JACC: Heart Failure
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 1, No. 4, 2013
ISSN 2213-1779/$36.00
http://dx.doi.org/10.1016/j.jchf.2013.04.004

CLINICAL RESEARCH

Effect of Amlodipine on the Survival of Patients With Severe Chronic Heart Failure Due to a Nonischemic Cardiomyopathy

Results of the PRAISE-2 Study (Prospective Randomized Amlodipine Survival Evaluation 2)

Milton Packer, MD, Peter Carson, MD, Uri Elkayam, MD, Marvin A. Konstam, MD, Gordon Moe, MD, Christopher O'Connor, MD, Jean-Lucien Rouleau, MD, Douglas Schocken, MD, Susan A. Anderson, MS, David L. DeMets, PHD, for the PRAISE-2 Study Group

Dallas, Texas

Objectives This study was designed to test the hypothesis of whether amlodipine reduces the risk for death in patients with heart failure due to a nonischemic cardiomyopathy.

Background A pre-specified subgroup analysis in an earlier, large-scale, placebo-controlled study suggested that amlodipine might reduce the risk for death in patients with heart failure due to a nonischemic cardiomyopathy.

Methods To evaluate this hypothesis, 1654 patients with severe heart failure due to a nonischemic cardiomyopathy (ejection fraction <30%) were randomly assigned to amlodipine (target dose: 10 mg/d) or placebo added to conventional therapy for heart failure for a median of 33 months.

Results There were 278 deaths in the amlodipine group and 262 deaths in the placebo group (hazard ratio: 1.09; 95% confidence interval [CI]: 0.92 to 1.29; p = 0.33). The differences between the 2 groups in the risks for cardiovascular death and hospitalization were also not significant. When the results from patients with a nonischemic cardiomyopathy in both the earlier trial and in the current study were combined, there was no evidence of a favorable or unfavorable effect of amlodipine on mortality (hazard ratio: 0.97; 95% CI: 0.83 to 1.13; p = 0.66). Both trials, however, observed higher frequencies of peripheral edema and pulmonary edema and lower frequencies of uncontrolled hypertension and chest pain in patients treated with amlodipine.

Conclusions These results of the current trial, viewed together with the results from the earlier study, indicate that amlodipine does not exert favorable effects on the clinical course of patients with heart failure, regardless of the presence or absence of underlying coronary artery disease. These findings indicate the need for great caution when striking benefits are observed in subgroups of patients or in trials not primarily designed to assess such effects. (J Am Coll Cardiol HF 2013;1:308–14) © 2013 by the American College of Cardiology Foundation

From the Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, Texas. This research was supported by a grant from Pfizer, Inc. Dr. Packer has received consultant's fees from Actelion, Amgen, BioControl, Janssen, Johnson & Johnson, Cardiorentis, CardioKinetix, CardioMEMS, Novartis, Onyx, Pfizer, Piramal, Polyphor, and Sanofi. Dr. Konstam has received research support and/or consultant's fees from Amgen, Johnson & Johnson, Merck, Otsuka, and Pfizer, Inc. Dr. Rouleau has received consultant's fees from Novartis. Dr. Schocken has received speaker's honoraria from Otsuka America Pharmaceutical. Dr. DeMets has served on data-monitoring committees and has received honoraria for several industry-sponsored trials. The authors have reported that they have no other relationships relevant to the contents of this paper to disclose. Paul Armstrong, MD, acted as Guest Editor for this paper. The PRAISE-2 study investigators and coordinators are listed in the Online Appendix.

Manuscript received January 2, 2013; revised manuscript received April 4, 2013, accepted April 11, 2013.

Most calcium-channel blockers have been reported to worsen heart failure and to increase the risk for death in patients with advanced left ventricular dysfunction (1–5). Despite their vasodilatory actions on peripheral vessels, these drugs can depress cardiac function and activate endogenous neurohormonal mechanisms (6), both of which may adversely affect the course of patients with chronic heart failure. As a result, physicians have been advised to avoid the use of calcium-channel blockers in patients with heart failure (7), even when these drugs are being considered for the therapy of coexistent angina or hypertension.

