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Special Communication

What Are Heart Failure With Preserved Ejection Fraction Mimics and What Are They Mimicking? Insights Into Our Conceptualization of Heart Failure With Preserved Ejection Fraction as a Disease

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ABSTRACT

During the initial workup of a patient with chronic heart failure, increased left ventricular filling pressures at rest or during exercise, and a left ventricular ejection fraction ≥50%, physicians are expected to exclude the presence of established diseases that masquerade as heart failure with preserved ejection fraction (HFpEF), referred to as "HFpEF mimics." These diseases include (1) cardiac amyloidosis; (2) hypertrophic cardiomyopathy; (3) infiltrative, restrictive, and inflammatory cardiomyopathies (sarcoidosis, hemochromatosis, Fabry disease, and radiation- and chemotherapy-induced restrictive disorders); (4) hemodynamically significant valvular heart disease; (5) pericardial diseases (particularly constrictive pericarditis); (6) high-output heart failure; and (7) end-stage kidney disease. These diseases were recognized long before HFpEF was defined as a disorder, have specific targeted treatments, and have generally been excluded from randomized controlled trials of new drugs for HFpEF. Interestingly, after the exclusion of HFpEF mimics, patients demonstrate the typical clinical and pathophysiologic features of cardiometabolic HFpEF, with an exceptionally high prevalence of central adiposity, dysglycemia, hypertension, and systemic inflammation—even though large-scale trials did not require participants to have any feature of a cardiometabolic disorder. The homogeneity of the phenotypic presentations of these patients is consistent with the lack of observed heterogeneity in the responses to broad-based treatments (ie, sodium-glucose cotransporter 2 inhibitors, finerenone and incretins). Importantly, many patients with adiposity-related HFpEF were not permitted to participate in large-scale trials, which

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excluded patients with severe obesity, lower natriuretic peptides and without manifest echocardiographic diastolic filling abnormalities. In conclusion, the exclusion of HFpEF mimics from the broad population of patients with left-sided heart failure and an ejection fraction ≥50% yields a relatively homogeneous patient population with the features of adiposity-related HFpEF. (*J Cardiac Fail 2026;32:1475–1481*)

Key Words: Heart failure with preserved ejection fraction, HFpEF mimics, cardiometabolic HFpEF.

When physicians encounter a patient with chronic heart failure, symptoms, signs or laboratory evidence of congestion, increased left ventricular (LV) filling pressures at rest or during exercise, and a LV ejection fraction ≥50%, they are reminded, first and foremost, to consider and to exclude the presence of established diseases that present in a manner akin to patients with heart failure with preserved ejection fraction (HFpEF). These diseases include (1) cardiac amyloidosis; (2) hypertrophic cardiomyopathy; (3) infiltrative, restrictive, and inflammatory cardiomyopathies (sarcoidosis, hemochromatosis, Fabry disease, endomyocardial fibrosis, and radiation- and chemotherapy-induced restrictive disorders); (4) hemodynamically significant valvular heart disease; (5) pericardial diseases (particularly constrictive pericarditis); (6) high-output heart failure; and (7) end-stage kidney disease. By convention, these diseases are referred to as "HFpEF mimics," "HFpEF mimickers," or "HFpEF masqueraders."[1-4] Other diseases that are characterized by exertional dyspnea, LV ejection fraction ≥50% but have normal LV filling pressures or LV morphology (eg, pulmonary arterial hypertension, chronic lung disease, severe anemia, rapid atrial fibrillation, deconditioning) can be grouped together as "non-left-heart HFpEF mimics," and they are not considered further in this perspective.

At first, the use of the term "HFpEF mimic" might seem to represent a highly unusual and inexplicable naming convention. Why are diseases that mimic HFpEF referred to as "HFpEF mimics"? What are "HFpEF mimics" actually mimicking?

HFpEF mimics were recognized as diseases before HFpEF was defined

When the modern era of heart failure emerged in the 1970s, trials focused on patients with systolic dysfunction, generally defined at the time as an ejection fraction of ≤35% or meaningful LV enlargement, typically caused by an ischemic or nonischemic dilated cardiomyopathy. In the 1980s, it was recognized that some patients with heart failure did not exhibit substantial systolic dysfunction.[5–7] With the advent of routine laboratory tests, echocardiography, cardiac catheterization, and myocardial biopsy, clinicians were able to identify patients with cardiac amyloidosis; hypertrophic, infiltrative, restrictive, and inflammatory cardiomyopathies; hemodynamically significant valvular heart disease; constrictive pericarditis; high-output heart failure; and end-stage kidney disease, and these diseases were recognized as specific causes of heart failure in patients without a low ejection fraction. Such patients were excluded from participation in trials of direct-acting vasodilators, positive inotropic agents, angiotensin-converting enzyme inhibitors, beta-adrenergic blockers, and mineralocorticoid receptor antagonists, which focused on patients with heart failure with reduced ejection fraction (HFrEF).

