cohort, the small changes in risk estimates despite increasingly comprehensive statistical models, and the close agreement between our results and previous research make this less likely.

Second, our analyses are based on participants’ self-reported alcohol consumption. Although self-reported mild-to-moderate alcohol consumption is generally reliable, heavy drinkers tend to underreport their alcohol use (25). We attempted to minimize the effect of this possible underreporting by excluding participants with alcoholic cardiomyopathy; but even if a substantial number of heavy drinkers were incorrectly included with the light-to-moderate drinkers, our results would overestimate, rather than underestimate, any harmful effect of alcohol consumption.

Third, patients may have altered their drinking habits after entering the trial, an occurrence for which we could not adjust. Fourth, research in other patient populations has demonstrated that approximately 50% of the benefit of alcohol consumption with regard to coronary heart disease is brought about by its effects on high density lipoprotein.
(HDL) cholesterol levels (4). Because blood lipid values were not collected in the SOLVD trials, we were unable to analyze this relationship. Finally, the average duration of follow-up in SOLVD was only about three years. Therefore, we lack information on the long-term effects of alcohol consumption in this population.

Conclusions. Light-to-moderate alcohol consumption appears to be safe in patients with LV systolic dysfunction, and it may reduce the risk of death and the risk of fatal MI in patients with ischemic LV dysfunction. Patients with LV dysfunction who consume ≤2 drinks per day should not be advised to discontinue drinking alcohol for the purpose of reducing cardiovascular morbidity or mortality. However, there is insufficient evidence to recommend the use of alcohol to patients with LV dysfunction who do not currently drink alcohol. Heavy alcohol consumption should continue to be discouraged for patients with LV systolic dysfunction, because of the clear increase in noncardiovascular and total mortality shown in previous studies (19,23,24) and because of the strong evidence that heavy alcohol consumption can lead to impairment of LV contractile function (1,2,12).

Reprint requests and correspondence: Dr. Howard A. Cooper, Two Rockledge Centre, Room 8149, 6701 Rockledge Drive, MSC 7936, Bethesda, Maryland 20892. E-mail: Cooperha@nih.gov.

REFERENCES