

## CLINICAL PRACTICE

## Systolic Heart Failure

John J.V. McMurray, M.D.

*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

**A 74-year-old man with a history of hypertension and myocardial infarction that occurred 5 years previously presents with breathlessness on exertion. His current medications include a statin and aspirin. On examination, his pulse is 76 beats per minute and regular, and his blood pressure is 121/74 mm Hg. There is jugular venous distention, lateral displacement of the apex beat, and edema in his lower limbs. The lung examination is normal. An echocardiogram shows left ventricular dilatation, globally reduced contractility, and an ejection fraction of 33%. How should his case be managed?**

## THE CLINICAL PROBLEM

From the Western Infirmary and the British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom. Address reprint requests to Dr. McMurray at the British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Pl., Glasgow G12 8TA, United Kingdom, or at j.mcmurray@bio.gla.ac.uk.

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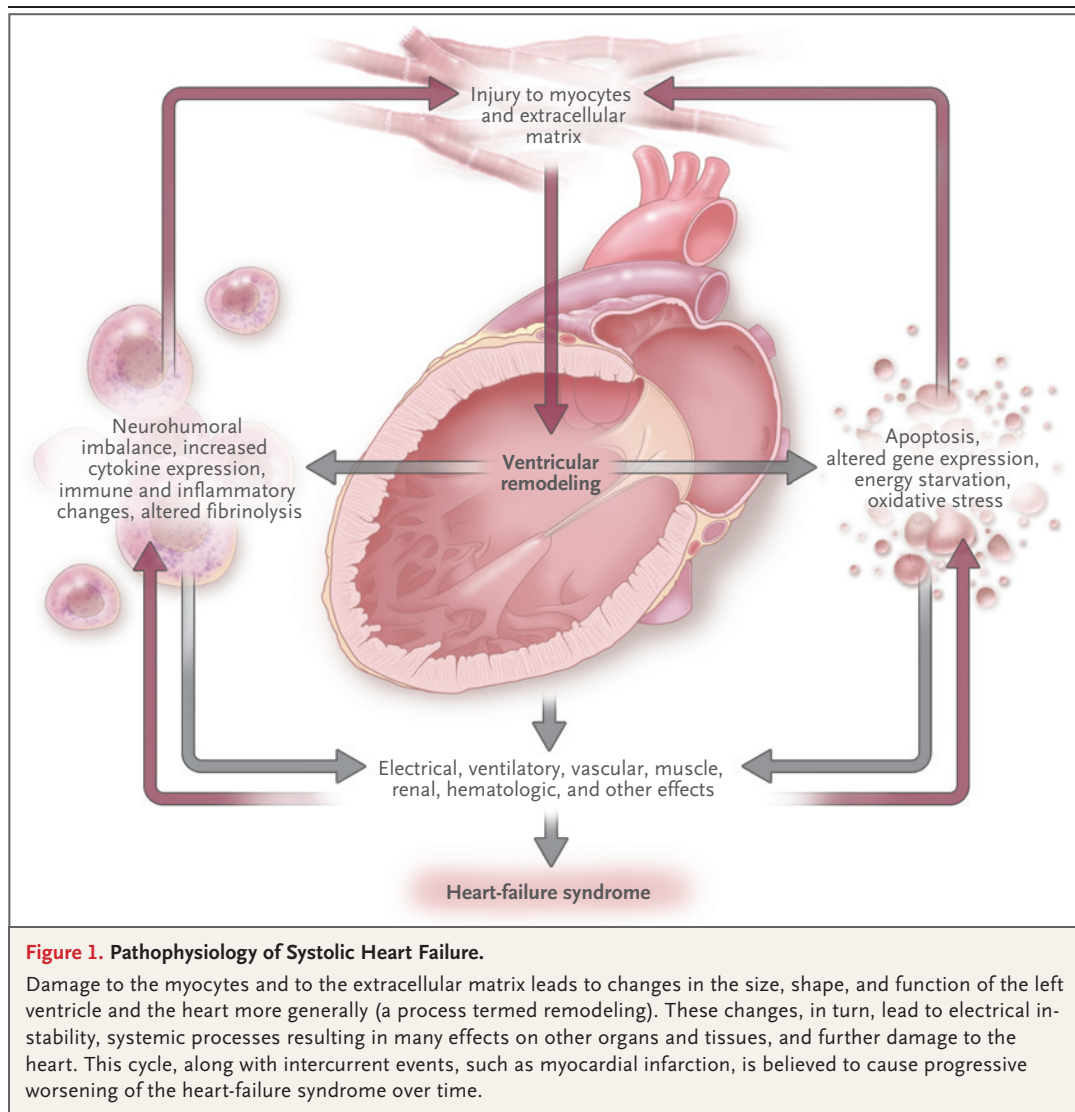


