Beta-Adrenergic Blocking Agent Use and Mortality in Patients With Asymptomatic and Symptomatic Left Ventricular Systolic Dysfunction: A Post Hoc Analysis of the Studies of Left Ventricular Dysfunction

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OBJECTIVES
This analysis was performed to assess whether beta-adrenergic blocking agent use is associated with reduced mortality in the Studies of Left Ventricular Dysfunction (SOLVD) and to determine if this relationship is altered by angiotensin-converting enzyme (ACE) inhibitor use.

BACKGROUND
The ability of beta-blockers to alter mortality in patients with asymptomatic left ventricular dysfunction is not well defined. Furthermore, the effect of beta-blocker use, in addition to an ACE inhibitor, on these patients has not been fully addressed.

METHODS
This retrospective analysis evaluated the association of baseline beta-blocker use with mortality in 4,223 mostly asymptomatic Prevention trial patients, and 2,567 symptomatic Treatment trial patients.

RESULTS
The 1,015 (24%) Prevention trial patients and 197 (8%) Treatment trial patients receiving beta-blockers had fewer symptoms, higher ejection fractions and different use of medications than patients not receiving beta-blockers. On univariate analysis, beta-blocker use was associated with significantly lower mortality than nonuse in both trials. Moreover, a synergistic reduction in mortality with use of both a beta-blocker and enalapril was suggested in the Prevention trial. After adjusting for important prognostic variables with Cox multivariate analysis, the association of beta-adrenergic blocking agent use with reduced mortality remained significant for Prevention trial patients receiving enalapril. Lower rates of arrhythmic and pump failure death and risk of death or hospitalization for heart failure were observed.

CONCLUSIONS
The combination of a beta-blocker and enalapril was associated with a synergistic reduction in the risk of death in the SOLVD Prevention trial. (J Am Coll Cardiol 1999;33:916–23) © 1999 by the American College of Cardiology

The Studies of Left Ventricular Dysfunction (SOLVD) Treatment trial (1) and other studies (2,3) have demonstrated that angiotensin-converting enzyme (ACE) inhibitors reduce mortality in patients with symptomatic heart failure. Furthermore, the SOLVD Prevention trial (4) demonstrated that ACE inhibitors reduced the combined incidence of death or hospitalization for heart failure in patients with asymptomatic left ventricular (LV) systolic dysfunction.

There are a number of reasons why the combined use of an ACE inhibitor and a beta-adrenergic blocking agent might improve survival in patients with LV dysfunction to a greater extent than the use of an ACE inhibitor alone. Although ACE inhibitors seem to have a modest effect on reducing arrhythmic deaths (5,6), beta-blockers have potent antifibrillatory (7,8), anti-ischemic (9) and possibly anti-thrombotic (10) properties that may reduce the incidence of sudden cardiac death. Furthermore, some beta-blockers have vasodilatory (11), antioxidant (12,13) and reverse remodeling (14–16) properties that would be anticipated to favorably alter survival. Several trials have suggested that beta-blockers, in addition to ACE inhibitors, reduce mortality in patients with symptomatic LV dysfunction (17,18).
However, it is less certain whether beta-blockers confer additional benefit to asymptomatic patients treated with ACE inhibitors (19–22).

This analysis was performed to evaluate whether the baseline use of beta-blockers was independently associated with reduced mortality in SOLVD and specifically, to determine whether Prevention trial patients randomized to enalapril had an incremental reduction in mortality with beta-blocker use.

**METHODS**

**Studies of left ventricular dysfunction trials.** Patients 21 to 80 years of age with no prior history of intolerance to enalapril and a LV ejection fraction ≤0.35 measured by radionuclide angiography, echocardiography or contrast angiography were eligible for enrollment in SOLVD (1,4,23). Those with a recent myocardial infarction (≤30 days), significant valvular heart disease or another serious comorbid illness were excluded. The specific inclusion and exclusion criteria have been published (23). All SOLVD participants (n = 6,797) had a detailed evaluation at entry. Patients were classified as asymptomatic or symptomatic and were then enrolled in the Prevention or Treatment trial, respectively (23). There were 4,228 patients in the Prevention trial, approximately one third of whom had New York Heart Association (NYHA) functional class II symptoms (4). The Treatment trial included 2,569 patients with mostly NYHA functional class II and III symptoms (1). Patients were randomized to enalapril or placebo in each trial and followed for an average of 35 ± 14 and 33 ± 15 months in the Prevention and Treatment trials, respectively (1,4).

