

## CLINICAL PRACTICE

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# Heart Failure with Preserved Ejection Fraction

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*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.*

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N Engl J Med 2016;375:1868-77.

DOI: 10.1056/NEJMc1511175

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**A 73-year-old woman with a history of dyspnea on exertion presents for a follow-up visit after hospitalization for acute worsening of dyspnea and orthopnea. On admission to the hospital, the patient had atrial fibrillation with a ventricular rate of 120 beats per minute, and chest radiography revealed pulmonary venous hypertension. Despite anticoagulation, rate control with a beta-blocker, and administration of loop diuretics during the hospitalization, she continues to have fatigue and exertional dyspnea. On physical examination, the body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) is 39, pulse 76 beats per minute, and blood pressure 160/70 mm Hg. There is jugular venous distention and lower-extremity edema but no third heart sound, murmurs, or rales. The serum creatinine level is 1.4 mg per deciliter (124  $\mu$ mol per liter), estimated glomerular filtration rate (GFR) 37 ml per minute per 1.73 m<sup>2</sup> of body-surface area, and N-terminal pro–brain natriuretic peptide (NT-proBNP) level 300 pg per milliliter (age-specific and sex-specific normal range, 10 to 218 pg per milliliter). Echocardiography reveals an ejection fraction of 70%, a normal left ventricular cavity dimension and wall thickness, and left atrial enlargement. Doppler echocardiography shows elevated left atrial pressure (E/e' ratio, 22) and an estimated pulmonary-artery systolic pressure of 52 mm Hg. How should this patient's condition be managed?**

## THE CLINICAL PROBLEM

**E**PIDEMIOLOGIC STUDIES INDICATE THAT UP TO 50% OF PATIENTS WITH heart failure have a preserved ejection fraction, and this proportion has increased over time.<sup>1</sup> In observational studies, rates of hospitalization and death among patients who have heart failure with a preserved ejection fraction approach those among patients who have heart failure with a reduced ejection fraction,<sup>1</sup> but in clinical-trial populations, outcomes are better in patients who have heart failure with a preserved ejection fraction.<sup>2</sup> Death from noncardiovascular causes is more common in patients who have heart failure with a preserved ejection fraction than in those with a reduced ejection fraction.<sup>3,4</sup>

Ventricular diastolic dysfunction (impaired relaxation and increased diastolic stiffness) that is present at rest or induced by stress (from exercise, tachycardia, or hypertension) is a central perturbation in heart failure with a preserved ejection fraction.<sup>1,5-9</sup> Although the ejection fraction is normal at rest, the ejection fraction does not increase appropriately with stress,<sup>1</sup> and other measures of systolic function are abnormal.<sup>10</sup> Endothelial dysfunction, arterial stiffening, and increased ventricular systolic

## KEY CLINICAL POINTS

**HEART FAILURE WITH PRESERVED EJECTION FRACTION**

- In patients who have signs and symptoms of heart failure but a preserved ejection fraction, objective evidence of abnormal cardiac structure and function should be confirmed by means of echocardiography, electrocardiography, chest radiography, and measurement of natriuretic peptide levels.
- Natriuretic peptide levels may be normal in patients who have heart failure with a preserved ejection fraction, particularly in obese patients or those with symptoms only on exertion.
- Right heart catheterization may be required in patients in whom there is indeterminate noninvasive testing or evidence of pulmonary hypertension.
- Medications that improve outcomes in patients who have heart failure with a reduced ejection fraction have not been shown to be of benefit in those who have heart failure with a preserved ejection fraction.
- Treatment of heart failure with a preserved ejection fraction should include diuretics for volume overload, treatment for cardiovascular and noncardiovascular coexisting conditions, aerobic exercise training to increase exercise tolerance, education regarding self-care, and disease management programs for patients with refractory symptoms or frequent hospitalizations for heart failure.

stiffness are also common and may result in heightened sensitivity to changes in load; this sensitivity manifests as rapid-onset pulmonary edema with increases in load and excessive hypotension with decreases in load.<sup>1</sup> Exercise performance is impaired owing to impaired chronotropic, vasodilatory, and ventricular diastolic and systolic reserve functions and impaired oxygen uptake and utilization in the peripheral muscles.<sup>5,11,12</sup>

The fundamental pathophysiological perturbation leading to heart failure with a preserved ejection fraction remains incompletely defined, but traditionally it has been attributed to hypertensive left ventricular remodeling<sup>1</sup> (Fig. 1). Systemic microvascular endothelial inflammation related to coexisting conditions has been proposed as an additional mechanism leading to myocardial inflammation and fibrosis, increases in oxidative stress, and alterations in cardiomyocyte signaling pathways. These alterations promote cardiomyocyte remodeling and dysfunction (Fig. 1)<sup>13,14</sup> as well as microvascular dysfunction and rarefaction in cardiac<sup>15,16</sup> and skeletal<sup>11,12</sup> muscle (Fig. 1).

