

Congestive Heart Failure: Guidelines for the Primary Care Physician

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Abstract

Heart failure is a common medical condition affecting nearly 5 million people each year in the United States, of whom 500,000 are newly diagnosed. The impact of this disease on society and the health care system is immense. Inpatient and outpatient costs are approximately \$40 billion annually, almost \$500 million of which is spent on heart failure medications alone. Beyond the problem of financial costs, however, it is imperative for us as health care professionals to improve our ability to prevent disease progression, decrease morbidity and mortality, and optimize patients' quality of life.

The use of a broad spectrum of treatments is reviewed in the context of a patient case study. Primary data justifying the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, digoxin, as well as beta blockers and spironolactone, is reviewed, with special reference to the stage of heart failure.

Key Words: Congestive heart failure, heart failure, treatment, guidelines, case study.

Background

HEART FAILURE (HF) is a common medical condition affecting nearly 5 million Americans each year in the United States, of whom 500,000 are newly diagnosed (1). The impact of this disease on society and the health care system is immense. Inpatient and outpatient costs are approximately \$40 billion annually, almost \$500 million of which is spent on heart failure medications alone (2). Beyond the problem of financial costs, however, it is imperative for us as health care professionals to improve our ability

to prevent disease progression, decrease morbidity and mortality, and optimize patients' quality of life. The data and guidelines presented here are intended to assist in realizing these goals.

Heart failure affects 1.5–2.0% of the total US population, but the prevalence increases to 6–10% for Americans over the age of 65 (3–6). It is estimated that as many as 20 million people with clinically silent cardiac impairment will probably develop symptoms of HF in the next 1–5 years. Heart failure is the leading cause of hospitalization in the US, and approximately 80% of hospitalized patients with HF are over 65 years old (3–6).

The clinical syndrome of heart failure arises from the heart's inability to fill/relax and/or eject blood from the ventricle. The inability of the ventricle to fill with blood, due to a problem with ventricular relaxation, is referred to as diastolic dysfunction. This definition of diastolic dysfunction is based upon an elevated end-diastolic pressure in an otherwise normal ventricle. The inability of the ventricle to empty/eject blood is referred to as systolic dysfunction, typically defined as an ejection fraction $\leq 45\%$. Left ventricular dysfunction classically presents as pulmonary congestion (rales), an S3 gallop, dyspnea on exertion, shortness of

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Dr. Baran has given six sponsored lectures in the past two years for Glaxo Smith Kline, which markets carvedilol. He received an honorarium for each lecture. The total received did not exceed the amount allowed by the policy of The Mount Sinai School of Medicine.

breath, paroxysmal nocturnal dyspnea, and/or orthopnea. It is important to note that the absence of rales does not rule out pulmonary venous congestion or left-sided HF, since patients with chronic HF can have specific adaptive compensatory mechanisms (7). If the right side of the heart is involved, patients may manifest signs and symptoms such as jugular venous distension, a pulsatile liver, and/or peripheral edema. A recent article evaluated the prognostic importance of elevated jugular venous pressure and a third heart sound in those patients with heart failure (8). The database was from the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial (9). In this analysis, elevated jugular venous pressure was associated with an increased risk of hospitalization for HF and death from HF. The presence of a third heart sound was associated with a similarly increased risk of the previously mentioned outcomes (9). There is a wide spectrum of disease that can cause ventricular dysfunction. While two-thirds of patients have HF from ischemic heart disease, others have identifiable causes such as hypertension, valvular disease, thyroid disease, alcohol use, myocarditis, sepsis, anemia, and nonischemic cardiomyopathy. A small percentage of people will have no identifiable cause for ventricular dysfunction (idiopathic dilated cardiomyopathy) (10). "Ventricular dysfunction" and "cardiomyopathy" refer only to the mechanism of dysfunction; the phrase "heart failure," as it will be used in this article, refers to the specific syndrome of signs and symptoms.

Symptomatic heart failure is described by functional limitation, using a New York Heart Association (NYHA) classification system. "NYHA class I" refers to patients who have no symptoms at any level of exertion. Normal physical activity does not cause them undue fatigue, or dyspnea, but such patients (as well as the patients in the other functional classes) have ventricular dysfunction. NYHA functional class II patients have symptoms with ordinary exertion, while class III patients have symptoms with less-than-ordinary exertion, and class IV patients have symptoms at rest. A simple rule to differentiate class II heart failure from class III heart failure is a "rule of 2's." In general, NYHA functional class II patients can walk two blocks and/or climb 2 flights of stairs without dyspnea, but class III or IV heart failure patients cannot. The system has several flaws: (a) inter-observer variability; (b) the inability to detect small changes in clinical status; and (c)

the implicit assumption that all symptoms are secondary to heart failure.

Despite its flaws, the NYHA classification is important for choosing treatments, as well as predicting prognosis. A common misconception is that ejection fraction is the greatest predictor of outcome. For patients with a low NYHA class (such as class I), the ejection fraction may help estimate survival. However, at ejection fractions less than 25%, the predictive value diminishes. The NYHA classification is one of the best predictors of survival. Only 50% of patients remain alive 5 years after the diagnosis of heart failure, and those with severe symptoms (NYHA functional class III or IV) have a 1-year survival rate of only 40% (1, 2, 11).

Medical Therapies

This article will explore the rationale for therapies chosen for a patient with chronic heart failure. At times, we will touch upon important clinical "pearls" for managing these patients in an outpatient setting.

The treatment of heart failure begins with an extensive and complete evaluation of the patient. An initial visit should begin with a history and physical examination, to establish the etiology of ventricular dysfunction. One should inquire about a history of hypertension; diabetes; hyperlipidemia; coronary, valvular, or peripheral vascular disease; rheumatic fever; chest irradiation; exposure to cardiotoxic agents; and recent or current pregnancy. The practitioner should also inquire about the signs and symptoms of heart failure. Some baseline studies are important for guiding therapy and determining the etiology of ventricular dysfunction. These include, but are not limited to, the tests for levels of various constituents of blood and other body fluids, thyroid function tests, glycosylated hemoglobin if diabetic, lipid profile, liver function tests, complete blood count, and transferrin saturation and serum ferritin if considering hemochromatosis. In addition, initial evaluation should include an electrocardiogram (ECG) and a chest radiograph (although ECG and chest radiograph have low sensitivity and specificity in terms of determining the etiology of HF), and often, an echocardiogram.