Clinical experience with the long-acting calcium-channel blocker amlodipine, however, has suggested that

administration of the drug might not be associated with the adverse effects reported with other agents in this class. In controlled trials that focused on exercise tolerance, amlodipine did not adversely affect the clinical status of patients with mild to moderate heart failure (8). Furthermore, in a large-scale, long-term study (PRAISE [Prospective Randomized Amlodipine Survival Evaluation]), amlodipine did not increase the combined risk for death or cardiovascular hospitalization in patients with severe heart failure (9). Instead, a prospectively defined subgroup analysis suggested that patients treated with amlodipine appeared to have a lower risk for death if their heart failure was due to a nonischemic cardiomyopathy. Although this finding was consistent with those from experimental and clinical studies suggesting that coronary vasoconstriction may play a role in the pathogenesis of nonischemic cardiac dysfunction (10,11), a survival benefit in this subgroup was not anticipated, and both the investigators and the sponsor believed that the subgroup finding required confirmation in a second trial before any favorable effect of amlodipine could be considered to have been established.

See page 315

As a result, we conducted the second PRAISE-2. The primary objective of this trial was to assess the long-term effect of amlodipine on survival in patients with severe chronic heart failure due to a nonischemic cardiomyopathy.

Methods

Patients were eligible if they had New York Heart Association (NYHA) functional class III or IV symptoms of heart failure due to a nonischemic cardiomyopathy. Patients were required to have symptoms at rest or, if symptoms were present only on effort, they could not walk more than 375 m during a 6-min corridor walk test. The diagnosis of nonischemic cardiomyopathy was based on the finding of a left ventricular ejection fraction <30% in the absence of any clinical or physiological evidence of coronary artery disease. Patients with a history of angina or of any test (exercise test, cardiac imaging or ambulatory monitoring) suggestive or indicative of myocardial ischemia were excluded unless they had undergone coronary angiography that demonstrated the absence of coronary artery disease (no coronary stenosis >50%). Symptoms of heart failure had persisted despite treatment with digoxin, diuretics, and an angiotensin-converting enzyme (ACE) inhibitor for at least 3 months. Patients were allowed to be treated with nitrates or hydralazine, but were not allowed to have received any other vasodilator, an angiotensin II antagonist, or a beta-blocker within the previous 4 weeks.

Patients were excluded if they had a reversible cause of cardiomyopathy or uncorrected primary valve disease; a history of sudden death or sustained ventricular tachycardia or fibrillation within the previous year; were receiving an antiarrhythmic agent known to adversely affect cardiac function or survival; had evidence of digitalis toxicity; and/or had a clinical indication for cardiac pacing (but were not paced). Patients were also not allowed to participate if they had severe pulmonary, renal, or hepatic disease or any disease (other than heart failure) that might have limited survival, within the previous 3 years; systolic blood pressure <85 or ≥160 mm Hg and/or diastolic blood pressure ≥90 mm Hg; serum creatinine >3.0 mg/dl and/or potassium <3.5 or >5.5 mmol/l; any liver function test result that was >3 times the upper limit of normal; and/or a white or red cell count >30% outside of the normal range. Before randomization, patients were not to have received intravenous diuretics or vasodilators within the previous 24 h, intravenous positive inotropic agents within the previous 72 h, or routine intermittent positive inotropic therapy within the previous month. The protocol was approved by the institutional review boards at all participating institutions. Written informed consent was obtained from all patients.

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme

NYHA = New York Heart Association

PRAISE = Prospective Randomized Amlodipine Survival Evaluation

Study design. Following the initial evaluation, patients were randomly assigned in a double-blind manner to receive either oral amlodipine or matching placebo in addition to their usual medications. The initial dose of amlodipine was 5 mg once daily for 2 weeks, which was then increased (if tolerated) to 10 mg once daily for the remainder of the study. If an adverse event occurred, the dose of the study medication could be reduced or discontinued, but investigators were encouraged to reinstitute treatment at a later time. In an effort to replicate the conditions of the first PRAISE trial, the utilization of beta-blockers was discouraged, particularly in view of the lack of evidence, at the time the trial was carried out, that beta-blockers were effective in patients with heart failure, and in light of evidence suggesting the existence of an adverse hemodynamic interaction between calcium-channel blockers and beta-blockers (12). However, if a patient's condition warranted, physicians could utilize any clinically indicated intervention (including beta-blockers), with the exception of open-label amlodipine.

Endpoints. The primary endpoint of the study was all-cause mortality. The effect of treatment on the primary endpoint was prospectively assessed in subgroups defined by the following 4 baseline variables: age, sex, NYHA functional class, and ejection fraction. The major secondary endpoints of the study were cardiovascular mortality and the frequency and cause of hospitalization.