**Beta-blocker use.** Beta-blocker use was determined at the time of enrollment. Information on the baseline use of beta-blockers was available for all but five of the Prevention trial (n = 4,223) and all but two of the Treatment trial (n = 2,567) participants. Furthermore, the use of beta-blockers was neither encouraged nor discouraged in the SOLVD protocol (23). Information on the specific agents used and their doses was not collected.

**End points.** Deaths and hospitalizations for heart failure were collected for all participants. Causes of death were evaluated in a masked fashion by the SOLVD investigators (23) and were classified as due to worsening heart failure (with or without an arrhythmia), an arrhythmia in the absence of worsening heart failure, a myocardial infarction, another cardiovascular cause or a noncardiovascular cause. For the present analysis, pump failure death includes deaths classified as “worsening heart failure, with or without arrhythmia”; arrhythmic deaths include only those deaths attributed to “arrhythmia without worsening heart failure.”

**Coding of variables.** Age, heart rate, mean arterial blood pressure, LV ejection fraction and serum sodium, potassium and creatinine values were assessed as continuous variables. The use of beta-blockers, study drug allocation (enalapril/placebo) and gender were coded dichotomously. New York Heart Association functional class symptoms were coded as class I, II or III/IV. The etiology of LV systolic dysfunction was coded as ischemic or other. All remaining variables were coded dichotomously, indicating the presence or absence of a characteristic or the use of a drug at baseline.

**Statistical analysis.** Continuous characteristics are presented as mean ± SD. Pair-wise differences were evaluated using a chi-square test or t test. Because all-cause mortality is the most definitive test of a therapeutic agent’s efficacy, it was used as the primary end point in this analysis, and separate analyses were performed for the classified modes of death. As an index of heart failure progression the composite end point of death or hospitalization for heart failure was evaluated.

Outcomes were assessed by Kaplan–Meier survival analysis and the log-rank test statistic. A Cox proportional hazards model that included baseline beta-blocker use, study drug allocation, age, gender, NYHA functional class, LV ejection fraction, etiology of LV dysfunction, history of prior coronary artery bypass surgery, history of angina or history of hypertension and the baseline use of diuretics, digoxin, aspirin and antiarrhythmic drugs was used to investigate the independent association of beta-blockers with mortality. This same model, absent study drug allocation, was used to assess the independent association of beta-blockers with the predefined end points in patients randomized to enalapril and placebo. Relative risk (RR) estimates and 95% confidence intervals (CIs) were obtained from the Cox models. Two-way interaction between each of the covariates and beta-blocker use was evaluated. All analyses were performed using Stata: Release 5.0 (College Station, Texas).

**RESULTS**

**Prevention trial patient baseline characteristics.** Beta-blockers were used in 1,015 (24%) of the Prevention trial participants (Table 1). Compared with patients not receiving beta-blockers, participants who received beta-blockers were somewhat younger, and were less likely to be women or have NYHA functional class II symptoms. Furthermore, patients receiving beta-blockers had slower heart rates,
lower blood pressure values and higher LV ejection fractions. Patients receiving beta-blockers were also more likely to have their LV systolic dysfunction classified as due to an ischemic etiology or have a history of angina or hypertension, but were less likely to have a history of atrial fibrillation. Baseline serum potassium levels and the use of antiarrhythmic drugs, antiocoagulants, aspirin, digoxin and nitrates were different in the two groups.

**Treatment trial patient baseline characteristics.** Beta-blockers were used in only 197 (8%) of the Treatment trial participants, a rate significantly lower than in the Prevention trial (p < 0.0001) (Table 2). Compared with patients not receiving beta-blockers, Treatment trial participants who received beta-blockers were less likely to have NYHA functional class III/IV symptoms. Baseline heart rates were lower, whereas ejection fractions were higher in patients receiving beta-blockers. Participants receiving beta-blockers were also more likely to have their LV dysfunction classified as due to an ischemic etiology, and have a history of angina or hypertension. The baseline use of aspirin, calcium channel blocking agents, digoxin and diuretics also differed between those who did versus those who did not receive beta-blockers.

