Halting the progression of heart failure: Finding the optimal combination therapy

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ABSTRACT

Finding the optimal combination of drugs in the correct dosages, which requires careful monitoring over time, is key to slowing the disease process and prolonging life. For most patients, treating heart failure involves correcting underlying left ventricular dysfunction, thereby slowing the remodeling process.

Heart failure patients should probably receive at most two neurohormonal blockers

WITH NEW FINDINGS about the nature of heart failure, physicians have been told that they need to treat their heart failure patients with a panoply of drugs—angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, angiotensin II receptor blockers, and aldosterone antagonists. Thus, one of the biggest challenges facing physicians treating heart failure patients is how to find the optimal combination of these agents that can slow the progression of the disease while minimizing side effects.

THE NEW VIEW OF HEART FAILURE

Understanding of the natural history of heart failure has evolved dramatically in the last decade and resulted in much more efficient therapy. Formerly, the principal goal was to control the hemodynamic derangements and the resulting symptoms. Now, new drugs and combinations of drugs aim to slow the progression of left ventricular dysfunction and lessen the resulting injurious neurohormonal cascade.

Heart failure affects 4.6 million people in the United States, resulting in nearly 1 million hospitalizations and 260,000 deaths each year.[1] It carries a grim prognosis. Patients with asymptomatic systolic dysfunction on echocardiography or multiple gated acquisition scanning have a 20% risk of dying of heart failure within 5 years.[1] Once a patient has symptoms at rest, ie, New York Heart Association (NYHA) class IV heart failure, the 1-year mortality rate climbs to 50%.

DIASTOLIC VS SYSTOLIC

Heart failure is classified as either diastolic or systolic. However, the signs and symptoms of diastolic failure may be virtually indistinguishable from those of systolic failure.

The two can be differentiated only on the basis of ejection fraction. An ejection fraction of 40% or less generally is diagnostic of systolic dysfunction, while an ejection fraction greater than 60% is characteristic of diastolic dysfunction. The entities can occur simultaneously, although the superimposed diastolic dysfunction may go unrecognized.

Because there is no trial-based evidence of the best way to treat diastolic dysfunction, this article focuses on the natural history and treatment of systolic disease.

THE NEUROHORMONAL MILIEU: WHAT GOES WRONG?

Neurohormonal derangements are responsible for the progression of heart failure.[2] Left ventricular dysfunction results in decreased car-

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diac efficiency and reduced blood pressure, activating baroreceptors that control the renin-angiotensin system and the sympathetic nervous system.

Initially, this neurohormonal reaction is an adaptive process meant to protect against the hemodynamic abnormalities that occur in heart failure. However, long-term elevation of these neurohormones is maladaptive and harms the myocardium.[3] Elevated levels of renin, angiotensin, and norepinephrine are associated with high 5-year mortality rates.

HYPERTENSION IS A MAJOR RISK FACTOR

Risk factors for heart failure include hypertension, diabetes, left ventricular hypertrophy, valvular heart disease, and ischemic disease. Because of its high prevalence in the general population, hypertension is the greatest population-attributable risk factor after adjustment for all other factors[4,5]; it is a significant factor in 40% of men and 60% of women with heart failure. In Framingham patients,[6] hypertension preceded the development of heart failure in 91% of cases.

Heart failure is a preventable illness as evidenced in studies where blood pressure was maintained at less than 140/90 mm Hg, or a lower goal if tolerated. No study has produced striking evidence that one class or agent is more effective than another in preventing heart failure. Once heart failure occurs, blood pressure should be maintained at less than 130/85 mm Hg.

In the Antihypertensive and Lipid-Lowering Treatment To Prevent Heart Attack Trial (ALLHAT),[7] the method used to lower blood pressure affected the risk for the development of heart failure. Those individuals randomized to doxazosin had a doubling in the risk for heart failure compared to those on the diuretic chlorthalidone. Accordingly, alpha-blocker therapy should not be used as monotherapy in those with hypertension.

TARGETED TREATMENT OF HEART FAILURE

The best-studied and most-prescribed neurohormonal blockers are ACE inhibitors, beta-blockers, and, more recently, angiotensin receptor blockers (ARBs). The aldosterone antagonist spironolactone also is commonly used, although its role in the treatment of heart failure is less clear. These drugs have been shown to be well tolerated when dosages are closely monitored and adjusted as needed.

