CLINICAL PRACTICE

Patrick G. O'Malley, M.D., M.P.H., *Editor*

Heart Failure with Preserved Ejection Fraction

Antonio Cannata, M.D., and Theresa A. McDonagh, 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 authors' clinical recommendations.*

A 75-year-old woman with a history of type 2 diabetes mellitus, resistant hypertension, obesity, and chronic obstructive pulmonary disease (COPD) is admitted with severe peripheral edema and exertional dyspnea on minimal effort. After an evaluation that rules out an acute coronary syndrome, she receives a diagnosis of heart failure. The N-terminal pro–B-type natriuretic peptide (NT-proBNP) level is 1529 pg per milliliter. Echocardiography reveals left ventricular dimensions within the normal range, left ventricular hypertrophy, left ventricular ejection fraction of 52%, dilated atria, right ventricular size and function within the normal range, and a pulmonary arterial systolic pressure of 65 mm Hg (normal, <35). How would you further evaluate and treat this patient?

From King's College Hospital, London (A.C., T.A.M.) and the British Heart Foundation Centre of Research Excellence, School of Cardiovascular Medicine, Faculty of Life Science, King's College London, London (A.C., T.A.M.). Dr. McDonagh can be contacted at theresa.mcdonagh@kcl.ac.uk or at King's College Hospital, Denmark Hill, London SE5 9RS, United Kingdom.

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CME

THE CLINICAL PROBLEM

Heart failure has been defined physiologically as the inability of the heart to supply sufficient oxygen to the metabolizing tissues despite an adequate filling pressure.[1] It is not a single pathological diagnosis but rather a clinical syndrome of symptoms and signs of cardiac origin. Most definitions require the presence of cardinal symptoms (e.g., breathlessness, ankle swelling, and fatigue), which may be accompanied by signs (jugular venous distension, pulmonary rales, and peripheral edema) and the presence of cardiac dysfunction. These definitions are independent of the presence or absence of systolic dysfunction traditionally based on the percentage of the left ventricular ejection fraction (LVEF).[2-4]

Our contemporary phenotypic classification of chronic heart failure according to left ventricular function is based on a cutoff point of an LVEF above or below 50%. Although the ejection-fraction cutoff for heart failure with preserved ejection fraction has changed, the current nomenclature defines heart failure with reduced ejection fraction as heart failure with an LVEF of 40% or less, heart failure with preserved ejection fraction as heart failure with an LVEF of 50% or greater, and heart failure with mildly reduced ejection fraction as heart failure with an LVEF of 41 to 49%.

When the contemporary definition is applied, heart failure with preserved ejection fraction is present in up to 50% of all adult patients who are hospitalized for heart failure. That prevalence increased from 38% in the late 1980s to 54% in the early 2000s.[5-9] The incidence of the condition among adults is between 7 per 1000 and 18 per 1000 persons per year.[10-12] Owing to the aging of the global population and the increased prevalence of coexisting conditions such as obesity, the incidence

KEY POINTS

HEART FAILURE WITH PRESERVED EJECTION FRACTION

- Heart failure with preserved ejection fraction is a heterogeneous syndrome.
- The diagnosis of the condition requires ruling out potential confounders such as respiratory disease, ischemic heart disease, hypertensive or valvular heart disease, cardiomyopathies, and amyloidosis.
- Symptoms and signs of heart failure, a left ventricular ejection fraction of 50% or greater, and evidence of cardiac structural abnormalities at rest or with exercise are required for the diagnosis.
- Contemporary guidelines recommend diuretic therapy and treatment with sodium–glucose cotransporter 2 (SGLT2) inhibitors for acute heart failure to reduce congestion and the continuation of SGLT2 inhibitors to reduce the risk of hospitalization for heart failure.
- New cardiometabolic drugs such as glucagon-like peptide-1 agonists have been shown to reduce symptoms and improve quality of life and exercise tolerance in patients with both heart failure with preserved ejection fraction and obesity.
- No available medical therapy has resulted in a reduction in mortality among patients with heart failure with preserved ejection fraction. Therefore, the current aims of medical treatment are to reduce the risk of hospitalization and improve quality of life.

of heart failure with preserved ejection fraction is expected to increase.[13]

Heart failure with preserved ejection fraction is heterogeneous and caused by multiple pathophysiological mechanisms, including cardiac aging and cardiometabolic disorders (Fig. 1).[14,15] Patients with the condition are often older and female. In addition, there is a higher prevalence of obesity, type 2 diabetes mellitus, hypertension, atrial fibrillation, chronic kidney disease, and other noncardiovascular conditions among patients with heart failure with preserved ejection fraction than among those with heart failure with reduced ejection fraction.[16] These multiple coexisting conditions have a substantial effect on outcomes.[17] Mortality associated with heart failure with preserved ejection fraction ranges between 15% at 1 year to 75% at 5 to 10 years after hospitalization.[5,15,18]

When both clinical trials and community-based studies are considered, the risk of death from any cause among patients with heart failure with preserved ejection fraction is lower than that among patients with heart failure with reduced ejection fraction after adjustment for age, sex, and causes of heart failure (hazard ratio, 0.68; 95% confidence interval [CI], 0.64 to 0.71).[19] Each year, approximately 6 to 10% of patients with heart failure with preserved ejection fraction are hospitalized for decompensated heart failure.

