ESC European Society of Cardiology

European Journal of Heart Failure (2022) **24**, 1158–1161
doi:10.1002/ejhf.2576

VIEWPOINT

Left ventricular ejection fraction as the primary heart failure phenotyping parameter

Lars H. Lund[1,2]*, Bertram Pitt[3], and Marco Metra[4]

[1]Karolinska Institutet, Department of Medicine, Unit of Cardiology, Stockholm, Sweden; [2]Karolinska University Hospital, Heart and Vascular Theme, Stockholm, Sweden; [3]Department of Medicine, University of Michigan School of Medicine, Ann Arbor, MI, USA; and [4]Cardiology, ASST Spedali Civili and University of Brescia, Brescia, Italy

Heart failure (HF) is the most common cause of hospitalization and among the most common causes of death.[1] Left ventricular ejection fraction (LVEF) measured by echocardiography has for decades been and remains the standard parameter for diagnosing and categorizing HF. Classification and treatment of patients remain based on ejection fraction.[2,3] Every time we encounter a patient with suspected or manifest HF, the first thing we ask is 'what is the ejection fraction?'.

So it is surprising the extent to which LVEF and HF categorization based on LVEF has come under criticism in recent years.[4–6] LVEF has limitations.[4] With improved understanding of the complexity of the HF syndrome, and with improved clinical, biomarker, imaging, invasive haemodynamic, and composite score and big-data analytical tools to characterize HF, the LVEF has been increasingly viewed as too primitive. But in no instance have critics of the LVEF provided a validated alternative to LVEF. Decades of progress in HF treatment remain based on studies where reduced LVEF was the main inclusion criterion. In this viewpoint therefore, as has also recently been done by others,[7] we provide a pragmatic rationale for why echocardiography with measurement of LVEF and categorization of HF into HF with reduced ejection fraction (HFrEF, LVEF ≤40%); HF with mildly reduced ejection fraction (HFmrEF, LVEF 41–49%), and HF with preserved ejection fraction (HFpEF, LVEF ≥50%)[2] remains the primary clinical tool in assessment of patients with suspected or manifest HF, until better and actionable alternatives emerge (*Figure 1*).

Is echocardiography useful?

Echocardiography is easy to perform, inexpensive, safe and can be performed without discomfort for the patient. Echocardiography provides an extensive array of structural and functional measurements. Parameters such as left ventricular mass and left atrial size, myocardial strain and measures of left ventricular diastolic function, right ventricular function and valvular heart disease are useful in characterizing patients with HF and potentially as adjunct eligibility criteria and surrogate endpoints in clinical trials. However, they are complementary to and do not substitute for LVEF.[2]

Technological advancements are providing alternatives to echocardiography. However, echocardiography has also evolved, and is now widely available with small, portable and inexpensive devices for point-of-care ultrasonography.[8] These are proving useful for reproducible point-of-care assessment of cardiac structure and function, but also of other parameters relevant in HF, such as lung ultrasound for interstitial fluid (B-lines) or pleural effusion.[9] Interpretation of echocardiography has also evolved, with machine learning and artificial intelligence able to provide accurate automated LVEF measurements.[10] Echocardiography is nearly universally available at least in high and medium income countries.[11] Costs of standard transthoracic echocardiography are highly variable but generally much lower in comparison to most medical diagnostics or therapeutics. Thus echocardiography remains a firmly established diagnostic technology in HF and cardiovascular medicine.

Is left ventricular ejection fraction useful?

The LVEF parameter is familiar to all clinicians regardless of training and specialty. Together with other structural and functional parameters from the echocardiogram (but even to some extent alone), it provides not definitive answers but important clues as to the aetiology of, severity of, prognosis of, and therapeutic possibilities in HF. A common criticism is that LVEF is variable and the implication is that it is therefore unreliable. LVEF varies according to imaging technology and measurement methods. LVEF has inter- and intra-observer variability. When healthy volunteers had separate-day measurements, the coefficient of variation was 11%, compared to 7% for cardiac magnetic resonance imaging (CMR). Interestingly, in this study the reproducibility of global longitudinal and circumferential strain was more reproducible with echocardiography than with CMR.[12] In addition, measurements

*Corresponding author. Department of Medicine, Karolinska Institutet, and Heart Vascular and Neurology Theme, Karolinska University Hospital, Norrbacka, S1:02, 171 76 Stockholm, Sweden, Tel: +46 8 51770000, Fax: +46 8 311044, Email: lars.lund@alumni.duke.edu