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Approximately 1 to 2% of the population in developed countries has heart failure, with the prevalence rising to 10% or more among persons 70 years of age or older.<sup>1</sup> At least half the patients with heart failure have a low ejection fraction (40% or less).<sup>1</sup> This review focuses on the recommended treatment for ambulatory patients with systolic heart failure; heart failure with preserved ejection fraction was reviewed previously in this series.<sup>2</sup>

Coronary artery disease is the cause of approximately two thirds of cases of systolic heart failure, although hypertension and diabetes are likely to be contributing factors in many cases. Dilated cardiomyopathy may also result from a genetic cause, previous viral infection (recognized or unrecognized), alcohol abuse, or occasionally, chemotherapy (e.g., doxorubicin or trastuzumab).<sup>2</sup>

The maladaptive changes that occur in surviving myocytes and in the extracellular matrix after myocardial injury lead to pathologic remodeling of the left ventricle, with dilatation and impaired contractility. If these changes are left untreated, they worsen over time, exacerbated by additional injury (e.g., myocardial infarction)<sup>3</sup> and by systemic responses to left ventricular systolic dysfunction, notably activation of the sympathetic and renin-angiotensin-aldosterone systems.<sup>4</sup> All these responses have detrimental systemic effects, accounting for the clinical manifestations of the syndrome of heart failure, including the development and worsening of symptoms, declining functional capacity, episodes of frank decompensation that result in the need for hospitalization, myocardial electrical instability, and premature death, usually due to pump failure or a ventricular arrhythmia (Fig. 1). Since the limited cardiac reserve of patients with systolic heart failure depends on atrial contraction and synchronized contraction of the left ventricle, events that affect these functions (e.g., the development of atrial fibrillation or left bundle-branch block) or that impose an additional hemodynamic load on the failing heart (e.g., anemia) can lead to acute deterioration. Interruption of left ventricular remodeling and of the systemic responses to it is the basis of much of the effective treatment of heart failure.



Before 1990, as many as 60 to 70% of patients died within 5 years after the diagnosis of systolic heart failure, and hospitalization owing to the exacerbation of symptoms was frequent.<sup>5</sup> Effective treatment has improved both outcomes, with a relative reduction in mortality in recent years of 20 to 30%.<sup>6</sup>

## STRATEGIES AND EVIDENCE

### DIAGNOSIS AND EVALUATION

The cardinal symptoms (i.e., dyspnea and fatigue) and signs (i.e., peripheral edema) of heart failure are nonspecific and must be evaluated in light of the patient's history, the findings on examination,

and the results of additional testing.<sup>1,7,8</sup> Other symptoms (e.g., orthopnea and paroxysmal nocturnal dyspnea) and signs (e.g., jugular venous distention, cardiac enlargement, and a third heart sound) have 70 to 90% specificity for the diagnosis but only 11 to 55% sensitivity.<sup>9</sup>

Routine cardiac investigations, such as electrocardiography and chest radiography, are also insensitive, although they may provide other useful information (Table 1).<sup>7,8</sup> For example, left ventricular systolic dysfunction may be seen without cardiomegaly on a chest radiograph. Measurement of the plasma concentration of natriuretic peptides is recommended, since natriuretic peptides are secreted in increased amounts by the failing heart,

**Table 1. Possible Findings in Patients with Left Ventricular Systolic Dysfunction and Recommendations for Treatment.\***

Test and Possible Finding	Recommendation
Electrocardiography	
Atrial fibrillation or flutter	Slow the ventricular rate if it is rapid, and consider prophylactic anticoagulation therapy for thromboembolism.
QRS duration $\geq 120$ msec	Consider cardiac-resynchronization therapy.
Sinus bradycardia	Administer beta-blocker and digoxin with caution.
Chest radiography	
Pulmonary congestion, edema, or pleural effusion	Provide adequate diuresis.
Primary pulmonary pathology (e.g., COPD, fibrosis, or tumor)	Look for alternative cause of dyspnea and provide therapy specific to that cause.
Hematologic tests	
Anemia	Perform a diagnostic workup; treat iron deficiency, if present.
Biochemical tests	
Increased creatinine	Administer RAAS blockers with caution.
Hypokalemia	Add or increase the dose of RAAS blocker; consider potassium replacement.
Hyperkalemia	Stop potassium replacement and supplements; reduce dose of or withdraw RAAS blocker.
Hyponatremia	Reduce the dose of or discontinue use of thiazide diuretic; reduce water intake; consider treatment with tolvaptan, if hyponatremia is severe.
Hyperuricemia	Consider reducing the dose of the diuretic as much as possible; administer prophylaxis for gout with a xanthine oxidase inhibitor.