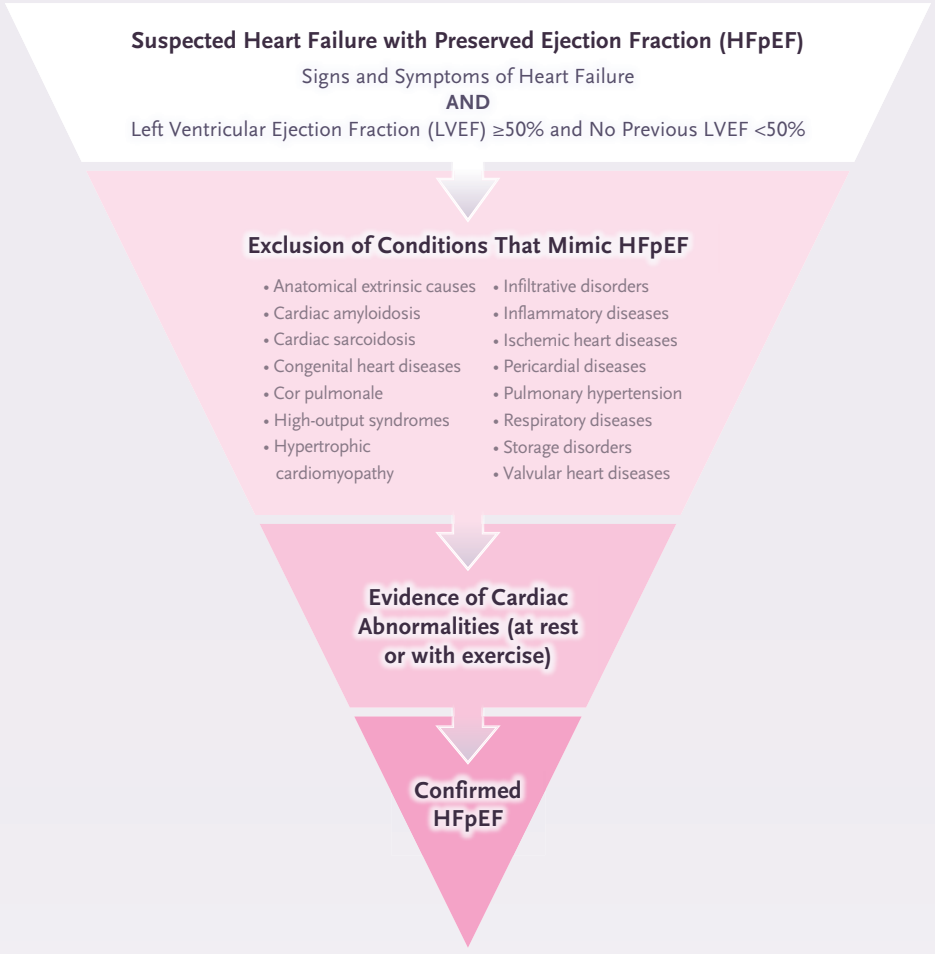
Until recently, specific etiologic factors that are associated with a poorer prognosis, such as cardiac amyloidosis (average prevalence of 6.3% among patients with heart failure with preserved ejection fraction and up to 21% among patients >90 years of age[20]) and hypertrophic cardiomyopathy, were considered part of the spectrum of conditions defined as heart failure with preserved ejection fraction. Diagnosis of these conditions is important because there are now targeted treatments available.