In addition to the signs already mentioned, one should examine the patient for any jugular venous distension and/or a third heart sound, since their presence has been shown to have prognostic significance (9).

Therapy for heart failure begins by treating the underlying mechanism of ventricular dys-

function. One should also encourage coronary artery disease risk factor modification (treating lipid disorders and encouraging smoking cessation, regular exercise, weight loss, and limiting alcohol intake). Current American Heart Association guidelines (7) divide therapy according to the following criteria: high risk for heart failure (HF) but without structural heart disease or symptoms of HF (Stage A); structural heart disease but without symptoms of HF (Stage B); structural heart disease with prior or current symptoms of HF (stage C); and refractory HF requiring specialized interventions (Stage D). This article will primarily focus on the patient with symptomatic heart failure in the outpatient setting (Stage C) and will describe how to initiate and titrate medications for this general population. In addition, we will comment on the evidence regarding the indication or contraindication for use of commonly prescribed HF medications. The figure (12) is a helpful graphic synopsis of heart failure treatment, according to NYHA functional class. The components of this figure will be discussed at length below.

To best understand the outpatient management of heart failure and ischemic cardiomyopathy, we will examine several scenarios for a hypothetical patient, “J.K.,” and assume that you are her primary care physician.

J.K. is a 62-year-old postmenopausal female with non-insulin-dependent diabetes, hypertension, and coronary artery disease (myocardial infarction 18 months ago, coronary artery bypass surgery also 18 months ago). She has a history of smoking 2 packs of cigarettes a day, but quit after her heart attack, and drinks a glass of red wine each night. Today, in your of-

fice, she has no complaints. She denies any signs or symptoms of heart failure. Her examination reveals blood pressure of 125/80 mm Hg, pulse of 78 per minute, and respiratory rate of 14 per minute. Her weight is 168 lbs and her height is 5’4”. The examination reveals no jugular venous distension and no carotid bruits. Cardiopulmonary examination reveals a 2/6 holosystolic murmur that is most prominent at the apex and radiates to the axilla. There are no extra heart sounds and no rales. A well-healed sternotomy scar is noted; there is no hepatosplenomegaly or peripheral edema. Laboratory results show a normal set of chemistries (BUN and creatinine are 15 and 1.0 mg/dL respectively) except for an elevated serum glucose of 168 mg/dL. The complete blood count and coagulation studies are normal. A fasting serum lipid profile is as follows: total cholesterol 168 mg/dL, triglycerides 120 mg/dL, HDL 45 mg/dL, and LDL 98 mg/dL. An electrocardiogram reveals an old anterior wall myocardial infarction (MI). A recent echocardiogram shows a moderately dysfunctional left ventricle (ejection fraction of 35%), moderate mitral regurgitation, mild tricuspid regurgitation, and a mildly enlarged left atrium. No thrombus was noted in the left atrium or ventricle. Her medications include metformin 1000 mg twice a day, two 81 mg aspirin tablets each day, a hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase inhibitor (simvastatin 10 mg each day), atenolol 25 mg each day, and a low dose of an angiotensin-converting enzyme (ACE) inhibitor (lisinopril 10 mg each day). Which cardiac medication should this patient be taking for her left ventricular dysfunction?

The patient illustrates a category of left ventricular dysfunction, after a myocardial infarction (non-acute setting), without symptoms of heart failure. In addition to a low-salt diet and daily exercise, her current medical regimen should be continued — but why?

There have been numerous studies looking at the use of ACE inhibitors in the setting of ventricular dysfunction and in the case of acute or recent MI. Before considering the clinical evidence for using ACE inhibitors, one should understand the physiologic rationale for using an ACE inhibitor. The renin-angiotensin-aldosterone system (RAAS) has evolved as an adaptive mechanism in the setting of hypovolemia. RAAS activation leads to salt and water retention. However, in the setting of heart failure, this compensatory mechanism is maladaptive. The kidneys perceive hypovolemia and hypo-

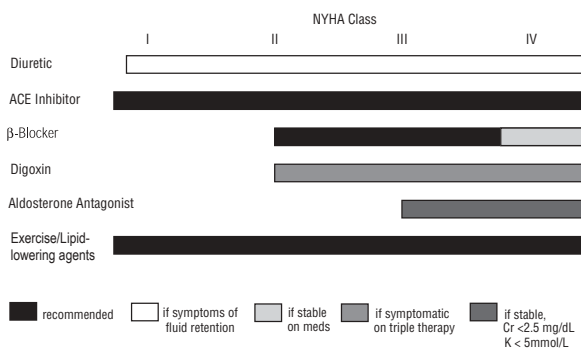


Figure. Recommended medication for heart failure patients. Adapted from Gomberg-Maitland M, Baran DA, Fuster V. Treatment of congestive heart failure: guidelines for the primary care physician and the heart failure specialist. Arch Intern Med 2001; 161(3):342–352 (12).

perfusion, and thus feed into a vicious cycle of increased RAAS activation and resulting increases in salt and water retention. This increased plasma volume results in more strain on the dysfunctional heart and a reduced cardiac output. In turn, there is worsening hypoperfusion of the kidneys and an increase in the degree of RAAS activation.

ACE inhibition inhibits (but does not completely stop) conversion of angiotensin I to angiotensin II. The effects of angiotensin II (via angiotensin II type 1 receptors) have been well studied (13–16); they include an increased load against which the left ventricle pumps (afterload), a stimulation of smooth muscle growth, and an increase in sodium and water retention. Angiotensin II also causes an increase in superoxide production, potentiates endothelin activity, causing vasoconstriction, and stimulates cardiac myocyte growth as well as interstitial and perivascular collagen synthesis, thus potentially contributing to ventricular remodeling and myocardial fibrosis. Therefore, ACE inhibition reduces ventricular remodeling and enlargement, and in this way acts to delay progression of left ventricular dysfunction.

