

## EFFECT OF AMLODIPINE ON MORBIDITY AND MORTALITY IN SEVERE CHRONIC HEART FAILURE

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## ABSTRACT

**Background** Previous studies have shown that calcium-channel blockers increase morbidity and mortality in patients with chronic heart failure. We studied the effect of a new calcium-channel blocker, amlodipine, in patients with severe chronic heart failure.

**Methods** We randomly assigned 1153 patients with severe chronic heart failure and ejection fractions of less than 30 percent to double-blind treatment with either placebo (582 patients) or amlodipine (571 patients) for 6 to 33 months, while their usual therapy was continued. The randomization was stratified on the basis of whether patients had ischemic or nonischemic causes of heart failure. The primary end point of the study was death from any cause and hospitalization for major cardiovascular events.

**Results** Primary end points were reached in 42 percent of the placebo group and 39 percent of the amlodipine group, representing a 9 percent reduction in the combined risk of fatal and nonfatal events with amlodipine (95 percent confidence interval, 24 percent reduction to 10 percent increase;  $P=0.31$ ). A total of 38 percent of the patients in the placebo group died, as compared with 33 percent of those in the amlodipine group, representing a 16 percent reduction in the risk of death with amlodipine (95 percent confidence interval, 31 percent reduction to 2 percent increase;  $P=0.07$ ). Among patients with ischemic heart disease, there was no difference between the amlodipine and placebo groups in the occurrence of either end point. In contrast, among patients with nonischemic cardiomyopathy, amlodipine reduced the combined risk of fatal and nonfatal events by 31 percent ( $P=0.04$ ) and decreased the risk of death by 46 percent ( $P<0.001$ ).

**Conclusions** Amlodipine did not increase cardiovascular morbidity or mortality in patients with severe heart failure. The possibility that amlodipine prolongs survival in patients with nonischemic dilated cardiomyopathy requires further study. (N Engl J Med 1996;335:1107-14.)

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**S**HORT-TERM or long-term treatment with calcium-channel blockers may worsen heart failure and increase the risk of death in patients with advanced left ventricular dysfunction.<sup>1-4</sup> The possibility of such effects has been noted with most drugs in this class, including many of the newer agents that have become available for clinical

use.<sup>2,5,6</sup> As a result, physicians have been advised to avoid the use of calcium-channel blockers in patients with heart failure, even if these drugs are being considered for the treatment of coexisting angina or hypertension.<sup>7</sup>

It is not clear, however, whether all calcium-channel blockers have deleterious effects in patients with heart failure. In two controlled trials, amlodipine did not adversely affect the clinical status of patients; in fact, the drug reduced symptoms and improved exercise tolerance.<sup>8,9</sup> These findings, however, did not allow definitive conclusions to be made about the safety of amlodipine in heart failure, since the trials enrolled fewer than 300 patients, who were treated for only 8 to 12 weeks, and patients with severe symptoms — those most likely to have clinical deterioration after treatment with a calcium-channel blocker — were not included.<sup>10</sup> To address these limitations, we conducted the Prospective Randomized Amlodipine Survival Evaluation (PRAISE). The primary objective of this trial was to assess the long-term effect of amlodipine on morbidity and mortality among patients with advanced chronic heart failure.

## METHODS

All patients had dyspnea or fatigue at rest or on minimal exertion (New York Heart Association class IIIB or IV) and a left ventricular ejection fraction of less than 30 percent despite treatment with digoxin, diuretics, and an angiotensin-converting-enzyme inhibitor. Treatment with nitrates was allowed, but other vasodilator drugs (e.g., hydralazine) were not permitted. Patients were excluded if they had uncorrected primary valvular disease, active myocarditis, or constrictive pericarditis; if they had a history of cardiac arrest or had had sustained ventricular tachycardia or fibrillation within the previous year, unstable angina or an acute myocardial infarction within the previous month, or a cardiac-revascularization procedure or stroke within the previous three

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**TABLE 1. PRETREATMENT CHARACTERISTICS OF 1153 PATIENTS WITH CHRONIC HEART FAILURE ASSIGNED TO TREATMENT WITH AMLODIPINE OR PLACEBO.\***