STRATEGIES AND EVIDENCE

DIAGNOSIS

Making the diagnosis of heart failure with preserved ejection fraction is challenging owing to the presence of multiple overlapping conditions that mimic it and several phenotypic subtypes that contribute to the pathophysiologic features of the condition (Fig. 1). Patients often present with dyspnea and signs of congestion. In these patients, a pragmatic approach to the diagnosis requires an echocardiographic estimate of an LVEF of 50% or greater (excluding patients with recovered LVEF) and objective evidence of left ventricular diastolic dysfunction or raised left ventricular filling pressures. In these patients, the ruling out of potential mimickers such as respiratory disease, hypertrophic cardiomyopathy, and storage and infiltrative disorders, such as Fabry's disease or cardiac amyloidosis, is pivotal.[4,21]

The presence of cardiac structural or functional abnormalities is fundamental for making the diagnosis and for ruling out noncardiovascular causes of the clinical presentation (Fig. 1). Measuring natriuretic peptide levels is useful when heart failure is suspected. In patients with suspected heart failure, levels of NT-proBNP of 125 pg per milliliter or greater are diagnostic of



Indicators of Cardiac Abnormalities — The greater the number of abnormalities present, the higher the likelihood of HFpEF

Variable	At Rest	With Exercise
Left ventricular mass index	For women ≥95 g/m^2 For men ≥115 g/m^2	— —
Relative wall thickness	>0.42	—
Left atrial volume index	Sinus rhythm >34 ml/m^2 Atrial fibrillation >40 ml/m^2	— —
E:e′ at rest	>9	>15
NT-proBNP	Sinus rhythm ≥125 pg/ml Atrial fibrillation >365 pg/ml	— —
Pulmonary-artery systolic pressure estimated with echocardiography	>35 mm Hg	—
Tricuspid-regurgitation velocity at rest	>2.8 m/sec	>3.4 m/sec
Pulmonary capillary wedge pressure (PCWP)	≥15 mm Hg	≥25 mm Hg or PCWP:CO slope ≥2 mm Hg/liter/min
Left ventricle end diastolic pressure	≥16 mm Hg	—

Figure 1 (facing page). A Pragmatic Approach to the Diagnosis of Heart Failure with Preserved Ejection Fraction.
CO denotes cardiac output, E:e′ the ratio of E-wave velocity to e′ velocity (as assessed with echocardiography), and NT-proBNP N-terminal pro–B-type natriuretic peptide.

heart failure, with a sensitivity of 0.98 and a specificity of 0.35; the negative predictive value is high (0.97) for the ruling out of the diagnosis.[22] However, it is important to note that natriuretic peptide levels may be either falsely elevated in specific conditions, such as renal impairment or atrial fibrillation, or inappropriately low, particularly in the presence of obesity.

The presence of noncardiovascular coexisting conditions, such as obesity, insulin resistance, cardiometabolic disorders, physical inactivity, and respiratory disease, also confounds the diagnosis of heart failure with preserved ejection fraction because these conditions cause exertional dyspnea.[23,24] Diagnostic scoring systems exist but lack robust diagnostic validation.[21,25] When these scores are used, the diagnosis of the condition remains in doubt in approximately 30% of patients. For these patients, either invasive left ventricular hemodynamic assessments at rest or during exercise or diastolic stress testing (or both) may confirm the diagnosis. In addition, cardiac magnetic resonance imaging may help to rule out other mimickers of heart failure with preserved ejection fraction, such as hypertrophic cardiomyopathy or cardiac amyloidosis.

TREATMENT

Goals of Treatment

The main goals of therapy for patients with heart failure with preserved ejection fraction are to address the signs and symptoms of heart failure, improve quality of life, and reduce the risk of hospitalization. To date, no treatment has shown a significant reduction in mortality. Until recently, treatment has been largely supportive, and several clinical trials of potential disease-modifying agents have not shown evidence of benefit (Fig. 2). Most clinical trials of the condition have recruited patients with LVEFs of greater than 40% or 45%, making it difficult to infer conclusions specific to heart failure with preserved ejection fraction when a threshold ejection fraction of 50% is used.

Treatment of the Underlying Cause and Coexisting Conditions

Treatment of the underlying cause and concomitant cardiovascular and noncardiovascular coexisting conditions (e.g., hypertension, atrial fibrillation, diabetes, respiratory disease, ischemic heart disease, valvular heart disease, and obesity) is the basis for the treatment strategies in patients with heart failure with preserved ejection fraction.