Interestingly, a few early trials allowed the enrollment of patients with an ejection fraction >35%. The V-HeFT and V-HeFT II trials (carried out from 1980 to 1991) enrolled a few hundred patients with a LV ejection fraction of >35%,[8] but the patients did not appear to respond favorably to hydralazine and isosorbide dinitrate. The number of patients with an LV ejection fraction of ≥50% in these 2 trials is not known but was likely to be few, because all patients were required to have meaningful LV enlargement. In the Digitalis Investigation Group (DIG) trial (carried out from 1991 to 1995), a small minority of patients—719 of 7788 (9.2%)—had an ejection fraction ≥50%,[9] and they did not exhibit a favorable effect of digoxin on cardiovascular death or heart failure hospitalization.

The emergence and design of large-scale trials dedicated to HFpEF

In 1999, the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) investigators first proposed the term HFpEF as identifying patients with heart failure who had a LV ejection fraction >40%,[10] but this numerical threshold represented an arbitrary value. The CHARM trials studied heart failure with a broad spectrum of ejection fractions, and the HFpEF and HFrEF trials were run in parallel.[11] Given the expected variance in ejection fraction measurements, the investigative sites likely had some discretion as to whether to enroll patients into one trial or the other. Subsequent work demonstrated that the pathophysiologic features of patients with an ejection fraction of 41%–49% (ie, those with mildly reduced ejection fraction) resembled that seen in patients with heart failure and an ejection fraction of ≤40% (ie, HFrEF).[12] As a result, the universal definition of HFpEF

currently defines HFpEF as requiring a LV ejection fraction ≥50%.[3]

The first stand-alone trials of patients with HFpEF with >1000 patients were the Irbesartan in Heart Failure with Preserved Systolic Function Trial (I-PRESERVE) trial (initiated in 2002)[13] and the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial (initiated in 2006)[14]; these trials enrolled patients with a LV ejection fraction of ≥45% and specifically excluded HFpEF mimics, that is, those with cardiac amyloidosis, hypertrophic and restrictive cardiomyopathies, hemodynamically significant valvular heart disease, constrictive pericarditis, and end-stage kidney disease, as well as those with chronic lung disease or cor pulmonale. All HFpEF trials initiated since 2002 specified eligibility criteria that excluded the participation of patients with HFpEF mimics. These large-scale trials subsequently demonstrated the efficacy of sodium-glucose cotransporter 2 inhibitors (SGLT2i), mineralocorticoid receptor antagonists, and incretin drugs.[15–19] Trials with similar exclusion criteria also reported the lack of efficacy of angiotensin receptor blockers and drugs that dilate peripheral veins and the pulmonary vasculature through a nitric oxide-cyclic guanosine monophosphate mechanism.[20–27] Ongoing prospective observational studies of HFpEF involving deep phenotyping are also excluding patients with HFpEF mimics.[28]

Therefore, HFpEF has been defined operationally by the criteria that were used to define patient eligibility into placebo-controlled trials that have established the evidence base for our treatment of the disease. Accordingly, true HFpEF is defined by symptoms and signs of heart failure, an LV ejection fraction ≥50%, and objective evidence of hemodynamic congestion, usually reflected by LV diastolic filling abnormalities, increased natriuretic peptides or increased LV filling pressures at rest or exercise, excluding HFpEF mimics.

HFpEF mimics are diseases with their own defined treatments

Why have patients who had HFpEF mimic diseases been excluded from participation in HFpEF trials? HFpEF mimics are well-defined disorders with a rich clinical history dating back for decades (and preceding the delineation of HFpEF as a clinical entity), a defined pathogenesis, and (most importantly) highly effective disease-specific treatments. Cardiac amyloidosis results from the infiltration of amyloid fibrils, and transthyretin forms respond favorably to treatment with drugs that suppress amyloid synthesis or stability.[29,30] Hypertrophic cardiomyopathy is frequently a monogenetic, polygenetic, or epigenetically driven disease that benefits symptomatically from cardiac myosin inhibitors.[31,32] Sarcoidosis is treated with immunosuppressive agents[33]; hemochromatosis responds to phlebotomy or iron chelation therapy[34]; and Fabry disease is managed with enzyme-replacement and pharmacologic chaperone therapies.[35,36] High-output heart failure responds to cause-specific treatments (eg, thiamine and arteriovenous shunt revisions) [37,38]; the cardiac abnormalities of end-stage kidney disease are reversed after renal transplantation[39,40]; and constrictive pericarditis and severe valvular disease benefit from surgical or device interventions that alleviate the primary hemodynamic derangement.[41,42] The established benefits of disease-specific treatments make it unethical to withhold treatment and randomize patients to placebo or an intervention being evaluated for the management of true HFpEF (Fig. 1).