CHARACTERISTIC	ALL PATIENTS		ISCHEMIC STRATUM		NONISCHEMIC STRATUM	
	PLACEBO (N=582)	AMLODIPINE (N=571)	PLACEBO (N=370)	AMLODIPINE (N=362)	PLACEBO (N=212)	AMLODIPINE (N=209)
Age (yr)	64.7±0.5	64.7±0.5	67.3±0.5	67.5±0.5	60.2±0.9	60.0±0.8
Sex (M/F)	453/129	422/149	304/66	287/75	149/63	135/74
NYHA class (no. of patients)						
III	471	460	295	287	176	173
IV	111	111	75	75	36	36
Blood pressure (mm Hg)						
Systolic	117.3±0.7	117.8±0.8	116.6±0.9	118.0±1.0	118.4±1.1	117.4±1.2
Diastolic	72.0±0.5	72.5±0.4	70.9±0.6	71.4±0.5	74.1±0.7	74.2±0.7
Heart rate (beats/min)	82.9±0.7	83.2±0.7	80.8±0.7	81.0±0.8	86.6±0.9	87.0±1.2
Cardiothoracic ratio	0.57±0.01	0.56±0.01	0.56±0.01	0.56±0.01	0.59±0.01	0.58±0.01
Left ventricular ejection fraction	0.21±0.01	0.21±0.01	0.21±0.01	0.21±0.01	0.20±0.01	0.20±0.01
Other medications (% of patients)						
Digitalis	99	99	99	99	100	100
Diuretics	100	100	100	100	100	100
ACE inhibitor	99	99	99	99	100	99
Dose of digoxin (mg/day)	0.20±0.01	0.20±0.01	0.19±0.01	0.19±0.01	0.22±0.01	0.22±0.01
Dose of captopril (mg/day)	81	74	71	66	95	86
Dose of enalapril (mg/day)	14	15	13	13	16	18

\*Plus-minus values are means ±SE. NYHA denotes New York Heart Association, and ACE angiotensin-converting enzyme.

months; or if they had severe pulmonary, renal, or hepatic disease. Other criteria for exclusion were systolic blood pressure lower than 85 mm Hg or higher than 159 mm Hg; diastolic blood pressure higher than 89 mm Hg; a serum creatinine concentration higher than 3.0 mg per deciliter (270 μmol per liter) or a potassium concentration lower than 3.5 or higher than 5.5 mmol per liter; or treatment with beta-blockers, calcium-channel blockers, or class IC antiarrhythmic agents. Eligible patients had not received intravenous diuretics or vasodilators within 24 hours before enrollment or intravenous positive inotropic agents within 72 hours.

The protocol was approved by the institutional review boards of all 105 participating institutions. Written informed consent was obtained from all patients.

### Study Design

After the initial evaluation, patients were randomly assigned (in a double-blind fashion) to receive either oral amlodipine or matching placebo, in addition to their usual medications. Because it was expected before the start of the study that amlodipine might have different effects on patients with different causes of heart failure, the randomization was stratified according to whether the cause of left ventricular dysfunction was coronary artery disease or nonischemic dilated cardiomyopathy. The presence of coronary artery disease was confirmed by coronary arteriography or suspected on the basis of a history of angina or myocardial infarction.

After randomization, patients received an initial dose of 5 mg of amlodipine or placebo once daily for two weeks; the dose was then increased (if tolerated) to 10 mg of amlodipine or placebo once daily for the remainder of the study. If side effects occurred, the dose of the study medication could be reduced or discontinued, but investigators were encouraged to reinstitute treatment at a later time. If the patient's condition changed, the physician could use any clinically indicated interventions, including adjustments of concomitant treatment with other drugs; however, patients could not receive open-label amlodipine.

### End Points

The primary end point of the study, as stated in the original protocol, was the combined risk of mortality from all causes and cardiovascular morbidity. Cardiovascular morbidity was defined as hospitalization for at least 24 hours for any of the following reasons: acute pulmonary edema, severe hypoperfusion, acute myocardial infarction, or sustained or hemodynamically destabilizing ventricular tachycardia or fibrillation. The criteria used to evaluate these end points were established at the start of the study, and all events were reviewed by an end-points committee without knowledge of the treatment assignments. The principal secondary end point of the study was mortality from all causes. The effect of amlodipine on survival was also assessed in subgroups of patients defined on the basis of the following seven prerandomization variables: age, sex, ejection fraction, New York Heart Association class, serum sodium concentration, and the presence or absence of a history of angina or a history of hypertension. All subgroup analyses (except that involving age) were prospectively planned in the original protocol.