ACE inhibitors

ACE inhibitors work by blocking conversion of angiotensin I to angiotensin II, which results in lower blood pressure, increased peripheral vasodilation, and reduced afterload. These agents may inhibit left ventricular remodeling, with a reduction in aldosterone that results in less fluid retention. ACE inhibitors also help regulate the sympathetic nervous system, which results in decreased serum levels of norepinephrine.

ACE inhibitors have been convincingly shown to reduce mortality rates, prolong life, and reduce the incidence of pump failure and recurrent myocardial infarction in patients with heart failure. For example:

- The Studies of Left Ventricular Dysfunction (SOLVD),[8] in 2,569 patients with class II, III, or IV heart failure, demonstrated a 16% reduction in all-cause mortality with use of the ACE inhibitor enalapril vs placebo.
- The Vasodilator-Heart Failure Trial II (V-HeFT II),[9] in 804 patients with class II, III, or IV heart failure, found that enalapril reduced the all-cause mortality rate by 28% vs a combination of the vasodilators hydralazine hydrochloride and isosorbide dinitrate.

Only 15% to 25% of eligible patients receive a beta-blocker

Despite these positive results, only 40% to 70% of patients with heart failure who should be receiving an ACE inhibitor are actually receiving one.

Dosage. Patients who do receive these agents may not be getting adequate doses.[10] ACE inhibitors should be started at very low dosages (eg, captopril 6.25 mg two or three times daily, enalapril 2.5 mg daily, or lisinopril 2.5 or 5 mg daily), but these dosages should be doubled every 3 to 7 days as tolerated. Most patients tolerate long-term ACE inhibitor therapy, and daily doses of up to 150 mg of captopril, 20 mg of enalapril, or 20 to 40 mg of lisinopril are often prescribed.

Contraindications. ACE inhibitors should not be used in patients with hypotension, renal failure, hyperkalemia, renal artery stenosis, or past angioedema.

Beta-blockers

Beta-blockers have been shown to confer a survival advantage in patients with mild to moderate heart failure in several trials where they have been added to ACE inhibitor therapy.

- In the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II),[11] in 2,647 patients with NYHA class III or IV heart failure, bisoprolol resulted in a 34% reduction in all-cause mortality vs placebo.
- The Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF),[12] in 3,991 patients with NYHA class III or IV heart failure, showed a 34% reduction in all-cause mortality with metoprolol CR/XL vs placebo.
- The US Carvedilol Heart Failure Study,[13] in 1,094 patients with NYHA class II, III, or IV heart failure, demonstrated a 65% reduction in all-cause mortality with carvedilol vs placebo.
- The Carvedilol Prospective Randomized Cumulative Survival study (COPERNICUS),[14] in patients with NYHA class IV heart failure, recently was ended early because carvedilol reduced mortality rates by 35%.

While all ACE inhibitors appear approximately equally effective, this does not seem to be true of beta-blockers. Outcome may be tied to use of a particular agent and dosing strategy. Patients should not receive a generic beta-blocker simply because it is in their health maintenance organization's formulary. Each drug should be given in the dosage and formulation that have been shown in studies to improve outcome.

Unfortunately, even though beta-blockers confer a trial-proven benefit in patients receiving ACE inhibitor therapy, only 15% to 25% of heart failure patients under the care of a cardiologist receive beta-blockers. This is probably the result of the association of beta-blockers with left ventricular depression with short-term use. However, beta-blockers are now recommended for all patients with symptomatic mild to moderate heart failure who have no contraindications to them.

Dosage. Start beta-blockers at the lowest approved dosage (eg, 3.125 mg carvedilol twice daily). If tolerated, this dose can be doubled every 2 to 4 weeks. It is unclear whether low doses of beta-blockers are as beneficial as high doses because all trial doses were force-titrated, but studies have shown that patients can tolerate fairly high doses. For example, doses up to 200 mg of metoprolol CR/XL were used in the MERIT-HF. Of the patients in this trial, 66% tolerated 200 mg and 87% tolerated 100 mg.