Statistical analysis. The sample size of the study was estimated based on the following assumptions: the 1-year mortality rate in the placebo group would be 20%; the risk would be altered by 25% by treatment with amlodipine; and the study would have 90% power to detect a difference between the treatment groups (alpha = 0.05, 2-tailed). Because it was recognized that estimates of the event rate might be inaccurate, the trial was designed to continue until 264 deaths had occurred in the placebo group. To protect

against increasing a false positive error rate due to repeated interim analyses, the Lan-DeMets procedure (13) using an O'Brien-Fleming–type boundary (14) was utilized, which requires only the expected number of events and the significance level to be specified in advance. Using this procedure, comparisons of the 2 treatments at the scheduled end of the trial were considered significant if a z value >2.04 was attained. A data and safety monitoring board periodically reviewed the unblinded results and was empowered to recommend early termination of the program if it observed a treatment effect that exceeded the pre-specified boundaries.

The baseline characteristics of the 2 treatment groups were compared by the Wilcoxon test (for continuous and ordinal variables) and a chi-square statistic (for categorical variables). Differences in post-randomization events between the treatment groups were analyzed by the Wilcoxon or chi-square test, as appropriate. Cumulative survival curves were constructed by Kaplan-Meier survival methods (15), and differences between the curves were tested for significance by the log-rank statistic. Cox proportional hazards regression models (16) were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). The survival analyses included all randomized patients, and deaths were assigned to a patient's randomized treatment group (according to the intention-to-treat principle). Patients who underwent a cardiac transplantation were not censored at the date of transplantation but were followed up for survival.

The log-rank statistic for survival was also calculated in a pooled patient-level analysis that combined the nonischemic patients in PRAISE-1 and PRAISE-2, with *death* defined as in the original planned analysis for each trial (i.e., cardiac transplantations were considered deaths in PRAISE-1 but not in PRAISE-2).

Results

Between December 1995 and January 2000, 1654 patients were enrolled into the trial, with 827 randomized to each the amlodipine and placebo groups. The 2 treatment groups were similar with respect to baseline characteristics (Table 1).

Following the initiation of treatment, most patients underwent successful titration to, and were maintained on, target doses of the study medication. In general, concomitant therapy with digitalis, a diuretic, and an ACE inhibitor was maintained in all patients, but treatment with a beta-blocker was started in 141 and 171 patients in the amlodipine and placebo groups, respectively, at varying times following randomization. In nearly two-thirds of the patients who received a beta-blocker, treatment with the beta-blocker was started more than 1 year following randomization.

A total of 122 patients in the placebo group and 120 patients in the amlodipine group, were permanently discontinued from treatment with the study medication, most frequently because of a request by the patient, family, or referring physician. The median and maximum durations of follow-up were 33 and 52 months, respectively.

Table 1 Pretreatment Characteristics of Patients in the Study

Characteristic	Amlodipine (n = 827)	Placebo (n = 827)
Age, yrs	59 ± 14	59 ± 13
Male, %	66	66
Disease characteristics		
Cause of nonischemic cardiomyopathy		
Idiopathic	504	522
Hypertensive	159	128
Alcoholic	85	86
Infectious/viral	47	53
Other	32	38
NYHA functional class III/IV	661/166	668/158
LVEF, %	0.21 ± 0.06	0.21 ± 0.06
Physical examination		
SBP, mm Hg	120 ± 18	120 ± 17
HR, beats/min	80 ± 13	81 ± 14
Laboratory analysis		
SNa, mmol/l	140 ± 3	139 ± 3
SCr, mg/dl	1.2 ± 0.4	1.3 ± 0.4
Current treatment, %		
Amiodarone	10	10
Aspirin	29	26

Values are mean ± SD, %, or n.
HR = heart rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SBP = systolic blood pressure; SCr = serum creatinine concentration; SNa = serum sodium concentration.

Effect of amlodipine on survival. By intention to treat, there were 278 patients who died in the amlodipine group and 262 patients who died in the placebo group (HR: 1.09; 95% CI: 0.92 to 1.20; p = 0.33) (Table 2, Fig. 1). Prespecified and post hoc subgroup analyses failed to identify any baseline characteristic that exerted any significant influence on the magnitude or direction of the difference between the 2 treatment groups (all interaction p values >0.10) (Table 3).