There are several reasons why this patient should be taking an ACE inhibitor, assuming that there is: (a) no history of angioedema or anuric renal failure (secondary to an ACE inhibitor); (b) no pregnancy; (c) no increased creatinine ≥ 3 mg/day; (d) no bilateral renal artery stenosis, or (e) potassium level > 5.5 mmol/L. Three trials have shown a decrease in all-cause mortality and in the risk of developing heart failure for patients with a recent MI, as a result of using ACE inhibitors, while other trials have shown beneficial effects on left ventricular remodeling, and delayed progression to HF in the same group of patients (17–21).

The Survival and Ventricular Enlargement (SAVE) trial randomized patients with a recent MI and a left ventricular ejection fraction of $\leq 40\%$ to captopril (target of 150 mg/day) or placebo for an average of 42 months (22). The results showed that long-term therapy with captopril resulted in lower mortality and morbidity compared to placebo (20% vs. 25%, risk reduction = 29% [95% CI, 3–32, $p=0.019$] for overall reduction in mortality and reduction in risk of death from cardiovascular causes of 21% [95% CI, 20–50, $p=0.014$]). The result was seen for all patients, regardless of whether they received beta-blockers, aspirin, and/or thrombolytics.

The Acute Infarction Ramipril Efficacy (AIRE) (23) and the Acute Infarction Ramipril

Efficacy Extension (AIREX) (24) trials showed similar reductions for patients with an acute MI and clinical or radiographic evidence of HF by randomizing patients to ramipril (goal of 5 mg/day) or placebo. The Trandolapril Cardiac Evaluation Study (TRACE) (19) was similar to the SAVE trial, but randomized patients with a recent MI and an ejection fraction of $\leq 35\%$ to trandolapril (goal of 4 mg/day) or placebo. This trial showed similar reductions in the aforementioned endpoints. Also, other trials have shown the benefit of ACE inhibition after an MI, regardless of left ventricular function (16, 25, 26). There is one trial that fits our patient's profile, which is asymptomatic left ventricular dysfunction. The Studies of Left Ventricular Dysfunction (SOLVD)-prevention trial randomized patients with an ejection fraction $\leq 35\%$ and a remote history of ischemic or nonischemic infarct and with no (or minimal) symptoms of heart failure to enalapril (goal of 20 mg/day) or placebo (27). This trial showed a decrease in combined risk of death and hospitalization as well as decreased risk of hospitalization alone with enalapril. Although there was a trend toward a decrease in all-cause mortality, the results were not statistically significant (27).

Although there is clear evidence of the benefits of beta-blockers in the peri-myocardial infarction period and post-myocardial infarction periods, there is no evidence to support the use of beta-blockers for asymptomatic left ventricular dysfunction. The most recent evidence of the benefit of beta-blockers in the peri-/post-myocardial periods was seen in the Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) study (28). This trial investigated the long-term efficacy of carvedilol on morbidity and mortality in patients with left ventricular dysfunction after acute MI, treated according to current evidence-based practice (28). Patients with proven acute MI and a left ventricular ejection fraction of 40% or less were randomly assigned to carvedilol or placebo. Although there was no difference between the carvedilol and placebo groups in the number of patients with the primary endpoint, all-cause mortality alone was significantly lower in the carvedilol group than in the placebo group. The authors concluded that "in patients treated long-term after an acute myocardial infarction complicated by left ventricular systolic dysfunction, carvedilol reduced the frequency of all-cause and cardiovascular mortality, and recurrent, non-fatal myocardial infarctions. These beneficial effects are additional

to those of evidence-based treatments for acute myocardial infarction including ACE inhibitors.”

Eight months later, the same patient returns to your office at one of her regularly scheduled follow-up visits. Today, she complains of some shortness of breath with her normal daily activities. She notes that she has had to sleep on 2 pillows instead of only one, and she can only walk 4 blocks before becoming short of breath, whereas she used to be able to walk 8 blocks. Her examination reveals blood pressure of 110/70, pulse of 75, and a respiratory rate of 18. Her weight today is 173 lbs. (+5 lbs). The remainder of her examination reveals jugular venous distension 5 cm above the right clavicle at 30 degrees and no carotid bruits. Cardiopulmonary examination reveals a 2/6 holosystolic murmur that is most prominent at the apex and radiates to the axilla. An S₃ is noted, and she has mild bibasilar rales. There is neither hepatosplenomegaly nor peripheral edema. Laboratory tests report serum BUN and creatinine levels of 35 and 1.4 mg/dL respectively, an elevated serum glucose of 148 mg/dL, a normal complete blood count, and normal coagulation studies. An ECG is unchanged from the previous visit. Her medication list is also unchanged (metformin 1000 mg twice a day, two 81 mg aspirin tablets each day, an HMG CoA reductase inhibitor (simvastatin 10 mg each day), atenolol 25 mg each day, and a low dose of an (ACE) inhibitor (lisinopril 10 mg each day).

Questions:

- What medications should this patient be taking?
- What medications should be stopped?
- Does this patient need to be hospitalized?
- Does this patient need a repeat echocardiogram?

At this visit, the patient describes symptoms of heart failure, with left ventricular dysfunction. It is important to establish the etiology of this progression. Is there a new heart attack or injury, or is this volume overload alone? We will assume that this patient is manifesting the natural progression of ischemic cardiomyopathy and is volume overloaded after eating salty foods.