PHARMACOTHERAPY

Renin–Angiotensin–System Inhibitors

Inhibition of the renin–angiotensin system (RAS) in heart failure with preserved ejection fraction has been the focus of many treatment trials (Fig. 2). The CHARM (Candesartan in Heart Failure — Assessment of Reduction in Mortality and Morbidity)–Preserved trial did not show a significant benefit for the use of the angiotensin-receptor blocker (ARB) candesartan on the primary composite end point of death from cardiovascular causes or hospitalization for heart failure over a median follow-up of 36 months (hazard ratio, 0.89; 95% CI, 0.77 to 1.03); however, ARB therapy was associated with a lower incidence of hospitalizations for heart failure than placebo (15% vs. 18%; P=0.02).[26] The I-PRESERVE (Irbesartan in Heart Failure with Preserved Ejection Fraction) trial, using irbesartan, showed similar results to those in the CHARM–Preserved trial, which suggests no beneficial role for ARBs in patients with heart failure with preserved ejection fraction (hazard ratio for the composite end point, 0.95; 95% CI, 0.86 to 1.05) aside from their known benefit in the treatment of hypertension.[27] Likewise, in the PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure) trial of the angiotensin-converting enzyme (ACE) inhibitor perindopril, the incidence of death or hospitalization for heart failure (the primary composite end point), at a median follow-up of 2.1 years, was similar in patients who received perindopril and those who received placebo (hazard ratio, 0.92; 95% CI, 0.70 to 1.21). However, perindopril was associated with a lower risk of hospitalization for heart failure at 1 year (hazard ratio, 0.63; 95% CI, 0.41 to 0.97).[28,29] Despite the lack of significant benefit shown in trials of RAS inhibitors in heart failure with preserved ejection fraction specifically, these drugs are indicated for use in treating the underlying causes of heart failure and coexisting conditions, such as hypertension.

Angiotensin Receptor–Neprilysin Inhibitors

The PARAGON-HF (Prospective Comparison of ARNI [angiotensin receptor–neprilysin inhibitor] with ARB Global Outcomes in HF with

Preserved Ejection Fraction) trial evaluated the use of sacubitril–valsartan in 4822 patients with heart failure who had an LVEF of greater than 45%.[30,31] The trial did not show a significant reduction in the incidence of the primary end point of death from cardiovascular causes or hospitalization for heart failure (rate ratio, 0.87; 95% CI, 0.75 to 1.01; P=0.06). However, there was a signal of possible benefit in women (rate ratio, 0.73; 95% CI, 0.59 to 0.90) and patients with an LVEF below the median value of 57% (rate ratio, 0.78; 95% CI, 0.64 to 0.95). The PARAGLIDE-HF (Prospective Comparison of ARNI with ARB Given Following Stabilization in Decompensated HFpEF) trial, which involved 466 patients whose condition was stabilized after worsening heart failure with an LVEF of greater than 40%, showed that sacubitril–valsartan, as compared with valsartan alone, reduced the incidence of the primary outcome of neurohormonal activation (15% greater reduction in NT-proBNP level between baseline and week 8;

