JACC Vol. 19, No. 6
May 1992:1360–2

EDITORIALS

Vasodilator Therapy and Survival in Chronic Congestive Heart Failure*

MARRICK L. KUKIN, MD, FACC
New York, New York

The treatment of congestive heart failure has evolved considerably over the past 15 years. State of the art therapy utilizes a combination of three classes of medications: digitalis glycosides, diuretic drugs and vasodilators. There is not, as yet, a consensus of opinion on other often utilized medications for heart failure, including anticoagulant drugs, antiarrhythmic agents and beta-adrenergic blocking agents. In contrast, recent data have shown that some medications—oral phosphodiesterase inhibitors (1), some type I antiarrhythmic agents (2) and calcium channel blockers (3)—may actually be detrimental in heart failure.

In terms of the current conventional therapy in chronic heart failure, the clinician has several choices within the vasodilator category. Vasodilation can be achieved by direct-acting drugs that cause arteriolar dilation—hydralazine, for example—or by drugs that work through neurohormonal antagonism with subsequent vasodilation—converting enzyme inhibitors, for example. If the immediate results of vasodilation—decreased filling pressures and increased cardiac output—were the sole goals, one would select the most potent vasodilators to achieve these actions. However, the physician who wants to use vasodilation as a means of decreasing symptoms and increasing survival would choose the drugs not on the basis of immediate hemodynamic results, but on the basis of outcome of randomized, double-blind survival trials in the target population.

Survival trials. Five prospective randomized clinical trials over the past 6 years provide the physician with data concerning morbidity and mortality that can guide a rational approach to choosing appropriate vasodilator therapy. The V-HEFT I trial (4) in 1986 showed that, compared with placebo, the combination of hydralazine and isosorbide dinitrate had a favorable effect on mortality (with a borderline p value of 0.09) in patients in New York Heart Association functional classes II and III. The CONSENSUS trial (5) in 1987 showed a dramatic improvement in 6-month and 1-year survival in patients in functional class IV taking enalapril compared with results in patients taking placebo. After these trials, the next questions focused on the survival benefits of converting enzyme inhibitor therapy in mild and moderate heart failure and on a direct comparison of different vasodilators in matched populations (positive controlled trials). Three new survival trials have answered many questions that remained after the first two survival trials.

The SOLVD treatment trial (6), which is the third double-blind placebo-controlled heart failure survival trial with a vasodilator, found a significant reduction in mortality in patients in functional classes II and III taking enalapril compared with that in patients taking placebo. The V-HEFT II trial (7), using two active therapy arms to test whether direct-acting vasodilators (hydralazine) or vasodilators with neurohormonal antagonism (enalapril) would differentially affect mortality, found an improvement in survival in patients in functional classes II and III randomized to enalapril therapy compared with the group randomized to the combination of hydralazine and isosorbide dinitrate. At the same time, the combination of hydralazine and isosorbide dinitrate improved exercise capacity (oxygen consumption) compared with that in the patients treated with enalapril.

Hydralazine-captopril comparison. The Hy-C trial (8), recently reported in this Journal, although not blinded, is the latest survival trial to complement the previously published data. This trial randomized patients with class III and IV heart failure either to the combination of captopril and isosorbide dinitrate or to the combination of hydralazine and isosorbide dinitrate. Unlike the previous trials, this study was designed and completed at a single center.

This trial carefully tried to randomize patients to therapy that was both tolerable and immediately effective in order to test the effect on survival of actually taking the different drugs. A total of 117 patients with class III and IV heart failure referred to the transplant evaluation unit at the University of California at Los Angeles with an elevated mean pulmonary artery pressure or a depressed cardiac output were randomly assigned to one of the two drug

From the Division of Cardiology, Mount Sinai Medical Center, New York, New York. Dr. Kukin is the Arthur Ross Scholar in Cardiovascular Medicine at The Mount Sinai School of Medicine, New York, New York.

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

Address for reprints: Marrick L. Kukin, MD, Division of Cardiology, Mount Sinai Medical Center, Box 1030, 1 Gustave L. Levy Place, New York, New York 10029.