Diuretics

There are several medications that this patient should continue to take, or begin to take, which have been shown to improve mortality, morbidity, or both. To begin with, diuretics are

imperative. Each heart failure patient should know his or her optimal weight. This weight is based upon clinical trial and error and is optimal while the patient is clinically euvolemic and asymptomatic. Diuretics work by decreasing the reabsorption of sodium or chloride by the kidney. Loop diuretics, such as bumetanide, furosemide and torsemide are most commonly used and are the preferred agents. Other diuretics, such as thiazides, metolazone, and potassium-sparing diuretics may also be used alone or in conjunction with loop diuretics. Table 1 lists common loop diuretics used to treat HF, as well as the initial and maximum daily doses. Although there have been no long-term trials of diuretics (excluding spironolactone) and heart failure with regard to mortality and morbidity, these medications have become a cornerstone in the maintenance of volume status and symptom relief. Diuretics have been shown to improve cardiac function, symptoms, and exercise tolerance in intermediate-term trials (29–31). Trials evaluating the use of diuretics as monotherapy for heart failure have concluded that diuretics should not be used as monotherapy for HF, since they do not reduce mortality, unlike other therapeutic agents. While a patient is taking diuretics, it is important to maintain serum electrolyte values and to monitor renal function.

Angiotensin-Converting Enzyme Inhibitors

Once again, the use of ACE inhibitors is paramount. (The clinical rationale for the use of ACE inhibition was described above.) While there have been numerous trials evaluating the use of ACE inhibitors for NYHA classes I–IV, it is important to note that most trials excluded patients with a systolic blood pressure of 90 mm Hg or less, or impaired renal function

TABLE 1
Oral Loop Diuretics Commonly Used for Heart Failure

Medication	Initial Dose	Maximum Dose
bumetanide	0.5–1.0 mg once or twice daily	Titrate to achieve dry weight (up to 10 mg daily)
furosemide	20–40 mg once or twice daily	Titrate to achieve dry weight (up to 400 mg daily)
torsemide	10–20 mg once or twice daily	Titrate to achieve dry weight (up to 200 mg daily)

(serum creatinine greater than 2.5 mg/mL). Assuming that there is no contraindication to an ACE inhibitor (typically, systolic blood pressure less than 80 mm Hg, serum creatinine greater than 3 mg/mL, or a serum potassium greater than 5.5 mmol/L, angioedema, or pregnancy), a low dose should be initiated and increased slowly toward target levels (see Table 2). Not all ACE inhibitors are FDA-approved for heart failure. The ones that have been approved in the United States include enalapril, captopril, quinapril, lisinopril, fosinopril, and ramipril.

In the Vasodilator Heart Failure Trial-2 (V-HeFT-II) (32), patients with ischemic or non-ischemic cardiomyopathy and mild-to-moderate heart failure (NYHA class II and III) were randomized to enalapril (up to 20 mg/day) or a combination of hydralazine (300 mg/day) plus isosorbide dinitrate (160 mg/day). V-HeFT-I had already shown that the combination of hydralazine and isosorbide dinitrate, in contrast to placebo, or prazosin (33), decreased mortality and increased left ventricular ejection fraction in patients with a left ventricular ejection fraction of less than 45% (NYHA class II and III), when it was associated with reduced exercise tolerance or cardiomegaly on chest radiograph. The results of V-HeFT-II showed a 28% reduction in mortality in the enalapril group compared to the hydralazine and nitrate combination group at 2 years, but lost statistical significance at 5-year follow-up. The reduction in mortality was mostly due to a reduction in the incidence of sudden cardiac death, while death that was due to pump failure was unchanged

(32). The SOLVD Treatment study randomized patients with NYHA class II or III (ejection fraction of 35% or less) to enalapril or placebo (9). The enalapril group had an 11% reduction in mortality and a 30% reduction in hospitalizations for heart failure compared to placebo.

Enalapril was also studied in NYHA class IV patients in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) (33). Patients with NYHA functional class IV heart failure were randomized to placebo or enalapril (up to 40 mg each day). This trial was stopped prematurely because there was a 27% reduction in all-cause mortality at 6 months and 31% reduction at 12 months. Improvement in NYHA class was observed in 42% of patients in the enalapril group compared to only 22% of the placebo group. However, there was no effect on the combined risk of death and hospitalization for heart failure (34). Captopril was evaluated in the Captopril-Digoxin Multicenter Trial (35). Study patients were mostly NYHA class II, already taking a diuretic, and they were randomized to digoxin, captopril, or placebo. The captopril group had decreased emergency care visits, as well as fewer hospitalizations for worsening heart failure compared to placebo (34, 35).

Recommendations for Patient J.K.

In contrast to the above medical regimen, there are some medications that should not be used by acute or chronic heart failure patients, if possible. These medications include non-steroidal anti-inflammatory drugs, most anti-arrhythmics, thiazinediones, and metformin. Moreover, in acute decompensated heart failure, one must exercise caution when using beta-blockers. Beta-blockers should never be initiated in the setting of acute decompensated HF. In addition, if a patient is currently taking a beta-blocker and presents with an acute exacerbation, with evidence of hypoperfusion and low cardiac output, then consideration should be given to reducing the dose of beta-blocker or temporarily stopping it. For our patient, we could consider stopping the atenolol, since it is a low-dose beta-blocker.

This patient does not necessarily need to be hospitalized, since she is known to you (the primary care provider). Prescribing medications to provide symptomatic relief as well as to retard progression of HF can be done on an outpatient basis. If this patient were not known from prior visits, it would be best to send her for an inpatient evaluation to determine ischemic causes of

TABLE 2
ACE Inhibitors Commonly Used for Heart Failure

Medication	Initial Dose	Maximum Dose
captopril	6.25 mg 3 times daily	50 mg 3 times daily
enalapril	2.5 mg twice daily	10–20 mg twice daily
fosinopril	5–10 mg once daily	40 mg once daily
lisinopril	2.5–5 mg once daily	20–40 mg once daily
quinapril	10 mg twice daily	40 mg twice daily
ramipril	1.25–2.5 mg once daily	10 mg once daily

heart failure, as well as to rule out other causes of left ventricular dysfunction.

Additional questions to ask are: “What dose of ACE inhibitor should one use to treat heart failure? Does one get the same effect if the patient cannot tolerate the dose used in clinical trials?”

