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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)

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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

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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.

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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