Effects of amlodipine on secondary endpoints. By intention to treat, there were 239 cardiovascular deaths in the amlodipine group and 215 cardiovascular deaths in the placebo group (HR: 1.14; 95% CI: 0.95 to 1.37; p = 0.17).

A total of 505 patients were hospitalized for a total of 1,433 admissions in the amlodipine group, and 529 patients were hospitalized for a total of 1,520 admissions in the placebo group. The observed differences between the 2 groups in the numbers of patients and the numbers of hospitalizations were not significant (p = 0.22 and p = 0.42, respectively). A total of 324 patients were hospitalized for heart failure, for a total of 749 heart failure admissions in the amlodipine group; 316 patients were hospitalized for heart failure, for a total of 723 heart failure admissions in the placebo group. The observed differences between the 2 groups in the numbers of patients and the numbers of hospitalizations for heart failure were not significant (p = 0.69 and p = 0.56, respectively).

Safety. Systolic blood pressure decreased more in the amlodipine group than in the placebo group at both 12 and 26 weeks of follow-up (12 weeks: −3.5 vs. +1.7 mm Hg; 26

Table 2 Effects of Amlodipine on Mortality in Patients With Severe Heart Failure Due to a Nonischemic Cardiomyopathy

Study	Amlodipine	Placebo	HR (95% CI)	p Value†
PRAISE-1 (9)	45/209	74/212	0.54 (0.37–0.78)	0.001
PRAISE-2	278/827	262/827	1.09 (0.92–1.29)	0.3
PRAISE-1 (9) + PRAISE-2‡	322/1036	332/1039	0.97 (0.83–1.13)	0.6

*In both trials and in both treatment groups, only the results from patients with a nonischemic cardiomyopathy are shown. As per protocol, patients who received transplants were classified as deaths in PRAISE-1 but as survivors in PRAISE-2 (unless a patient actually died following transplantation). In PRAISE-1, cardiac transplantation was performed in 1 patient in the amlodipine group and in 4 patients in the placebo group; in PRAISE-2, these values were 29 (of whom 7 died) and 39 (of whom 5 died), respectively. †All p values are unadjusted and nominal. ‡In the pooled analysis of PRAISE-1 and PRAISE-2, only deaths were counted as events, thus explaining why the event counts in the pooled analysis are not the sum of the event counts in PRAISE-1 + the event counts in PRAISE-2.

HR = hazard ratio; PRAISE = Prospective Randomized Amlodipine Survival Evaluation.

weeks: −2.9 vs. +1.1 mm Hg; both, $p < 0.001$). A similar pattern was observed with respect to diastolic blood pressure (12 weeks: −2.2 vs. +0.1 mm Hg; 26 weeks: −2.1 vs. +0.1 mm Hg; both, $p < 0.001$). There were no significant differences in heart rate between the 2 groups at these time points.

Adverse events related to the cardiovascular system and occurring in >3% of patients are summarized in Table 4. Two cardiovascular reactions occurred more frequently (nominal $p < 0.05$) with amlodipine than with placebo (peripheral edema [$p < 0.001$] and pulmonary edema [$p < 0.001$], and 3 cardiovascular reactions were seen less frequently (nominal $p < 0.05$) in the amlodipine group (uncontrolled hypertension [$p = 0.002$], chest pain/angina [$p = 0.011$], and stroke [$p = 0.029$]). The 2 groups were similar in the nature and frequency of noncardiovascular adverse events. The study drug was withdrawn due to an adverse event in 3.9% of the amlodipine group and in 3.3% of the placebo group and ($p = 0.97$).

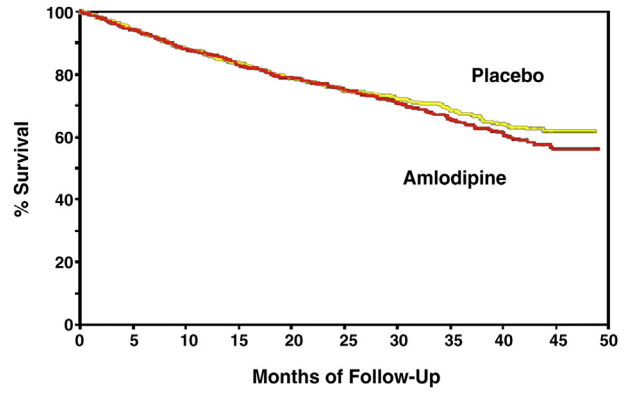

Figure 1 Kaplan-Meier Survival Curves in Patients With a Nonischemic Cardiomyopathy

Survival curves in patients enrolled in PRAISE-2 (Second Prospective Randomized Amlodipine Survival Evaluation) who received amlodipine or placebo.