Dosing of ACE Inhibitors

Two trials have addressed these questions (36, 37). Regardless of the high doses used in the large, randomized clinical trials, the NETWORK study showed that there was no difference in benefit between enalapril 2.5 mg bid, 5 mg bid, or 10 mg bid in patients with NYHA class II–IV (36). The study looked at a primary combined endpoint (death, HF-related hospitalizations, and progression of HF), as well as several individual secondary endpoints (death, HF-related hospitalizations, and progression of HF) and found no statistically significant correlation between doses and outcomes. The Accupril Congestive Heart Failure Investigation and Economic Variable Evaluation (ACHIEVE) trial is currently evaluating the effects of different doses of quinapril on mortality (38). Finally, the Assessment of Treatment with Lisinopril and Survival (ATLAS) looked at the differences between high-dose and low-dose lisinopril (37). The results of this trial showed no difference in mortality for patients with class II through IV heart failure. However, there were fewer hospitalizations ($p=0.002$) for all causes and HF hospitalization in the high-dose group. Although one would like to achieve the high doses used in the large, randomized clinical trials, one must also try to minimize potential side effects. These include hypotension, worsening renal function, potassium retention, cough, and angioedema. Yet, while lower doses may minimize some of these side effects, it is important to realize that lower doses may produce smaller differences in outcome. In patient J.K.’s case the blood pressure is not low, and attempts should be made, at successive visits, to increase ACE inhibitor dosage.

What if this same patient developed a cough, and could not tolerate an ACE inhibitor? Is there any evidence that an angiotensin II receptor blocker (ARB) has equivalent or superior effects in the same group of patients?

Angiotensin Receptor Blockers

This clinical question has been addressed in several clinical trials. The first direct comparison of an angiotensin II receptor blocker (ARB) to an ACE inhibitor was the Evaluation of

Losartan in the Elderly (ELITE) study (39). This trial randomized elderly patients with NYHA class II–IV heart failure, who had never been treated with an ACE inhibitor, to either losartan or captopril for 48 weeks. This trial was designed to compare the safety profile of ACE inhibitors and ARBs in the treatment of HF. Unexpectedly, there was a trend to decreased mortality in the ARB group (4.8% vs. 8.7%), a risk reduction of 46% ($p=0.035$) (39). The lower mortality rate resulted mainly from a reduction in sudden cardiac death. Also, losartan was shown to be better tolerated than captopril (37). These results led to ELITE II (40), which was designed to confirm the survival advantage seen in ELITE. However, this trial failed to demonstrate any survival benefit in the losartan group compared to placebo. Ironically, it showed a trend toward an increase in mortality in the losartan group compared to the captopril group, especially in regard to sudden cardiac death. Losartan was again shown to be better tolerated than the ACE inhibitor.

ACE inhibitors have clearly been shown to reduce mortality and morbidity across all classes of heart failure as well as for asymptomatic left ventricular dysfunction. In addition, ARBs have not been shown to be either superior, or equivalent, in the treatment of heart failure compared to ACE inhibitors. Thus, one must use these ARBs with caution and mainly for those patients who cannot tolerate an ACE inhibitor.

However, does a combination of the two (ACE inhibition and angiotensin II receptor blockade) have an equivalent or superior effect?

Combination Therapy with ACE Inhibitors and ARBs

The rationale for this approach is based on the pharmacology of ACE inhibitors. The blockade of ACE inhibitors is not complete, since there is some “escape” of angiotensin I, which is converted to angiotensin II. Thus, it is believed that blocking the renin-angiotensin cascade in multiple spots will improve overall patient outcomes. One of the first studies to look at this was the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) trial (41). This trial compared candesartan, enalapril, and combination candesartan plus enalapril for patients with NYHA class II–IV heart failure, an ejection fraction of less than 40%, and a 6-minute walk distance of less than 500 meters. Although there was no differ-

ence in 6-minute walk, ejection fraction, ventricular volumes, neurohormonal levels, quality of life, or NYHA functional class, there was a nonsignificant increase in ejection fraction in the combination group. Also, there was no significant difference in death, hospitalization for HF, or any hospitalizations, but there was a nonsignificant difference in mortality between the combination, candesartan, and enalapril groups (8.7%, 6.1%, and 3.7% respectively) (41).

The Valsartan Heart Failure Trial (Val-HeFT) was the next trial to compare ARBs, ACE inhibitors, and combination therapy (42). Patients with NYHA classes II–IV heart failure were randomized to valsartan or placebo. In this trial some patients were on ACE inhibitors (92.6% valsartan vs. 92.8% placebo) and/or beta-blockers (34.5% in the valsartan group on beta-blockers vs. 35.3% placebo). This study showed the overall mortality rate between treatment groups to be similar, while the combined endpoint of mortality and morbidity was significantly lower in the valsartan group (28.8% vs. 32.1%; $p=0.009$). The combined endpoint was defined as cardiac arrest with resuscitation, hospitalization for HF, or administration of intravenous inotropic or vasodilator drugs for four hours or more with or without hospitalization. There was also a significant improvement in the secondary endpoints (NYHA class, ejection fraction, signs and symptoms of HF, and quality of life) in the valsartan group compared to placebo ($p<0.01$) (42).

The benefits of valsartan were not seen in the heterogeneous black study population, and there was a worrisome trend toward increased mortality with valsartan in this group. A post hoc analysis divided the study population into four groups, based upon whether or not the patient was on an ACE inhibitor and/or a beta-blocker. For those patients receiving both an ACE inhibitor and a beta-blocker, the addition of valsartan had an adverse effect on mortality and a trend toward an increase in combined mortality and morbidity. For patients who were receiving neither an ACE inhibitor nor a beta-blocker, there was a significantly lower mortality rate in the valsartan group than the placebo group (42). One can conclude from this trial that if a patient is receiving neither an ACE inhibitor nor a beta-blocker, valsartan will decrease the likelihood of mortality with a probability of decreased combined mortality and morbidity. However, for patients on both a beta-blocker and an ACE inhibitor, the addition of

valsartan will have an adverse effect on the combined endpoint and on mortality. The Candesartan in Heart failure — Assessment of Reduction in Mortality and morbidity (CHARM) trial — is currently evaluating candesartan in heart failure, and will contain one arm that will treat patients with a combination of candesartan and an ACE inhibitor (43).

