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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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 μmol per liter), estimated glomerular filtration rate (GFR) 37 ml per minute per 1.73 m² 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?

An audio version of this article is available at NEJM.org

THE CLINICAL PROBLEM

Epidemiologic studies indicate that up to 50% of patients with heart failure have a preserved ejection fraction, and this proportion has increased over time.[1] 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,[1] but in clinical-trial populations, outcomes are better in patients who have heart failure with a preserved ejection fraction.[2] 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.[3,4]

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.[1,5-9] Although the ejection fraction is normal at rest, the ejection fraction does not increase appropriately with stress,[1] and other measures of systolic function are abnormal.[10] 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.[1] 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.[5,11,12]

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[1] (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)[13,14] as well as microvascular dysfunction and rarefaction in cardiac[15,16] and skeletal[11,12] muscle (Fig. 1).

STRATEGIES AND EVIDENCE

DIAGNOSIS AND EVALUATION

Since signs and symptoms of heart failure are nonspecific, 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%.[17,18] An ejection fraction of 40 to 49% is a gray area.[17] 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.[8,19] Doppler echocardiographic evidence of diastolic dysfunction (slowed ventricular relaxation and increased diastolic stiffness or elevated left atrial pressure) is common

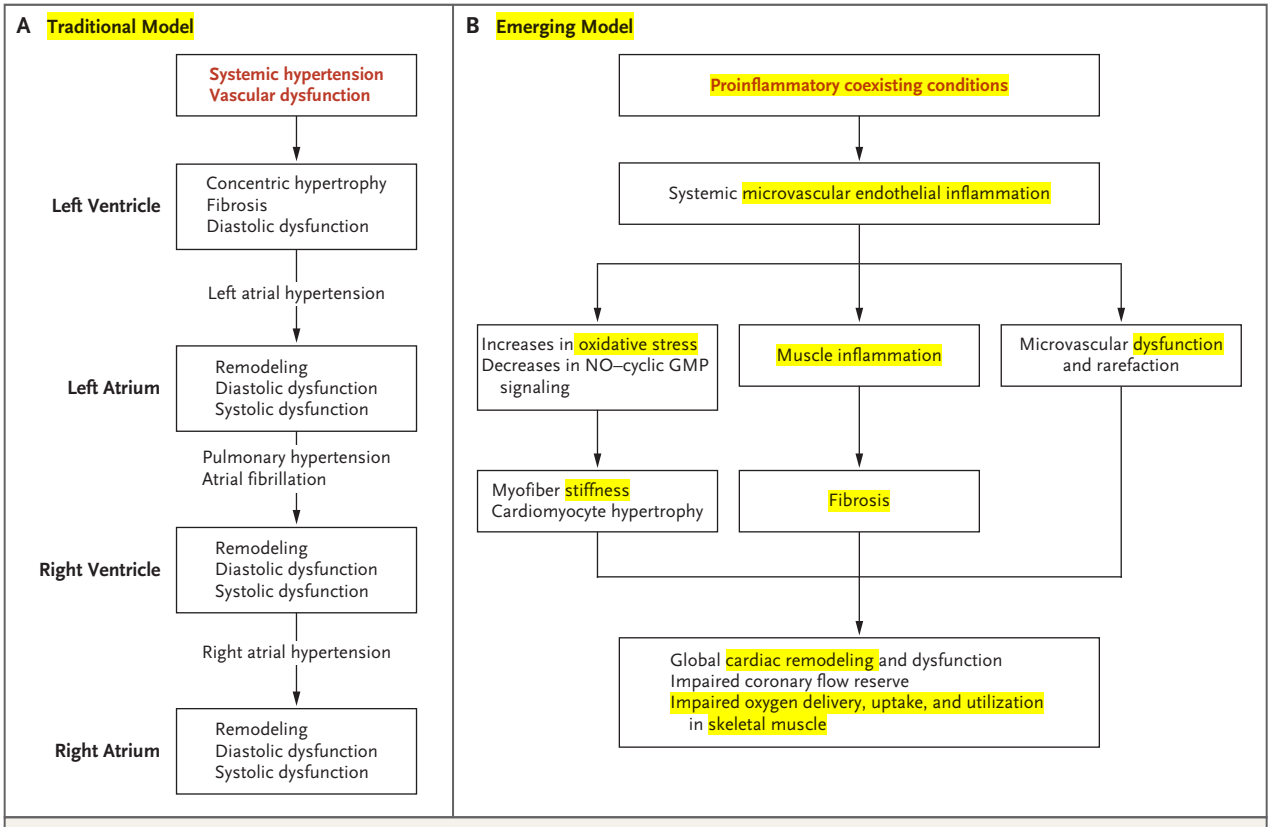

Figure 1. Traditional and Emerging Pathophysiological Models of Heart Failure with Preserved Ejection Fraction.