## STRATEGIES AND EVIDENCE

**DIAGNOSIS AND EVALUATION**

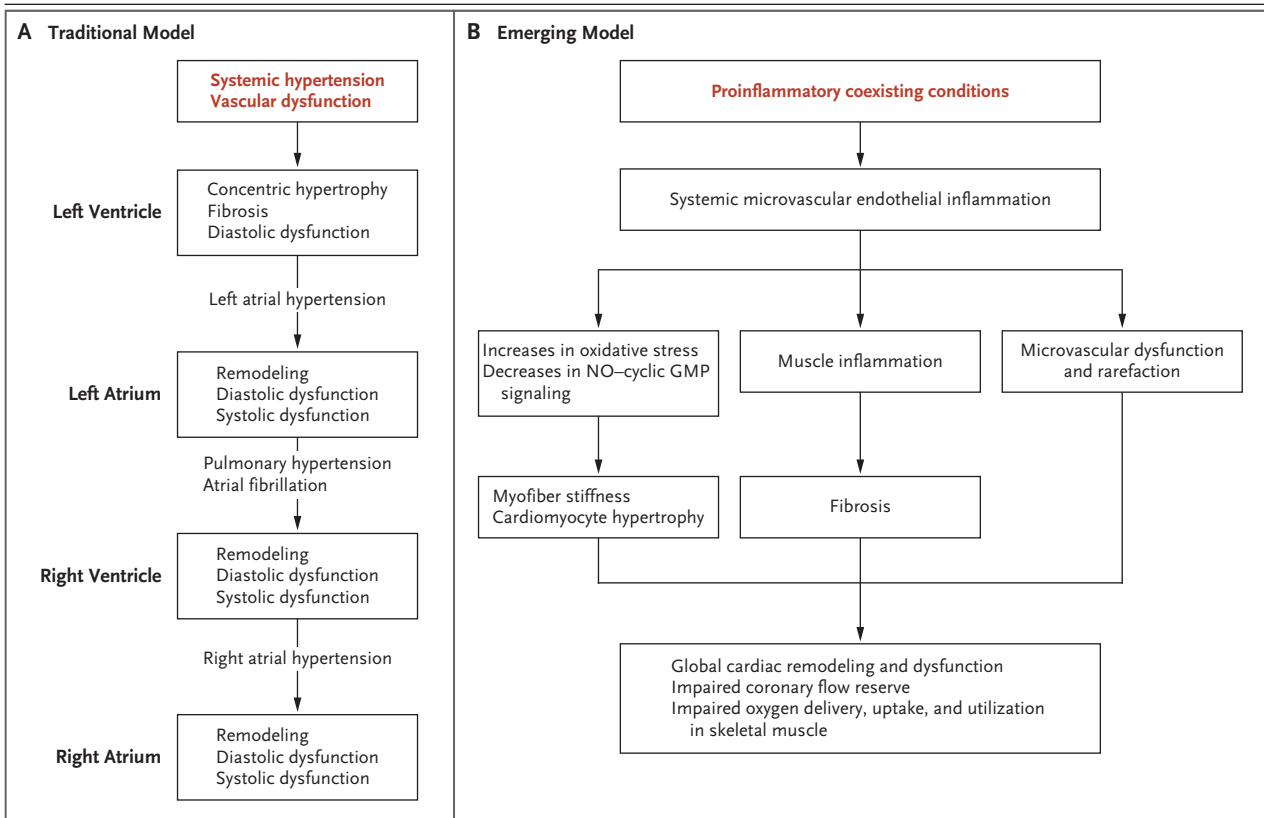
Since signs and symptoms of heart failure are non-specific, clinicians should maintain a high index of suspicion for heart failure in patients with risk factors, but they also should consider alternative or contributing diagnoses (Fig. 2). The clinical history should include ascertainment of reduced symptoms in response to diuretic therapy and

previous hospitalizations for or complicated by heart failure. In some patients, heart failure manifests as “unexplained” exertional dyspnea. In such patients, differentiating heart failure from noncardiac dyspnea or deconditioning can be challenging. In patients with suspected heart failure, comprehensive Doppler echocardiography should be performed.