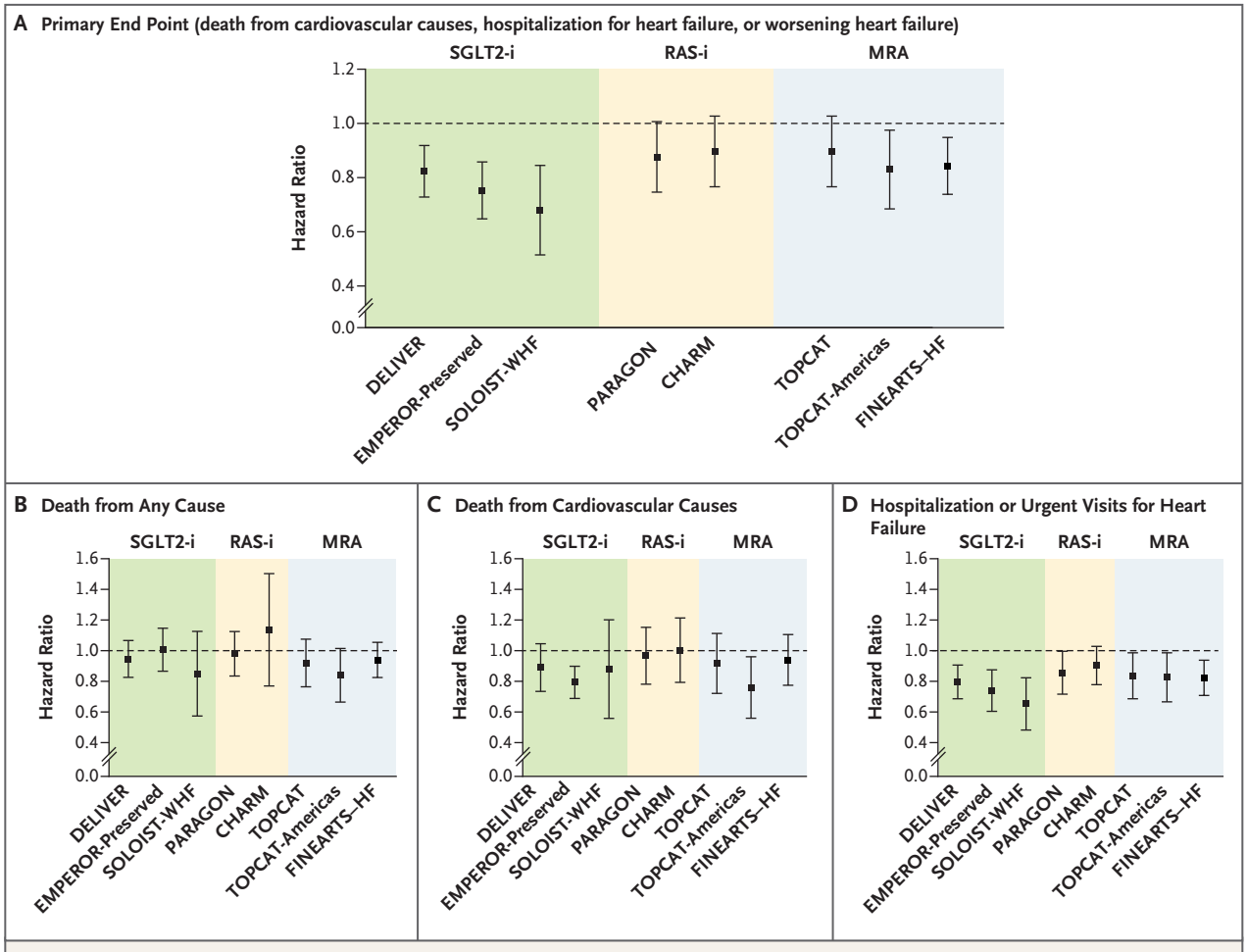


Figure 2. Treatment Effect Shown in Trials of Recommended Drug Therapies in Heart Failure with Preserved Ejection Fraction.

Shown are hazard ratios or risk ratios, from the results of eight clinical trials, for the primary composite end point of death from cardiovascular causes, hospitalization for heart failure, or worsening heart failure (Panel A), and for death from any cause, death from cardiovascular causes, and hospitalization or urgent visits for heart failure (Panels B through D), in patients with heart failure with preserved ejection fraction who were treated with a sodium–glucose cotransporter 2 inhibitor (SGLT2-i), renin–angiotensin–system inhibitor (RAS-i), or mineralocorticoid receptor antagonist (MRA). The trials, and the treatments they investigated, were DELIVER (dapagliflozin), EMPEROR-Preserved (empagliflozin), SOLOIST-WHF (sotagliflozin, in patients with heart failure with reduced ejection fraction and patients with heart failure with preserved ejection fraction), PARAGON (sacubitril and valsartan), CHARM (candesartan), TOPCAT and TOPCAT-Americas (spironolactone), and FINEARTS-HF (finerenone). Hazard ratios are shown for all trials except for hospitalizations or urgent visits for heart failure in the PARAGON trial, for which risk ratios are shown (Panel D). I bars indicate 95% confidence intervals.

geometric mean ratio, 0.85; 95% CI, 0.73 to 0.10), with a greater effect in patients with an LVEF of less than 60%. However, this reduction was at the expense of a greater incidence of symptomatic hypotension (odds ratio, 1.73; 95% CI, 1.09 to 2.76).[32] Similarly, the PARALLAX (Prospective Comparison of ARNI versus Comorbidity-Associated Conventional Therapy on Quality of Life and Exercise Capacity) trial, which involved 2572 patients with heart failure and an LVEF of greater than 40%, showed a greater reduction in the first primary end point of change in the NT-proBNP level at 12 weeks with sacubitril–valsartan than with standard medical therapy (i.e., either enalapril or valsartan) or placebo (geometric mean ratio, 0.84; 95% CI, 0.80 to 0.88). However, there was no change in the other primary end point of improvement in 6-minute walk distance from baseline to week 24.[33] The data from these trials support the indication from the Food and Drug Administration for the potential use of sacubitril–valsartan on the basis of the results of the subgroup of patients with LVEFs below the normal range.

Mineralocorticoid Receptor Antagonists

The evidence for the use of mineralocorticoid receptor antagonists (MRAs) in the treatment of heart failure with preserved ejection fraction comes mainly from three trials. Aldo-DHF (Aldosterone Receptor Blockade in Diastolic Heart Failure) was a phase 2 trial that involved 422 patients and investigated the effect of spironolactone at a daily dose of 25 mg on diastolic and functional characteristics. It showed a reduction in left ventricular mass and natriuretic peptide levels and improvements in measures of diastolic function but no changes in the symptoms and signs of heart failure or in quality of life.[34] In the larger phase 3 TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial, patients with heart failure with preserved ejection fraction and an LVEF of greater than 45% were randomly assigned to receive either spironolactone or placebo.[35] This trial did not show a reduction in the primary outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for heart failure.[36] However, FINEARTS-HF (Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients with Heart Failure) recently showed that in patients with an LVEF of 40% or greater, finerenone increased to a maximum dose of 40 mg daily reduced the incidence of the primary composite end point of death from cardiovascular causes and total heart-failure events, thus supporting its use in patients with heart failure with preserved ejection fraction.[37]