©1992 by the American College of Cardiology

0735-1097/92/$5.00

groups (combination therapy with captopril and isosorbide dinitrate or with hydralazine and isosorbide dinitrate). The patients received "tailored therapy" (9) in which the hemodynamic values achieved with nitroprusside and intravenous furosemide were then matched by the oral drug regimen assigned. If the assigned drug did not produce "acceptable" hemodynamic status or caused significant side effects, the alternate drug regimen was tried. Of 55 patients initially randomized to treatment with captopril plus isosorbide dinitrate, 22 (40%) crossed over to the hydralazine plus isosorbide dinitrate group. Only 11 (22%) of 49 patients assigned to the combination of hydralazine and isosorbide dinitrate crossed over to the captopril-isosorbide dinitrate regimen (p = NS). The survival data are taken from 104 patients discharged on drug therapy—the 44 patients treated with captopril plus isosorbide (33 plus 11 who crossed over to this regimen) and the 60 patients treated with hydralazine plus isosorbide (38 plus 22 who crossed over to this regimen).

Patients were followed up closely as outpatients. At 1 year, the survival in the captopril-isosorbide group was 81% compared with 51% in the hydralazine-isosorbide group (p = 0.05). By a Cox regression analysis, three variables independently predicted survival: a low pulmonary capillary wedge pressure with vasodilator therapy, serum sodium and captopril therapy.

Study limitations. The results of this trial are consistent with our expectations after the previous survival trials. However, the methodology could have skewed the results because of the crossover design of this trial (8) based on the immediate hemodynamic goals of tailored therapy. Tailoring long-term therapy on the basis of short-term hemodynamic results can limit the use of drugs that have delayed hemodynamic effects, and favor the use of drugs that provide dramatic immediate hemodynamic effects. This bias may be particularly significant with the converting enzyme inhibitors, which may take several weeks to show maximal hemodynamic benefits (10–13).

In this study, 20 of the 22 patients who crossed over from the captopril-isosorbide to the hydralazine-isosorbide regimen could conceivably have received long-term treatment with captopril if tailored therapy had not been the initial goal. Eight of the 20 patients changed regimens because of hypotension with short-term captopril therapy and 12 changed because the systemic vascular resistance could not be lowered to "acceptable" levels. The former group may have received too high an initial dose of captopril, which is a particular problem in patients with marked activation of the renin-angiotensin system because their blood pressure is dependent on renin (14). These patients often require and tolerate a gradual increase in the dose of captopril over several days. If the latter group had continued treatment with the captopril-isosorbide combination for several weeks, they might have shown a delayed (long-term) hemodynamic response to captopril not found in the short term. Of particular significance, this group of patients comprised the sickest patients, as demonstrated by hyponatremia (15). If the serum sodium was <135 mEq/liter in this trial, hemodynamic goals were achieved in only 6 (33%) of the 18 patients receiving the captopril-isosorbide combination compared with 12 (71%) of the 17 patients receiving the hydralazine-isosorbide combination (p = 0.04). Furthermore, among patients whose pulmonary capillary wedge pressure after vasodilator therapy was >16 mm Hg, 1-year survival was 82% in those given captopril compared with only 18% in those given hydralazine (p = 0.01). One can only speculate about long-term or delayed improvement in this hemodynamic variable (and subsequently in survival) in the captopril-treated group.

Tailored therapy and the use of short-term hemodynamic studies to guide the choice of a drug for long-term treatment is based on two assumptions. The first is that tolerance does not develop to the acute hemodynamic effects of the drug. But this assumption is not always true; for example, prazosin produces excellent immediate hemodynamic benefits in patients with heart failure, but these effects are not sustained during long-term treatment (16). Tolerance has been shown to develop during long-term hydralazine therapy (17), whereas captopril therapy has been shown to produce sustained hemodynamic benefit (12).

A second assumption is that the hemodynamic effects of drugs are correlated with their clinical effects. This assumption is also not necessarily valid; certain arterial vasodilators—minoxidil, for example—produce increases in cardiac output but are associated with clinical deterioration rather than clinical improvement (18).