\* COPD denotes chronic obstructive pulmonary disease, and RAAS renin–angiotensin–aldosterone system.

and a normal concentration virtually rules out a diagnosis of heart failure (although this observation may not hold true in the case of obese persons).<sup>10</sup>

Transthoracic Doppler echocardiography allows for confirmation of the diagnosis, provides information on myocardial and valvular structure and function, and may reveal other important findings, such as the presence of a thrombus in a cardiac chamber.<sup>7,8</sup> Cardiac magnetic resonance imaging is an alternative to echocardiography in difficult cases, such as those in which the quality of the ultrasonic image is poor, or in cases in which characterization of the tissue is particularly important (e.g., when myocarditis or an infiltrative myocardial disease is suspected).<sup>11</sup> Investigations that are recommended routinely, as well as those that are useful in selected circumstances, are summarized in Table 1.<sup>7,8</sup>

Patients' symptoms, including limitations in activity, can be quantified with the use of the New York Heart Association (NYHA) functional

classification or the more recent American Heart Association–American College of Cardiology classification (Table 2).<sup>7,8,12</sup>

Coexisting conditions that are common in patients with heart failure and that may influence the prognosis and affect treatment decisions should be routinely assessed (Table 1). These include conditions that may have led to the heart failure (e.g., ischemic heart disease, hypertension, or diabetes) or that may result from either the heart failure itself (e.g., atrial fibrillation, cachexia, or depression) or the treatment (e.g., gout induced by diuretics). Other common coexisting conditions include renal impairment, anemia, and sleep-disordered breathing.

#### TREATMENT OPTIONS

The goals of treatment are the reduction in symptoms, a decrease in the rate of hospitalization, and the prevention of premature death. The cornerstone of treatment is pharmacologic therapy

**Table 2. Clinical Classifications of Heart Failure Severity.\***

NYHA Functional Classification		ACC–AHA Stages of Heart Failure	
Class I	No limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea	Stage A	At high risk for heart failure; no identified structural or functional abnormality; no signs or symptoms
Class II	Slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea	Stage B	Developed structural heart disease that is strongly associated with the development of heart failure but without signs or symptoms
Class III	Marked limitation of physical activity; comfortable at rest, but less than ordinary activity results in fatigue, palpitation, or dyspnea	Stage C	Symptomatic heart failure associated with underlying structural heart disease
Class IV	Unable to carry on any physical activity without discomfort; symptoms present at rest; if any physical activity is undertaken, discomfort is increased	Stage D	Advanced structural heart disease and marked symptoms of heart failure at rest despite maximal medical therapy

\* The American College of Cardiology (ACC)–American Heart Association (AHA) classification is from Hunt et al.<sup>8</sup> The New York Heart Association (NYHA) functional classification is from the Criteria Committee of the New York Heart Association.<sup>1,2</sup>

(Fig. 2). Lifestyle modification such as exercise training, implantable devices, and in selected cases, surgery may also be needed.

#### PHARMACOLOGIC THERAPY

Pharmacologic agents include those that provide relief of symptoms only (i.e., diuretics) and those that also modify the course of the disease (see below). The dosing and key side effects of medications that have been shown in randomized trials to be effective are listed in Table 3. The randomized trials are summarized in Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. Detailed information that provides guidance on prescribing and monitoring treatments is available.<sup>32</sup>