Beta-Blockers

According to observational data, up to 80% of patients with heart failure with preserved ejection fraction receive beta-blockers for other clinical indications. However, trials involving patients with the condition who have received either nebivolol or carvedilol have not shown a reduction in death or hospitalizations for heart failure or an improvement in quality of life.[38-45]

Diuretics

Until recently, diuretics were the only pharmacologic therapy indicated for heart failure with preserved ejection fraction despite a lack of randomized clinical trials. For patients with the condition, diuretics are recommended to reduce congestion, symptoms, and the risk of hospitalization for heart failure.[3,4] Loop diuretics are used in approximately 90% of patients with acute heart failure.[46] Guidelines recommend the use of the lowest possible dose of diuretics and possible discontinuation when euvolemia is achieved.[3,4] In patients with concomitant hypertension, thiazide diuretics are also an option.[3]

SGLT2 Inhibitors

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are a group of drugs first studied for type 2 diabetes mellitus, and they have subsequently been shown to be effective in reducing adverse events in patients with heart failure. The evidence for their use in patients with heart failure with preserved ejection fraction comes from two large trials, EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) and DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure).[47,48] In these trials, SGLT2 inhibitors showed a reduction in the primary outcome of death from cardiovascular causes or hospitalization for heart failure as compared with placebo — empagliflozin at a dose of 10 mg

daily in the EMPEROR-Preserved trial (hazard ratio, 0.79; 95% CI, 0.69 to 0.90; P<0.001) and dapagliflozin at a dose of 10 mg daily in the DELIVER trial (hazard ratio, 0.82; 95% CI, 0.73 to 0.92; P<0.001). There was no heterogeneity in the treatment effect on the basis of sex or ejection fraction. A subsequent meta-analysis of both trials corroborated the results and showed a consistent reduction in death from cardiovascular causes or hospitalization for heart failure (hazard ratio, 0.80; 95% CI, 0.73 to 0.87; P<0.001). However, the reduction in the incidence of the primary end point was driven by fewer hospitalizations for heart failure (hazard ratio, 0.74; 95% CI, 0.67 to 0.83; P<0.001), and the reduction in death from cardiovascular causes was not significant (hazard ratio, 0.88; 95% CI, 0.77 to 1.00; P=0.052). Current guidelines recommend the use of SGLT2 inhibitors in patients with heart failure with preserved ejection fraction on the basis of the composite primary end points used in the trials but stress that the observed effect is mainly owing to the reduction in hospitalizations for heart failure.

Glucagon-like Peptide-1 Receptor Agonists

Heart failure with preserved ejection fraction is often associated with cardiometabolic derangement and a high prevalence of diabetes and obesity, both of which may reduce exercise capacity. Therefore, improvement in the cardiometabolic profile, weight loss, and reduction in inflammation may also be therapeutic targets. A recent trial, STEP-HFpEF (Effect of Semaglutide 2.4 mg Once Weekly on Function and Symptoms in Subjects with Obesity-related Heart Failure with Preserved Ejection Fraction), showed that, as compared with placebo, a weekly injection of 2.4 mg of semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, improved quality of life (mean change in score on the Kansas City Cardiomyopathy Questionnaire [KCCQ; scores range from 0 to 100, with higher scores indicating better health status], 16.6 points with semaglutide vs. 8.7 points with placebo; P<0.001), led to significant weight loss (mean percentage change in body weight, −13.3% vs. −2.6%; P<0.001), improved exercise tolerance (mean change in 6-minute walk distance, 21.5 m vs. 1.2 m; P<0.001), and reduced inflammation (mean percentage change in C-reactive protein level, −43.5% vs. −7.3%; P<0.001).[49] In a similar trial involving patients with heart failure with preserved ejection fraction and type 2 diabetes, semaglutide therapy led to a greater reduction in heart failure–related symptoms and more weight loss than placebo at 1 year.[50] In a pooled analysis of both these trials, semaglutide was associated with a significant reduction in major adverse cardiac events.[51] The recent SUMMIT trial showed the efficacy of tirzepatide, a long-acting agonist of glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors. In this trial, in which 364 patients with heart failure with preserved ejection fraction (LVEF >50%) and obesity received tirzepatide, treatment with tirzepatide led to a lower risk of a composite of death from cardiovascular causes or worsening heart failure than placebo (hazard ratio, 0.62; 95% CI, 0.41 to 0.95; P=0.026) and improved health status (between-group difference in change in KCCQ score, 6.9 points; 95% CI, 3.3 to 10.6; P<0.001).[52]

These trials have shown efficacy for GLP-1 receptor agonism in patients with heart failure with preserved ejection fraction and obesity. However, we await further trials to expand the evidence.