**Modes of death.** The incidence of death from any cause was lower in patients receiving beta-blockers in both trials (Table 3). In the Prevention trial, most deaths were due to pump failure or an arrhythmic cause; pump failure accounted for most of the Treatment trial deaths. Prevention trial participants receiving beta-blockers had a lower death rate (p < 0.01), due to reductions in arrhythmic (p < 0.05) and pump failure deaths (p < 0.05), compared with those not receiving beta-blockers. Likewise, Treatment trial participants receiving beta-blockers were less likely to die (p < 0.01) specifically from pump failure (p < 0.01) compared to participants not receiving beta-blockers.

**Survival curves.** As shown in Figure 1, Prevention trial participants receiving both enalapril and a beta-blocker had the lowest overall mortality. Prevention trial participants receiving both therapies were less likely to die compared with participants receiving enalapril alone (log-rank p = 0.003), a beta-blocker alone (log-rank p = 0.03) or neither of these therapies (log-rank p = 0.001).

Figure 2 illustrates that Treatment trial participants receiving both enalapril and a beta-blocker had similar survival compared with patients receiving a beta-blocker.
alone (log-rank p = 0.8), but tended to have greater survival compared with participants receiving enalapril alone (log-rank p = 0.06) or neither of these therapies (log-rank p = 0.005).

**Interaction between enalapril and beta-blockers.** On univariate analysis, beta-blocker use was associated with a significant reduction in the risk of death in both the Prevention (RR = 0.77; 95% CI 0.63 to 0.94; p < 0.01) and in the Treatment trial (RR = 0.65; 95% CI 0.49 to 0.86; p < 0.01) (Table 4).

Prevention trial participants receiving enalapril had a significant unadjusted reduction in the risk of death associated with beta-blocker use, whereas patients randomized to placebo did not. Evidence of statistical interaction between active study drug (enalapril) and beta-blocker use on mortality was present in the Prevention trial (p = 0.08).

In Treatment trial participants beta-blocker use was associated with a reduced risk of death, independent of study drug allocation. No evidence of interaction was observed in the Treatment trial (p = 0.70). However, the small number of patients receiving beta-blockers in this trial (Table 2) significantly limited the ability to detect interaction.

**Table 3.** Mortality Rates and Modes of Death

<table>
<thead>
<tr>
<th>Mode of Death</th>
<th>Beta-Blocker</th>
<th>No Beta-Blocker</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths</td>
<td>Incidence*</td>
</tr>
<tr>
<td>Prevention trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>12.4%</td>
<td>4.3</td>
</tr>
<tr>
<td>Pump failure</td>
<td>3.3%</td>
<td>1.2</td>
</tr>
<tr>
<td>Arrhythmic</td>
<td>3.6%</td>
<td>1.3</td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>2.5%</td>
<td>0.9</td>
</tr>
<tr>
<td>Other cardiovascular</td>
<td>1.3%</td>
<td>0.4</td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td>1.7%</td>
<td>0.6</td>
</tr>
<tr>
<td>Treatment trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>26.9%</td>
<td>8.8</td>
</tr>
<tr>
<td>Pump failure</td>
<td>11.7%</td>
<td>3.8</td>
</tr>
<tr>
<td>Arrhythmic</td>
<td>7.6%</td>
<td>2.5</td>
</tr>
<tr>
<td>Fatal myocardial infarction</td>
<td>4.6%</td>
<td>1.5</td>
</tr>
<tr>
<td>Other cardiovascular</td>
<td>1.5%</td>
<td>0.5</td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td>1.5%</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*Incidence rate per 100 person-years of follow-up. †Log rank p value < 0.01. ‡Log rank p value < 0.05.

**Figure 1.** Unadjusted all-cause mortality survival curves for Prevention trial participants. Patients receiving neither enalapril nor a beta-blocker (neither) are represented by the broken gray line, those receiving enalapril alone by the solid gray line, patients receiving beta-blockers alone by the broken black line and those receiving both enalapril and a beta-blocker (both) by the solid black line. The number of patients at risk of death during each 365-day period is shown. Patients with asymptomatic left ventricular dysfunction who received both a beta-blocker and enalapril had the lowest mortality (p ≤ 0.03).