The proportion of patients with heart failure, increased LV filling pressures, and an ejection fraction of ≥50% who have a disease classified as a HFpEF mimic is not known. Cohort studies have not defined the prevalence of HFpEF mimics in any representative patient population that presents to a clinician with complaints of exertional dyspnea and is found to have heart failure and an ejection fraction of ≥50% on their initial assessment. Two-dimensional Doppler echocardiography, when performed and interpreted with experience and when considered together with other features (age and accompanying conditions), should be able to identify most patients with HFpEF mimics. However, many patients do not undergo additional definitive diagnostic testing for cardiac amyloidosis or sarcoidosis. The medical literature is replete with reports of patients with HFpEF mimics who were initially diagnosed and treated as if they had true HFpEF[42–44]—an unfortunate occurrence because HFpEF mimics require disease-specific treatments.

It should be noted that some patients with coronary artery disease experience exertional dyspnea (rather than angina) as the primary symptom of effort-induced ischemia. These patients likely represent a very small minority of patients with epicardial artery disease, and there is no noninvasive test that can reliably elucidate the potential contribution of ischemia to complaints of exertional dyspnea. At the present time, such patients can only be defined retrospectively, on the basis of the observation that coronary revascularization has led to resolution of symptoms of effort-induced breathlessness in an individual patient. However, in general, the completeness of coronary revascularization (when applied routinely) has not been associated with improved exertional dyspnea and a reduced risk of heart failure hospitalizations among patients with heart failure and an ejection fraction ≥50%.[45] In light of these diagnostic difficulties and therapeutic uncertainties, patients with exertional dyspnea as the primary symptom of effort-induced ischemia were not excluded from participation in large-scale trials. Therefore, we have not included this disorder in our listing of HFpEF mimics, a decision that is aligned with an identical decision made by scientific statements, consensus documents and guidelines.

Interestingly, a similar exclusionary principle has been applied to trials of HFrEF. For most of the past 40 years,

trials of new agents for HFrEF have typically excluded patients with reversible causes or requiring disease-specific interventions. These have included drug-related cardiomyopathies; tachycardia-induced cardiomyopathy; malignant hypertension; hyper- or hypothyroidism; acute myocarditis or peripartum cardiomyopathy; nutritional deficiencies (thiamine, selenium, etc); cardiac amyloidosis with a reduced ejection fraction; or cardiomyopathy potentially related to acute ischemia or hibernating myocardium. These disorders were generally excluded from large-scale trials of HFrEF; they have disease-specific treatments; and the role of neurohormonal activation and the efficacy of neurohormonal antagonism in these disorders is not known.

Patient characteristics and treatment responses in dedicated HFpEF trials

What are the features of the trial participants who have been enrolled in randomized controlled trials in HFpEF? Nearly all the patients have had abdominal obesity[46,47] and a history of hypertension; >80% have had overweight or obesity; one-half have had type 2 diabetes,[15–17] with dysglycemia and insulin resistance in ≈75%[48,49]; and the vast majority have had evidence for systemic inflammation.[15–17,50] These features correspond closely to what has been referred to as "cardiometabolic HFpEF," an endotype that has been causally linked to the upstream influence of excess and dysfunctional visceral fat.[51,52] According to the 2023 American College of Cardiology Scientific Statement on HFpEF,[3] the vast majority of patients with HFpEF can be considered to have "cardiometabolic HFpEF." Aging (through its effects to promote visceral adiposity), hypertension (mediated through adiposity-related arterial stiffness), and atrial fibrillation (through adiposity-mediated atrial myopathy) may be considered components of adiposity-related HFpEF (Fig. 1). The mechanistic importance of these pathophysiological derangements (independent of adiposity) remains to be demonstrated.[53,54]

The homogeneity of the cardiometabolic features of patients enrolled in HFpEF trials is consistent with the lack of heterogeneity in the observed treatment responses in

