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.2013.05.005

EDITORIAL COMMENT

PRAISE (Prospective Randomized Amlodipine Survival Evaluation) and Criticism*

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Once upon a time, there was a clinical trial of 1,153 patients with severe heart failure (New York Heart Association class IIIB or IV and left ventricular ejection fraction <30%) who were randomized to receive either amlodipine or placebo. Enrolled patients were receiving digoxin and angiotensin-converting enzyme inhibitors; appropriate for the time of the study, beta-blockers were prohibited (1). After a median follow-up of 13.8 months, the incidence of the primary endpoint of all-cause mortality or cardiovascular hospitalization was similar in both groups (amlodipine: 222 of 571 [39%]; placebo: 246 of 582 [42%]; hazards ratio [HR] [95% confidence interval] (CI): 0.91 [0.76 to 1.10]). This neutral effect on the primary composite endpoint was also reported on the most important secondary endpoint: death from all causes (amlodipine: 190 of 571 [33%]; placebo: 223 of 582 [38%]; HR [95% CI]: 0.84 [0.69 to 1.02]) (2). However, further probing of the data exploring multiple subgroups led to a potentially important observation: amlodipine seemed to reduce the risk of experiencing the primary composite endpoint as well as almost cutting in half the risk of death in

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those classified in the nonischemic stratum (HR [95% CI] for mortality: 0.54 [0.37 to 0.79]) but not those in the ischemic group (HR [95% CI]: 1.02 [0.81 to 1.29]; p value for interaction = 0.004). Although resulting from a subgroup analysis with all the known potential pitfalls (3–5), the importance of the endpoint (death) and the striking magnitude of the apparent benefit (between 21% and 63% reduction) if true, could have important public health consequences for this large group of patients with nonischemic cardiomyopathy.

Between the time the results of this trial were presented (at the American College of Cardiology Scientific Sessions in March 1995) and published (in October 1996) (2), the follow-up hypothesis-testing trial had already commenced enrolling patients with nonischemic cardiomyopathy (December 1995). Indeed, the last line in the PRAISE-1 (Prospective Randomized Amlodipine Survival Evaluation-1 study) paper stated "…*That study, known as PRAISE-2, is now in progress.*" The celerity demonstrated by the investigators and the sponsor to test the hypothesis that they generated from a subgroup in the original neutral trial is PRAISEworthy.

This second trial, PRAISE-2 was specifically crafted to test the hypothesis observed in the pre-specified subgroup analysis of a secondary outcome in the original PRAISE study; that is, that amlodipine would reduce the rates of death from all causes in heart failure patients with the same symptom status and left ventricular ejection fraction but now exclusively in those with an etiology attributed to nonischemic cardiomyopathy. PRAISE-2 enrolled 1,654 patients selected to resemble the original PRAISE patients in terms of demographic characteristics and background therapies (including digoxin and angiotensin-converting enzyme inhibitors while discouraging the use of beta-blockers). There was a tightening in the designation of nonischemic etiology by excluding those with angina or any test result suggestive or indicative of myocardial ischemia unless coronary angiography was performed and revealed no disease or nonobstructive disease (coronary stenosis <50%).

PRAISE-2 was an event-driven trial that went to completion until ~260 deaths had occurred in the placebo group. There was no imbalance in baseline characteristics between the randomization arms, and, as designed, the baseline characteristics were similar between the 2 PRAISE trials. After a median follow-up of 33 months, 540 (32.6%) deaths had occurred among all the consenting enrolled patients. Allocation to the amlodipine group did not favorably influence the primary endpoint of all-cause mortality (placebo: 262 of 827 [32%]; amlodipine: 278 of 827 [34%]; HR [95% CI]: 1.09 [0.92 to 1.29], p = 0.3), thus refuting the observation from the subgroup analysis in the initial PRAISE (6).

The PRAISE-1 and PRAISE-2 experience serves as an important reminder to the medical community regarding the difference between hypothesis-generating and practice-changing data. Another prominent example (7) in cardiovascular medicine in which a significant p value for an important irrefutable endpoint such as all-cause mortality from a secondary analysis was not confirmed by a more definitive randomized controlled trial directly testing the

*Editorials published in the *Journal of the American College of Cardiology: Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC: Heart Failure* or the American College of Cardiology.

From the Division of Cardiovascular Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts. Dr. Pfeffer receives honoraria and/or research grants or serves as a consultant for Aastrom, Amgen, Bristol-Myers Squibb, Cerenis, Genzyme, Hamilton Health Sciences, Keryx, Medtronic, Merck, Novartis, Roche, Sanofi-Aven sanofi-aventis, Servier, Teva, University of Oxford, and Xoma. The Brigham and Women's Hospital has patents for the use of inhibitors of the renin-angiotensin system in survivors of myocardial infarction with Novartis and Boehringer Ingelheim. Dr. Pfeffer's shares are irrevocably transferred to charity. Dr. Skali has reported that he has no relationships relevant to the contents of this paper to disclose.