Discussion

The hypothesis that amlodipine might favorably affect survival in patients with nonischemic cardiomyopathy was derived from the findings from a subgroup analysis of a secondary endpoint of a large-scale trial (PRAISE-1 [9]), which enrolled patients with and without coronary artery disease. Treatment with amlodipine was associated with a favorable trend on survival ($p = 0.07$) in the trial overall, which was particularly marked in patients with a nonischemic cardiomyopathy ($p < 0.001$). Not only was this subgroup analysis pre-specified in the statistical plan, but also the original trial was actually designed as a stratified study in which patients were allocated to amlodipine or placebo in separate strata defined by the presence or absence of coronary artery disease. The effect of amlodipine on mortality in the strata of patients with a nonischemic cardiomyopathy was significant in its own right, and the magnitude of the effect in patients without coronary artery disease was significantly greater than in patients with the disease (treatment-by-etiology interaction: $p = 0.004$). Furthermore, although the a priori hypothesis was that amlodipine might be particularly useful in patients with an ischemic cardiomyopathy, the possibility that the drug might favorably modify the natural history of patients with a nonischemic cardiomyopathy was consistent with experimental and clinical data suggesting that coronary vasoconstriction or vasospasm plays an important role in the pathogenesis of cardiomyopathies that are associated with no apparent structural disease of the coronary vessels (10,11).

The findings of the current study, however, indicate that the administration of amlodipine in patients with moderate to severe heart failure due to a nonischemic cardiomyopathy does not prolong survival or reduce the risk for hospitalization. Although the drug exerted vasodilatory effects that resulted in an expected decrease in blood pressure, treatment with amlodipine did not reduce morbidity or mortality in the population as a whole or in any pre-specified or post-hoc subgroup. When the mortality data in the patients with a nonischemic cardiomyopathy in both the earlier PRAISE-1 trial and the current PRAISE-2 trial were combined, there was no evidence of a favorable or unfavorable effect of amlodipine on mortality (Table 2). Therefore, the results of the current trial, viewed either alone or together with the results of the earlier trial (9), failed to confirm the earlier finding that amlodipine might be effective in reducing the risk for death in patients with heart failure who do not have coronary artery disease.

Why did the results of the PRAISE-1 and PRAISE-2 trials differ? Differences in the results of clinical studies are frequently attributed to differences in trial design or in the study patients. However, the baseline characteristics of nonischemic patients in the 2 trials were similar (Table 5), and the trials were carried out using virtually

JACC: Heart Failure Vol. 1, No. 4, 2013
August 2013:308–14

Table 3 Effects of Amlodipine on Mortality in Pre-Specified Subgroups Defined by Baseline Characteristics

Subgroup	Amlodipine	Placebo	HR (95% CI)	p Value*
Age				0.38
≤60 yrs	121/417	109/434	1.19 (0.92–1.55)	
>60 yrs	157/410	153/393	0.99 (0.79–1.24)	
Sex				0.60
Male	200/547	191/549	1.08 (0.88–1.31)	
Female	78/280	71/278	1.12 (0.81–1.54)	
LVEF				0.14
≤20%	159/344	144/369	1.26 (1.00,1.58)	
>20%	119/483	118/458	0.96 (0.75,1.24)	
NYHA functional class				0.48
III	192/661	193/668	1.03 (0.84,1.26)	
IV	86/166	69/158	1.21 (0.88,1.67)	

*Calculated from 2 degrees of freedom chi-square statistic, which was used to test simultaneously for the presence of treatment effect and treatment–covariate interaction.
Abbreviations as in Table 1.