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).[8,9,20] However, diastolic dysfunction also may be present in patients who do not have heart failure[21] and absent in patients who have received aggressive treatment for heart failure or those with predominantly exertional symptoms.[6,7] The left atrium is usually enlarged. Pulmonary-artery systolic pressure, estimated by means of Doppler echocardiography, is often elevated (>35 mm Hg).[22] Right ventricular systolic dysfunction is present in 20 to 30% of patients, often in association with atrial fibrillation.[23] 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.[24] 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.[25] Levels of natriuretic peptides may be normal in up to 30%

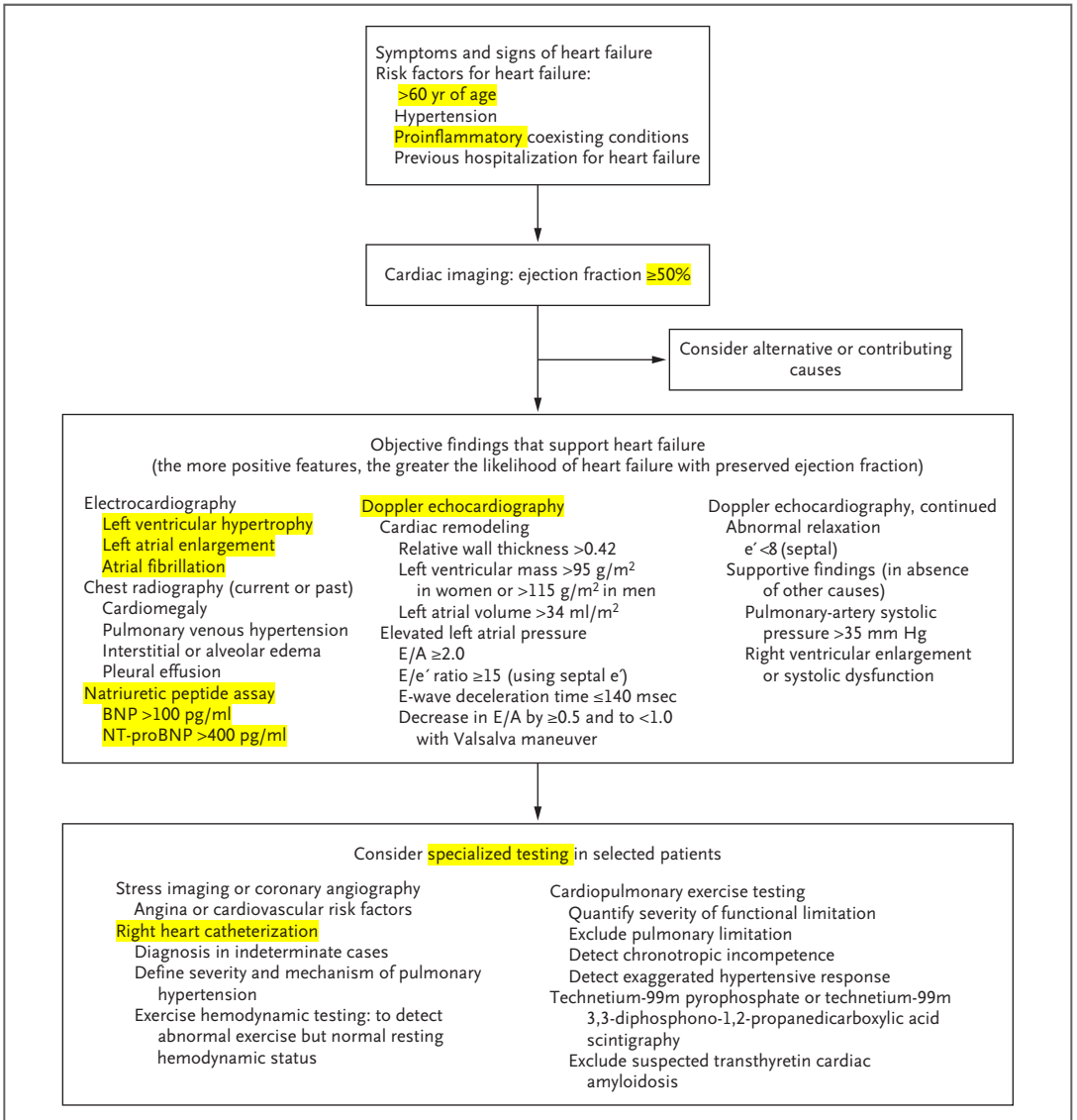

Figure 2. Systematic Approach to the Diagnosis of Heart Failure with Preserved Ejection Fraction.