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Table 1 Mortality and Treatment Effect in Hypothesis-Generating Studies and Definitive Trials

Variable	Hypothesis-Generating		Definitive Test	
Trial	PRAISE 1 (nonischemic) Total deaths = 119		PRAISE 2 Total deaths = 540	
Arm	Placebo	Amlodipine	Placebo	Amlodipine
n/N (%)	74/212 (35%)	45/209 (22%)	262/827 (32%)	278/827 (34%)
HR (95% CI)	0.54 (0.37–0.78), p = 0.001		1.09 (0.92–1.29), p = 0.3	
Trial	ELITE 1 Total deaths = 49		ELITE 2 Total deaths = 530	
Arm	Captopril	Losartan	Captopril	Losartan
n/N (%)	32/370 (9%)	17/352 (5%)	250/1,574 (16%)	280/1,578 (18%)
HR (95% CI)	0.46 (0.05–0.69), p = 0.04		1.13 (0.95–1.35), p = 0.2	

CI = confidence interval; HR = hazards ratio; n/N = numbers of deaths/number of patients.

hypothesis generated from the initial study (8) is shown in Table 1. Several authors have previously described potential reasons why findings from a subgroup analysis may not be reliable (3,4,9). These reasons include, among others, lack of prespecification of subgroups, multiple testing (lack of appropriate p value adjustment), and lack of biological plausibility, as well as potential misclassification due to blurred subgroup phenotypes. Although results from a subgroup could be spurious and require confirmation, there are circumstances involving patient safety, in which clinical practice changes without repeat testing. In the Multicenter Diltiazem Postinfarction Trial (10), randomization to receive diltiazem (compared with the placebo group) did not influence the primary endpoint of all-cause mortality in the cohort of 2,466 patients enrolled after a myocardial infarction. However, diltiazem was associated with an increase in the risk of death among the subgroup of patients with pulmonary congestion. When patients were also grouped according to depressed left ventricular function or acute anterior myocardial infarction, a qualitatively similar interaction was again demonstrated, thus reinforcing the finding that diltiazem was to be avoided in post–myocardial infarction patients with these high-risk features: pulmonary congestion, systolic dysfunction, or anterior Q waves. In this example, a subgroup analysis indicating potential harm was sufficient to alter medical practice without the medical community requiring a corroborating trial (11).

We, again, commend the PRAISE-2 investigators for promptly conducting the definitive trial to test the hypothesis generated from the subgroup analysis from the first PRAISE trial. Unfortunately, equally deserved is the criticism regarding the 13-year incubation between the completion of the trial with neutral results (January 2000), the oral presentation (American College of Cardiology Scientific Sessions in March 2000), and the long overdue first publication of the results in this issue of the *Journal* (6). Although standards for conduct and reporting of clinical trials have improved since 2000, the failure to fully vet the results of a clinical trial of human volunteers in a peer-reviewed journal was and remains unacceptable. Selective peer review reporting of good news relative to less favorable results, especially of a therapy on the market for other indications, undermines public trust, regardless of the reason for the delay (12).

A similar issue of tardy publication of nonfavorable outcomes of another therapy for patients with severe heart failure from a different randomized controlled trial was the subject of a recent editorial in this *Journal* by Califf (13). He appropriately reviewed the privileges of conducting human research along with the responsibilities and—indeed—obligations of the sponsors and lead investigators to share with the public the knowledge gained from the consenting subjects in the form of a peer-reviewed publication. The required clinical trial registration (14) was a move to ensure greater awareness and transparency of studies randomizing human subjects with the goal of, among other things, reducing such selective reporting (12,15). However, there is currently no requirement for a prompt and full report of study results. Our institution, as others, currently requires, in the contract with sponsors of randomized controlled trials, that the results be presented and published within a reasonable period, and if the study leadership has not fulfilled this important responsibility, the dataset is to be transferred to other coinvestigators for this purpose. If the investigators and sponsors somehow shirk this important responsibility (which would hopefully be a rare situation), we propose an additional consideration that, as a safeguard to this "obstruction of information," the Data Safety Monitoring Board of the trial be empowered to fulfill this important responsibility to society. Although these situations are less common in cardiovascular medicine than in other fields (12,15), we must remain vigilant to minimize this communication bias. Only then will our once upon a time story conclude with a happily ever after….

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