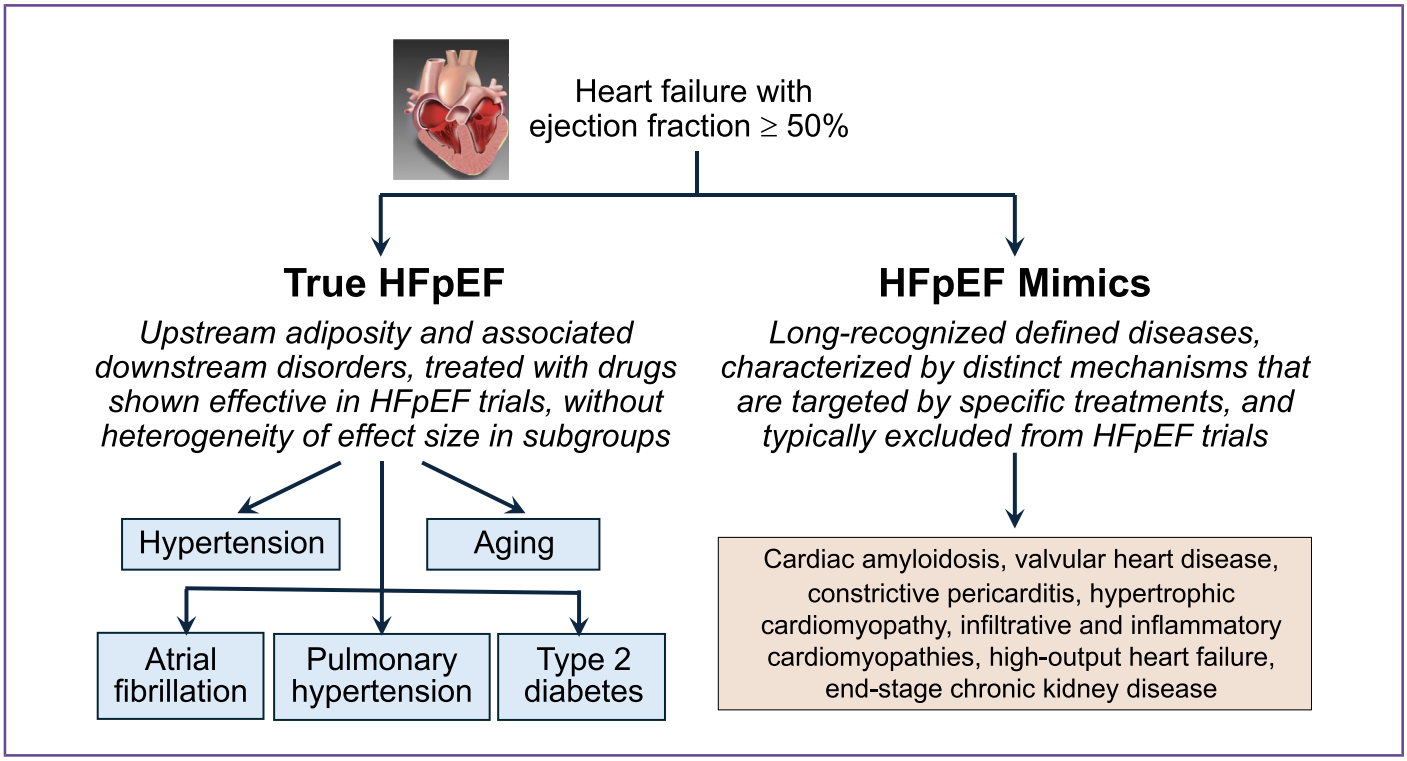

Fig 1. Clinical, pathophysiologic, and therapeutic features that distinguish patients with HFpEF mimics from patients with true HFpEF. Patients with heart failure, increased left ventricular filling pressures, and an ejection fraction ≥50% can be grouped into those with (1) "true HFpEF," which is generally characterized by the presence of central adiposity (and associated [typically downstream] cardiometabolic disorders) and whose participation has dominated large-scale trials that demonstrated the efficacy of sodium-glucose cotransporter 2 inhibitors, finerenone, and incretin drugs, without evidence of heterogeneity of the treatment benefit across subgroups; and (2) "HFpEF mimics," which comprise defined diseases, recognized long before HFpEF was identified as a clinical entity, with distinct pathophysiologic mechanisms and which respond favorably to targeted disease-specific treatments. Because of the need to provide disease-specific treatments that were expected to provide considerable benefits, patients with HFpEF mimics were generally not allowed to be recruited into large-scale HFpEF trials. The patients who participated in these trials had all the features of an adiposity-related disorder, even though the eligibility criteria for these trials did not require patients to have any cardiometabolic abnormality. Interestingly, many patients with adiposity-related HFpEF were also not allowed to participate in large-scale trials, because these trials excluded patients with severe obesity or who did not have meaningful increases in natriuretic peptides. HFpEF, heart failure with preserved ejection fraction.