identical protocols and similar investigators. Yet, despite the apparent and intended similarities in patients and protocols, the annual mortality rate in the placebo group in the nonischemic patients in PRAISE-1 was twice that seen in the placebo group in the nonischemic patients in PRAISE-2 (26% vs. 12%) (Fig. 2), a difference that could not be explained by the infrequent and delayed use of beta-blockers in PRAISE-2 or to potential (but unrecorded) differences in the dosing of diuretics or ACE inhibitors between the 2 trials. Instead, our findings indicate that the PRAISE-2 investigators enrolled patients with less advanced disease than did the PRAISE-1 investigators, possibly because they were pressed to recruit large numbers of difficult-to-find patients without coronary artery disease who had advanced symptoms. Could this have explained the differences in results? Subgroup analyses of PRAISE-2 based on NYHA class and ejection fraction (Table 2) do not support the hypothesis that patients with more advanced disease responded better to amlodipine than did patients with less advanced disease. These observations highlight the difficulties of using baseline characteristics or features of the protocol design to predict event rates in clinical trials and the dangers of reaching conclusions using data from historical controls. Indeed, if PRAISE-2 had been carried out as an uncontrolled trial with amlodipine and not as a randomized comparison against placebo, one might have been tempted to compare the mortality rates with amlodipine in PRAISE-2 with the mortality rates with placebo in PRAISE-1 (using the latter as the historical control)—a comparison that might have seemed reasonable given the similarity in the baseline characteristics and the study conditions of the 2 cohorts. Such a comparison would have led to the incorrect conclusion that amlodipine reduced mortality.

Table 4 Most Frequently* Reported Adverse Events Related to the Cardiovascular System

Adverse event	Amlodipine (n = 1156)	Placebo (n = 1133)	p Value
Cardiac arrest	81 (9.8)	72 (8.7)	0.445
Chest pain/angina	178 (21.5)	222 (26.8)	0.011
Peripheral edema	230 (27.8)	133 (16.1)	0.001
Atrial fibrillation	86 (10.4)	88 (10.6)	0.873
Hypotension/dizziness	161 (19.5)	163 (19.7)	0.901
Palpitation	64 (7.9)	75 (9.1)	0.329
Pulmonary edema	55 (6.7)	20 (2.4)	0.001
Stroke	20 (2.4)	36 (4.4)	0.029
Syncope/pre-syncope	77 (9.3)	87 (10.5)	0.411
Ventricular tachycardia	96 (11.6)	93 (11.2)	0.817
Ventricular fibrillation	32 (3.9)	31 (3.7)	0.898
Hypertension	28 (3.4)	55 (6.7)	0.002
Worsening heart failure	478 (57.8)	464 (56.1)	0.487
Shortness of breath	81 (9.8)	96 (11.6)	0.233
Abnormal renal function	126 (15.2)	99 (12.0)	0.053

Values are n (%) of patients. *Overall frequency >3%.

Table 5 Pretreatment Characteristics of Patients With a Nonischemic Cardiomyopathy Treated With Placebo in the PRAISE-1 and PRAISE-2 Studies

Characteristic	PRAISE-1 [9] (n = 212)	PRAISE-2 (n = 827)
Age, yrs	60 ± 14	59 ± 13
Male, %	70	66
Disease characteristics		
NYHA functional class III/IV, %	17	19
LVEF, %	0.20 ± 0.06	0.21 ± 0.06
Physical examination		
SBP, mm Hg	118 ± 17	120 ± 17
HR, beats/min	87 ± 14	81 ± 14
Laboratory analysis		
SNa, mmol/l	139 ± 3	139 ± 3
SCr, mg/dl	1.3 ± 0.5	1.3 ± 0.4
Current treatment, %		
Digitalis	100	99
Diuretic	100	99
ACE-I	100	99
Amiodarone	6	10
Aspirin	19	26

Values are mean ± SD or %.
ACE-I = angiotensin-converting enzyme inhibitor; other abbreviations as in Table 1.

The totality of available evidence suggests that the benefits of amlodipine seen in PRAISE-1 were related to chance. The encouraging findings in PRAISE-1 were based on a subgroup analysis of a secondary endpoint in a trial that failed to achieve its primary endpoint. Furthermore, the observation that mortality rates were lower in patients treated with amlodipine in PRAISE-1 was based on a small number of recorded deaths in patients with a nonischemic cardiomyopathy. Previous experience in clinical trials of other treatments of chronic heart failure has demonstrated that striking effects on mortality in subgroups of patients or in trials not specifically designed or powered to observe an