#### *Diuretics for Relief of Symptoms*

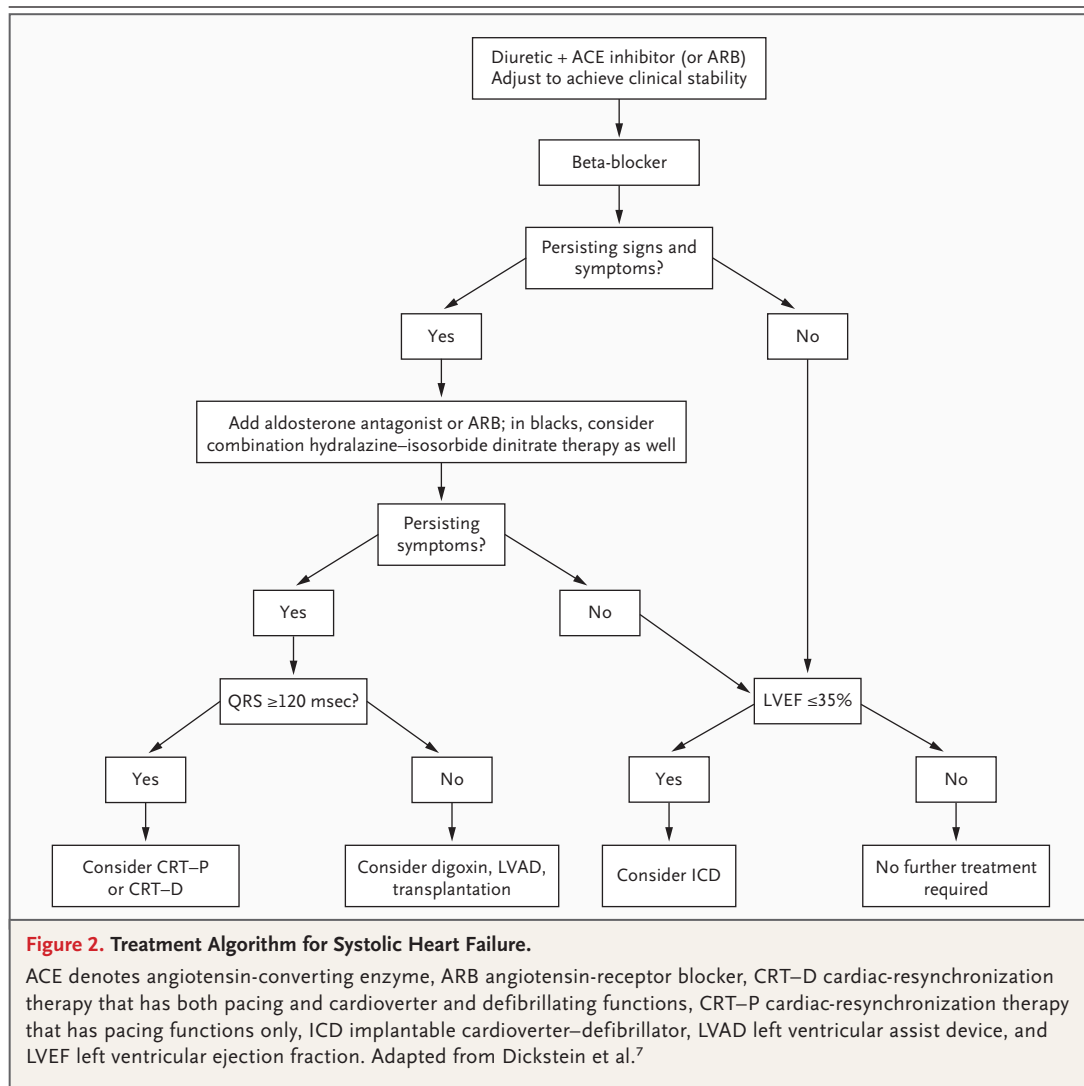
Diuretics provide rapid relief of dyspnea and fluid retention.<sup>7,8</sup> The lowest dose of diuretic needed to achieve an edema-free state (“dry weight”) is used. The patient’s weight should be measured daily, and the dose of the diuretic adjusted to maintain the dry weight. Patients can alter the timing of the doses for social convenience.

The combination of a loop diuretic and a thiazide-like diuretic (e.g., metolazone), often in conjunction with an aldosterone antagonist — treatment that is termed sequential nephron blockade — may be needed to control fluid retention in cases of severe heart failure, although

this treatment requires close monitoring of blood levels of electrolytes because of the risk of disturbances such as hyponatremia. Patients with refractory edema often have impaired absorption of oral diuretics and require intravenous therapy. The requirement for diuretics may decrease as the patient’s condition improves. Although patients who have recently presented with symptoms may quickly become symptom-free with diuretic therapy, treatment with agents that also modify the course of the disease is needed to reduce the risk of progression of the disease.

#### *Agents That Modify the Course of the Disease*

**Angiotensin-Converting–Enzyme (ACE) Inhibitors**  
ACE inhibitors are the first-line therapy for patients with systolic heart failure; therapy should be initiated promptly after diagnosis and continued indefinitely. ACE inhibitors reduce ventricular size, increase the ejection fraction modestly, and reduce symptoms.<sup>7,8</sup> Two large trials showed that when patients with NYHA class II, III, or IV heart failure were treated with enalapril, as compared with placebo, in addition to diuretics and digoxin, the rates of admission to the hospital were reduced, and there was a relative risk reduction for death of 16 to 40%.<sup>14,15</sup> In a placebo-controlled trial, enalapril therapy reduced the risk of the development of symptomatic heart failure among asymptomatic (NYHA class I) patients with left ventricular systolic dysfunction<sup>33</sup> and was su-



perior to the combination of hydralazine and isosorbide dinitrate in a head-to-head trial assessing mortality (18% vs. 25% mortality at 2 years,  $P < 0.02$ ).<sup>34</sup> ACE inhibitors also reduce the risk of myocardial infarction.<sup>15,33</sup> Treatment with ACE inhibitors is recommended for all patients who have left ventricular systolic dysfunction, irrespective of the cause of the condition or the severity of the symptoms (i.e., whether they are in NYHA class I, II, III, or IV).

