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 I 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 trial, 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. 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 studies 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 ATLAS\(^7\), 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 II\(^8\).

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 trial\(^9\) 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 setting.

Address:
Edward K. Kasper, MD
Johns Hopkins Cardiomyopathy and Heart Transplant Service, Johns Hopkins School of Medicine, Baltimore, MD, USA

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 dos-
es 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 be-
ta-blocker unless they are intolerant or have a con-
traindication. 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 advan-
tage to being on 25 mg per day of spironolactone as com-
pared to placebo in patients with class IV CHF.

In summary, ACE-inhibitors have become the foun-
dation of the management of patients with systolic dys-
function. They should be used at the maximally toler-
ated dose. Alternative medications are angiotensin II re-
ceptor blockers or the less well tolerated combination
of isosorbide dinitrate plus hydralazine. Loop diuretics
are used to control edema and the addition of spirono-
lactone 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 crit-
ical role in the development and progression of this
disorder. The next 15 years will certainly highlight im-
portant discoveries at both the bench and the bedside.

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