**ECHOCARDIOGRAPHIC FINDINGS AND NATRIURETIC PEPTIDE LEVELS**

In observational studies and clinical trials, the value used to define a “preserved” ejection fraction has ranged from 40 to 55%, but current guidelines recommend a partition value of 50%.<sup>17,18</sup> An ejection fraction of 40 to 49% is a gray area.<sup>17</sup> Patients who previously had an ejection fraction of less than 40% but in whom the ejection fraction increased with therapy for heart failure are considered to have “recovered” heart failure with a reduced ejection fraction. In these patients, medications for heart failure that have a proven benefit in patients with a reduced ejection fraction should be continued.

If the ejection fraction is preserved, evidence of altered cardiac structure and function should be sought to provide further objective evidence of heart failure (Fig. 2). The size of the left ventricular cavity is usually normal. Evidence of left ventricular hypertrophy (Fig. 2) is common but absent in many patients.<sup>8,19</sup> Doppler echocardiographic evidence of diastolic dysfunction (slowed ventricular relaxation and increased diastolic stiffness or elevated left atrial pressure) is common

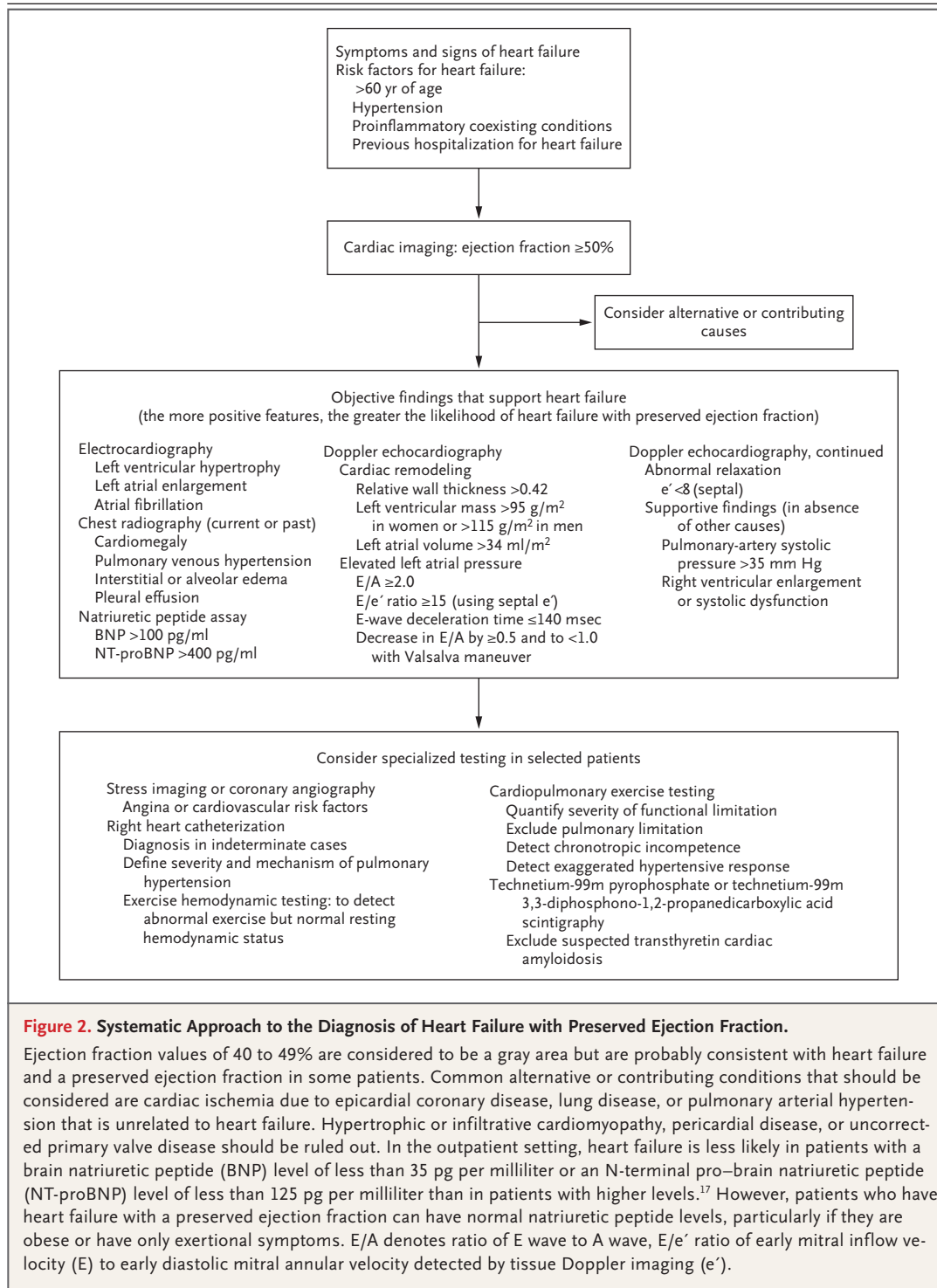


**Figure 1. Traditional and Emerging Pathophysiological Models of Heart Failure with Preserved Ejection Fraction.**

Most patients who have heart failure with a preserved ejection fraction have a history of hypertension. In the traditional pathophysiological model, pressure overload leads to concentric left ventricular hypertrophic and fibrotic remodeling and diastolic dysfunction. Ultimately, the left ventricular diastolic dysfunction leads to left atrial hypertension and remodeling, pulmonary venous hypertension, and right ventricular and atrial remodeling and dysfunction. Atrial fibrillation is common because of the chronic left atrial hypertension and subsequent structural and electrical remodeling. In the emerging model, proinflammatory cardiovascular and noncardiovascular coexisting conditions (e.g., hypertension, obesity, diabetes, the metabolic syndrome, lung disease, smoking, and iron deficiency) lead to systemic microvascular endothelial inflammation, global cardiac and skeletal-muscle inflammation, and subsequent fibrosis. These conditions also lead to increases in oxidative stress that limit nitric oxide–cyclic guanosine monophosphate (NO–cyclic GMP)–protein kinase G signaling, promoting global cardiomyocyte hypertrophy and intrinsic myofiber stiffness. Finally, coronary microvascular inflammation results in microvascular dysfunction and rarefaction with reduced microvascular density and coronary flow reserve. Similar changes occur in the skeletal-muscle vasculature with reduced oxygen delivery and utilization.