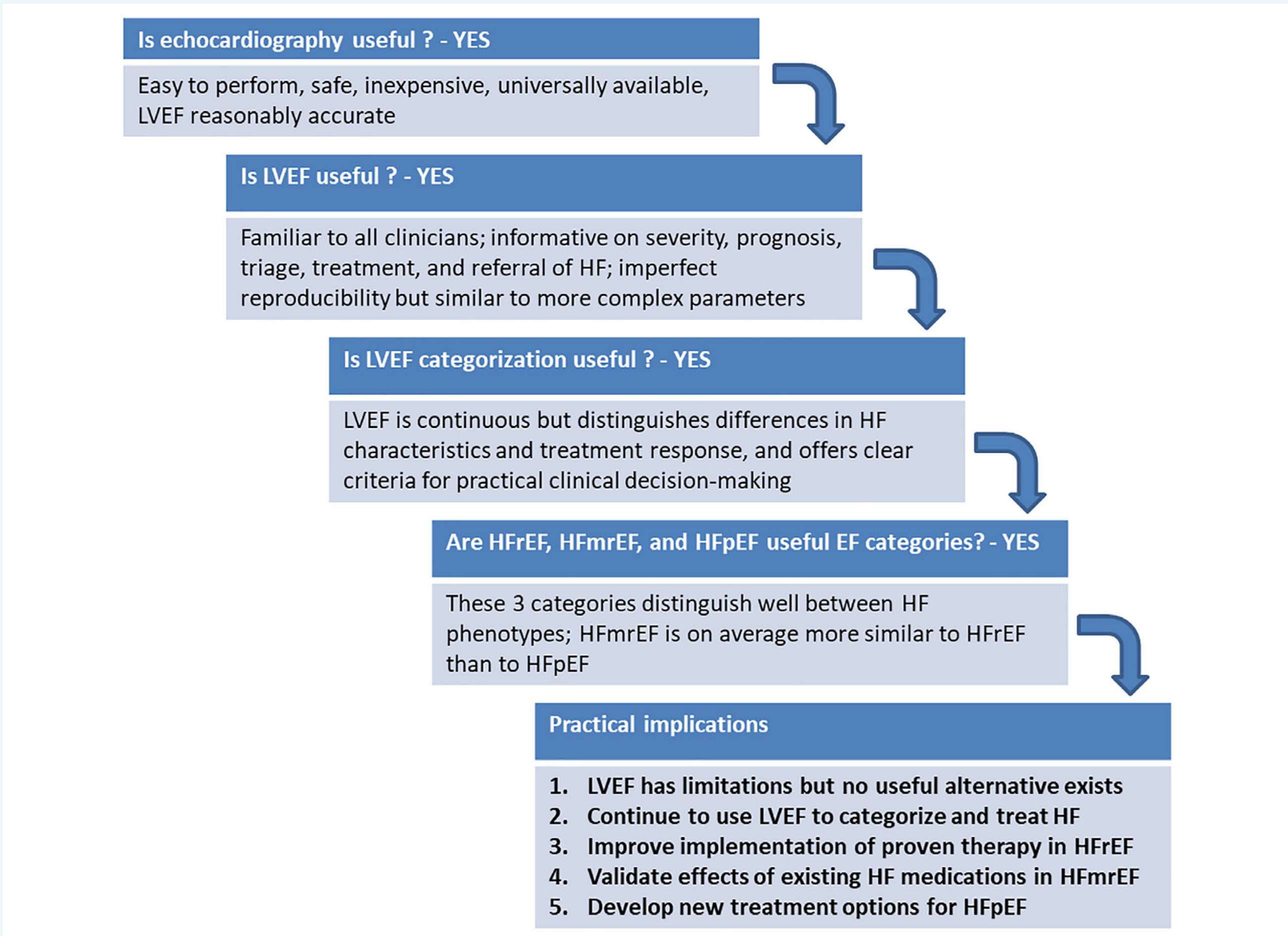

Figure 1 Rationale for continued use of left ventricular ejection fraction (LVEF) in heart failure (HF). EF, ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

were on separate days. A well-established parameter of HF severity, such as N-terminal pro-B-type natriuretic peptide (NT-proBNP), has low variability when repeated on the same sample, but is very variable over even short periods of time in the same patient, and low values may be difficult to interpret in patients with HFpEF or obesity. A prospective study aimed at the use of changes in NT-proBNP levels to predict and prevent acute HF events was stopped prematurely for slow enrolment and the belief that an algorithm for assessing natriuretic peptide trends was needed. B-type natriuretic peptide (BNP) values were highly variable within a patient with dispersion between serial BNPs values of 39.3%, 57.7%, and 73.6% for 1, 60, and 120 days between measures, respectively.[13] In another study, the intra-individual coefficient of variation of NT-proBNP levels measured at a 6-week interval was of 21.8% with a reference change value that may indicate a relevant change of 61.7%.[14] LVEF for clinical trial entry has been reported to differ and often be higher when adjudicated as compared to reported by investigators,[15] but some authors have argued that local interpretation in clinical trials is a strength since it reflects routine care and improves generalizability.[7]

Is categorization of patients with heart failure according to left ventricular ejection fraction useful?