Unfortunately, in the Hy-C study (8), a large number of patients crossed over to the alternate therapy during the initial "tailored" treatment. Such crossover may have biased the data by preselecting "survivors" to be maintained on captopril therapy and placing the most hyponatremic patients (those who could not tolerate large doses of captopril or meet hemodynamic targets) on hydralazine therapy. There are no long-term hemodynamic data to demonstrate continued hemodynamic efficacy (or tolerance) with either of the drug groups. It is possible that the long-term hemodynamic effects of hydralazine or captopril are not comparable with their early effects.

Finally, the data on sudden death must be interpreted with caution. Holter ambulatory electrocardiographic data were obtained in 64 patients and amiodarone therapy was initiated for high grade asymptomatic ventricular arrhythmias. Approximately 66% of patients in this study were taking an antiarrhythmic drug (either a type I agent or amiodarone). However, there were more patients in the captopril-isosorbide group (48%) who were taking the hemodynamically safer and perhaps less proarrhythmic amiodarone than there were in the hydralazine-isosorbide group (38%).

Implications. This is the first survival trial (8) to show the categoric value of converting enzyme inhibitors; in the Hy-C trial, captopril was given, whereas the previous trials used

enalapril. When viewed with the other vasodilator-heart failure studies (with both placebo and positive controls), we now have compelling evidence not only that vasodilators as a class increase survival in heart failure, but that using converting enzyme inhibitors in patients in functional classes II, III and IV improves survival compared with that achieved with either placebo or direct-acting vasodilators. The probable mechanism for this enhanced survival is the neurohormonal antagonism that is pharmacologically achieved with captopril and enalapril. Given this preponderance of clinical, hemodynamic and survival data, the vasodilator of choice in patients with mild, moderate or severe congestive heart failure should be a converting enzyme inhibitor.

References

1. Packer M, Carver JR, Chesebro JH, et al, and the PROMISE Study Investigators and Coordinators. Effect of milrinone on mortality in severe chronic heart failure: The Prospective Randomized Milrinone Survival Evaluation (PROMISE). N Engl J Med 1991;325:1468–75.
2. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989;321:406–12.
3. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. N Engl J Med 1988;319:385–92.
4. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. N Engl J Med 1986;314:1547–52.
5. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study. N Engl J Med 1987;316:1429–35.
6. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. N Engl J Med 1991;325:293–302.
7. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303–10.
8. Fonarow GC, Chelimsky-Fallick C, Stevenson LW, et al. Effect of direct vasodilation with hydralazine versus angiotensin-converting enzyme inhibition with captopril on mortality in advanced heart failure: the Hy-C trial. J Am Coll Cardiol 1992;19:842–50.
9. Stevenson LW, Dracup KA, Tillisch JH. Efficacy of medical therapy tailored for severe congestive heart failure in patients transferred for urgent cardiac transplantation. Am J Cardiol 1989;63:461–4.
10. Massie BM, Kramer BL, Topic N. Lack of relationship between short-term hemodynamic effects of captopril and subsequent clinical responses. Circulation 1984;69:1135–41.
11. Kramer B, Topic N, Massie B. Acute and long-term effects of captopril on exercise cardiac performance and exercise capacity in congestive heart failure. Br J Clin Pharmacol 1982;14:143S–51S.
12. Kramer B, Massie BM, Topic N. Controlled trial of captopril in chronic heart failure: a rest and exercise hemodynamic study. Circulation 1983; 67:807–16.
13. Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. J Am Coll Cardiol 1983;2:755–63.
14. Packer M, Medina N, Yushak M. Relationship between serum sodium concentration and the hemodynamic and clinical responses to converting enzyme inhibition with captopril in severe heart failure. J Am Coll Cardiol 1984;3:1035–43.
15. Lee WH, Packer M. Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe chronic heart failure. Circulation 1986;73:257–67.
16. Packer M, Meller J, Gorlin R, Herman MV. Clinical and hemodynamic tachyphylaxis to prazosin-mediated afterload reduction in severe congestive heart failure. Circulation 1979;59:531–9.
17. Packer M, Meller J, Medina N, Yushak M, Gorlin R. Hemodynamic characterization of tolerance to long-term hydralazine therapy in severe chronic heart failure. N Engl J Med 1982;306:57–62.
18. Franciosa JA, Jordan RA, Wilen MM, Leddy CL. Minoxidil in patients with chronic left heart failure: contrasting hemodynamic and clinical effects in a controlled trial. Circulation 1984;70:63–8.