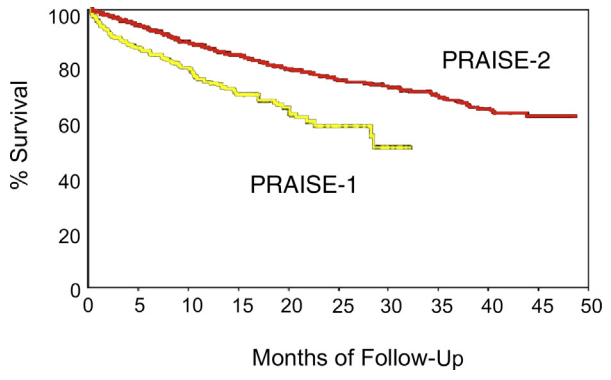

Figure 2 **Kaplan-Meier Survival Curves in Patients With a Nonischemic Cardiomyopathy**

Survival curves in patients enrolled in PRAISE-1 (9) and PRAISE-2 who received placebo.

effect on mortality are frequently not reproduced when a larger trial is carried out to confirm the encouraging observation. Specifically, an initial observation that vesnarinone reduced mortality in patients with heart failure was based on an analysis of a secondary endpoint in a trial (17) that recorded only 46 deaths and was not designed to evaluate the effect of the drug on the risk for death. In a larger trial (18) that was designed to look at mortality, vesnarinone was shown to increase mortality rates. Similarly, the initial observation that losartan reduced mortality when compared to captopril was based on an analysis of a secondary endpoint in a trial (19) that recorded only 49 deaths and was not designed to compare the survival effects of 2 drugs. Two larger trials (20,21) that were specifically designed to compare the mortality effects of losartan and captopril failed to confirm the earlier finding. These experiences—when taken together with the results of the current trial—indicate that great caution is needed in the interpretation of findings when striking benefits are observed in trials not designed to discern them. A conservative approach is warranted even when the observed benefit is a reduction in a seemingly unbiased endpoint (i.e., mortality), as was the case in PRAISE-1.

Interestingly, the results of PRAISE-2 were similar to those of PRAISE-1 with respect to the safety of amlodipine in patients with severe heart failure. Both trials reported decreases in the frequencies of uncontrolled hypertension and chest pain/angina and increases in the frequencies of peripheral edema and pulmonary edema in patients treated with amlodipine. The reduction in reports of chest pain and uncontrolled hypertension may not be surprising given the efficacy of amlodipine in the treatment of angina and hypertension. However, it is noteworthy that patients in the current trial did not have coronary artery disease, although it might be postulated that some may have had symptomatic myocardial ischemia related to coronary vasoconstriction (10,11). Peripheral edema is a well-established adverse effect of amlodipine in patients with hypertension or angina, especially when the drug is prescribed at the target doses used in the current study (22). The frequency of pulmonary edema was increased with amlodipine in both PRAISE-1 and PRAISE-2, even though neither trial demonstrated an increased risk for worsening heart failure, hospitalization for heart failure, or mortality in the amlodipine groups. This apparent paradox suggested that the occurrence of pulmonary edema with amlodipine may not reflect the progression of heart failure. Calcium-channel blockers can cause pulmonary edema by dilating pulmonary arterioles rather than by adversely affecting the heart (23,24); in doing so, these drugs interfere with the restraint that pulmonary vasoconstriction normally exerts on blood flow into the lungs and the transudation of fluid into alveoli when pulmonary venous pressures are increased (25–27). Finally, it is of interest that the PRAISE-2 trial reported fewer strokes in amlodipine-treated patients, particularly in light of evidence that antihypertensive agents may reduce the risk for stroke even in patients without hypertension (28). However, given the retrospective nature of this observation and the small number of events, no conclusions regarding the existence of such a benefit would be warranted.

Conclusions

The results of the current trial, viewed either alone or together with the results of earlier studies, indicate that amlodipine does not exert favorable effects on the clinical course of patients with heart failure, regardless of the presence or absence of underlying coronary artery disease. The findings of the current trial indicate the need for great caution when striking benefits are observed in subgroups of patients or in trials not primarily or specifically designed to assess such effects.

Reprint requests and correspondence: Dr. Milton Packer, Department of Clinical Sciences, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, Texas 75390. E-mail: Milton.Packer@UTSouthwestern.edu.