The definition of the HF syndrome does not require any specific cut-off for (or even knowledge of) LVEF. Categorization based on LVEF was dictated since the 1980s by clinical trial design requiring an LVEF generally below 30–40%.[2] In patients with HF but a normal LVEF, diagnosis of HF was unreliable (and sometimes remains so). It was understood that patients with lower LVEF had greater HF severity and greater risk of cardiovascular and HF events, and thus enriching trials by setting cut-offs at LVEF 30–40% would ensure the presence of HF and reduce sample size and increase trial feasibility. In addition, it was believed that maladaptive neurohormonal activation was relevant predominantly in patients with lower LVEF. These considerations certainly proved prescient. They set the stage for an era of fantastically successful clinical trials in HFrEF, delivering immensely effective therapy for a common and severe syndrome and helping countless patients to better and longer lives.

Are the HFrEF (≤40%), HFmrEF (41–49%) and HFpEF (≥50%) categories useful?

Categorization of LVEF has been criticized because it is a continuous parameter that reflects a spectrum of HF characteristics and severity and therefore cut-offs are by necessity arbitrary. However, the relation between LVEF and outcomes, namely mortality, is not linear but rather U-shaped, with higher mortality with lower ejection fraction, lower mortality with normal LVEF, and again higher mortality with supernormal values, above 70%.[16] Even though it may have been necessary for enrichment, by excluding patients with HFmrEF from the landmark HFrEF trials, an opportunity was perhaps missed to provide effective therapy also for this group. Categorization of HF into HFrEF, HFmrEF and HFpEF (and more recently also into HF with improved ejection fraction [HFimpEF], and HF with supra-normal ejection fraction [HFsnEF]) is a relatively recent development. The 2012 European Society of Cardiology (ESC) HF guidelines defined LVEF in the range of 35–50% as a 'grey area'. Subsequent commentary largely considered this range as 'the middle child' intermediate between HFrEF and HFpEF,[17] and the 2016 ESC HF guidelines coined a new term – HFmrEF. As intended, this new category prompted extensive clinical research and renewed interest in previously conducted and overall neutral randomized trials in HFpEF (≥40%, which included HFmrEF).[18] This research proved this classification to be prescient but that HFmrEF was 'intermediate' in some but not in many other important respects, and led the 2021 ESC HF guidelines to conclude that 'patients with HFmrEF have, on average, features that are more similar to HFrEF than HFpEF'.[2,18]

Finally and of great relevance for clinical care and clinical trial design, patients with HFmrEF appear to respond similarly to patients with HFrEF to neurohormonal antagonists (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists [MRAs]) and neurohormonal modulators (the angiotensin receptor–neprilysin inhibitor sacubitril/valsartan).[18] In post-hoc and sub-group analyses of HFpEF trials (which included patients with LVEF down to 40–45%), patients in the HFmrEF range had similar relative risk reduction (and because HFmrEF is milder, lower absolute risk reduction), generally on the order of 20% lower risk of the primary trial endpoint, as did patients with HFrEF in the analogous HFrEF trials. In contrast, patients with HFpEF derived no benefit at all. This was especially distinct in the CHARM programme,[19] the beta-blocker meta-analysis consortium,[20] and in PARAGON-HF.[21] For MRAs, the TOPCAT trial hinted at a potential benefit among patients in the lower range of HFmrEF/HFpEF, but there are ongoing trials with generic and proprietary MRAs that should determine whether MRAs are effective in HFmrEF, and potentially in HFpEF, with greater certainty.

For catheter-based, device, and surgical interventions in HF, the LVEF is an important component in the comprehensive assessment of potential indications. Decisions for advanced HF interventions are based on sophisticated multifactorial considerations beyond LVEF,[22] but referral to advanced HF centres are very much determined by LVEF.[23] Thus, not only has ejection fraction categorization proven useful, but also the cut-offs for HFrEF, HFmrEF and HFpEF do also appear to be appropriate. The normal and lower limit of normal LVEF is around 62% and 52% in men and 64% and 54% in women, respectively.[24] Drugs that appear effective in HFmrEF may possibly be effective also into the low 50% range, or even higher in women. There have been calls to return to using the term HF with normal ejection fraction (HFnEF) instead of HFpEF,[25] but whether this should be 50% for reasons of consistency and practicality, or whether it should be higher and/or different in men and women remains a matter of debate.