(Fig. 2).<sup>8,9,20</sup> However, diastolic dysfunction also may be present in patients who do not have heart failure<sup>21</sup> and absent in patients who have received aggressive treatment for heart failure or those with predominantly exertional symptoms.<sup>6,7</sup> The left atrium is usually enlarged. Pulmonary-artery systolic pressure, estimated by means of Doppler echocardiography, is often elevated (>35 mm Hg).<sup>22</sup> Right ventricular systolic dysfunction is present in 20 to 30% of patients, often in association with atrial fibrillation.<sup>23</sup> Atrial remodeling can lead to annular dilatation and functional mitral and tricuspid regurgitation, but primary valvular disease should be ruled out.

Atrial fibrillation is very common and may precede, present concurrently with, or occur subsequent to the onset of heart failure with a preserved ejection fraction.<sup>24</sup> Radiographic evidence of heart failure (Fig. 2) is common in patients who present with acute heart failure, but radiographic evidence of heart failure is not necessarily present in patients who are in stable condition. Ventricular wall stress and thus circulating levels of natriuretic peptides are lower in patients who have heart failure with a preserved ejection fraction than in patients who have heart failure with a reduced ejection fraction.<sup>25</sup> Levels of natriuretic peptides may be normal in up to 30%



**Figure 2. Systematic Approach to the Diagnosis of Heart Failure with Preserved Ejection Fraction.**

Ejection fraction values of 40 to 49% are considered to be a gray area but are probably consistent with heart failure and a preserved ejection fraction in some patients. Common alternative or contributing conditions that should be considered are cardiac ischemia due to epicardial coronary disease, lung disease, or pulmonary arterial hypertension that is unrelated to heart failure. Hypertrophic or infiltrative cardiomyopathy, pericardial disease, or uncorrected primary valve disease should be ruled out. In the outpatient setting, heart failure is less likely in patients with a brain natriuretic peptide (BNP) level of less than 35 pg per milliliter or an N-terminal pro-brain natriuretic peptide (NT-proBNP) level of less than 125 pg per milliliter than in patients with higher levels.<sup>17</sup> However, patients who have heart failure with a preserved ejection fraction can have normal natriuretic peptide levels, particularly if they are obese or have only exertional symptoms. E/A denotes ratio of E wave to A wave, E/e' ratio of early mitral inflow velocity (E) to early diastolic mitral annular velocity detected by tissue Doppler imaging (e').