### Statistical Analysis

The sample size for the study was estimated on the basis of the following assumptions: the event rate (morbidity and mortality combined) in the placebo group at one year would be 40 percent; the risk would be reduced by 25 percent in the amlodipine group; 10 percent of the patients would withdraw permanently from the assigned treatment group; and the power to detect a difference between the treatment groups would be 90 percent or higher (alpha level of 0.05 by a two-tailed test). Since we recognized that estimates of the event rate might be inaccurate, the trial was designed to continue until 190 fatal or nonfatal events had occurred in the placebo group, with all patients subsequently followed for an additional six months. To reduce the likelihood of false positive results due to repeated interim analyses, we used the Lan-DeMets procedure<sup>11</sup> with an O'Brien-Fleming boundary,<sup>12</sup> which requires only the expected number of events and the significance level to be specified in advance. With this procedure, differences

between the two treatment groups at the scheduled end of the trial were considered significant if the z score was higher than 2.06 (corresponding to nominal  $P < 0.0424$ ). The Data and Safety Monitoring Board periodically reviewed the unblinded results and was empowered to recommend early termination of the study if the treatment effect exceeded the prespecified boundaries.

The base-line characteristics of the two treatment groups were compared with use of the Wilcoxon test (for continuous and ordinal variables) or chi-square test (for categorical variables). Cumulative survival curves for the two groups were constructed by the Kaplan–Meier method,<sup>13</sup> and differences between the curves were tested for significance with both the log-rank test and a Cox proportional-hazards regression model.<sup>14</sup> The survival analyses included all patients randomly assigned to a treatment group, and all deaths were analyzed on the basis of the original group assignments (according to the intention-to-treat principle). Changes in vital signs and differences in the frequency of adverse reactions were analyzed by the Wilcoxon or chi-square test, as appropriate. All P values are two-tailed.

## RESULTS

The PRAISE trial began on March 9, 1992; 1153 patients were enrolled, and follow-up was completed on December 31, 1994. Of the 732 patients with ischemic heart disease, 370 were assigned to placebo and 362 to amlodipine. Of the 421 patients with nonischemic cardiomyopathy, 212 were assigned to placebo and 209 to amlodipine.

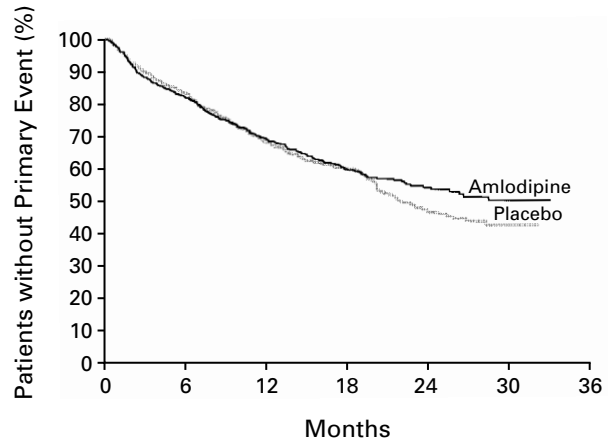
The two treatment groups were similar with respect to all pretreatment characteristics (Table 1). One month after randomization, patients were receiving an average daily dose of  $8.8 \pm 0.6$  mg of amlodipine or  $8.9 \pm 0.6$  mg of placebo; these doses were maintained at similar levels throughout the follow-up period. Compliance with the study regimen (assessed by pill counts) averaged over 90 percent at all visits. The duration of follow-up ranged from 6 to 33 months (median, 13.8); no patients were lost to follow-up.

### Effect of Amlodipine in the Combined Strata

A primary fatal or nonfatal event occurred in 222 of the 571 patients in the amlodipine group (39 percent) and in 246 of the 582 patients in the placebo group (42 percent). Cumulative survival curves are shown in Figure 1. Amlodipine therapy was associated with a 9 percent reduction in the risk of a primary fatal or nonfatal event (95 percent confidence interval, 24 percent reduction to 10 percent increase;  $P = 0.31$  by the log-rank test). There were 190 deaths from all causes (33 percent) in the amlodipine group and 223 (38 percent) in the placebo group. This difference reflected a 16 percent reduction in the risk of death in the amlodipine group (95 percent confidence interval, 31 percent reduction to 2 percent increase;  $P = 0.07$ ) (Fig. 2).