TREATMENT DEVICES

Monitoring pulmonary pressures to control fluid status is a potential strategy for reducing hospitalization in patients with heart failure. The CardioMEMS system is a small, invasive, remote monitoring system that constantly measures pulmonary arterial pressure and transmits the readings to clinicians who then adjust medical therapy in response. In the single-blind CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial involving 550 patients, CardioMEMS-guided optimization of medical therapy was associated with a significant reduction in hospitalizations for heart failure as compared with standard care, irrespective of the LVEF.[53] Similarly, the MONITOR-HF trial, an open-label trial involving 348 patients with chronic heart failure (28% with an LVEF of >40%), showed that hemodynamic monitoring with CardioMEMS improved the primary end point of change in quality of life (mean change in KCCQ score, 7.05) as compared with usual care (mean change in KCCQ score, −0.08).[54]

Treatment with another device, an iatrogenic interatrial shunt, did not show a difference in

Table 1. Guideline Recommended Treatment for Heart Failure with Preserved Ejection Fraction.*

Treatment	Initial Daily Dose	Maximum Daily Dose	Use	ACC–AHA 2022	ESC 2021, 2023	CCS–CHFS 2017, 2020	JCS–JHFS 2017, 2021	NHFA–CSANZ 2018	Common Side Effects and Contraindications
				Class of Recommendation					
Diuretics				Class I	Class I	Recommend	Class I	Recommend	
Loop diuretics			To relieve congestion; minimum dose possible						Hypokalemia, hyponatremia, hypovolemia, worsening renal function
Furosemide	20–40 mg	600 mg							
Bumetanide	0.5–1 mg	10 mg							
Torsemide	10–20 mg	200 mg							
Thiazides			To relieve congestion and reduce blood pressure						Hypokalemia, hypochloremia, hyperglycemia, hyperuricemia, nausea, postural hypotension
Chlorthalidone	25 mg	200 mg							
Hydrochlorothiazide	25 mg	200 mg							
Bendroflumethiazide	2.5 mg	10 mg							
Indapamide	2.5 mg	5 mg							
Metolazone	2.5 mg	20 mg							
SGLT2 inhibitors			To reduce the risk of hospitalization	Class IIa†	Class I	NS‡	NS‡	NS‡	Diabetes ketoacidosis, UTI
Empagliflozin	10 mg	10 mg							
Dapagliflozin	10 mg	10 mg							
Sotagliflozin	200 mg	400 mg	SGLT1/2 inhibitor; for use in patients with diabetes and heart failure						
MRAs									
Spironolactone	12.5–25 mg	100 mg	For coexisting conditions; can decrease hospitalization among patients with low LVEF	Class IIb	For coexisting conditions§	Suggest¶	Class IIb	Consider	Hyperkalemia, worsening renal function, gynecomastia
Finerenone	10 mg	40 mg		NA	NA	NA	NA	NA	Hyperkalemia, worsening renal function

RAS inhibitors			For coexisting conditions; can decrease hospitalization, particularly among patients with LVEF lower than the normal range	Class IIb	For coexisting conditions§	Suggest	Class IIb	For coexisting conditions	Worsening renal function, hypotension, renal-artery stenosis
Candesartan	4 mg	32 mg							
Irbesartan	75 mg	300 mg							
Losartan	25 mg	150 mg							
Valsartan	20 mg	160 mg							
Sacubitril–valsartan‖	24–26 mg BID	97–103 mg BID							
Beta-blockers			For coexisting conditions; careful dose adjustment necessary; may exacerbate respiratory disease	For coexisting conditions	For coexisting conditions	For coexisting conditions	Class IIb	For coexisting conditions	Severe asthma, bradycardia, hypotension
Bisoprolol	1.25 mg	10 mg							
Nebivolol	1.25 mg	10 mg							
Carvedilol	3.125 mg BID	25 mg BID							
Metoprolol	12.5–25 mg	200 mg							
GLP-1 receptor agonist				NA	NA	NA	NA	NA	Diabetic ketoacidosis, nausea, vomiting
Semaglutide	2.4 mg weekly								
GLP-1 and GIP receptor agonist				NA	NA	NA	NA	NA	Alopecia, nausea, vomiting, asthenia, constipation, diarrhea, dizziness, lethargy, malaise
Tirzepatide	2.5 weekly	15 mg weekly							

* Recommendation classifications are as follows: I, recommended; IIa, should be considered; IIb, may be considered; and III, not recommended or harmful. ACC denotes American College of Cardiology, AHA American Heart Association, BID twice daily, CCS Canadian Cardiovascular Society, CHFS Canadian Heart Failure Society, CSANZ Cardiac Society of Australia and New Zealand, ESC European Society of Cardiology, GIP glucose-dependent insulinotropic polypeptide, GLP-1 glucagon-like peptide 1, JCS Japanese Circulation Society, JHFS Japanese Heart Failure Society, LVEF left ventricular ejection fraction, MRA mineralocorticoid-receptor antagonist, NA not available, NHFA National Heart Foundation of Australia, RAS renin–angiotensin system, SGLT2 sodium–glucose cotransporter 2, and UTI urinary tract infection.