these studies. In the patients enrolled in the DELIVER and EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved) trials (which studied SGLT2i), the Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure (FINEARTS-HF) trial (which studied finerenone) and the incretin trials (which studied semaglutide and tirzepatide), patients showed consistent responses across all prespecified and post hoc subgroups.[15–19] Patients with coronary artery disease, atrial fibrillation, or elevated blood pressure (with presumed arterial stiffness) did not show differential responses to treatment, even though they were well-represented in the trials and have been hypothesized (by some) to produce HFpEF by cardiometabolic- and adiposity-independent pathways. It is noteworthy that SGLT2i, mineralocorticoid receptor antagonists, and incretin drugs reduce visceral adiposity and mute the activation of deleterious molecular signaling pathways that accompany an expansion of visceral fat mass.[52] However, the degree to which these actions contribute to their clinical benefits in patients with HFpEF has not been defined.

Lack of full representation of adiposity-related HFpEF in large-scale trials

Even though patients with HFpEF who have been eligible for clinical trials have had all the typical features of a cardiometabolic disorder, it should be noted that large-scale trials did not require participants to have any feature of an adiposity-related disease. In fact, the eligibility criteria of these trials systematically excluded many patients with adiposity-related HFpEF. In most trials, patients were not permitted to participate if they had a body mass index >40 to 45 kg/m^2 or if they did not have meaningfully elevated levels of natriuretic peptides.[13–18] Suppression of circulating natriuretic peptides is a typical feature of obesity-related HFpEF.[55,56] In addition, many trials required patients to have evidence of diastolic filling abnormalities on echocardiography, but this finding is present in a minority of patients who have demonstrable HFpEF.[57] The SUMMIT trial did not restrict the participation of patients with marked obesity and did not require patients to have diastolic filling abnormalities or a threshold level of natriuretic peptides, and it reported striking clinical benefits aftertreatment with a drug that caused meaningful decreases in body weight and metrics of central adiposity.[19] The exclusion of patients with marked adiposity may have attenuated the reported magnitude of clinical benefit in large-scale trials.[46,58–60]

Summary and conclusions

The term "HFpEF mimics" refers to a group of distinct diseases that have pathophysiologic mechanisms and therapeutic responses that are fundamentally different from true HFpEF. HFpEF mimics refer to specific disorders that were recognized long before HFpEF was defined as a clinical entity, should be identified during a patient's initial clinical evaluation, and have their own disease-specific treatments. Importantly, patients with HFpEF mimics have been systematically excluded from large-scale placebo-controlled trials of therapeutic interventions for HFpEF for the past 20 to 25 years.

After the exclusion of patients with HFpEF mimics, the patients who remained eligible for participation in large-scale HFpEF trials showed the characteristic features of adiposity-related HFpEF—even though the eligibility criteria for these trials did not require patients to have any cardiometabolic feature. Importantly, these trials demonstrated clinical benefits of drugs that are known to favorably influence adipose tissue biology—without evidence for heterogeneity of the treatment benefit across subgroups.

Therefore, the exclusion of HFpEF mimics from the broad population of patients with heart failure and an ejection fraction ≥50% yields a relatively homogeneous patient population with the clinical and pathophysiologic features of a cardiometabolic- and adiposity-related disorder, even though these trials generally excluded many patients with severe adiposity. Patients with adiposity-related HFpEF—referred to as "true HFpEF"—have dominated participation in trials that established the efficacy of SGLT2 inhibitors, finerenone, and incretin drugs. Diseases that are grouped together as "HFpEF mimics" are singled out, because they masquerade as adiposity-related HFpEF.

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Disclosures

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CRediT authorship contribution statement

MILTON PACKER: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **JAVED BUTLER:** Writing – review & editing. **JENNIFER E. HO:** Writing – review & editing. **CAROLYN S.P. LAM:** Writing – review & editing. **MARK C. PETRIE:** Writing – review & editing. **GABRIELE G. SCHIATTARELLA:** Writing – review & editing. **MUTHIAH VADUGANATHAN:** Writing – review & editing. **FAIEZ ZANNAD:** Writing – review & editing. **BARRY A. BORLAUG:** Writing – review & editing.