#### Angiotensin-Receptor Blockers (ARBs)

The efficacy of ARBs is similar to that of ACE inhibitors, as evidenced by findings from a single large trial in which candesartan was used<sup>24</sup> and a subgroup analysis from a study of valsartan ther-

apy (Table 1 in the Supplementary Appendix).<sup>26</sup> Since ARBs are generally more expensive than ACE inhibitors, they are used as an alternative to ACE inhibitors primarily in patients in whom a cough develops as a result of ACE-inhibitor therapy.

ARBs are also used as additional therapy in patients who have symptoms that persist (i.e., patients who remain in NYHA class II, III, or IV) despite receiving an optimal dose of an ACE inhibitor and a beta-blocker. In two placebo-controlled, randomized trials (one in which valsartan was used<sup>26</sup> and one in which candesartan was used<sup>25</sup>), the addition of an ARB reduced the rate of hospitalization for heart failure by 17 to 22%; candesartan also reduced cardiovascular mortality by 16%.<sup>25</sup>



**Table 3. Evidence-Based Pharmacologic Treatment of Heart Failure.\***

Treatment	Starting Dose	No. of Doses per Day†	Dosing Target Total Daily Dose†	Mean Total Daily Dose Achieved in Outcome Studies	Contraindications, Cautions, and Adverse Events
<b>ACE inhibitors</b>					
Captopril <sup>13</sup>	6.25 mg	3	150 mg	121 mg	Contraindications include a history of angioedema and bilateral renal-artery stenosis. Be alert for serum potassium >5.0 mmol/liter, serum creatinine >2.5 mg/dl (220 μmol/liter), or symptomatic hypotension or systolic blood pressure <90 mm Hg. Possible adverse events include cough, angioedema, a rise in creatinine or blood urea nitrogen, hyperkalemia, and symptomatic hypotension.
Enalapril <sup>14,15</sup>	2.5 mg	2	20–40 mg	16.6 mg	
Lisinopril <sup>16</sup>	2.5–5.0 mg	1	20–35 mg	NA‡	
Ramipril <sup>17</sup>	2.5 mg	1 or 2	10 mg	8.7 mg§	
Trandolapril <sup>18</sup>	1.0 mg	1	4 mg	3 mg	Contraindications include asthma and second- or third-degree atrioventricular block. Be alert for recent decompensated heart failure and heart rate <55 bpm. Possible adverse events include bradycardia and atrioventricular block, bronchospasm, worsening heart failure during initiation of treatment or increase in dosage, and symptomatic hypotension.
Beta-blockers					
Bisoprolol <sup>19</sup>	1.25 mg	1	10 mg	6.2 mg	
Carvedilol <sup>20</sup>	3.125 mg	2	50–100 mg	37 mg¶	
Metoprolol CR/XL <sup>21</sup>	12.5 or 25 mg	1	200 mg	159 mg	Contraindications include bilateral renal-artery stenosis. Be alert for serum potassium >5.0 mmol/liter, serum creatinine >2.5 mg/dl, symptomatic hypotension, or systolic blood pressure <90 mm Hg. Possible adverse events include a rise in creatinine or blood urea nitrogen, hyperkalemia, and symptomatic hypotension.
Nebivolol <sup>23</sup>	1.25 mg	1	10 mg	7.7 mg**	
Angiotensin-receptor blockers					
Candesartan <sup>24,25</sup>	4 mg	1	32 mg	24 mg††	
Valsartan <sup>26</sup>	40 mg	2	320 mg	254 mg	Contraindications include serum potassium >5.0 mmol/liter and serum creatinine >2.0 mg/dl (175 μmol/liter). Be alert for serum potassium >4.5 mmol/liter and serum creatinine >2.0 mg/dl (175 μmol/liter). Possible adverse events include hyperkalemia, rise in creatinine or blood urea nitrogen, and gynecomastia and breast pain in men (more common with spironolactone).
Losartan <sup>27</sup>	50 mg	1	150 mg	129 mg‡‡	
Aldosterone blockers					
Eplerenone <sup>28</sup>	25 mg	1	50 mg	43 mg	
Spironolactone <sup>29</sup>	25 mg	1	25–50 mg	26 mg	Contraindications include lupus syndrome. Be alert for symptomatic hypotension or systolic blood pressure <90 mm Hg. Possible adverse events include headache, symptomatic hypotension, arthralgia, and lupus-like syndrome.
Hydralazine–isosorbide dinitrate§§	37.5 mg	3	225 mg	143 mg	
Hydralazine	20 mg	3	120 mg	60 mg	
Isosorbide dinitrate <sup>30</sup>					

\* The information in this table is based on randomized, controlled trials involving patients with chronic heart failure or with heart failure, left ventricular systolic dysfunction, or both after myocardial infarction. ACE denotes angiotensin-converting enzyme; metoprolol CR/XL metoprolol succinate, controlled release or extended release, and NA not available.