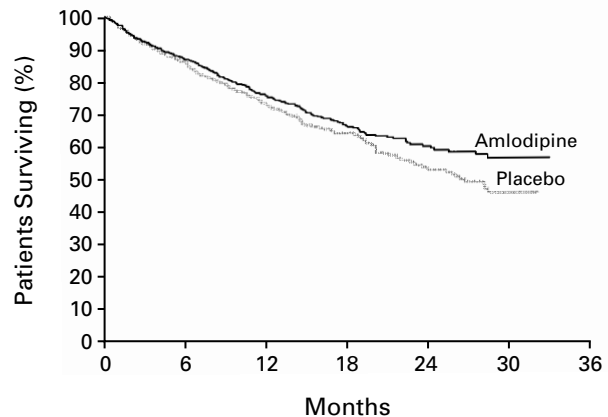
### Effect of Amlodipine in Individual Strata

The results noted above were based on the assumption that the effects of amlodipine in the patients with ischemic heart disease were similar to the



**Figure 1.** Kaplan–Meier Plots of the Time to the First Primary Event (Death or Cardiovascular Morbidity) among 571 Patients with Chronic Heart Failure Receiving Amlodipine and 582 Receiving Placebo.

As compared with the placebo group, the amlodipine group had a 9 percent lower risk of a primary event (95 percent confidence interval, 24 percent lower to 10 percent higher;  $P = 0.31$ ).

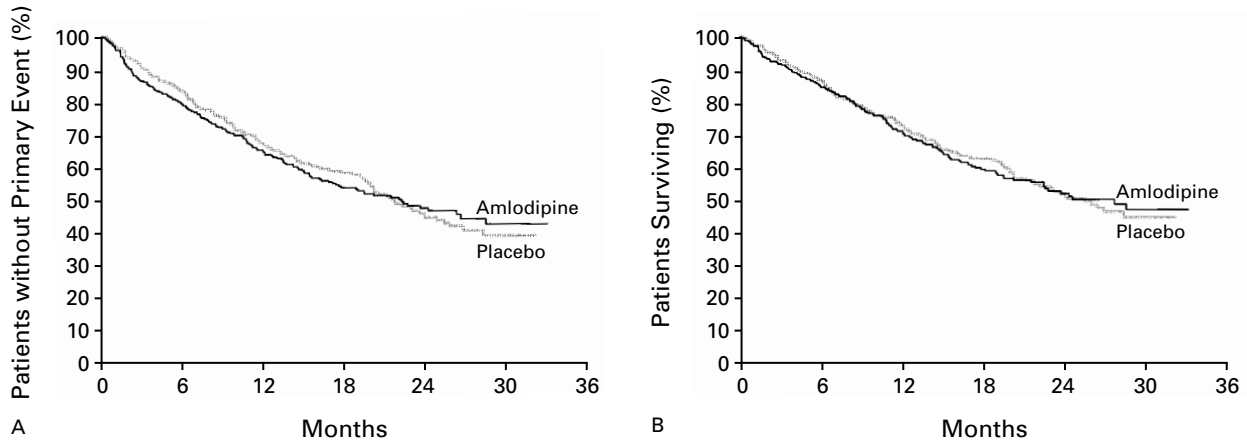


**Figure 2.** Kaplan–Meier Plots of Cumulative Survival in the Amlodipine and Placebo Groups.

As compared with the placebo group, the amlodipine group had a 16 percent lower risk of death (95 percent confidence interval, 31 percent lower to 2 percent higher;  $P = 0.07$ ).