Contraindications. Do not start beta-blockers in patients who have significant chronic obstructive pulmonary disease, reactive airway disease that has required an emergency department visit, a forced expiratory volume in 1 second (FEV_1) less than 2 L, or a resting heart rate less than 68.

Angiotensin II receptor blockers

Unlike ACE inhibitors, ARBs do not inhibit the breakdown of bradykinin. However, they do block angiotensin II at the receptor level in all pathways. ARBs selectively block the AT_1 receptor, thereby inhibiting muscle cell growth and promoting vasodilation. ARBs may also have a positive effect on left ventricular remodeling.

Studies of the benefits of ARBs in the treatment of heart failure have been conflicting, however, and no ARBs are currently indicated in treating heart failure.

- The year-long Evaluation of Losartan in the Elderly trial (ELITE)[15] assigned 722 patients with NYHA class II, III, or IV heart failure to receive either 50 mg of the ACE inhibitor captopril three times daily or 50 mg of the ARB losartan potassium once daily. There was no difference between the two groups in the study's primary end point of renal function. However, rates of death, hospitalization for heart failure, or both were 32% less in patients who received losartan. In addition, about three fourths of the patients tolerated the maximum dose of losartan.
- The follow-up ELITE II study,[16] in 3,152 patients, did not confirm the findings of the first study. In this superiority trial, the mortality rates (the primary end point) of the two groups were comparable: 15.9% with captopril and 17.7% with losartan. Accordingly, there was no evidence of superiority in using losartan.
- In the Valsartan Heart Failure Trial (Val-HeFT),[17] in 5,010 patients with NYHA class II, III, or IV heart failure, the addition of