The side effects of ARBs are similar to those seen with ACE inhibitors. However, since angioedema and cough are bradykinin mediated, these two side effects generally do not occur in patients treated with ARBs.

Assuming that this patient can tolerate an ACE inhibitor and that she is stable on her current regimen, but still complains of shortness of breath with daily activities, are there any other medications from which this patient would benefit? (Also, assume that the patient does not have any signs or symptoms of acutely decompensated heart failure.)

Digoxin

Another medication frequently mentioned in the treatment of heart failure is digoxin. This medication is traditionally considered as a positive inotrope via cardiac sodium/potassium adenosine triphosphatase (ATPase) pump inhibition. However, digoxin is also a neurohumoral modulator, causing a decrease in sympathetic tone and an increased vagal/parasympathetic tone. Other trials of positive inotropes have uniformly shown excess cardiac mortality, but digoxin has no excess mortality effect (possibly due to its weak inotropic effect). The Digitalis Investigation Study group (DIG trial) examined NYHA class II–IV HF patients who had not received digoxin and randomized them to either digoxin or placebo (44). While there was no difference in mortality, arrhythmias, or occurrence of myocardial ischemia, the digoxin group did have a lower rate of overall hospitalization and hospitalization due to HF (44).

Withdrawal of Digoxin

The flip-side of this equation is the patient with HF who is withdrawn from digoxin therapy. Both the Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin (PROVED) (45) and the Randomized Assessment of Digoxin and Inhibitors of Angiotensin-Converting Enzyme (RADIANCE) (46) showed detrimental effects of withdrawing digoxin in a stable heart failure patient. The patients in RA-

DIANCE were already on diuretics and an ACE inhibitor in addition to digoxin. The withdrawal of digoxin for three months led to clinically significant worsening of HF as assessed by NYHA class, patient's subjective assessment, left ventricular ejection fraction and left ventricular end diastolic dimension, compared to those who continued digoxin (46). PROVED showed similar results (45).

If digoxin does not improve mortality, then why use it at all for patients with a normal sinus rhythm?

In the current recommendations for heart failure management, digoxin should be added to achieve improvement in clinical status for those patients with HF who are already treated with diuretics, ACE inhibitors, and a beta-blocker. Withdrawal of digoxin may do more potential harm than the benefits seen after starting the medication for heart failure therapy.

Side effects of digoxin include cardiac arrhythmias (ectopic and re-entrant rhythms and heart block), gastrointestinal symptoms (anorexia, nausea, and vomiting), and neurologic complaints (visual disturbances, disorientation, and confusion). The potential side effects are more commonly associated with elevated serum concentrations. However, these effects may manifest at lower serum levels in the setting of hypokalemia, hypomagnesemia, or hypothyroidism.

The same patient returns to your office and is now euvolemic by weight and by examination. Her BUN and creatinine values are now 15 and 1.1 mg/dL respectively. Her potassium is normal, her blood pressure is 120/80 mm Hg, and her pulse beats 72 per minute. Are there any additional medications from which this patient would benefit? Her current regimen includes: an oral anti-hypoglycemic agent (glipizide 10 mg each day), two 81 mg aspirin tablets each day, furosemide 80 mg po qd, an HMG CoA reductase inhibitor (simvastatin 10 mg each day), digoxin 0.125 qd, and a low dose (lisinopril 10 mg each day) of an ACE inhibitor. The atenolol had been stopped when the patient presented with an acute exacerbation of heart failure, and was never restarted.

Beta-Blockers

Initially beta-blockers were thought to be detrimental to HF patients. However, one of the hallmarks of severe heart failure is activation of the sympathetic nervous system, and high serum catecholamine levels. Beta-blockers inhibit

these effects. Strong evidence (discussed below) supports the role of beta-blockers for HF patients, with resultant improvement in morbidity, mortality, and delay of HF progression.

Another misconception about treating heart failure is that the beneficial effects of beta-blockers are a "class-effect." While there are certain classes of medications that have the same effect on a certain illness or produce the same side effects, this is not true for beta-blockers and heart failure. Beta-blockers from three classes, β 1-selective, β 1- β 2 nonselective, and β -nonselective + α -blockade, have been studied in the setting of heart failure. The four drugs studied have been metoprolol, bisoprolol, bucindolol, and carvedilol.

Two trials have looked at the utility of the β 1-selective agent metoprolol. The Metoprolol in Dilated Cardiomyopathy (MDC) trial (47) randomized patients with NYHA functional classes II–IV (who were already taking digitalis, diuretics, nitrates, and/or ACE inhibitors designed to achieve optimal compensation of their heart failure). Diabetics, patients with significant coronary artery disease, and patients with other serious illnesses (including chronic obstructive pulmonary disease) were excluded from this trial. The investigators found that those treated with metoprolol did not have a significant decrease in mortality, but had significantly lower need for heart transplantation, and had improved left ventricular ejection fraction, exercise capacity, and NYHA functional class, compared to placebo at an 18-month follow-up.

As the results of the MDC trial were promising, it led to the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) study (48, 49). Nearly 4,000 patients with NYHA classes II–IV were randomized to a sustained-release preparation of metoprolol or placebo. This trial was stopped early because of the favorable results in the sustained-release metoprolol-treated group. MERIT-HF demonstrated decreased mortality with metoprolol (specifically resulting from sudden cardiac death or pump failure) regardless of ischemic or nonischemic etiology. This difference was seen across most demographic groups. The metoprolol group also had a reduced requirement for hospitalization, improved NYHA functional class, and improved patient-assessed well-being.