**Figure 2.** Unadjusted all-cause mortality survival curves for Treatment trial participants. Patients receiving neither enalapril nor a beta-blocker (neither) are represented by the broken gray line, those receiving enalapril alone by the solid gray line, patients receiving beta-blockers alone by the broken black line and those receiving both enalapril and a beta-blocker (both) by the solid black line. The number of patients at risk of death during each 365-day period is shown.
Adjusted survival. Prevention trial participants receiving both a beta-blocker and enalapril had a significant, independent reduction in the risk of death (Table 5). This favorable outcome was the result of reductions in cardiovascular deaths (RR = 0.67; 95% CI 0.48 to 0.94; p = 0.02), notably arrhythmic and pump failure deaths. Progression to symptomatic heart failure, as assessed by the composite end point of death or hospitalization for heart failure, was also significantly reduced in Prevention trial participants receiving beta-blockers and enalapril. In contrast, no significant independent reduction in the risk of death was associated with beta-blocker use in Treatment trial participants.

Incremental effect of beta-blockers. In the entire SOLVD cohort, beta-blocker use was associated with an incremental mortality reduction in patients receiving enalapril. In the prespecified multivariate model, the reduced risk of death associated with the use of a beta-blocker and enalapril (RR = 0.74) was greater than that observed for beta-blockers alone (RR = 0.89) or enalapril alone (RR = 0.88). Figure 1 illustrates the synergistic reduction in mortality observed with the use of both agents in Prevention trial participants.

Comorbid conditions. Because specific conditions or comorbid illnesses probably influenced which patients were or were not prescribed beta-blockers in SOLVD, we evaluated whether these covariates altered the association of beta-blocker use with reduced mortality that was observed in the Prevention trial (Table 5). The association of beta-blocker use with reduced mortality in Prevention trial participants randomized to enalapril was unchanged when history of previous myocardial infarction (RR = 0.72; 95% CI 0.53 to 0.98), the presence of atrial fibrillation (RR = 0.72; 95% CI 0.53 to 0.98) or a history of diabetes (RR = 0.72; 95% CI 0.53 to 0.97) was added to the multivariate model. Likewise, the association of beta-blockers with reduced mortality in these patients was not significantly altered when use of calcium channel blockers (RR = 0.68; 95% CI 0.48 to 0.95) was added. Moreover, this association remained significant when all of these covariates (RR = 0.72; 95% CI 0.50 to 0.99) were collectively added to the multivariate model.

Ischemic and nonischemic subgroups. Although the etiology of LV dysfunction was included in all of the multivariate models, we separately assessed the association of beta-blocker use with mortality in these subgroups, because some studies have suggested that patients with nonischemic LV dysfunction derive greater benefit from beta-blockers (24,25). Due to the relatively small number of patients with nonischemic LV dysfunction in SOLVD (Tables 1 and 2),

### Table 4. Mortality Reduction Associated With the Use of Beta-Blockers in Patients Randomized to Enalapril and Placebo

<table>
<thead>
<tr>
<th>Trial</th>
<th>Placebo</th>
<th>Relative Risk* (95% CI)</th>
<th>Enalapril</th>
<th>Relative Risk* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention</td>
<td>2,116</td>
<td>0.91 (0.70 to 1.18)</td>
<td>2,107</td>
<td>0.64 (0.48 to 0.86)†</td>
</tr>
<tr>
<td>Treatment</td>
<td>1,282</td>
<td>0.62 (0.41 to 0.93)‡</td>
<td>1,285</td>
<td>0.69 (0.47 to 1.01)§</td>
</tr>
</tbody>
</table>

*Unadjusted (univariate). †p < 0.01. ‡p < 0.05. §p < 0.10. CI = confidence interval.

### Table 5. Independent Association of Beta-Blocker Use With Modes of Death and Composite End Point of Death or Hospitalization for Heart Failure