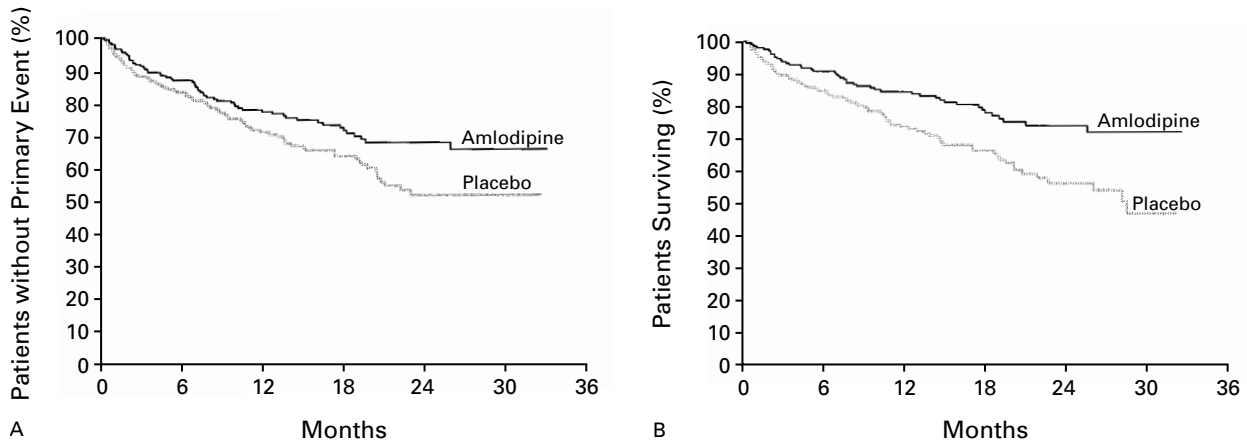
effects in those with nonischemic cardiomyopathy, but this was not the case. There was a significant interaction between the effect of treatment and the cause of heart failure, both for mortality from all causes ( $P = 0.004$ ) and for the combined end point of fatal and nonfatal primary events ( $P = 0.04$ ). As a result, the effects of amlodipine were evaluated separately in the two strata.

Among the patients with ischemic heart disease, treatment with amlodipine did not affect the combined risk of morbidity and mortality or the risk of



**Figure 3.** Kaplan–Meier Plots of the Time to the First Primary Event (Panel A) and the Time to Death (Panel B) among Patients with Ischemic Cardiomyopathy in the Amlodipine and Placebo Groups.

There was no significant difference between the two groups in the risk of primary or secondary events.



**Figure 4.** Kaplan–Meier Plots of the Time to the First Primary Event (Panel A) and the Time to Death (Panel B) among Patients with Nonischemic Dilated Cardiomyopathy in the Amlodipine and Placebo Groups.

As compared with the placebo group, the amlodipine group had a 31 percent lower risk of a primary event (95 percent confidence interval, 2 percent to 51 percent lower;  $P=0.03$ ) and a 45 percent lower risk of death (95 percent confidence interval, 21 percent to 63 percent lower;  $P<0.001$ ).

mortality from any cause. Forty-five percent of the patients in both treatment groups had a fatal or nonfatal event (hazard ratio for the amlodipine group as compared with the placebo group, 1.04; 95 percent confidence interval, 0.83 to 1.29), and 40 percent of the patients in both groups died (hazard ratio, 1.02; 95 percent confidence interval, 0.81 to 1.29). Cumulative survival curves for the ischemic stratum are shown in Figures 3A and 3B.

In contrast, treatment with amlodipine reduced the frequency of primary and secondary events in patients with nonischemic dilated cardiomyopathy. There were 78 fatal or nonfatal events in the placebo group but only 58 in the amlodipine group, reflecting a 31 percent reduction in risk in the amlodipine group (95 percent confidence interval, 2 to 51 percent reduc-

tion;  $P=0.04$ ). There were 74 deaths from all causes in the placebo group but only 45 in the amlodipine group, reflecting a 46 percent reduction in risk in the amlodipine group (95 percent confidence interval, 21 to 63 percent reduction;  $P<0.001$ ). Cumulative survival curves for the nonischemic stratum are shown in Figures 4A and 4B.

The fatal and nonfatal primary events that occurred in the two treatment groups are shown in Table 2 for all patients and for those in the two strata.