The U.S. Carvedilol Heart Failure Program, consisting of 4 coordinated studies (50–53) of patients with NYHA class II, III, or IV who had an ejection fraction of less than 35%, and the

Australia and New Zealand Heart Failure Research Collaborative Group (54), consisting of one trial of patients with NYHA class I, II, or III and an ejection fraction of less than 45%, have shown the efficacy of carvedilol in HF patients. The Australia/New Zealand group showed that for patients with heart failure secondary to ischemic cardiomyopathy, at 6 months the carvedilol group had improved left ventricular function, but slightly worsened symptoms compared to the placebo group (54). At 12 months, the carvedilol group still had an improvement in left ventricular function and a decrease in the combined endpoint of death or hospitalization. However, there was no effect on mortality, exercise performance, symptoms, or episodes of worsening heart failure.

The U.S. Carvedilol Heart Failure Study (50) showed that carvedilol reduces the risk of death and risk of hospitalization for cardiovascular causes in patients with HF who are receiving treatment with digoxin, diuretics, and an ACE inhibitor. Overall mortality was 7.8% in the placebo group compared to 3.2% in the carvedilol group ($p < 0.001$) (50). Death from progressive heart failure was 3.3% in the placebo group and 0.7% in the carvedilol group (50).

The Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA) study (51) showed that in those subjects with mild-to-moderate HF due to systolic dysfunction, treatment with carvedilol resulted in dose-dependent improvement in left ventricular function and reduction in mortality and hospitalization rates (51). The US Carvedilol Heart Failure Study (52) showed that for patients with mildly symptomatic stable HF due to systolic dysfunction, carvedilol reduced clinical progression of heart failure and mortality. There was no difference in quality of life scores and the distance walked in a 9-minute treadmill test between the carvedilol group and a placebo group. The mortality rate for the placebo group was 4% vs. 0.9% in the carvedilol group (95% CI 0.045 to 1.174, $p = 0.048$) (52). Finally, the Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise (PRECISE) trial (53) showed that while there was no statistically significant difference in hospitalization for cardiovascular etiology or death, there was a statistically significant difference in combined death and cardiovascular hospitalization. The authors concluded that for patients who tolerate drug treatment and are being treated with diuretics, ACE inhibitors and digoxin for moderate-to-severe

stable heart failure due to systolic dysfunction, the addition of carvedilol decreased death or cardiovascular hospitalization (53).

The collaborative US Carvedilol Heart Failure Program was terminated early as a result of a reduction in mortality among patients treated with carvedilol. According to intention-to-treat analysis, overall mortality risk was reduced significantly (by 65%) in the carvedilol group as compared to the placebo group (3.2% vs. 7.8%). Mortality was significantly lower in patients with NYHA class II symptoms (1.9% vs. 5.9%) and 65% lower among those with NYHA III symptoms (4.2% vs. 11%). One of the criticisms is that a reduction in mortality includes data from some trials in which the primary endpoints were not achieved (55, 56).

Most recently the Carvedilol Prospective Randomized Cumulative Survival Trial (COPERNICUS) (57) evaluated the safety and efficacy of carvedilol in NYHA class IV patients. When the results showed a 35% reduction in death in the carvedilol group compared to the group with placebo, and the trial was stopped early. Patients were excluded from this study if uncorrected primary valve disease or a form of reversible cardiomyopathy caused the heart failure; if they were likely to receive cardiac transplantation; if they had severe primary pulmonary, renal, or hepatic disease; or if they had a contraindication to beta-blocker therapy. Patients who received intensive care, had marked fluid retention, or were receiving intravenous vasodilator or intravenous positive inotropic agents were not enrolled. Such patients may not have a favorable response to carvedilol.

Currently, the Carvedilol or Metoprolol European Trial (COMET) (58) is comparing the use of carvedilol and metoprolol for heart failure. This trial represents the first direct, randomized comparison of these two FDA-approved beta-blockers for the treatment of HF. The trial is ongoing, with results expected in the next 1–2 years.

Nonselective beta-blockers have also been studied in large, randomized trials. Bisoprolol was studied in two trials, and a third is currently planned. The Cardiac Insufficiency Bisoprolol Study (CIBIS-I) (59) was a placebo-controlled trial of bisoprolol for patients with symptomatic ischemic or nonischemic cardiomyopathy, who had NYHA function class III or IV, were treated with diuretics and vasodilators, and had an ejection fraction of less than 40%. A 20% reduction in mortality was observed, but this did not reach statistical significance due to insuffi-

cient patient numbers (the trial was underpowered). The observed benefit was limited to those with nonischemic cardiomyopathy. An improvement in functional status and a decrease in hospitalization for cardiac decompensation was observed in the bisoprolol group (59). These promising results prompted the CIBIS-II study (60), which was stopped early (after 18 months) because of a 32% reduction ($p < 0.001$) in all-cause mortality in the bisoprolol-treated group. The CIBIS-II trial showed that bisoprolol was well tolerated and reduced mortality and hospitalization rates for patients with stable HF (60). The results of this trial are impressive, and the trial itself constitutes a landmark in the development in beta-blockade as a treatment for heart failure (56).

The Beta-blocker Evaluation of Survival Trial (BEST) (61) evaluated bucindolol for patients with advanced heart failure. This trial also enrolled a large subset of patients who were either women or minorities. A total of 2,708 patients, mostly of class III (92%) heart failure and some of class IV (8%), who were already optimized on a heart failure regimen but not taking a beta-blocker, were randomized to bucindolol or placebo. The trial was terminated after the seventh interim analysis showed no mortality difference between the two groups. The results of this trial are based on a completed follow-up of 2 years. The BEST study concluded that there was no significant improvement in overall survival for patients in the bucindolol group (61). The authors hypothesized that the lack of significant reduction in overall mortality was secondary to a different patient population, since there was a significant decrease in mortality in a subgroup of non-black patients. There was actually an increase in mortality in the black population in the BEST study, in contrast to the metoprolol or carvedilol studies, where this was not observed. It is possible that different racial groups may have different pharmacological responses to beta-blockers (61).