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References

1. Hamo CE, DeJong C, Hartshorne-Evans N, Lund LH, Shah SJ, et al. Heart failure with preserved ejection fraction. Nat Rev Dis Primers 2024;10:55.
2. Obokata M, Reddy YNV, Borlaug BA. Diastolic dysfunction and heart failure with preserved ejection fraction: understanding mechanisms by using noninvasive methods. JACC Cardiovasc Imaging 2020;13:245–57.
3. Kittleson MM, Panjrath GS, Amancherla K, Davis LL, Deswal A, Dixon DL, et al. 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2023;81:1835–78.
4. Desai AS, Lam CSP, McMurray JJV, Redfield MM. How to manage heart failure with preserved ejection fraction: practical guidance for clinicians. JACC Heart Fail 2023;11:619–36.
5. Dougherty AH, Naccarelli GV, Gray EL, Hicks CH, Goldstein RA. Congestive heart failure with normal systolic function. Am J Cardiol 1984;54:778–82.
6. Luchi RJ, Snow E, Luchi JM, Nelson CL, Pircher FJ. Left ventricular function in hospitalized geriatric patients. J Am Geriatr Soc 1982;30:700–5.
7. Topol EJ, Traill TA, Fortuin NJ. Hypertensive hypertrophic cardiomyopathy of the elderly. N Engl J Med 1985;312:277–83.
8. Carson P, Johnson G, Fletcher R, Cohn J. Mild systolic dysfunction in heart failure (left ventricular ejection fraction >35%): baseline characteristics, prognosis and response to therapy in the Vasodilator in Heart Failure Trials (V-HeFT). J Am Coll Cardiol 1996;27:642–9.
9. Abdul-Rahim AH, Shen L, Rush CJ, Jhund PS, Lees KR, McMurray JJV. VICCTA-Heart Failure Collaborators. Effect of digoxin in patients with heart failure and mid-range (borderline) left ventricular ejection fraction. Eur J Heart Fail 2018;20:1139–45.
10. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777–81.
11. Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, et al. CHARM Investigators and Committees. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 2003;362:759–66.
12. Savarese G, Stolfo D, Sinagra G, Lund LH. Heart failure with mid-range or mildly reduced ejection fraction. Nat Rev Cardiol 2022;19:100–16.
13. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008;359:2456–67.
14. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383–92.
15. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al. DELIVER Trial Committees and Investigators. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med 2022;387:1089–98.
16. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385:1451–61.
17. Solomon SD, McMurray JJV, Vaduganathan M, Claggett B, Jhund PS, Desai AS, et al. FINEARTS-HF Committees and Investigators. Finerenone in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med 2024;391:1475–85.
18. Butler J, Shah SJ, Petrie MC, Borlaug BA, Abildstrøm SZ, Davies MJ, et al. STEP-HFpEF Trial Committees and Investigators. Semaglutide versus placebo in people with obesity-related heart failure with preserved ejection fraction: a pooled analysis of the STEP-HFpEF and STEP-HFpEF DM randomised trials. Lancet 2024;403:1635–48.
19. Packer M, Zile MR, Kramer CM, Baum SJ, Litwin SE, Menon V, et al. SUMMIT Trial Study Group. Tirzepatide for heart failure with preserved ejection fraction and obesity. N Engl J Med 2025;392:427–37.
20. Borlaug BA, Anstrom KJ, Lewis GD, Shah SJ, Levine JA, Koepp GA, et al. Effect of inorganic nitrite vs placebo on exercise capacity among patients with heart failure with preserved ejection fraction: the INDIE-HFpEF randomized clinical trial. JAMA 2018;320:1764–73.
21. Zamani P, Shah SJ, Cohen JB, Zhao M, Yang W, Afable JL, et al. Potassium nitrate in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA Cardiol 2025;10:284–9.
22. Udelson JE, Lewis GD, Shah SJ, Zile MR, Redfield MM, Burnett Jr J, et al. Effect of praliciguat on peak rate of oxygen consumption in patients with heart failure with preserved ejection fraction: the CAPACITY HFpEF randomized clinical trial. JAMA 2020;324:1522–31.