REFERENCES

1. Elkayam U, Amin J, Mehra A, et al. A prospective randomized, double-blind crossover study to compare the efficacy and safety of chronic nifedipine therapy to isosorbide dinitrate and their combination in the treatment of chronic congestive heart failure. Circulation 1990; 82:1954–62.
2. Barjon JN, Rouleau J-L, Bichet D, et al. Chronic renal and neurohormonal effects of the calcium entry blocker nisoldipine in patients with congestive heart failure. J Am Coll Cardiol 1987;9:622–30.
3. Goldstein RE, Boccuzzi SJ, Cruess D, et al. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. Circulation 1991;83:52–60.
4. Tan LB, Murray RG, Littler WA. Felodipine in patients with chronic heart failure: discrepant hemodynamic and clinical effects. Br Heart J 1987;58:122–8.

5. Littler WA, Sherdian DJ. Placebo controlled trial of felodipine in patients with mild to moderate heart failure. Br Heart J 1995;73:428–33.
6. Packer M. Pathophysiologic mechanisms underlying the adverse effects of calcium channel blocking drugs in patients with chronic heart failure. Circulation 1989;80 Suppl IV:59–67.
7. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA Guidelines for the evaluation and management of chronic heart failure in the adult. J Am Coll Cardiol 2001;38:2101–13.
8. Udelson JE, DeAbate CA, Berk M, et al. Effects of amlodipine on exercise tolerance, quality of life, and left ventricular function in patients with heart failure from left ventricular systolic dysfunction. Am Heart J 2000;139:503–10.
9. Packer M, O'Connor CM, Ghali JK, et al., for the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) Study Group. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. N Engl J Med 1996;335:1107–14.
10. Sole MJ, Liew CC. Catecholamines, calcium and cardiomyopathy. Am J Cardiol 1988;62:20G–4G.
11. Weismuller S, Czernin J, Sun KT, et al. Coronary vasodilatory capacity is impaired in patients with dilated cardiomyopathy. Am J Card Imaging 1996;10:154–62.
12. Packer M, Meller J, Medina N, et al. Hemodynamic consequences of combined beta-adrenergic and slow calcium channel blockade in man. Circulation 1982;65:660–8.
13. Lan KKG, DeMets DL. Discrete sequential boundaries of clinical trials. Biometrika 1983;70:59–63.
14. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979;35:549–56.
15. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457–81.
16. Cox DR. Regression models and life-tables. J R Stat Soc B 1972;34:187–202.
17. Feldman AM, Bristow MR, Parmley WW, et al. Effects of vesnarinone on morbidity and mortality in patients with heart failure. N Engl J Med 1993;329:149–55.
18. Cohn JN, Goldstein SO, Greenberg BH, et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. N Engl J Med 1998;339:1810–6.
19. Pitt B, Segal R, Martinez FA, et al. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet 1997;349:747–52.
20. Pitt B, Poole-Wilson PA, Segal R, et al. Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial—the Losartan Heart Failure Survival Study ELITE II. Lancet 2000;355:1582–7.
21. Dickstein K, Kjekshus J; OPTIMAAL Steering Committee of the OPTIMAAL Study Group. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction. Lancet 2002;360:752–60.
22. Andresdottir MB, van Hamersvelt HW, van Helden MJ, et al. Ankle edema formation during treatment with the calcium channel blockers lacidipine and amlodipine: a single-centre study. J Cardiovasc Pharmacol 2000;35 Suppl 1:S25–30.
23. Gillmer DJ, Kark P. Pulmonary oedema precipitated by nifedipine. Br Med J 1980;280:1420–1.
24. Batra AK, Segall PH, Ahmed T. Pulmonary edema with nifedipine in primary pulmonary hypertension. Respiration 1985;47:161–3.
25. Yoran C, Glassman E. The paradoxical effect of tolazoline hydrochloride on the pulmonary hypertension of mitral stenosis. Chest 1973;63:843–6.
26. Semigran MJ, Cockrill BA, Kacmarek R, et al. Hemodynamic effects of inhaled nitric oxide in heart failure. J Am Coll Cardiol 1994;24:982–8.
27. Haywood G, Sneddon J, Bashin Y, et al. Adenosine infusion for the reversal of pulmonary vasoconstriction in biventricular failure, a good test but a poor therapy. Circulation 1992;86:896–902.
28. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet 2001;358:1033–41.

Key Words: amlodipine ■ clinical trials ■ heart failure ■ nonischemic cardiomyopathy.

APPENDIX

For the list of PRAISE-2 study investigators and coordinators, please see the online version of this article.