#### Effect of Amlodipine in Specific Subgroups

To determine whether amlodipine has an adverse effect in some patients with heart failure, the influence of treatment on mortality was examined in subgroups defined on the basis of pretreatment charac-

**TABLE 2.** FREQUENCY OF FATAL AND NONFATAL PRIMARY EVENTS IN ALL PATIENTS AND IN THE ISCHEMIC AND NONISCHEMIC STRATA.\*

PRIMARY EVENT	ALL PATIENTS		ISCHEMIC STRATUM		NONISCHEMIC STRATUM	
	PLACEBO (N=582)	AMLODIPINE (N=571)	PLACEBO (N=370)	AMLODIPINE (N=362)	PLACEBO (N=212)	AMLODIPINE (N=209)
	no. of patients (%)					
Fatal	192 (33)	160 (28)	126 (34)	123 (34)	66 (31)	37 (18)
Nonfatal						
Pulmonary edema	15 (3)	35 (6)	13 (4)	21 (6)	2 (1)	14 (7)
Severe hypoperfusion	11 (2)	10 (2)	8 (2)	8 (2)	3 (1)	2 (1)
Myocardial infarction	10 (2)	7 (1)	9 (2)	4 (1)	1 (<1)	3 (1)
Sustained ventricular tachycardia or fibrillation	18 (3)	10 (2)	12 (3)	8 (2)	6 (3)	2 (1)
Total	246 (42)	222 (39)	168 (45)	164 (45)	78 (37)	58 (28)

\*Fatal primary events include only the deaths considered by the end-points committee to be primary end points and do not include the deaths that followed the occurrence of a nonfatal primary event.

teristics. The point estimates for the hazard ratios (with 95 percent confidence intervals) are shown in Table 3. For all characteristics except the presence or absence of angina, the point estimates for the treatment effect within each subgroup were similar to those for the overall study group. Amlodipine did not have an adverse effect on survival in any of the subgroups. The drug was associated with a favorable effect on survival in patients without angina ( $P=0.002$  for the comparison with the patients with angina). This finding is consistent with the risk reduction noted among patients with nonischemic cardiomyopathy.

#### Safety and Adverse Reactions

In both treatment groups, there were only minor changes in vital signs. After three months, systolic and diastolic blood pressure, measured with the patient standing, was slightly lower (by 2.0 mm Hg) in the amlodipine group, as compared with base-line values and the values in the placebo group ( $P<0.01$  for both comparisons), but the heart rate did not change in either group.

Adverse reactions are shown in Table 4, and those requiring the discontinuation of double-blind therapy are shown in Table 5. Two cardiovascular reactions occurred more frequently in the amlodipine group than in the placebo group: peripheral edema ( $P<0.001$ ) and pulmonary edema ( $P=0.01$ ). In contrast, two cardiovascular reactions occurred less frequently in the amlodipine group: uncontrolled hypertension ( $P=0.03$ ) and symptomatic cardiac ischemia (angina and chest pain). In the patients with ischemic heart disease, the risk of angina or chest pain was lower among those in the amlodipine group (25 percent) than among those in the placebo group (31 percent,  $P=0.07$ ). The frequency of myocardial infarction in the two groups was similar.

**TABLE 3.** EFFECT OF TREATMENT ON MORTALITY, ACCORDING TO PRETREATMENT CHARACTERISTICS.\*

CHARACTERISTIC	PLACEBO (N=582)	AMLODIPINE (N=571)	HAZARD RATIO† (95% CI)
		no. of deaths/total no. of patients	
Age			
>65 yr	141/327	112/305	0.86 (0.67–1.11)
≤65 yr	82/255	78/266	0.84 (0.61–1.15)
Sex			
Male	176/453	152/422	0.92 (0.74–1.15)
Female	47/129	38/149	0.62 (0.40–0.96)
Left ventricular ejection fraction			
>0.20	98/304	82/289	0.87 (0.65–1.17)
≤0.20	125/278	108/282	0.80 (0.62–1.04)
NYHA class			
III	166/471	136/459	0.80 (0.64–1.01)
IV	57/111	53/111	0.93 (0.63–1.36)
Serum sodium concen- tration			
>137 mmol per liter	144/401	125/412	0.84 (0.66–1.08)
≤137 mmol per liter	78/180	65/159	0.85 (0.60–1.18)
History of angina			
Absent	108/265	71/266	0.59 (0.44–0.81)
Present	115/317	119/305	1.09 (0.84–1.42)
History of hypertension			
Absent	104/249	99/259	0.93 (0.70–1.23)
Present	119/333	91/312	0.75 (0.57–0.99)

\*All deaths were included in the analysis, whether they occurred as a fatal primary event or after a nonfatal primary event. None of the interactions between treatment and characteristic were statistically significant, except for the absence or presence of a history of angina. CI denotes confidence interval, and NYHA New York Heart Association. Data were not available on NYHA class for one patient in the amlodipine group and on serum sodium concentration for one patient in the placebo group.