of patients who have heart failure with a preserved ejection fraction,<sup>26</sup> particularly in those who are obese<sup>27</sup> or have purely exertional symptoms.<sup>6</sup> The higher the natriuretic peptide level,

the more likely it is that the patient has heart failure (Fig. 2). However, some elderly patients<sup>28,29</sup> or patients who have atrial fibrillation<sup>30</sup> without heart failure may have natriuretic peptide levels

that are similar to those of patients with heart failure.

#### SPECIALIZED TESTING IN SELECTED PATIENTS

Specific cardiac conditions that can cause heart failure when a preserved ejection fraction is present (e.g., pericardial disease and hypertrophic or infiltrative cardiomyopathies) must be considered in the differential diagnosis in patients who have heart failure with a preserved ejection fraction (Fig. 2). Epicardial coronary atherosclerosis can account for symptoms of heart failure with exertional dyspnea or angina, but angina is also common in patients who do not have coronary disease.<sup>31</sup> In most patients with coronary disease, the coronary disease is of insufficient severity to account for the severity of heart failure, but it is a risk factor for future coronary events and death.<sup>31</sup>

Stress testing, coronary angiography, or both should be performed if the patient has symptoms of or risk factors for coronary artery disease and is a candidate for anti-ischemic medications or revascularization. Standard exercise stress testing provides information about functional limitation and about the possibility of chronotropic incompetence or exaggerated hypertensive response to exercise. Cardiopulmonary exercise testing can be useful to rule out noncardiac limitations to exercise such as poor effort, deconditioning, and pulmonary disease. Pulmonary-artery catheterization with or without exercise may be needed to establish the diagnosis in patients in whom the findings of noninvasive studies are indeterminate or to document the severity and mechanism of pulmonary hypertension when pulmonary-artery systolic pressure estimated with Doppler echocardiography is significantly elevated (>50 mm Hg).

Pulmonary hypertension in heart failure is due to pulmonary venous hypertension and sometimes modest increases (2 to 4 Wood units) in pulmonary vascular resistance<sup>22</sup>; higher values should spur evaluation of other causes contributing to pulmonary hypertension. Large “V waves” (twice the mean pulmonary arterial wedge pressure value and >25 mm Hg) in the pulmonary arterial wedge pressure wave forms at rest or with stress (in the absence of marked mitral regurgitation) indicate reduced left atrial compliance, a hemodynamic hallmark of this condition.<sup>32,33</sup>

Cardiac magnetic resonance imaging may be useful if infiltrative cardiomyopathy (amyloidosis) or inflammatory cardiomyopathy (sarcoidosis) is

suspected. Scintigraphy with specific radioactive tracers can also assist in the recognition of transthyretin cardiac amyloidosis<sup>34</sup> and should be considered in older patients with increased ventricular-wall thickness ( $\geq 12$  mm) on echocardiography.<sup>35</sup>