† At the time the guideline was published, only results from the EMPEROR-Preserved trial were available.

the incidence of the composite primary end point of death from cardiovascular causes, stroke, hospitalization for heart failure, and quality of life in patients with heart failure with preserved ejection fraction in the phase 3 REDUCE LAP-HF II (Study to Evaluate the Corvia Medical IASD System II to Reduce Elevated Left Atrial Pressure in Patients with Heart Failure).[55] Moreover, the preliminary results of the RELIEVE-HF (Reducing Lung Congestion Symptoms in Advanced Heart Failure) trial, which did not show a significant difference in the primary outcome (win ratio, 0.86; 95% CI, 0.61 to 1.22; P=0.20), suggested that in patients with an LVEF of greater than 40%, implantation of interatrial shunt systems may be harmful on the basis of the incidence of adverse events among patients with preserved ejection fraction who received shunts (60.2%) as compared with patients who did not (35.9%) (P=0.001).[56]

AREAS OF UNCERTAINTY

There is uncertainty regarding heart failure with preserved ejection fraction classification and the precise diagnostic criteria that should be used. More disease-modifying therapies are needed. The term "heart failure with preserved ejection fraction" is nonspecific and based on an arbitrary LVEF cutoff value and therefore may not provide adequate nomenclature for this heterogenous disease.[57,58] Although patients with the condition share many common characteristics, distinct subgroups are emerging. Patients with specific phenotypic features of the condition, such as obesity, may benefit from specific medical treatment. We do not know whether GLP-1 receptor agonists and GIP agonists are useful in treating patients with heart failure with preserved ejection fraction who are not obese.[20] Beneficial treatments are now available for patients with cardiac amyloidosis, but more are needed. More specific noninvasive diagnostic tools would improve diagnostic accuracy and rule out confounding diagnoses. New biomarkers and techniques to measure increases in intracardiac pressures and volumes could improve diagnostic pathways. Treatment of coexisting conditions and use of preventive strategies may also reduce the incidence of the condition and resultant medical treatment.

Despite recent reductions in composite morbidity and mortality end points in clinical trials, no single trial of therapy has yet shown a significant reduction in mortality or in death from cardiovascular causes in patients with heart failure with preserved ejection fraction. Several clinical trials are ongoing in this area (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

GUIDELINES

Therapies for heart failure with preserved ejection fraction that are recommended in international guidelines are summarized in Table 1.[3,4,59-61] All international guidelines recommend diuretic treatment for patients with the condition. The main difference among the guidelines is the strength of recommendations for the use of SGLT2 inhibitors in patients with heart failure with preserved ejection fraction, which reflects the timing of trial publications relative to the guideline publications. The more recent 2023 focused update of the European guidelines indicates the use of SGLT2 inhibitors as a class I recommendation ("recommend").

The U.S. and the Japanese guidelines give a class IIb recommendation ("may be considered") for the use of ARNIs and MRAs in patients with heart failure with preserved ejection fraction. The Canadian guidelines suggest the use of RAS inhibitors and MRAs, but the European Society of Cardiology guideline does not give any recommendations on these agents because the task force avoided issuing recommendations that were based on subgroup analyses of trials in which the primary outcomes showed no benefit.

CONCLUSIONS

Regarding the patient in the vignette, we would introduce guideline-directed therapies for heart failure with preserved ejection fraction. First, we would address the patient's pulmonary and vascular congestion with intravenous diuretics. Once euvolemia had been reached, we would switch to an oral loop diuretic. We would also add an SGLT2 inhibitor to reduce symptoms and the risk of subsequent hospitalization for heart failure. Effective decongestion should result in the reduction of her pulmonary arterial pressure and respiratory symptoms. We would target treatments to control both her hypertension and her obesity. Because the patient has resistant hypertension, with a blood pressure of greater than

130/80 mm Hg despite treatment with ramipril and amlodipine, we would add spironolactone. For her obesity, we could consider introducing a GLP-1 receptor agonist. We would assess her for sleep-disordered breathing and treat any obstructive sleep apnea found. In the longer term, promotion of a healthy lifestyle, monitoring of disease progression, and treatment of coexisting conditions may avoid hospitalizations in the future and improve her quality of life.

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

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