23. Armstrong PW, Lam CSP, Anstrom KJ, Ezekowitz J, Hernandez AF, O'Connor CM, et al. Effect of vericiguat vs placebo on quality of life in patients with heart failure and preserved ejection fraction: the VITALITY-HFpEF randomized clinical trial. JAMA 2020;324:1512–21.
24. Redfield M, Anstrom K, Levine J, Koepp GA, Borlaug BA, Chen HH, et al. Isosorbide mononitrate in heart failure with preserved ejection fraction. N Engl J Med 2015;373:2314–24.
25. Dachs TM, Duca F, Rettl R, Binder-Rodriguez C, Dalos D, Ligios LC, et al. Riociguat in pulmonary hypertension and heart failure with preserved ejection fraction: the haemoDYNAMIC trial. Eur Heart J 2022;43:3402–13.
26. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2013;309:1268–77.
27. Borlaug BA, Testani JM, Petrie MC, Wang Z, Cunningham J, Adams Jr KF, et al. Effects of volenrelaxin in worsening heart failure with preserved ejection fraction: a phase 2 randomized trial. Nat Med 2025;31:3853–61.
28. Borlaug BA, Chirinos JA, Lewis GD, Redfield MM, Bertoni AG, Cadeiras M, et al. Rationale and design of the HeartShare/AMP-HF deep phenotyping study to improve understanding of heart failure with preserved ejection fraction. JACC Heart Fail 2025;13:102714.
29. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, et al. ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 2018;379:1007–16.
30. Fontana M, Berk JL, Gillmore JD, Witteles RM, Grogan M, Drachman B, et al. HELIOS-B Trial Investigators. Vutrisiran in patients with transthyretin amyloidosis with cardiomyopathy. N Engl J Med 2025;392:33–44.
31. Rossano JW, Canter C, Wolf CM, Papez A, Gambra M, Bryant RM, et al; SCOUT-HCM Investigators. Mavacamten in adolescents with obstructive hypertrophic cardiomyopathy. N Engl J Med, in press.
32. Maron MS, Masri A, Nassif ME, Barriales-Villa R, Arad M, Cardim N, et al. SEQUOIA-HCM Investigators. Aficamten for symptomatic obstructive hypertrophic cardiomyopathy. N Engl J Med 2024;390:1849–61.
33. Imamura Y, Momose M, Yamamoto A, Suzuki A, Serizawa N, Uto K, et al. Long term prognosis in cardiac sarcoidosis under FDG-PET guided immunosuppressive therapy. Int J Cardiol 2025;432:133273.
34. Murphy CJ, Oudit GY. Iron-overload cardiomyopathy: pathophysiology, diagnosis, and treatment. J Card Fail 2010;16:888–900.
35. Pande S, Varzideh F, Gambardella J, Jankauskas SS, Cerasuolo FA, Spinelli L, et al. Fabry disease cardiomyopathy: a state-of-the-art review. Prog Cardiovasc Dis 2025;92:43–65.
36. Pogoda C, Brand SM, Duning T, Schmidt-Pogoda A, Sindermann J, Lenders M, et al. Impact of enzyme replacement therapy and migalastat on left atrial strain and cardiomyopathy in patients with Fabry disease. Front Cardiovasc Med 2023;10:1223635.
37. Nisar S, Mohi-U-Din K, Tak SI, Andrabi SMA, Tanvir M, Muzaffer U, et al. Thiamine responsive high output heart failure of adults: an under-recognized entity. Eur J Clin Nutr 2023;77:757–60.
38. Cristiano F, Lodi M. The management of high flow arteriovenous fistula and possible solutions. J Vasc Access 2025;26:1748–53.
39. Qi L, Ni X, Schoepf UJ, Varga-Szemes A, McGill L, Wang W, et al. Time-dependent cardiac structural and functional changes after kidney transplantation: a multiparametric cardiac magnetic resonance study. Eur Radiol 2022;32:5265–75.
40. Tian Z, Bergmann K, Kaufeld J, Schmidt-Ott K, Melk A, Schmidt BMW. Left ventricular hypertrophy after renal transplantation: systematic review and meta-analysis. Transplant Direct 2024;10:e1647.
41. Doldi P, Stolz L, Orban M, Karam N, Praz F, Kalbacher D, et al. Transcatheter mitral valve repair in patients with atrial functional mitral regurgitation. JACC Cardiovasc Imaging 2022;15:1843–51.
42. Rayamajhi K, Parul F, Yavari M, Brummel K, Scoma C. A near-miss event: constrictive pericarditis misdiagnosed as heart failure with preserved ejection fraction. Cureus 2025;17:e99563.
43. AbouEzzeddine OF, Davies DR, Scott CG, Fayyaz AU, Askew JW, McKie PM, et al. Prevalence of transthyretin amyloid cardiomyopathy in heart failure with preserved ejection fraction. JAMA Cardiol 2021;6:1267–74.