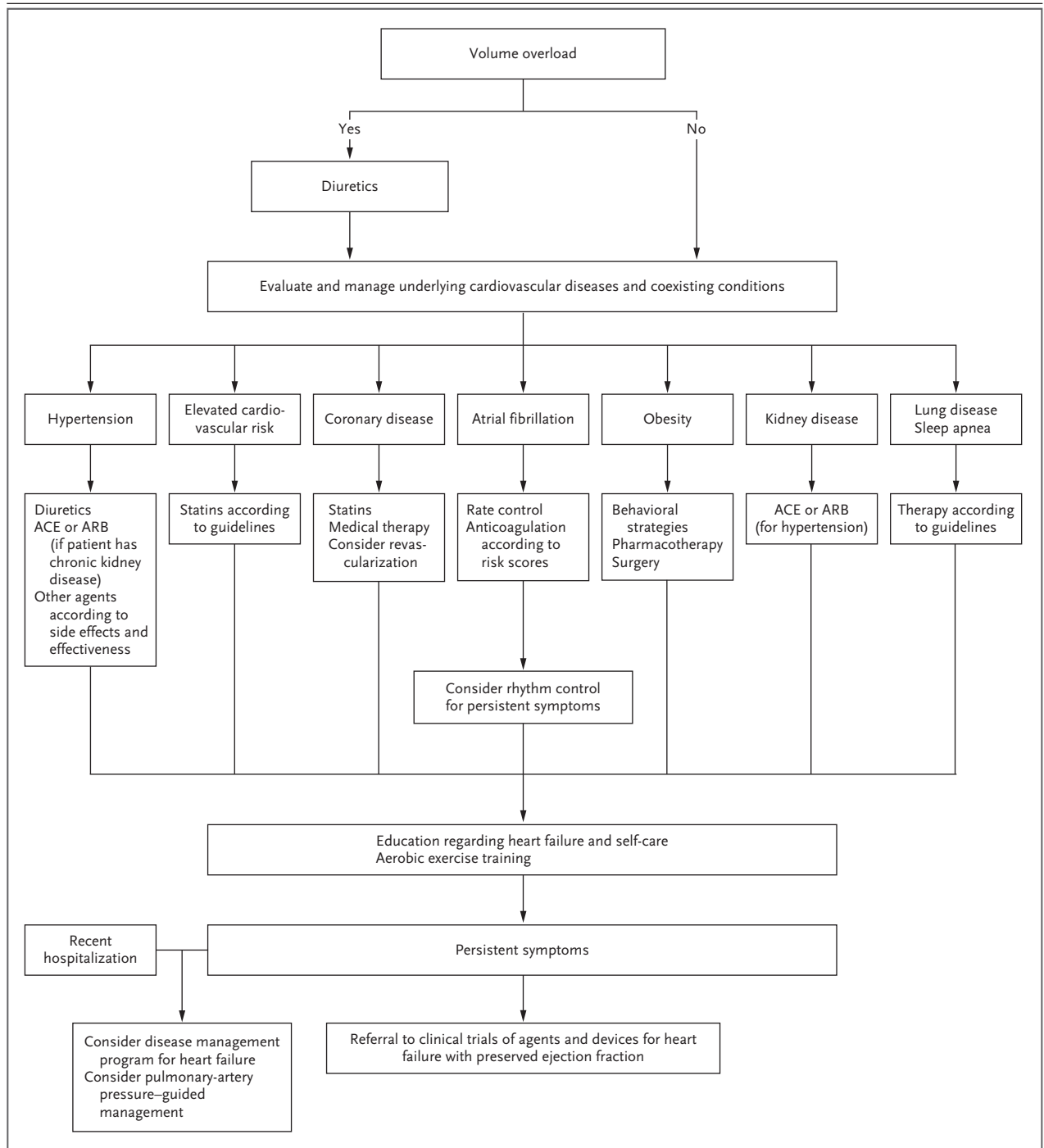
Renal artery stenosis should be considered in patients with risk factors for this condition (e.g., renal dysfunction or peripheral vascular disease) and a history of recurrent acute episodes of heart failure with a preserved ejection fraction.<sup>36</sup> In patients who have a normal or only mildly elevated creatinine level, the requirement for a high dose of a diuretic should prompt further evaluation of renal function (e.g., measurement of the cystatin C level).

#### TREATMENT

Since no therapy has been shown to improve outcomes in patients who have heart failure with a preserved ejection fraction, current therapy (Fig. 3) includes the relief of volume overload (when present), treatment of coexisting conditions, additional strategies that may increase exercise tolerance or reduce symptoms, and strategies to manage chronic disease and prevent hospitalizations.

#### *Trials of Therapies to Improve Outcomes*

Individually or in a meta-analysis, three randomized trials of angiotensin antagonists (angiotensin-converting-enzyme [ACE] inhibitors or angiotensin-receptor antagonists) involving patients who had heart failure with a preserved ejection fraction did not show significant effects of these agents on composite end points of all-cause or cardiovascular mortality and hospitalizations for heart failure.<sup>37</sup> The mineralocorticoid-receptor antagonist spironolactone did not reduce rates of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure in these patients.<sup>38</sup> Spironolactone reduced the rate of hospitalization for heart failure but not the rate of death from any cause or hospitalization for any cause, and it increased the rate of renal dysfunction and hyperkalemia. Analyses that were limited to patients who were enrolled in centers in the Americas (which had higher event rates) showed beneficial effects of spironolactone on the composite primary end point, but these post hoc analyses must be interpreted with caution.<sup>39</sup> The effect of beta-blockers in patients with heart failure and a pre-



**Figure 3. Treatment Algorithm for Heart Failure with Preserved Ejection Fraction.** ACE denotes angiotensin-converting-enzyme inhibitor, and ARB angiotensin-receptor blocker.

served ejection fraction has not been evaluated in an adequately powered study, and the limited available data are conflicting.<sup>40-43</sup>

Thus, the use of angiotensin antagonists and

beta-blockers in the treatment of patients who have heart failure with a preserved ejection fraction should be limited to patients who have alternative indications for their use. The use of

spironolactone in patients who have heart failure with a preserved ejection fraction remains controversial.