<table>
<thead>
<tr>
<th>Mode of Death</th>
<th>Placebo</th>
<th>Relative Risk* (95% CI)</th>
<th>Enalapril</th>
<th>Relative Risk* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention trial</td>
<td>0.98 (0.76 to 1.29)</td>
<td>0.70 (0.52 to 0.95)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment trial</td>
<td>0.79 (0.52 to 1.18)</td>
<td>0.86 (0.58 to 1.27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmic death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention trial</td>
<td>0.85 (0.52 to 1.39)</td>
<td>0.57 (0.32 to 0.99)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment trial</td>
<td>0.70 (0.31 to 1.59)</td>
<td>1.17 (0.58 to 2.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pump failure death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention trial</td>
<td>1.04 (0.64 to 1.70)</td>
<td>0.54 (0.29 to 1.01)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment trial</td>
<td>0.89 (0.49 to 1.60)</td>
<td>0.78 (0.42 to 1.45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or hospitalization for heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention trial</td>
<td>0.89 (0.72 to 1.12)</td>
<td>0.64 (0.49 to 0.83)§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment trial</td>
<td>0.85 (0.62 to 1.17)</td>
<td>0.82 (0.59 to 1.13)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Multivariate model included use of beta-blocker at baseline, age, gender, New York Heart Association functional class, left ventricular ejection fraction, etiology of left ventricular dysfunction, history of coronary artery bypass, history of angina, history of hypertension and use of digoxin, diuretics, aspirin and antiarrhythmic drugs. †p < 0.05. ‡p < 0.10. §p < 0.01. CI = confidence interval.
the Prevention and Treatment trials were combined for this analysis. Using the same multivariate model, beta-blocker use tended to be independently associated with reduced mortality in both patients with ischemic (RR = 0.80; 95% CI 0.62 to 1.03; p = 0.08) and patients with nonischemic LV dysfunction (RR = 0.43; 95% CI 0.16 to 1.17; p = 0.10) who were randomized to enalapril.

**DISCUSSION**

The present analysis demonstrates that the use of beta-blockers, in addition to enalapril, is independently associated with a significant reduction in the risk of death for patients with asymptomatic LV systolic dysfunction. This favorable outcome was the result of reductions in arrhythmic death, pump failure death and progression to symptomatic heart failure. Moreover, the reduction in mortality associated with the use of both a beta-blocker and enalapril was greater than that of either agent alone.

**Rationale for a beneficial effect of beta-blockers, in addition to ACE inhibitors, to reduce arrhythmic death.** Neurohormonal activation occurs in both patients with asymptomatic (26) and patients with symptomatic (27) LV systolic dysfunction. Prognosis in these patients is related to plasma norepinephrine concentrations, with decreased survival and increased morbidity being associated with higher catecholamine concentrations (27,28). Furthermore, preferential activation of cardiac sympathetic outflow in mild heart failure has been linked to the development of life-threatening ventricular arrhythmias (29), and increases in plasma catecholamines in these patients have been observed to precede the occurrence of sudden cardiac death (30). The ability of beta-blockers to reduce the direct and indirect impact of catecholamines on the human heart (13) seems to be an important mechanism for the reduced incidence of sudden cardiac death in patients with moderately symptomatic LV dysfunction treated with carvedilol (17). Most important, because the susceptibility to ventricular fibrillation, at least in the setting of acute ischemia, is related to functional alterations in the beta2 receptor (8), nonselective agents such as carvedilol may be particularly effective in reducing arrhythmic deaths.

**Effect on remodeling.** Although myocardial remodeling is initially an adaptive response, it results in progressive LV dysfunction in the long term (31). Myocyte hypertrophy, apoptosis, alterations in the extracellular matrix and increases in alpha- and beta-adrenergic activity are all features of this process (13,32). Furthermore, circulating catecholamines have been demonstrated to have direct toxic effects on the heart (33), and a variety of inflammatory cytokines have been shown to be elevated in patients with LV dysfunction (32), including the patients in SOLVD (34). Both ACE inhibitors (35) and beta-blockers (13) have been shown to favorably alter these processes. However, because these agents act through different mechanisms, their combination might be anticipated to be additive or possibly synergistic. The association of beta-blocker use with reductions in death from pump failure and death or hospitalization for heart failure in Prevention trial patients receiving enalapril supports the notion that beta-blockers reduce the progression to overt heart failure in patients with asymptomatic LV dysfunction already receiving an ACE inhibitor.

**Synergistic effect of combination therapy.** Qualitative interactions, differences in direction of effect, are infrequently observed when subgroups in clinical trials are analyzed because the smaller sample sizes limit the power to detect these effects (36). However, when a qualitative interaction is observed, it likely represents a true effect (36). The observed association of beta-blocker use with reduced mortality in the Prevention trial patients randomized to enalapril was present in both the univariate (unadjusted) and multivariate (adjusted) models. Furthermore, the beneficial association of beta-blockers was observed for arrhythmic death, pump failure death and the composite end point of death or hospitalization for heart failure. Finally, similar point estimates were obtained when additional, potentially confounding covariates were individually and collectively added to the prespecified multivariate model. These findings suggest that the association between beta-blocker use and reduced mortality in Prevention trial patients receiving enalapril is likely a true effect.