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.[17] 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,[26] particularly in those who are obese[27] or have purely exertional symptoms.[6] The higher the natriuretic peptide level, the more likely it is that the patient has heart failure (Fig. 2). However, some elderly patients[28,29] or patients who have atrial fibrillation[30] 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.[31] 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.[31]

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[22]; 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.[32,33]

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[34] and should be considered in older patients with increased ventricular-wall thickness (≥12 mm) on echocardiography.[35]

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.[36] 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.[37] 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.[38] 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.[39]The effect of beta-blockers in patients with heart failure and a pre-

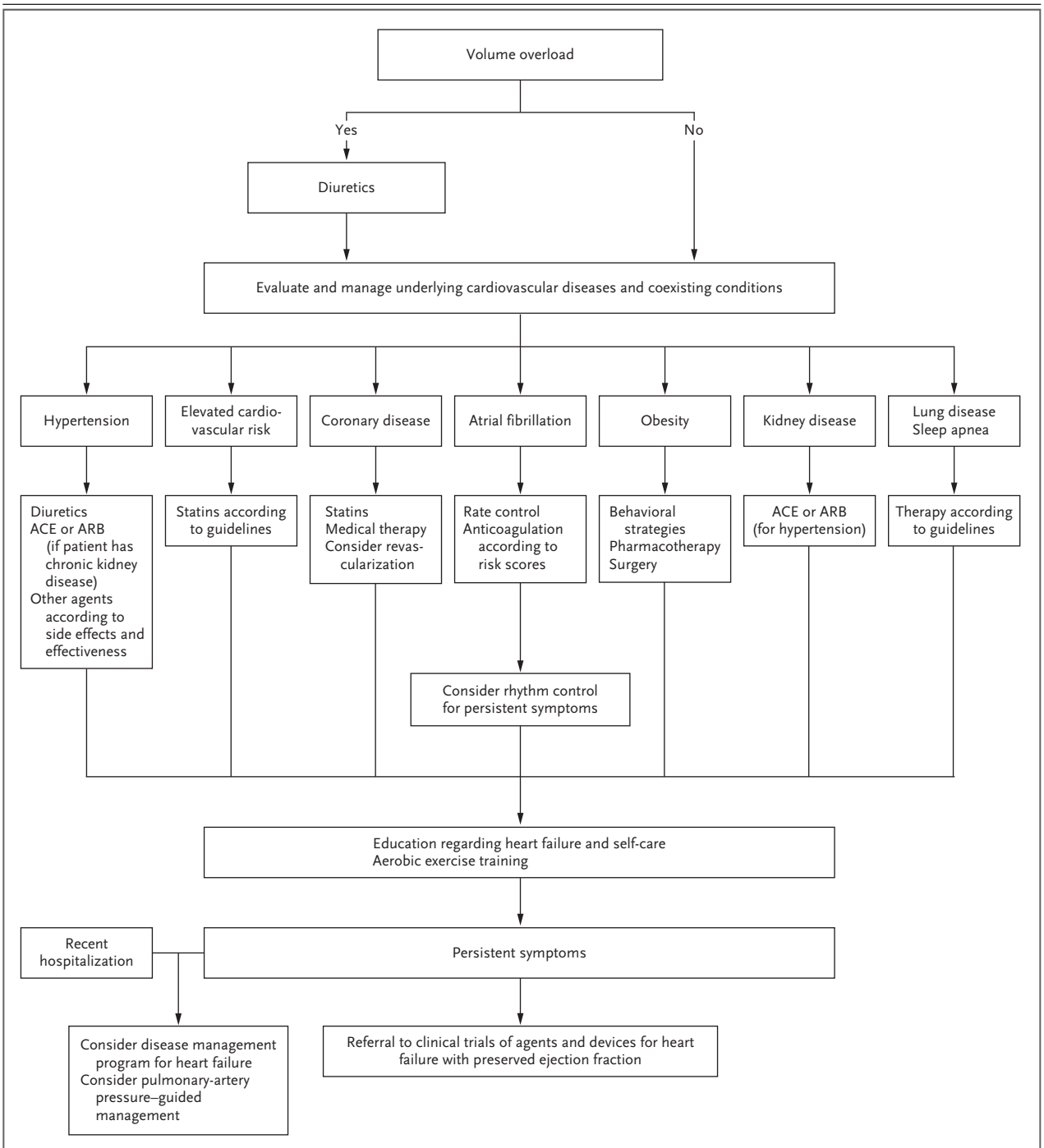

Figure 3. Treatment Algorithm for Heart Failure with Preserved Ejection Fraction.