† Doses are based on the total daily dose, taken as one pill daily or split into two or three equal portions (e.g., the target total daily dose of captopril is 150 mg, taken as 50 mg three times a day on the basis of results of the Survival and Ventricular Enlargement [SAVE] study).<sup>13</sup>

‡ The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial compared high-dose lisinopril (32.5 to 35.0 mg) to low-dose lisinopril (2.5 to 5.0 mg); guidelines recommend 20 mg daily as a single dose.<sup>16</sup>

§ This value is based on the results of the Acute Infarction Ramipril Efficacy (AIRE) study, in which ramipril was prescribed twice daily (with a target total daily dose of 10 mg).<sup>17</sup>

¶ This value is based on the results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) study, in which the target total daily dose was 50 mg.<sup>20</sup>

|| This value is based on results for metoprolol succinate. The Carvedilol or Metoprolol European Trial (COMET) showed that low doses of metoprolol tartrate are inferior to carvedilol.<sup>22</sup>

‡‡ This value is based on the results of the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORES) trial.<sup>23</sup>

‡‡‡ This value is based on the results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM)-Added trial (ClinicalTrials.gov number, NCT00634309).<sup>25</sup>

§§ losartan once daily were compared.<sup>27</sup>

||| These data are based on the African-American Heart Failure Trial (A-HeFT; NCT00047775)<sup>30</sup>; this combination was given four times daily in the 1st Vasodilator Heart Failure Trial (V-HeFT I).<sup>31</sup>

### Beta-Blockers

Along with ACE inhibitors, beta-blockers are essential first-line therapy in patients with heart failure and left ventricular systolic dysfunction, regardless of the cause of the condition.<sup>7,8,19-21</sup> Treatment with beta-blockers improves systolic function, resulting in an increase in ejection fraction of 5 to 10%, and reduces symptoms. In three placebo-controlled trials, beta-blocker therapy (with bisoprolol,<sup>19</sup> carvedilol,<sup>20</sup> or metoprolol CR/XL [metoprolol succinate, controlled release or extended release]<sup>21</sup>) reduced the rate of hospital admissions and reduced mortality by 34%, when it was added to an ACE inhibitor, diuretic, and digoxin among patients with NYHA class II, III, or IV symptoms. Among patients hospitalized with acute decompensation who are not already taking a beta-blocker, beta-blocker therapy should be deferred until the patient's condition improves but should be initiated before the patient's discharge from the hospital. Long-term beta-blocker therapy should not be stopped during episodes of decompensation unless the patient has severe systemic underperfusion, in which case it should be withdrawn until the patient is hemodynamically stable and his or her condition is improved.<sup>35</sup>

### Aldosterone Antagonists

In a large, placebo-controlled, randomized trial in which patients received spironolactone in addition to a diuretic, digoxin, and an ACE inhibitor, a reduction in symptoms and in hospital admissions, and a 30% reduction in mortality, were seen among patients with severe systolic heart failure (NYHA class III or IV).<sup>29</sup> Therefore, the addition of an aldosterone antagonist should be considered for any patient who remains in NYHA class III or IV despite treatment with a diuretic, an ACE inhibitor (or ARB), and a beta-blocker. Either an aldosterone antagonist or an ARB (but not both, because of the risk of renal dysfunction and hyperkalemia) may be added to an ACE inhibitor.

### Hydralazine and Isosorbide Dinitrate

Retrospective subgroup analyses from two trials of hydralazine and isosorbide dinitrate<sup>36</sup> (one a placebo-controlled trial<sup>31</sup> and the other a comparison of hydralazine–isosorbide dinitrate with enalapril<sup>34</sup>) and from the Studies of Left Ventricular Dysfunction<sup>37</sup> (in which enalapril was compared with placebo) suggested that black patients did not have as good a response to an ACE inhibitor as did

white patients, but had a better response to hydralazine–isosorbide dinitrate than did white patients. In a subsequent randomized, placebo-controlled trial involving patients with NYHA class III or IV heart failure who self-identified as African American,<sup>30</sup> treatment with hydralazine–isosorbide dinitrate, when added to an ACE inhibitor, a beta-blocker, and, in some cases, an aldosterone antagonist, resulted in a reduced rate of hospitalization for heart failure, improved quality of life, and increased survival.<sup>30</sup>