In Framingham, high blood pressure preceded heart failure in 91% of cases

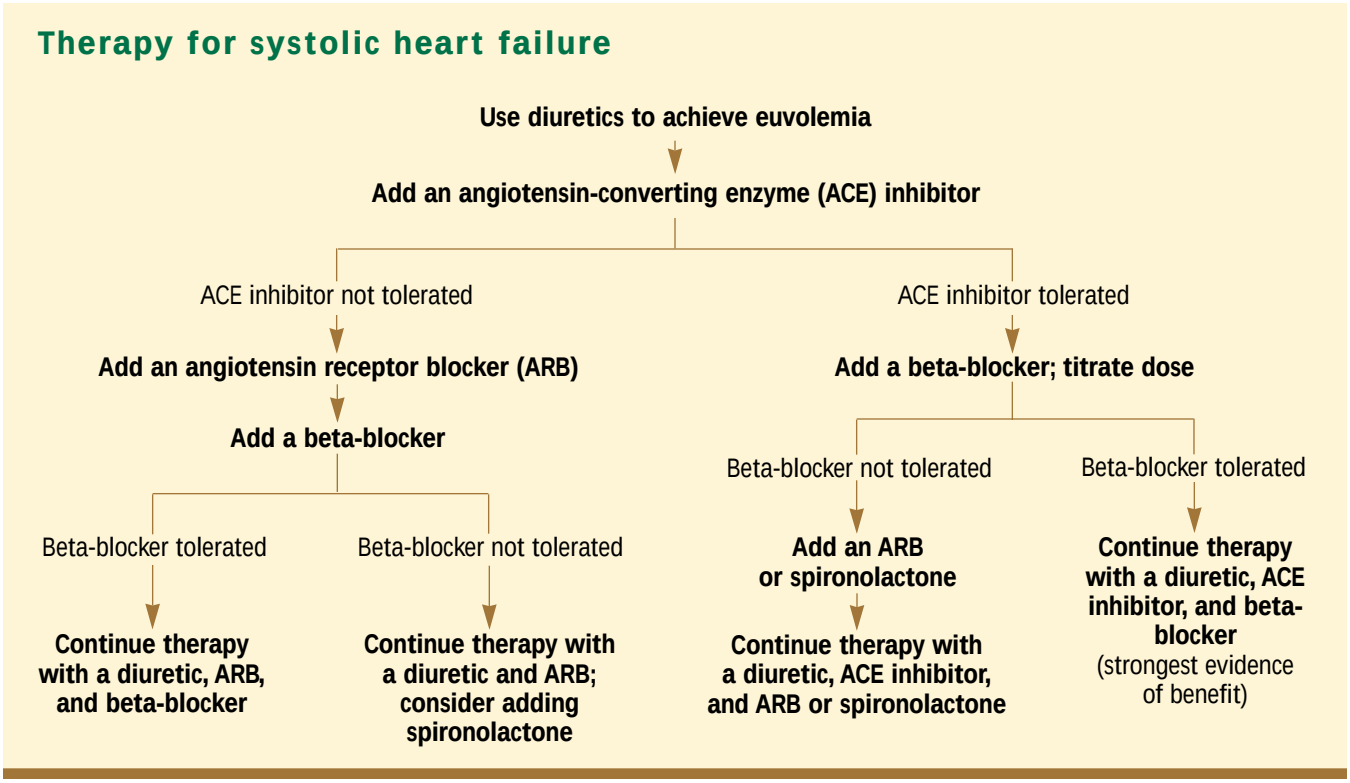

FIGURE 1

Reserve ARBs for patients who cannot tolerate ACE inhibitors

the ARB valsartan to a standard regimen of ACE inhibitors (93%), beta-blockers (35%), diuretics (86%), and digoxin (67%) did not significantly affect the all-cause mortality rate. However, it did reduce hospitalizations for heart failure by 27.5% and morbidity and mortality rates by 13.2% (a primary end point).

In addition, valsartan reduced the risk of morbidity and mortality by 45% in the 7% of patients who could not tolerate an ACE inhibitor. This finding provided evidence for reserving ARBs for patients who cannot tolerate an ACE inhibitor.

Aldosterone antagonists

The role of spironolactone in the treatment of heart failure is unclear, although its use with ACE inhibitors would seem to be bolstered by the Randomized Aldactone Evaluation Study (RALES).[18] This study, in 1,663 patients with NYHA class III or IV heart failure, found that spironolactone, added to a standard background regimen of an ACE inhibitor with or without digoxin and diuretics, reduced the mortality rate by 30% and hospitalization for heart failure by 35%. Most patients in the spironolactone group received 25 mg daily.

Because only 11% of the patients were also receiving a beta-blocker, spironolactone's role in combination with beta-blockade is unclear.

The right combination

The Val-HeFT suggested that patients should receive at most two neurohormonal blockers. This was demonstrated in patients who received valsartan in addition to background therapy with a beta-blocker plus an ACE inhibitor. Those patients did not do as well as patients who had been receiving *either* a beta-blocker or an ACE inhibitor when valsartan was added to the regimen.

Thus, the evidence suggests that patients should start with a loop diuretic, when there is volume overload, plus an ACE inhibitor (FIGURE 1). If the ACE inhibitor is well tolerated and euvolemia maintained, a beta-blocker can be added. Only if the patient does not tolerate the ACE inhibitor should an ARB be started. The initial dosage of valsartan is 40 mg twice daily, adjusted upward at 2-week intervals to 80 and then 160 mg, all given twice daily.

Patients who cannot tolerate beta-blockers may receive either an ARB or spironolactone in addition to an ACE inhibitor.

ADJUNCTIVE HEART FAILURE THERAPY

Some drugs, once used as monotherapy, are now always used in combination with neurohormonal blockers.

Digoxin and diuretics

Digoxin may improve exercise capacity and reduce heart failure hospitalizations, but it does not appear to improve prognosis. Digoxin, which is used in patients with persistent symptoms of heart failure and rapid atrial fibrillation, remains important even though lower doses are needed when used in the new drug combinations. Most patients begin with 0.25 mg daily, or 0.125 mg in elderly patients or in those with renal impairment.

Patients receiving diuretics need to weigh themselves daily and to contact their physicians and increase the dose of diuretic if they gain more than 2 to 3 pounds.

Calcium channel blockers

Many physicians prescribed calcium channel blockers before it was understood that drugs belonging to the nondihydropyridine subset are contraindicated in treatment of systolic dysfunction. (The dihydropyridines amlodipine or felodipine can be used in cases of angina or poorly controlled hypertension.) Calcium channel blockers as a class have been eclipsed by the neurohormonal blockers, which improve outcome and also relieve angina and improve blood pressure control.

Only 40% to 70% of eligible patients receive an ACE inhibitor

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