#### *Treatment of Volume Overload*

Diuretics, which should be used for relief of symptoms in patients with volume overload, should be adjusted according to the patient's body weight, symptoms, and electrolyte status. Intermittent use of a thiazide-like diuretic such as metolazone, administered before the dose of a loop diuretic, may be helpful in outpatients with volume overload that is refractory to higher doses of loop diuretics. However, the use of this agent calls for careful monitoring because of the risk of hypokalemia, hyponatremia, and worsening renal function. Persistent diuretic resistance may result from impaired diuretic absorption, necessitating intravenous administration of loop diuretics.

Although the evidence base is limited,<sup>17,18</sup> sodium restriction (to 2 g per day) may be helpful in patients who are prone to volume overload. At a minimum, high-sodium diets (>6 g per day) and rapid fluctuations in sodium intake should be avoided.<sup>17,18</sup>

#### *Treatment of Coexisting Conditions*

Data to guide treatment of coexisting conditions and risk factors specifically in patients with heart failure and a preserved ejection fraction are very limited. Hypertension can exacerbate heart failure and predispose patients to other adverse outcomes.<sup>18</sup> The Eighth Joint National Committee guidelines do not include a specific blood-pressure target for persons with heart failure. However, they recommend target blood pressures of less than 150/90 mm Hg in persons who are 60 years of age or older in the general population<sup>44</sup> and of less than 140/90 mm Hg in persons with kidney disease (estimated GFR, <60 ml per minute per 1.73 m<sup>2</sup> of body-surface area or >30 mg of albumin per gram of creatinine, regardless of diabetic status) and for persons with diabetes, regardless of age. A recent trial showed that lower rates of cardiovascular events and death were associated with blood-pressure targets lower than those recommended by current guidelines, but the trial did not enroll patients with heart failure.<sup>45</sup>

Most patients with heart failure and hypertension will require a diuretic. All patients with

hypertension and concomitant kidney disease should receive an angiotensin antagonist, regardless of their race or diabetic status<sup>44</sup> (Fig. 3). In patients who do not have concomitant kidney disease, a thiazide-like diuretic, angiotensin antagonist, or calcium-channel blocker for non-blacks and a thiazide-like diuretic or calcium-channel blocker for blacks are appropriate for initial management.<sup>44</sup> Aggressive use of vasodilators may lead to unacceptable side effects in patients with heart failure with a preserved ejection fraction. The choice of additional agents to achieve blood-pressure control should be guided by the presence of coexisting conditions, the patient's ability to receive the agent without adverse effects, and the effect of the agent on blood pressure.

Patients should be treated with statins according to the usual criteria. Observational studies, including a propensity-score-matched analysis,<sup>46</sup> have shown lower mortality among patients with heart failure with a preserved ejection fraction who have received statins than among those who have not received statins, but it remains unclear whether this association is causal.

Patients with coronary artery disease should receive medical therapies according to current guidelines.<sup>47</sup> Limited (and potentially confounded) observational data in patients who have heart failure with a preserved ejection fraction and coronary disease have suggested better outcomes among those who have undergone complete revascularization than among those who have not.<sup>31</sup> Revascularization can be considered for symptom relief in patients who are otherwise eligible for this procedure and who have clinically significant angina or in whom clinically significant ischemia is evident and thought to contribute to dyspnea as an angina equivalent.<sup>18</sup>

Atrial fibrillation should be managed according to current guidelines, which recommend rate control and anticoagulation initially, and a trial of rhythm control should be considered if symptoms persist despite adequate rate control.<sup>17,18,48</sup> Patients may be most likely to benefit from rhythm control if the symptoms of heart failure started or worsened after the onset of atrial fibrillation.