44. Liu J, Wang D, Ruan J, Wu G, Xu L, Jiang W, et al. Identification of heart failure with preserved ejection fraction helps risk stratification for hypertrophic cardiomyopathy. BMC Med 2022;20:21.
45. Fu M, Wang Y, Han X, Yuan S, Liu Y, Qian J, et al. Revascularization for patients with heart failure with preserved ejection fraction and coronary artery disease. Am J Cardiol 2024;213:86–92.
46. Peikert A, Vaduganathan M, Claggett BL, Kulac IJ, Litwin S, Zile M, et al. Near-universal prevalence of central adiposity in heart failure with preserved ejection fraction: the PARAGON-HF trial. Eur Heart J 2025;46:2372–90.
47. Ostrominski JW, Højbjerg Lassen MC, Butt JH, Claggett BL, Anand IS, Desai AS, et al. Adiposity-related anthropometrics and clinical outcomes in heart failure with mildly reduced or preserved ejection fraction: a participant-level pooled analysis of randomized clinical trials. J Am Coll Cardiol 2025;86:1760–77.
48. Jackson AM, Rørth R, Liu J, Kristensen SL, Anand IS, Claggett BL, et al. PARAGON-HF Committees and Investigators. Diabetes and pre-diabetes in patients with heart failure and preserved ejection fraction. Eur J Heart Fail 2022;24:497–509.
49. Reddy YNV, Frantz RP, Hemnes AR, Hassoun PM, Horn E, Leopold JA, et al. PVDOMICS Study Group. Disentangling the impact of adiposity from insulin resistance in heart failure with preserved ejection fraction. J Am Coll Cardiol 2025;85:1774–88.
50. Packer M. What causes inflammation in heart failure with a preserved ejection fraction? Potential role of eicosanoid adipokines. JACC Heart Fail 2025;13:102638.
51. Packer M, Schiattarella GG, Borlaug BA. What exactly is cardiometabolic HFpEF: a phenotype or an endotype? Circ Heart Fail 2026;19:e014031.
52. Packer M. The adipokine hypothesis of heart failure with a preserved ejection fraction: a novel framework to explain pathogenesis and guide treatment. J Am Coll Cardiol 2025;86:1269–373.
53. Packer M, Butler J, Lam CSP, Zannad F, Vaduganathan M, Borlaug BA. Central adiposity or hypertension: which drives heart failure with a preserved ejection fraction? J Am Coll Cardiol 2025;86:1935–49.
54. Packer M, Ho J, Petrie MC, Schiattarella GG, Butler J, Lam CSP, et al. Excess and dysfunctional fat as a primary driver of heart failure with preserved ejection fraction: from institutional recognition to clinical integration. JACC Heart Fail 2026;14:103046.
55. Reddy YNV, Tada A, Obokata M, Carter RE, Kaye DM, Handoko ML, et al. Evidence-based application of natriuretic peptides in the evaluation of chronic heart failure with preserved ejection fraction in the ambulatory outpatient setting. Circulation 2025;151:976–89.
56. Sorimachi H, Verbrugge FH, Omote K, Omar M, Obokata M, Reddy YNV, et al. Longitudinal evolution of cardiac dysfunction in heart failure and preserved ejection fraction with normal natriuretic peptide levels. Circulation 2022;146:500–2.
57. Harada T, Sorimachi H, Obokata M, Naser JA, Ibe T, Tada A, et al. Echocardiographic diastolic function grading in HFpEF: testing the updated 2025 ASE criteria. J Am Coll Cardiol 2026;87:1261–75.
58. Butt JH, Henderson AD, Jhund PS, Claggett BL, Desai AS, Lay-Flurrie J, et al. Finerenone, obesity, and heart failure with mildly reduced/preserved ejection fraction: prespecified analysis of FINEARTS-HF. J Am Coll Cardiol 2025;85:140–55.
59. Siddiqi TJ, Anker SD, Filippatos G, Ferreira JP, Pocock SJ, Böhm M, et al. Health status across major subgroups of patients with heart failure and preserved ejection fraction. Eur J Heart Fail 2023;25:1623–31.
60. Borlaug BA, Zile MR, Kramer CM, Ye W, Ou Y, Hurt K, et al. SUMMIT Trial Study Group. Impact of body mass index, central adiposity, and weight loss on the benefits of tirzepatide in HFpEF: the SUMMIT trial. J Am Coll Cardiol 2025;86:242–55.