One reason often suggested for why HFpEF trials failed has been that HFpEF is 'heterogeneous'. Indeed, the range of and confounding by comorbidities, age and frailty has confounded clinical trial design. For example, recently it has become clear that many patients with HFpEF have transthyretin amyloidosis. These patients may benefit from specific therapy[2] and it has been assumed that they do not benefit from standard HF drugs, although recent exploratory data suggest that in fact they may.[26] An alternative view may be that this perceived heterogeneity reflects inclusion of both HFmrEF and HFpEF, where HFmrEF resembles HFrEF, and HFpEF is different from but no more heterogeneous than any other category. According to this theory, HFrEF and HFmrEF are results of some initial myocardial injury, followed by maladaptive neurohormonal activation and secondary remodelling, whereas HFpEF is a consequence of long-standing comorbidity-driven systemic inflammation, leading to progressive changes in the heart as well as in other organs.[27]

Recently, the SOLOIST-WHF trial demonstrated efficacy with the sodium–glucose cotransporter type 2/1 (SGLT2/1) inhibitor sotagliflozin in patients with type 2 diabetes mellitus across the LVEF spectrum,[28] and EMPEROR-Preserved demonstrated efficacy of the SGLT2 inhibitor empagliflozin in HFmrEF and HFpEF.[29] Thus SGLT2/1 inhibitors appear to be the first class of drugs effective in HF regardless of LVEF, which is consistent with the many putative mechanisms of action that extend well beyond neurohormonal antagonism and modulation, and targets the cardiac, kidney and vascular remodelling that occurs in HF generally, whether it is secondary to an initial myocardial injury as in HFrEF and HFmrEF, or part of the primary disease process as in HFpEF.

Conclusions

Left ventricular ejection fraction is the most commonly used and comprehensive parameter for HF diagnosis, characterization, prognosis, monitoring, therapeutic decision making, and eligibility for HF clinical trials (*Figure 1*). LVEF categorization into HFrEF, HFmrEF and HFpEF has been criticized as arbitrary but has proven remarkably prescient, properly characterizing patients with HF into different aetiologies, characteristics, risk of different cause-specific outcomes, and response to therapy. It is hard to imagine what more one could ask of a simple, inexpensive, safe and widely available clinical tool. Critics of the LVEF parameter have proposed many but not demonstrated utility of any alternative parameters to manage patients with HF. There are indeed many unmet needs in HF: wider implementation of proven HFrEF therapy, verification of potential effects of standard HF drugs in HFmrEF, and development of novel treatments in HFpEF; but a replacement for LVEF is not one of them. However, we still encourage the search and validation of new biomarkers that will add insight and predictive ability to subsets within the LVEF categories, HFrEF, HFmrEF and HFpEF.

Conflict of interest: L.H.L Related to the present work: None. Unrelated to the present work: Grants: AstraZeneca, Vifor, Boston Scientific, Boehringer Ingelheim, Novartis. Consulting: Merck, Vifor, AstraZeneca, Bayer, Pharmacosmos, MedScape, Sanofi, Lexicon, Myokardia, Boehringer Ingelheim, Servier. Speaker's honoraria: Abbott, MedScape, Radcliffe, AstraZeneca, Novartis, patent AnaCardio Stock ownership: AnaCardio. B.P Related to the present work; none. unrelated to the present work: consulting fees from Bayer, Astra Zeneca, Boehringer Ingelheim/Lilly, and Phasebio; consulting fees and stock options from SCPharmaceuticals, SQinnovations, G3pharmaceuticals, Relypsa/Vifor, Cereno scientific, KBP Pharmaceuticals, Sarfez, Tricida, Proton Intel, and Brainstorm Medical. M.M Related to the present work: none. Unrelated to the present work: Personal fees from AstraZeneca, Abbott vascular, Amgen, Edwards Therapeutics, Actelion, Amgen, Servier, Livanova, Vifor pharma, and WindTree Therapeutics.