### Other Medications

In the single large trial involving patients with systolic heart failure who were in sinus rhythm, digoxin, when added to a diuretic and an ACE inhibitor, had no effect on mortality but reduced the risk of hospitalization for heart failure by 28% (Table 1 in the Supplementary Appendix).<sup>38</sup> A recent study showed that treatment with 1 gram of n-3 polyunsaturated fatty acid per day (850 to 852 mg of eicosapentaenoic acid and docosahexaenoic acid as ethyl esters in the average ratio of 1:1.2) led to a small reduction in cardiovascular complications and death in patients with heart failure (Table 1 in the Supplementary Appendix).<sup>39</sup> The exact mechanism of action of this treatment is uncertain, although it may have beneficial antiinflammatory and electrophysiological effects (the latter reducing the risk of arrhythmias). Some conventional cardiovascular drugs (e.g., aspirin,<sup>40</sup> statins,<sup>41</sup> and erythropoiesis-stimulating agents<sup>42</sup>) are of uncertain benefit in patients with heart failure, and some drugs can be harmful, including thiazolidinediones, nonsteroidal antiinflammatory drugs, and most antiarrhythmic drugs (including dronedarone<sup>43</sup>). Vitamin K antagonists reduce the risk of thromboembolism in patients with atrial fibrillation but have not been shown to be of value in other patients with heart failure.<sup>7,8,40</sup> Pneumococcal and influenza vaccinations are recommended.<sup>7,8</sup>

### ORGANIZATION OF CARE

A multidisciplinary intervention that is focused on both the patient and the caregiver results in a reduction in the rate of hospital admissions and has also been shown in a meta-analysis of trials to reduce mortality.<sup>44</sup> Educating patients, their families, and caregivers about heart failure, its treatment, and the early recognition of and response to clinical deterioration (e.g., new or wors-

ening symptoms or weight gain) appears to be of central importance. The importance of adhering to treatment should be emphasized, and guidance on flexible dosing of diuretics should be provided. These disease-management programs also provide the framework for optimizing evidence-based pharmacologic therapy and encouraging regular exercise. End-of-life palliative care should also be available for patients with end-stage heart failure.<sup>45</sup>

#### LIFESTYLE AND EXERCISE

Restriction of sodium intake is routinely recommended, although this recommendation is based on little evidence.<sup>7,8</sup> A recent trial showed that tailored, structured, aerobic exercise was safe and improved functional capacity and quality of life in patients with heart failure (Table 1 in the Supplementary Appendix).<sup>46</sup> That trial and a meta-analysis of smaller studies also suggested that exercise may reduce the risk of death and of hospitalization for heart failure.<sup>46</sup> The intervention used in the study, however, was labor-intensive.

#### DEVICES

##### *Implantable Cardioverter–Defibrillators*

About half the deaths that occur among patients with systolic heart failure are attributed to ventricular arrhythmias; the proportion is higher among patients with mild symptoms, whereas patients with severe heart failure are more likely to die from pump failure. An implantable cardioverter–defibrillator reduces the risk of sudden death in patients with left ventricular systolic dysfunction,<sup>47</sup> with no adverse effect on quality of life,<sup>48</sup> although the benefit is not apparent until a year or more after implantation of the device (Table 1 in the Supplementary Appendix).<sup>47</sup>

An implantable cardioverter–defibrillator is indicated for secondary prevention, in the case of any patient who survives an unprovoked episode of ventricular fibrillation or sustained ventricular tachycardia,<sup>7,8</sup> and for primary prevention, in the case of patients in NYHA functional class II or III who have an ejection fraction that is persistently 35% or less despite optimal medical therapy and who are expected to survive for at least 1 year with a reasonable quality of life and functional status.<sup>7,8,47</sup>

##### *Cardiac-Resynchronization Therapy*

Intraventricular conduction delays, identified by a QRS interval of 120 msec or more on a 12-lead

electrocardiogram, occur in up to a third of patients with severe systolic heart failure and are associated with dyssynchronous contraction of the left ventricle, leading to impaired emptying and, in some patients, mitral regurgitation.<sup>49,50</sup> Abnormal atrioventricular coupling (identified by a prolonged PR interval) and interventricular dyssynchrony, identified on an echocardiogram, may also occur. Cardiac-resynchronization therapy with atrial-synchronized biventricular pacing often improves cardiac performance immediately, by increasing stroke volume and reducing mitral regurgitation.<sup>7,8</sup> Randomized trials involving patients with severe heart failure showed that cardiac-resynchronization therapy resulted in a reduction in symptoms and improved functional capacity, a reduction in the number of hospitalizations for worsening heart failure, and increased survival.<sup>49,50</sup> On the basis of these trials, current guidelines recommend cardiac-resynchronization therapy for patients with severe symptoms (NYHA class III or IV), an ejection fraction that is persistently 35% or below, sinus rhythm, and a QRS duration of 120 msec or more.<sup>7,8</sup> Although cardiac-resynchronization therapy was not shown to be beneficial in patients with NYHA class III symptoms and a narrow QRS interval (<120 msec),<sup>51</sup> a recent randomized trial involving patients with NYHA class I or II symptoms, ejection fractions of 30% or less, and wide QRS intervals ( $\geq 130$  msec) showed that cardiac-resynchronization therapy in addition to an implantable cardioverter–defibrillator, as compared with an implantable cardioverter–defibrillator alone, improved ventricular function and reduced the risk of worsening heart failure; these effects were most pronounced in patients with a QRS interval of 150 msec or more (Table 1 in the Supplementary Appendix).<sup>52</sup> Cardiac-resynchronization therapy did not reduce the risk of death in this population with a relatively low mortality.<sup>52</sup>

