

Fifteen years of heart failure trials: lessons learned the hard way

Edward K. Kasper

Johns Hopkins Cardiomyopathy and Heart Transplant Service, Johns Hopkins School of Medicine, Baltimore, MD, USA

(Ital Heart J 2000; 1 (Suppl 3): S108-S109)

Address:

Edward K. Kasper, MD

*Johns Hopkins
Cardiomyopathy
and Heart Transplant
Service
Johns Hopkins School
of Medicine
Carnegie 568
Baltimore, MD 21281-6568
USA*

The management of patients with heart failure due to left ventricular systolic dysfunction has markedly changed during the past 15 years. Since 1985, angiotensin-converting enzyme (ACE)-inhibitors and beta-blockers have been shown to reduce mortality. Several medications have also been shown to increase mortality. Combined, these two findings led to the description of novel mechanisms to explain the results.

Vasodilators are not consistently beneficial for the amelioration of symptoms or improvement of survival for patients with heart failure due to systolic dysfunction.

V-HeFT I¹ was the first mortality trial performed in this patient population; 642 men with class II-III chronic heart failure (CHF) were randomized to prazosin, the combination of isosorbide dinitrate plus hydralazine, or placebo. A 25-30% reduction was seen only in the isosorbide dinitrate plus hydralazine combination. Prazosin was no different from placebo. In the PROFILE trial², 2304 patients with class III-IV CHF were randomized to flosequinan versus placebo. Mortality was increased by flosequinan and this resulted in withdrawal of the drug from the US market. Finally, epoprostenol, a pure vasodilator, increased mortality when compared to usual care. We thus have one vasodilator (prazosin) no better than placebo and two vasodilators that increase mortality (flosequinan and epoprostenol). We should understand, therefore, that it matters how you improve hemodynamics and that vasodilation alone may not be effective.

ACE-inhibitors have been shown to produce clinical benefits and improve survival in patients with left ventricular dysfunction.

The story of ACE-inhibitors unfolded dramatically in the 1980s. Multiple stud-

ies demonstrated the utility of these drugs in class I-IV CHF (CONSENSUS, SOLVD)³⁻⁵. ACE-inhibitors are clearly superior to the combination of isosorbide dinitrate plus hydralazine (V-HeFT II)⁶. The proper dose, as defined in ATLAS⁷, turns out to be the highest tolerable dose or upwards of 35 mg per day of lisinopril. This dose reduced the risk of CHF hospitalization by 24% while slightly reducing the risk of death when compared to 2.5 to 5 mg per day. Angiotensin II receptor blockers are better tolerated. To date, they have not been demonstrated to be better than ACE-inhibitors as demonstrated by ELITE II⁸.

Therefore, all patients with left ventricular dysfunction should be on an ACE-inhibitor unless they have been shown to be intolerant or have a contraindication. ACE-inhibitors are favored over the combination of isosorbide dinitrate plus hydralazine as well as angiotensin II receptor blockers.

Positive inotropic agents produce striking short-term benefits but increase mortality in patients with left ventricular dysfunction.

The only positive inotropic agent not shown to increase mortality when used as a chronic medication in this patient population is digoxin. The DIG trial⁹ showed no increase (or decrease) in mortality compared to placebo. It did demonstrate a 28% reduction in hospitalization for CHF in patients on digoxin.

Therefore, low-dose digoxin is used in the chronic management of heart failure in patients with systolic dysfunction. This agent is added to an ACE-inhibitor and a loop diuretic. Other positive inotropic agents have their role in the intensive care unit for the acute management of heart failure. They should be used in the chronic, outpatient

management of heart failure only for palliative care, if at all.

Beta-blockers consistently improve survival, clinical status and left ventricular ejection fraction when added to an ACE-inhibitor in class II-III CHF due to systolic dysfunction.

Three large clinical trials using carvedilol, long-acting metoprolol, and bisoprolol have demonstrated a survival advantage to being on a beta-blocker. The US Carvedilol Trial¹⁰, MERIT-HF¹¹ and CIBIS II¹² each demonstrated a survival advantage to being on a beta-blocker at high dose for a long period of time. The doses used in these trials were high and beta-blockers were almost always added to an ACE-inhibitor.

All stable, euvolemic patients with class II-III CHF due to systolic dysfunction should, therefore, be on a beta-blocker unless they are intolerant or have a contraindication. ACE-inhibitors and beta-blockers should be increased to the maximally tolerated dose¹³. Both are started at a low dose with the dose increased every week. Usually, the ACE-inhibitor is maximized first and then the beta-blocker is started.

Spironolactone is the only diuretic shown to improve survival in patients with severe CHF due to systolic dysfunction.

The RALES trial¹⁴ demonstrated a survival advantage to being on 25 mg per day of spironolactone as compared to placebo in patients with class IV CHF.

In summary, ACE-inhibitors have become the foundation of the management of patients with systolic dysfunction. They should be used at the maximally tolerated dose. Alternative medications are angiotensin II receptor blockers or the less well tolerated combination of isosorbide dinitrate plus hydralazine. Loop diuretics are used to control edema and the addition of spironolactone in the sickest patients is likely warranted. Digoxin is used in patients who remain symptomatic on an ACE-inhibitor and a loop diuretic. Beta-blockers should be added to the regimen of all patients with class II-III CHF and left ventricular dysfunction. They are started at a low dose with the goal of increasing the dose as tolerated.

We have learned much about the management of left ventricular systolic dysfunction in the past 15 years. Our concepts of pathophysiology have evolved from a purely hemodynamic explanation to an understanding of the cellular and molecular mechanisms that play a critical role in the development and progression of this

disorder. The next 15 years will certainly highlight important discoveries at both the bench and the bedside.

References

1. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. *N Engl J Med* 1986; 314: 1547-52.
2. Packer M, Rouleau J, Swedberg K, et al. Effect of flosequinan on survival in chronic heart failure: preliminary results of the PROFILE study. (abstr) *Circulation* 1993; 88: I-301.
3. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987; 316: 1429-35.
4. The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991; 325: 293-302.
5. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992; 327: 685-91.
6. 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.
7. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. *Circulation* 1999; 100: 2312-8.
8. 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.
9. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997; 336: 525-33.
10. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. US Carvedilol Heart Failure Study Group. *N Engl J Med* 1996; 334: 1349-55.
11. The MERIT-HF Study Group. Effect of metoprolol CX/XL in chronic heart failure: Metoprolol CX/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; 353: 2001-7.
12. CIBIS II Investigators. The Cardiac Insufficiency Bisoprolol Study II (CIBIS II): a randomised trial. *Lancet* 1999; 353: 9-13.
13. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *Circulation* 1996; 94: 2807-16.
14. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; 341: 709-17.