†The hazard ratio is for the risk of death in the amlodipine group as compared with the placebo group.

**TABLE 4. ADVERSE REACTIONS IN THE TWO TREATMENT GROUPS.**

ADVERSE REACTION	PLACEBO	AMLODIPINE
	(N=582)	(N=571)
	no. of patients (%)	
Cardiovascular disorder	435 (75)	437 (77)
Atrial arrhythmia	45 (8)	36 (6)
Bradycardia or atrioventricular block	9 (2)	9 (2)
Chest pain or angina	148 (25)	127 (22)
Hypotension	56 (10)	69 (12)
Uncontrolled hypertension	9 (2)	2 (<1)*
Myocardial infarction	18 (3)	16 (3)
Palpitation	29 (5)	21 (4)
Peripheral edema	103 (18)	155 (27)*
Presyncope or syncope	36 (6)	31 (5)
Pulmonary edema	58 (10)	85 (15)*
Ventricular arrhythmia	42 (7)	43 (8)
Worsening heart failure	240 (41)	239 (42)
Gastrointestinal disorder	172 (30)	149 (26)
Hematopoietic disorder	53 (9)	45 (8)
Liver or biliary disorder	27 (5)	11 (2)*
Metabolic or nutritional disorder	126 (22)	129 (23)
Musculoskeletal disorder	73 (13)	60 (11)
Nervous system disorder	169 (29)	161 (28)
Neoplasm	10 (2)	9 (2)
Psychiatric disorder	93 (16)	99 (17)
Respiratory disorder	257 (44)	236 (41)
Disorder of skin or skin appendages	73 (13)	81 (14)
Disorder of special senses	34 (6)	30 (5)
Urinary disorder	77 (13)	98 (17)

\*P<0.05 for the comparison with the placebo group.

**TABLE 5. REASONS FOR DISCONTINUATION OF STUDY MEDICATION.**

REASON	PLACEBO	AMLODIPINE
	(N=582)	(N=571)
	no. of patients	
Disease progression		
Cardiac transplantation	2	1
Heart block	1	1
Myocardial ischemia	4	4
Stroke	4	1
Ventricular arrhythmia	2	2
Worsening heart failure	32	40
Concurrent illness		
Gastrointestinal disorder	2	0
Neoplastic disorder	2	3
Neurologic or psychiatric disorder	2	1
Renal disorder	0	1
Respiratory disorder	2	2
Unspecified disorder	0	2
Adverse reaction		
Drug reaction	1	1
Edema	2	2
Gastrointestinal symptoms	4	1
Headache, weakness, or rash	3	1
Hypotension or dizziness	6	0
Administrative reason		
Patient's request	17	15
Physician's request	0	2
Other	8	2
Total	94	82

Although pulmonary edema occurred more frequently in the amlodipine group than in the placebo group (Tables 2 and 4), other events reflecting the clinical progression of heart failure (e.g., life-threatening arrhythmias and death) occurred less frequently in the amlodipine group (Table 2). The frequency of worsening heart failure was similar in the two groups (Table 4), as was the frequency of hospitalization for worsening heart failure (36 percent in the amlodipine group and 39 percent in the placebo group).

With respect to noncardiovascular side effects, the amlodipine group had a lower frequency of liver and biliary disorders than the placebo group (P=0.01) but a higher frequency of worsening renal function (7.7 percent vs. 3.6 percent, P=0.002). During the first six months, values for serum bilirubin and liver enzymes were higher in the placebo group (P<0.05), but the two groups had similar values for blood urea nitrogen and serum creatinine.

### DISCUSSION

The present study demonstrates that amlodipine does not adversely affect the natural history of chronic heart failure, even in patients with the most advanced disease. Administration of the drug for 6 to 33 months in patients who had symptoms at rest or on minimal exertion and an average left ventricular ejection fraction of only 21 percent was not associated with an increased frequency of worsening heart failure, myocardial infarction, or life-threatening arrhythmias or an increased risk of hospitalization for serious cardiovascular events. In addition, unlike several other vasodilator drugs,<sup>15</sup> amlodipine did not increase the risk of death. In fact, the mortality rate was 16 percent lower in the amlodipine group than in the placebo group (P=0.07), and worsening angina and uncontrolled hypertension were reported less frequently in the patients treated with amlodipine. Taken together, these observations indicate that amlodipine can be used with relative safety in patients with severe heart failure — an important finding, since angina and hypertension can be difficult to treat in patients with left ventricular dysfunction.<sup>16</sup>