**Differential effect in prevention trial.** The clinical use of beta-blockers has expanded significantly since the inception and conduct of the SOLVD trials. It is probable that most patients treated with beta-blockers in SOLVD received these agents for ancillary medical conditions, such as coronary artery disease, hypertension or rate control of atrial fibrillation, rather than LV dysfunction. Furthermore, in the late 1980s, when SOLVD was conducted, beta-blockers were largely avoided in patients with more significant symptoms or pronounced LV dysfunction (37,38). The less frequent use of beta-blockers in Treatment trial patients supports this. Also, Treatment trial participants receiving beta-blockers would be anticipated to be healthier than those who did not receive these agents in that trial. The finding that beta-blockers were associated with a significant reduction in mortality on univariate analysis, but not after adjustment for important, potentially confounding variables supports this notion as well. However, because patients in the Prevention trial were largely asymptomatic and had higher LV ejection fractions, the use of beta-blockers would be expected to be less related to the underlying degree of LV dysfunction. The observed similar associations of beta-blocker use with reduced mortality on univariate and multivariate analysis in the Prevention trial patients support this contention.

**Beta-blocker use.** Beta-blocker use was assessed at the time of enrollment in SOLVD. Although the use of these
agents and other medications probably changed during follow-up, it seems unlikely that this introduced a systematic bias into the present analysis.

Comparison with other studies. The Survival and Ventricular Enlargement (SAVE) trial randomized 2,231 patients with a recent (3 to 16 days) myocardial infarction and radionuclide LV ejection fraction \( \leq 0.40 \) to captopril or placebo (39). A post hoc analysis of SAVE demonstrated an independent association of beta-blocker use with reduced cardiovascular mortality(36). The primary endpoint of this trial was change in LV ejection fraction. Most patients (86%) received concurrent ACE inhibitor therapy, and the average follow-up was 19 months. After one year of follow-up, patients receiving carvedilol had a significant (+25%) improvement in LV ejection fraction compared with placebo patients (+5%; \( p = 0.001 \)). Furthermore, patients randomized to carvedilol had a 26% reduction in the risk of death or hospitalization compared to participants receiving placebo (\( p = 0.02 \)). The small size of this trial did not permit separate analyses of the symptomatic and asymptomatic groups.

Limitations. The present analysis is not a randomized comparison of outcome in patients who did versus those who did not receive concomitant beta-blocker therapy. Although adjustments were made for relevant differences, it is possible that the groups differed in other respects. However, the SOLVD cohort is a well characterized group of patients with comprehensive, long-term follow-up. Although residual confounding cannot be definitively excluded, the multivariate model allowed us to adjust for important prognostic variables. Moreover, the association between beta-blocker use and reduced mortality in Prevention trial participants receiving enalapril was consistent for all of the end points evaluated. Likewise, the point estimates for the effect of beta-blockers were similar when additional covariates were added to the prespecified multivariate model.

Although trends similar to those found in the Prevention trial were noted in Treatment trial participants, the small number of subjects receiving beta-blockers in the Treatment trial precludes a definitive statement regarding the benefit or lack of benefit in this group. Whether beta-blockers alter mortality in patients with NYHA class III or IV heart failure is unclear (22). Recent overviews of randomized trials suggest that beta-blockers reduce mortality in these patients (18,40). In addition, the Second Cardiac Insufficiency Bisoprolol Study (CIBIS II), a large (\( N = 2,647 \)) randomized trial of bisoprolol versus matched placebo in patients with NYHA class III or IV heart failure, recently reported a prominent reduction in mortality with the use of bisoprolol (\( RR = 0.66; 95\% CI 0.54 \) to 0.81; \( p < 0.0001 \)). Moreover, this mortality reduction was primarily the result of a 44% decrease in the incidence of sudden death (41).

Conclusions. The use of beta-blockers, in addition to ACE inhibitor therapy, was associated with a significant, independent reduction in the risk of death in SOLVD Prevention trial participants. This favorable outcome was the result of reductions in arrhythmic death and pump failure death. Progression to symptomatic heart failure was also significantly reduced in Prevention trial patients receiving both a beta-blocker and enalapril. Therefore, the combination of a beta-blocker and enalapril was associated with a synergistic reduction in mortality of patients with asymptomatic LV dysfunction in SOLVD.

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