Obesity may contribute to exercise intolerance. In a small randomized trial, intentional weight loss significantly increased exercise toler-

ance but did not increase a heart failure–specific quality-of-life score in obese patients who had heart failure with a preserved ejection fraction.<sup>49</sup> To increase exercise tolerance, weight loss in obese patients (BMI,  $\geq 35$ ) with heart failure should be considered.<sup>17</sup>

Lung disease and disordered breathing during sleep are common comorbid conditions in patients with heart failure, provoke symptoms (dyspnea and fatigue) that are similar to those of heart failure, and may exacerbate hypertension and heart failure. Thus, aggressive treatment of concomitant lung disease and sleep apnea according to current guidelines is reasonable.

#### *Other Therapies to Reduce Symptoms or Increase Exercise Tolerance*

Nitrates are often prescribed for patients who have heart failure and a preserved ejection fraction. However, a randomized, placebo-controlled trial of isosorbide mononitrate did not show increases in submaximal exercise capacity or quality-of-life scores in these patients.<sup>50</sup>

In small studies, exercise training has consistently been shown to produce clinically meaningful increases in exercise capacity and a reduction in symptoms.<sup>49,51</sup> Cardiac rehabilitation programs are reimbursed by U.S. government payers for patients who have heart failure with a reduced ejection fraction but not for those with a preserved ejection fraction. Clinicians should recommend a daily target of 30 minutes of aerobic exercise tailored to the abilities and resources particular to each patient and should monitor compliance and address barriers to exercise training in ongoing follow-up.<sup>17,18</sup>

#### *Disease Management*

All patients with heart failure should receive education regarding self-care. Self-care includes monitoring of weight and symptoms, adjustment of doses of diuretics, compliance with dietary restrictions, use of medications, exercise, and regular follow-up.

In patients with refractory symptoms or frequent hospitalizations for heart failure, referral to a disease management program should be considered. In patients who do not have a response to aggressive management, a palliative care program for symptom management and assistance in end-of-life planning should be considered.<sup>18</sup>

The effect of remote-monitoring strategies is unclear. However, a randomized trial of pulmonary-artery pressure–guided management in patients with heart failure showed that this strategy reduced hospitalizations for heart failure in patients with a reduced or a preserved ejection fraction.<sup>52</sup>

### AREAS OF UNCERTAINTY

Owing to positive findings in a phase 2 study,<sup>53</sup> a large outcomes trial of a neprilysin–angiotensin-receptor inhibitor (sacubitril–valsartan) in patients with heart failure and a preserved ejection fraction is ongoing (ClinicalTrials.gov number, NCT01920711). Information from ongoing phase 2, randomized trials of a variety of other drugs and medical devices in patients with heart failure and a preserved ejection fraction is needed.<sup>54</sup>

The incidence of ventricular arrhythmias and the role of implantable defibrillators are unknown. The most appropriate strategies for the treatment of hypertension, obesity, diabetes, atrial fibrillation, iron deficiency, anemia, and coronary disease in patients with heart failure and a preserved ejection fraction have not been defined.

### GUIDELINES

Recently updated guidelines for the management of heart failure with a preserved ejection fraction are available.<sup>17,18</sup> The recommendations in this article are largely consistent with those guidelines.

### CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette has heart failure with a preserved ejection fraction, exacerbated by, but probably predating, the onset of atrial fibrillation. The dose of diuretics should be increased to reduce the patient's clinical congestion. Given her hypertension and renal dysfunction, an angiotensin antagonist should be added and other agents used as needed to achieve a blood pressure of less than 140/90 mm Hg. She should receive education regarding self-care for heart failure. Anticoagulation should be continued. If symptoms persist, a trial of rhythm control should be considered.

The patient's atherosclerotic risk and the



presence of coronary disease should be assessed to guide the use of statins and other treatments for coronary disease. Evaluation for sleep apnea may also be reasonable, given her obesity, fatigue, hypertension, and atrial fibrillation. Once her condition is stable, exercise and weight-loss programs should be commenced. Persistent symptoms or recurrent hospitalizations should prompt referral to a disease management program for patients with heart failure. She should be in-

formed about clinical trials of therapeutic strategies for heart failure with a preserved ejection fraction.

Dr. Redfield reports serving as a member of a scientific committee for Novartis (unpaid) and receiving consulting fees from Merck, Eli Lilly, and Actelion, fees for serving on a data and safety monitoring board for Covaria, and grant support from St. Jude Medical and Medtronic. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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