The results with amlodipine differ from those reported in trials of other calcium-channel blockers in patients with chronic heart failure. Short-term treatment with verapamil, nifedipine, and diltiazem has produced clinical deterioration,<sup>10,17-19</sup> and long-term therapy with these drugs has increased the risk of worsening heart failure, myocardial infarction, and death in patients with left ventricular dysfunction.<sup>1,3,4,20</sup> These adverse reactions have been attributed to the propensity of the drugs to depress cardiac contractility and activate endogenous neurohormonal systems,<sup>21</sup> but the importance of these mechanisms remains uncertain, since the deleterious actions may be

minimized by the use of sustained-release formulations or vasoselective agents (e.g., nicardipine, nisoldipine, or felodipine). Neither approach, however, has prevented the development of cardiovascular complications. Immediate-release formulations of nicardipine<sup>22</sup> and nisoldipine<sup>2</sup> have resulted in worsening heart failure, as have sustained-release formulations of verapamil<sup>23</sup> and felodipine.<sup>6</sup>

An intriguing finding of the present study was that amlodipine reduced both mortality from all causes and the combined risk of fatal and nonfatal events in patients with nonischemic dilated cardiomyopathy. Although this benefit was seen only in a subgroup of patients, it is likely that it reflects a true effect of amlodipine, since the randomization procedure was stratified according to the cause of heart failure and a significant difference between the ischemic and nonischemic strata was noted for both the primary and secondary end points of the study. Yet, some caution is warranted, since our a priori expectation was that amlodipine would be more beneficial in patients with ischemic heart disease — a hypothesis that was not confirmed. Furthermore, the mechanism by which amlodipine may prolong survival remains unknown. Nevertheless, other trials of drugs in patients with heart failure have reported a treatment effect confined to those with nonischemic cardiomyopathy,<sup>24,25</sup> suggesting that this condition may be uniquely responsive to pharmacologic interventions.

If amlodipine has favorable effects in patients with heart failure, why was the risk of pulmonary edema higher with the drug than with placebo? Although this finding might suggest that amlodipine can exacerbate heart failure, such a conclusion would be inconsistent with other observations. First, amlodipine was associated with a decreased risk of most manifestations of disease progression (life-threatening arrhythmias and death) (Table 2). Second, the risk of worsening heart failure was similar in the placebo and amlodipine groups (Table 4). Third, pulmonary edema occurred more frequently in the amlodipine group, even among the patients with nonischemic cardiomyopathy, who had the most marked benefits from the drug. These observations suggest that the occurrence of pulmonary edema in patients treated 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<sup>26-28</sup>; 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.<sup>29,30</sup> Fortunately, the risk of pulmonary edema attributable to amlodipine is small (5 percent) (Table 4), so that this risk does not alter our finding that the drug has no overall effect on mor-

bidity and mortality in patients with severe chronic heart failure.

In the present study, the cause of heart failure was determined not by coronary arteriography but by the clinical judgment of the investigators. Hence, it is possible that some patients with silent coronary artery disease were included in the nonischemic stratum and some with angina but normal coronary arteries were included in the ischemic stratum. From a clinical viewpoint, such errors may raise doubts about our finding that amlodipine has a beneficial effect in patients with nonischemic cardiomyopathy. From a statistical viewpoint, however, such misclassifications would be expected to weaken (rather than strengthen) the ability to detect a stratum-specific treatment effect and are thus unlikely to account for the effect we observed. Furthermore, if the benefits of amlodipine in patients with nonischemic disease are confirmed by subsequent studies, our clinical (rather than angiographic) approach will make treatment recommendations readily applicable to most patients.

In conclusion, this trial establishes the safety of amlodipine for the treatment of angina or hypertension in patients with advanced left ventricular dysfunction. Should the drug be used for the treatment of heart failure in patients without these associated cardiovascular conditions? Although amlodipine may reduce the risk of death in patients with nonischemic dilated cardiomyopathy, we believe that such an effect requires confirmation in a second trial. That study, known as PRAISE-2, is now in progress.

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## APPENDIX

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