References

1. Savarese G, Lund LH. Global public health burden of heart failure. *Card Fail Rev*. 2017r;**3**:7–11.
2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al.; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2022;**24**: 4–131.
3. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of heart failure: endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail*. 2021;**23**: 352–80.
4. Ferreira JP, Packer M, Butler J, Zannad F. Reconsidering the ejection fraction centric view of pharmacologic treatment for heart failure. *Eur J Heart Fail*. 2022;**24**: 1148–53.
5. Lund LH, Vedin O, Savarese G. Is ejection fraction in heart failure a limitation or an opportunity? *Eur J Heart Fail*. 2018;**20**:431–2.
6. Mele D, Nardozza M, Ferrari R. Left ventricular ejection fraction and heart failure: an indissoluble marriage? *Eur J Heart Fail*. 2018;**20**:427–30.
7. Khan MS, Shahid I, Fonarow GC, Greene SJ. Classifying heart failure based on ejection fraction: imperfect but enduring. *Eur J Heart Fail*. 2022;**24**:1154–7.
8. Diaz-Gomez JL, Mayo PH, Koenig SJ. Point-of-care ultrasonography. *N Engl J Med*. 2021;**385**:1593–602.
9. Coiro S, Chouihed T, Girerd N. Lung ultrasound – the extension of clinical examination in patients with acute heart failure: reply. *Eur J Heart Fail*. 2016; **18**:215.
10. Tromp J, Seekings PJ, Hung CL, Iversen MB, Frost MJ, Ouwerkerk W, et al. Automated interpretation of systolic and diastolic function on the echocardiogram: a multicohort study. *Lancet Digit Health*. 2022;**4**:e46–54.
11. Seferovic PM, Vardas P, Jankowska EA, Maggioni AP, Timmis A, Milinkovic I, et al.; National Heart Failure Societies of the ESC member countries. The Heart Failure Association Atlas: heart failure epidemiology and management statistics 2019. *Eur J Heart Fail*. 2021;**23**:906–14.
12. Houard L, Militaru S, Tanaka K, Pasquet A, Vancraeynest D, Vanoverschelde JL, et al. Test-retest reliability of left and right ventricular systolic function by new and conventional echocardiographic and cardiac magnetic resonance parameters. *Eur Heart J Cardiovasc Imaging*. 2021;**22**:1157–67.
13. McDonald K, Troughton R, Dahlstrom U, Dargie H, Krum H, van der Meer P, et al. Daily home BNP monitoring in heart failure for prediction of impending clinical deterioration: results from the HOME HF study. *Eur J Heart Fail*. 2018;**20**:474–80.
14. Meijers WC, van der Velde AR, Muller Kobold AC, Dijck-Brouwer J, Wu AH, Jaffe A, et al. Variability of biomarkers in patients with chronic heart failure and healthy controls. *Eur J Heart Fail*. 2017;**19**:357–65.
15. Kutyifa V, Kloppe A, Zareba W, Solomon SD, McNitt S, Polonsky S, et al. The influence of left ventricular ejection fraction on the effectiveness of cardiac resynchronization therapy: MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). *J Am Coll Cardiol*. 2013;**61**:936–44.
16. Wehner GJ, Jing L, Haggerty CM, Suever JD, Leader JB, Hartzel DN, et al. Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie? *Eur Heart J*. 2020;**41**:1249–57.
17. Lam CSP, Solomon SD. The middle child in heart failure: heart failure with mid-range ejection fraction (40–50%). *Eur J Heart Fail*. 2014;**16**:1049–55.
18. 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.
19. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. *Eur J Heart Fail*. 2018;**20**:1230–9.
20. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, et al.; Beta-blockers in Heart Failure Collaborative Group. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J*. 2018;**39**:26–35.
21. Solomon SD, Vaduganathan M, Claggett BL, Packer M, Zile M, Swedberg K, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. *Circulation*. 2020;**141**:352–61.
22. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2018;**20**:1505–35.
23. Lund LH. Improving long-term outcomes with left ventricular assist devices – referral, selection, experience, and technology. *Eur J Heart Fail*. 2019;**21**:101–2.
24. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;**16**:233–70.
25. Kondo T, McMurray JJV. Re-emergence of heart failure with a normal ejection fraction? *Eur Heart J*. 2022;**43**:427–9.
26. Sperry BW, Hanna M, Shah SJ, Jaber WA, Spertus JA. Spironolactone in patients with an echocardiographic HFpEF phenotype suggestive of cardiac amyloidosis: results from TOPCAT. *JACC Heart Fail*. 2021;**9**:795–802.
27. Sanders-van Wijk S, Tromp J, Beussink-Nelson L, Hage C, Svedlund S, Saraste A, et al. Proteomic evaluation of the comorbidity-inflammation paradigm in heart failure with preserved ejection fraction: results from the PROMIS-HFpEF study. *Circulation*. 2020;**142**:2029–44.
28. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al.; SOLOIST-WHF Trial Investigators. Sotagliflozin in patients with diabetes and recent worsening heart failure. *N Engl J Med*. 2021;**384**:117–28.
29. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Bohm M, et al.; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;**385**:1451–61.