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.[40-43]

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,[17,18] 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.[17,18]

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.[18] 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[44] and of less than 140/90 mm Hg in persons with kidney disease (estimated GFR, <60 ml per minute per 1.73 m^2 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.[45]

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[44] (Fig. 3). In patients who do not have concomitant kidney disease, a thiazide-like diuretic, angiotensin antagonist, or calcium-channel blocker for nonblacks and a thiazide-like diuretic or calcium-channel blocker for blacks are appropriate for initial management.[44] 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,[46] 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.[47] 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.[31] 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.[18]

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.[17,18,48] 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.[49] To increase exercise tolerance, weight loss in obese patients (BMI, ≥35) with heart failure should be considered.[17]

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.[50]

In small studies, exercise training has consistently been shown to produce clinically meaningful increases in exercise capacity and a reduction in symptoms.[49,51] 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.[17,18]

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.[18]

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.[52]

AREAS OF UNCERTAINTY

Owing to positive findings in a phase 2 study,[53] 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.[54]

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.[17,18] 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 informed about clinical trials of therapeutic strategies for heart failure with a preserved ejection fraction.

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

REFERENCES

1. Gladden JD, Linke WA, Redfield MM. Heart failure with preserved ejection fraction. Pflugers Arch 2014;466:1037-53.
2. Campbell RT, Jhund PS, Castagno D, Hawkins NM, Petrie MC, McMurray JJ. What have we learned about patients with heart failure and preserved ejection fraction from DIG-PEF, CHARM-preserved, and I-PRESERVE? J Am Coll Cardiol 2012;60:2349-56.
3. Chan MM, Lam CS. How do patients with heart failure with preserved ejection fraction die? Eur J Heart Fail 2013;15:604-13.
4. Lee DS, Gona P, Albano I, et al. A systematic assessment of causes of death after heart failure onset in the community: impact of age at death, time period, and left ventricular systolic dysfunction. Circ Heart Fail 2011;4:36-43.
5. Borlaug BA. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction. Circ J 2014;78:20-32.
6. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. Circ Heart Fail 2010;3:588-95.
7. Franssen C, Paulus WJ. Normal resting pulmonary artery wedge pressure: a diagnostic trap for heart failure with preserved ejection fraction. Eur J Heart Fail 2015;17:132-4.
8. Lam CS, Roger VL, Rodeheffer RJ, et al. Cardiac structure and ventricular-vascular function in persons with heart failure and preserved ejection fraction from Olmsted County, Minnesota. Circulation 2007;115:1982-90.
9. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure — abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med 2004;350:1953-9.
10. Borlaug BA, Lam CS, Roger VL, Rodeheffer RJ, Redfield MM. Contractility and ventricular systolic stiffening in hypertensive heart disease: insights into the pathogenesis of heart failure with preserved ejection fraction. J Am Coll Cardiol 2009;54:410-8.
11. Dhakal BP, Malhotra R, Murphy RM, et al. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. Circ Heart Fail 2015;8:286-94.
12. Haykowsky MJ, Tomczak CR, Scott JM, Paterson DI, Kitzman DW. Determinants of exercise intolerance in patients with heart failure and reduced or preserved ejection fraction. J Appl Physiol 2015;119:739-44.
13. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013;62:263-71.
14. Shah SJ, Kitzman DW, Borlaug BA, et al. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. Circulation 2016;134:73-90.
15. Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. Circulation 2015;131:550-9.
16. Mohammed SF, Majure DT, Redfield MM. Zooming in on the microvasculature in heart failure with preserved ejection fraction. Circ Heart Fail 2016;9(7):e003272.
17. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2016;37:2129-200.
18. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;128(16):e240-327.
19. Zile MR, Gottdiener JS, Hetzel SJ, et al. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. Circulation 2011;124:2491-501.
20. Borlaug BA, Jaber WA, Ommen SR, Lam CS, Redfield MM, Nishimura RA. Diastolic relaxation and compliance reserve during dynamic exercise in heart failure with preserved ejection fraction. Heart 2011;97:964-9.
21. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 2003;289:194-202.
22. Thenappan T, Prins KW, Cogswell R, Shah SJ. Pulmonary hypertension secondary to heart failure with preserved ejection fraction. Can J Cardiol 2015;31:430-9.
23. Chatterjee NA, Steiner J, Lewis GD. It is time to look at heart failure with preserved ejection fraction from the right side. Circulation 2014;130:2272-7.
24. Zakeri R, Chamberlain AM, Roger VL, Redfield MM. Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction: a community-based study. Circulation 2013;128:1085-93.
25. Iwanaga Y, Nishi I, Furuichi S, et al. B-type natriuretic peptide strongly reflects diastolic wall stress in patients with chronic heart failure: comparison between systolic and diastolic heart failure. J Am Coll Cardiol 2006;47:742-8.
26. Anjan VY, Loftus TM, Burke MA, et al. Prevalence, clinical phenotype, and outcomes associated with normal B-type natriuretic peptide levels in heart failure with preserved ejection fraction. Am J Cardiol 2012;110:870-6.
27. Bishu K, Deswal A, Chen HH, et al. Biomarkers in acutely decompensated heart failure with preserved or reduced ejection fraction. Am Heart J 2012;164(5):763-770.e3.
28. Costello-Boerrigter LC, Boerrigter G, Redfield MM, et al. Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in the general community: determinants and detection of left ventricular dysfunction. J Am Coll Cardiol 2006;47:345-53.
29. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett

JC Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. J Am Coll Cardiol 2002;40:976-82.
30. Richards M, Di Somma S, Mueller C, et al. Atrial fibrillation impairs the diagnostic performance of cardiac natriuretic peptides in dyspneic patients: results from the BACH Study (Biomarkers in ACute Heart Failure). JACC Heart Fail 2013;1:192-9.
31. Hwang SJ, Melenovsky V, Borlaug BA. Implications of coronary artery disease in heart failure with preserved ejection fraction. J Am Coll Cardiol 2014;63:2817-27.
32. Pichard AD, Diaz R, Marchant E, Casanegra P. Large V waves in the pulmonary capillary wedge pressure tracing without mitral regurgitation: the influence of the pressure/volume relationship on the V wave size. Clin Cardiol 1983;6:534-41.
33. Rossi A, Gheorghiade M, Triposkiadis F, Solomon SD, Pieske B, Butler J. Left atrium in heart failure with preserved ejection fraction: structure, function, and significance. Circ Heart Fail 2014;7:1042-9.
34. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation 2016;133:2404-12.
35. González-López E, Gallego-Delgado M, Guzzo-Merello G, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J 2015;36:2585-94.
36. Anderson JL, Halperin JL, Albert NM, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127:1425-43.
37. Shah RV, Desai AS, Givertz MM. The effect of renin-angiotensin system inhibitors on mortality and heart failure hospitalization in patients with heart failure and preserved ejection fraction: a systematic review and meta-analysis. J Card Fail 2010;16:260-7.
38. Pfeffer MA, Pitt B, McKinlay SM. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;371:181-2.
39. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation 2015;131:34-42.
40. Conraads VM, Metra M, Kamp O, et al. Effects of the long-term administration of nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with diastolic dysfunction: results of the ELANDD study. Eur J Heart Fail 2012;14:219-25.
41. Liu F, Chen Y, Feng X, Teng Z, Yuan Y, Bin J. Effects of beta-blockers on heart failure with preserved ejection fraction: a meta-analysis. PLoS One 2014;9(3):e90555.
42. van Veldhuisen DJ, Cohen-Solal A, Böhm M, et al. Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: data from SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure). J Am Coll Cardiol 2009;53:2150-8.
43. Yamamoto K, Origasa H, Hori M. Effects of carvedilol on heart failure with preserved ejection fraction: the Japanese Diastolic Heart Failure Study (J-DHF). Eur J Heart Fail 2013;15:110-8.
44. James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507-20.
45. Wright JT Jr, Williamson JD, Whelton PK, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103-16.
46. Alehagen U, Benson L, Edner M, Dahlström U, Lund LH. Association between use of statins and mortality in patients with heart failure and ejection fraction of ≥50. Circ Heart Fail 2015;8:862-70.
47. Ohman EM. Chronic stable angina. N Engl J Med 2016;374:1167-76.
48. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014;130(23):e199-267.
49. Kitzman DW, Brubaker P, Morgan T, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2016;315:36-46.
50. Redfield MM, Anstrom KJ, Levine JA, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. N Engl J Med 2015;373:2314-24.
51. Pandey A, Parashar A, Kumbhani DJ, et al. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. Circ Heart Fail 2015;8:33-40.
52. Adamson PB, Abraham WT, Bourge RC, et al. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. Circ Heart Fail 2014;7:935-44.
53. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet 2012;380:1387-95.
54. Nanayakkara S, Kaye DM. Management of heart failure with preserved ejection fraction: a review. Clin Ther 2015;37:2186-98.