#### SURGERY

Although coronary revascularization is performed frequently, its role, especially in patients who do not have angina or reversible myocardial ischemia, is uncertain; this surgical treatment is currently being evaluated in a randomized trial.<sup>53</sup> Other procedures, such as repair of the mitral valve, are used empirically in selected patients. A recent trial showed that surgical ventricular reconstruction provided no benefit with respect to



symptoms or rates of death or hospitalization for cardiac causes.<sup>54</sup>

Cardiac transplantation is a last resort for patients with refractory heart failure. The patient must be otherwise fit for surgery and must be able to adhere to the intensive medical treatment and follow-up that are required postoperatively. Given the scarcity of donor organs,<sup>7,8</sup> there has been interest in left ventricular assist devices as a bridge to transplantation or even as definitive therapy. Whereas older pulsatile volume-displacement ventricular assist devices were not shown to improve 2-year survival in patients with end-stage heart failure who were ineligible for transplantation (Table 1 in the Supplementary Appendix) and were associated with relatively high rates of bleeding, infection, stroke, and repeat surgery to repair or replace the device,<sup>55</sup> newer ventricular assist devices appear to be more effective and safer.<sup>7,8</sup> In a recent trial comparing a continuous-flow device with an older pulsatile volume-displacement device in patients with end-stage heart failure who were ineligible for transplantation,<sup>56</sup> the 2-year survival without disabling stroke or the need for repeat surgery to repair or replace the device was significantly greater with the new device than with the older device (46% vs. 11%).

#### AREAS OF UNCERTAINTY

Randomized trials (e.g., the Reduction of Events with Darbepoetin Alfa in Heart Failure trial [RED-HF; NCT00358215]<sup>42</sup> and the Surgical Treatment for Ischemic Heart Failure trial [STICH; NCT00023595]<sup>53</sup>) are in progress to assess the benefit of an aldosterone antagonist as treatment for patients who are categorized as NYHA functional class II and to define the roles that correction of anemia and coronary revascularization play in the treatment of patients with systolic heart failure. The optimal content of disease-management programs is uncertain.<sup>44</sup> It is not known whether telemonitoring, implanted monitoring devices, or therapy guided by the measurement of natriuretic peptides improves the outcomes.<sup>57,58</sup> Whether persons with a narrow QRS interval, mild symptoms, or atrial fibrillation benefit from cardiac-resynchronization therapy is uncertain, nor is it clear which patients benefit from cardiac-resynchronization therapy alone and which patients need a device that provides both cardiac-resynchronization therapy and implantable car-

dioversion–defibrillation. The effectiveness and cost-effectiveness of ventricular assist devices require further evaluation.

#### GUIDELINES

The recommendations in this article are consistent with international guidelines.<sup>7,8</sup>

#### CONCLUSIONS AND RECOMMENDATIONS

The patient in this vignette presented with typical symptoms and signs of heart failure. Although systolic dysfunction is the likely diagnosis, given the patient's previous myocardial infarction, confirmation by echocardiography (or other imaging) is essential. In cases in which heart failure is a less likely diagnosis, measurement of natriuretic peptides may be useful as a first step, since a normal concentration suggests an alternative diagnosis.

A diuretic will quickly alleviate the patient's dyspnea and edema, but it is insufficient therapy alone. Both an ACE inhibitor and a beta-blocker should be prescribed at doses that have been shown in randomized trials to be effective; if symptoms persist, an aldosterone antagonist or ARB should be added. With these treatments, I would expect the patient's ejection fraction to improve over the course of 3 to 6 months, but if it remains at 35% or below, an implantable cardioverter–defibrillator should be considered. If the patient's 12-lead electrocardiogram shows QRS prolongation, I would consider a device that provides both cardiac-resynchronization therapy and implantable cardioversion–defibrillation instead, especially if he continues to have functional limitations owing to his symptoms.

Close monitoring is warranted, particularly during the initiation of therapy and the adjustment of the doses. I would encourage participation in a disease-management program, which would provide him and his family education<sup>59,60</sup> regarding heart failure and appropriate dietary, exercise, and other self-care interventions.

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