Contemporary Medical Options for Treating Patients With Heart Failure

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Case study: A 72-year-old woman presented with shortness of breath. Three months earlier, she had begun to notice dyspnea on exertion. This dyspnea progressed to the point that she noted dyspnea at rest in the 24 hours before presentation. She had a history of long-standing mild hypertension, treated with a calcium-channel antagonist, and type 2 diabetes. She denied chest pain, lightheadedness, and abdominal or ankle swelling, although she believed that she had gained between 5 and 10 pounds in recent weeks. On examination, she had a blood pressure of 150/90 mm Hg, a regular pulse at a rate of 90 min⁻¹, jugular venous pressure of about 8 cm water, faint bibasilar crackles, a prominent and displaced apical impulse, and a summation gallop, with no murmurs, no organomegaly, or ascites, but with 1+ ankle edema. Laboratory findings were notable for a creatinine level of 2.0 mg/dL, a random blood sugar level of 220 mg/dL, and proteinuria (protein:creatinine=400 mg/g). Her ECG showed sinus rhythm, left atrial enlargement, left ventricular hypertrophy (LVH), Q waves in the inferior leads, and inferolateral ST- and T-wave changes. The ECG findings were unchanged, except for a heart rate that had increased from a tracing taken 6 months earlier. Her chest x-ray showed a mildly enlarged cardiac silhouette and questionable evidence of pulmonary venous congestion. An echocardiogram showed a moderately dilated left ventricle with increased wall thickness, inferobasilar akinesis, and an ejection fraction estimated between 30% and 35%.

General Overview of Management
Our patient presented with signs and symptoms of heart failure. Her age was slightly below the average of patients hospitalized with heart failure.¹ She manifested each of the 3 principal factors linked to increased risk of developing heart failure, which are hypertension, ischemic heart disease, and diabetes.²

As we begin to treat our patient, we should also plan to evaluate the severity of her coronary disease and its potential for revascularization.³,⁴ Once her condition is stabilized, provocative testing should be performed to map the viability of myocardial segments and identify inducible ischemia. Depending on the results, we should have a low threshold to perform coronary angiography.

Technically, our patient’s disease falls into the category of systolic dysfunction, or heart failure associated with ventricular dilatation, providing us with the luxury of being able to apply evidence derived from the principal clinical trials in heart failure. However, she has a mixed picture, and as we prescribe treatment, we might consider whether we would change anything if her ejection fraction were a few percentage points higher, as it might well be were it objectively calculated. Additional specific goals of treatment will be to bring her blood pressure and diabetes under optimal control. On the basis of current guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-6),⁵ the target blood pressure should be <130/85 mm Hg.

Specific Drug Recommendations
Recommendations for specific drug treatments are detailed in the published clinical practice guidelines for patients with heart failure (see the Figure).⁶,⁷ Because she shows evidence of volume overload, diuretics will represent an important early component of treatment, and her acute exacerbation should push us toward initial use of a loop diuretic instead of a thiazide. An angiotensin-converting enzyme (ACE) inhibitor, however, should be initiated early, before excessive diuresis. Although we should start slowly, perhaps with a small dose of a shorter-acting agent like captopril, we should...
Drug management for patients with heart failure, based on randomized, controlled trials in patients with left ventricular dilatation and reduced ejection fraction. not be deterred by a slight further rise in creatinine, which is an expected pharmacological effect of this class of agents. Indeed, the results of the first Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS-I) suggest that most patients with heart failure will experience a 10% to 15% rise in creatinine after starting an ACE inhibitor; however, in 65% of the patients, the creatinine will stabilize in 2 to 4 weeks. Although firm guidelines for discontinuing ACE inhibitors do not exist, it is prudent to stop ACE inhibitors or reduce the dose when the creatinine rises 30% above baseline values and/or the serum potassium exceeds 5.0 mEq/L.

At this time, ACE inhibitors remain a mainstay of treatment. Angiotensin-receptor blockers (ARBs), however, are clearly better tolerated than are ACE inhibitors, producing a far smaller incidence of cough or angioedema. It should not be expected that renal insufficiency, hypotension, or hyperkalemia will occur less frequently with ARBs compared with ACE inhibitors. Because of ethical concerns, it has been difficult to investigate the beneficial effects of ARBs compared with placebo in the absence of ACE inhibitors in patients with heart failure and reduced ejection fraction. Despite this limitation, recent trials support a significant benefit of ARBs.

The second Evaluation of Losartan in the Elderly Study (ELITE-2) showed similar rates of mortality and morbidity for losartan (target dose 50 mg/d) and captopril (50 mg three times daily), although the study was not powered for equivalence. The Valsartan Heart Failure Trial (Val-HeFT) showed significant reduction in a combined morbidity-mortality end point (driven entirely by a decreased frequency of heart failure-related hospitalization), with high-dose valsartan (target dose 160 mg twice daily) compared with placebo, in addition to existing treatment. This effect was particularly striking in the 7% of the population not receiving ACE inhibitors because of intolerance; there was an adverse trend when valsartan was added to the combination of an ACE inhibitor and β-blocker. On the basis of the extensive body of placebo-controlled data, ACE inhibitors remain the first-line treatment of choice. ARBs should be prescribed in patients intolerant of ACE inhibitors because of cough or angioedema. If renal insufficiency or hyperkalemia prove limiting factors for treatment, the combination of hydralazine and nitrates represents an alternative.