It is important to emphasize that the addition of beta-blockers is appropriate only for the regimen of the euvolemic, stabilized heart failure patient. The potential side effects of beta-blockers include fluid retention and worsening HF, fatigue, depression, bradycardia and heart block, hypotension, and bronchospasm (in those prone to, or diagnosed with, bronchospastic diseases). In an outpatient setting these medications can be safely titrated every 2–4 weeks. The initial and goal doses are listed in Table 3.

One last point concerning this patient is that, since she has a systolic blood pressure of 120 mm Hg, the ACE inhibitor should be up-titrated, perhaps alternating with up-titration of the beta-blocker. Since atenolol has not been shown to be of benefit for HF, the patient should be placed on carvedilol or metoprolol sustained release.

The same patient returns for her follow-up visits over the next several years and does well, but her heart failure progresses. She now complains of dyspnea at rest, but has no finding of acute or decompensated heart failure (rales, orthopnea, paroxysmal nocturnal dyspnea, elevated jugular venous pulse, increased lower extremity edema, or worsened dyspnea on exertion). Her medication regimen includes an oral glucose-control agent (not metformin), two 81 mg aspirin tablets each day, an HMG CoA reductase inhibitor, carvedilol 25 po bid, furosemide 100 mg po bid, and a moderate dose (lisinopril 40 mg each day) of an ACE inhibitor regimen. Are there any additional medications that might help this patient in regard to mortality, morbidity, or both? You remember reading something about aldosterone antagonism and HF, but cannot remember if this patient fits into the patient profile of the spironolactone trial. Is there a role for an aldosterone antagonist in the setting of heart failure? If so, for which patients?

To begin with, this patient has NYHA functional class IV heart failure. It is important now to refer this patient to a specialist, ideally to a cardiologist who specializes in the management of heart failure. Following is a review of additional therapies that can affect (positively or negatively) mortality and/or morbidity.

Spironolactone

The Randomized Aldactone Evaluation Study (RALES) trial (62) examined the use of

TABLE 3
Beta-Blockers Commonly Used for Heart Failure

Medication	Initial Dose	Maximum Dose
bisoprolol	1.25 once daily	10 mg once daily
carvedilol	3.125 mg twice daily	25 mg twice daily; 50 mg twice daily for patients more than 85 kg
metoprolol CR/XL	12.5–25 mg daily	200 mg once daily

aldactone in a select group of patients (63, 64). HF patients in NYHA functional class III or IV (and with a diagnosis of heart failure at least 6 weeks before enrollment), who received an ACE inhibitor and a loop diuretic, and had an ejection fraction of less than 35% within 6 weeks of enrollment were randomized to spironolactone (25 mg orally each day) or placebo. Some of the exclusion criteria included a serum creatinine level of greater than 2.5 mg/dL or a serum potassium level greater than 5.0 mmol/L. The trial was stopped early, due to a significant 31% decrease in cardiac death (specifically, progression of heart failure and sudden death) observed in the spironolactone (25 mg orally each day) group. Spironolactone patients also had decreased hospitalization for all cardiac causes, mostly due to a decrease in HF hospitalizations (64). Given decreases in sudden death, it is possible that an increase in serum potassium in the spironolactone group was at least partially responsible.

For this patient, if there are no contraindications to the medication and her serum creatinine and potassium levels are less than 2.5 mg/dL and 5.0 mmol/L respectively, then spironolactone should be added to the regimen. The recent ACC/AHA consensus HF guidelines suggest that spironolactone may be of benefit for a select group of patients (7). The addition of low doses of spironolactone (25 mg each day) should be considered for patients with recent or current symptoms at rest despite the use of digoxin, diuretics, ACE inhibitor, and a beta-blocker. Patients should also have levels of serum creatinine and potassium of less than 2.5 mg/dL and 5.0 mmol/L respectively, before therapy is initiated.

Calcium-Channel Blockers

Calcium-channel blockers have been studied in several large trials. The Prospective Randomized Amlodipine Survival Evaluation (PRAISE) trial (65) documented the safety of amlodipine for HF. In fact, this is the first calcium-channel blocker that was NOT associated with an increased mortality and morbidity among patients with severe heart failure. Amlodipine lowered mortality in a subgroup of patients with nonischemic cardiomyopathy. PRAISE-2 (enrolling only patients with nonischemic cardiomyopathy) failed to confirm these results, but at least it did not demonstrate increased mortality with this agent (66).

Other trials such as V-HeFT III (67) and Diltiazem in Dilated Cardiomyopathy (DiDi)

(68), also failed to show any benefit for HF patients treated with a calcium-channel blocker (felodipine and diltiazem respectively). While calcium-channel blockers do not have any beneficial effects for heart failure patients, if their use is indicated (angina or refractory hypertension), then only one shown to be safe should be employed (preferentially amlodipine).

Oral Phosphodiesterase III Inhibitors

Intravenous phosphodiesterase III inhibitors are used in acute, mostly inpatient, decompensated heart failure situations. There has been one trial, the Prospective Randomized Milrinone Survival Evaluation (PROMISE) trial (69), which compared oral milrinone to placebo for patients treated with digoxin, diuretics, and ACE inhibitors. Long-term therapy with oral milrinone increased the mortality and morbidity of treated patients with severe heart failure.

Exercise

Patients were once told that bedrest was an adjunct to medical therapy. Although this may be the case for an unstable patient, moderate exercise training for patients with heart failure has been shown to improve functional capacity, quality of life, and improved outcome compared to those without training (70).

Conclusions

Our understanding of heart failure continues to improve as new therapies are subjected to the rigors of multicenter trials. In this paper, we have attempted to cover numerous trials in the context of a typical patient presentation. One of the most important points to remember is that heart failure is a progressive, relentless, and eventually fatal illness. At each stage of the disease, the practitioner may have the opportunity to prescribe medications that will extend the longevity of the patient and/or at least improve the patient's quality of life. Therapies such as beta-blockade and ACE inhibition have been shown to reduce disease progression. A specific combination of medications discussed in this paper, applied to each individual heart failure patient, will help prolong life and reduce suffering. In addition, knowledge of the underlying evidence supporting the use of these agents will help the practitioner customize a medical regimen, selecting from the variety of medications available.

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