Once our patient’s condition has stabilized and her volume status has normalized, we should initiate a β-blocker. Evidence supporting the use of β-blockers for patients with reduced ejection fraction (LV dilatation) now includes a broad spectrum of patients extending from those who are asymptomatic to a subset of those who are symptomatic at rest. Patients who manifest overt volume overload and those who have required intravenous inotropic or vasodilator treatment within the previous 4 days have been excluded from study. It is likely that a far greater proportion of patients with heart failure can tolerate and will benefit from β-blockers than are presently being treated with these agents. The 3 β-blockers with clinical trial evidence for improved morbidity and mortality in patients with heart failure are carvedilol, long-acting metoprolol, and bisoprolol. There is no apparent decline in either safety or efficacy when β-blockers are given to diabetics with heart failure. We should attempt to titrate the patient’s dose of β-blocker upward over a number of weeks until we either reach target doses or are limited by adverse effects, such as bradycardia, hypotension, or bronchospasm.

Additional treatment options for our patient are digoxin and spironolactone. The Digoxin Investigators Group (DIG) trial showed that digoxin reduced the number of patients hospitalized with heart failure, although digoxin was not found to reduce mortality. Of interest is the fact that the magnitude of this effect seemed comparable in patients with low and preserved ejection fractions, although the latter group did not contain enough patients to draw a definitive conclusion. We should have a low threshold for adding digoxin to our patient’s regimen if she remains symptomatic despite an ACE inhibitor, a β-blocker, and a diuretic.

In the Randomized Aldactone Evaluation Study (RALES), spironolactone was found to reduce mortality compared with placebo when added to ACE inhibitors in patients with low ejection fractions and severe symptoms of heart failure. Only a small percentage of patients in this study were receiving β-blockers, so the additive effect of spironolactone to the combination of ACE inhibitors and β-blockers is unknown. Ongoing trials are attempting to confirm these observations with newer generation aldosterone antagonists and to extend these results to healthier populations and to those receiving β-blockers. At this point, we should avoid addition of spironolactone, particularly because our patient has reduced renal function.

Heart Failure With Preserved Ejection Fraction (Nondilated Left Ventricle) What would we do differently if our patient’s ejection fraction were estimated to be just above 40% instead of 30% to 35%? Under these circumstances, our patient would not fit into the entry criteria for most of the major trials of patients with heart failure. Which drugs would still be beneficial? Certainly diuretics are useful for volume management in patients with heart failure, regardless of ejection fraction. In patients with smaller ventricular cavities and greater degrees of concentric LV hypertrophy, we would have to monitor diuretic effects even more carefully, because such patients are particularly sensitive to excessive preload reduction.
Beyond diuretics, if our patient had a more normal ejection fraction, a number of the same drug classes are still likely to be beneficial. For patients with atherosclerotic disease, or those with 2 cardiovascular risk factors, including diabetes, we may be guided by results of the Heart Outcomes Prevention Evaluation (HOPE) trial, which showed a reduction in a variety of cardiovascular end points with the ACE inhibitor ramipril. For patients with type 2 diabetes, abnormal renal function, and proteinuria, we might take guidance from the 2 recent studies that showed reduction in the progression of renal dysfunction with the ARBs losartan and irbesartan, respectively. The recently reported Losartan Intervention For Endpoint reduction in hypertension study (LIFE) showed a reduction in cardiovascular end points with losartan when compared with atenolol in patients with hypertension and electrocardiographic evidence of LVH. Although patients with heart failure generally were excluded from these trials, treatment with either an ACE inhibitor or an ARB should be strongly considered and would be an effective approach to treating our patient’s hypertension. Given her prior myocardial infarction, a ß-blocker is indicated. Even without this prior event, there would be strong rationale for use of a ß-blocker, which would slow her heart rate, prolong diastolic filling (a key goal in patients with heart failure and concentric LVH), and help treat her hypertension.

Conclusion

Our patient illustrates the important point that on the basis of existing clinical trial evidence and a rational approach to the underlying pathophysiology, ß-blockers and either ACE inhibitors or ARBs are justified, regardless of ejection fraction or the presence of ventricular dilatation) in many or most patients with heart failure (Figure).

Our patient benefits from a wealth of information that has been derived from recent clinical trials. In the coming years, ongoing clinical trials will further clarify the optimal role of many of the existing treatments, as well as others that are currently under investigation, and, we hope, will identify specific subsets of patients who will benefit from particular modes of treatment.

References

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