TIMOK MEDICAL GAZETTE

Vol. 47 (2022) No. 1 Review article

# PARADIGM CHANGE IN THE TREATMENT OF CHRONIC HEART FAILURE ACCORDING TO ESC GUIDE 2021 - NEW INNOVATIVE DRUGS IN FOCUS

*Dušan Bastać (1), Zoran Joksimović (1), Snežana Pavlović (2), Mila Bastać (3), Anastasija Raščanin (1), Igor Djordjioski (4)*

(1) OFFICE FOR INTERNAL MEDICINE "DR BASTAĆ", ZAJEČAR; (2) SPECIALIST OFFICE FOR INTERNAL MEDICINE "DR PAVLOVIĆ KARDIOLOGIJA" BELGRADE; (3) MEDSCAN TADIĆ DIAGNOSTICS, ZAJEČAR; (4) ZAJECAR HEALTH CENTER

**Summary:** Medical, primarily drug therapy directed by the New ESC Guide or Guidelines for Patients with Heart Failure (HF) brings significant innovations and changes in the treatment paradigm, from the gradual introduction of drugs to the simultaneous introduction of 5 main classes of drugs. Treatment of heart failure with reduced left ventricular ejection fraction (HFrEF) and symptoms of class II-New York Heart Association (NYHA) -dispnea at higher exertion and higher NYHA classes, now includes angiotensin receptor inhibitor neprilysin (ARNI) as a substitute for angiotenzin convertase enzyme inhibitor( ACEI). Another significant innovation is the addition of SGLT-2 inhibitors (SGLT2i = sodium-glucose channel cotransporter-2 inhibitors). SGLT2i: dapagliflozin or empagliflozin are now in the first line of therapy for heart failure, along with the introduction of beta-blockers (BB), ACEI or ARNI, mineralocorticotide receptor inhibitors (MRAs) and Henle's loop diuretics in fluid retention as recommended in Class I. Sacubitril-valsartan, a combined neprilysin and angiotensin inhibitor (ARNI), was introduced in the reduced left ventricular ejection fraction (HFrEF) and showed an additional reduction in CV mortality and hospitalization due to HFrEF compared to the ACE inhibitor enalapril. Dapagliflozin and empagliflozin reduce the risk of cardiovascular mortality or hospitalization due to HF in patients with HF and reduced left ventricular ejection fraction <40% (HFrEF), but empagliflozin has recently shown an effect in HFpEF with an ejection fraction of 65% of 40%.

**Key words:** heart failure, pharmaceuticals, left ventricular ejection fraction, heart failure with reduced left ventricular ejection fraction (HFrEF), heart failure with perserved left ventricular ejection fraction (HFpEF), hypertension, kidney disease, myocardial ichaemia, natriuretic peptide

The key points from the European Society of Cardiology (ESC) Guide for the Diagnosis and Treatment of Acute and Chronic Heart Failure (HF) from 2021 [1] are presented, as well as some views from the American ACC / AHA Guidelines from 2022 [2]:

Heart failure (HF) nomenclature with left ventricular ejection fraction (LVEF) of 41-49% has been revised in HF with mildly reduced EF (HFmEF). HF with LVEF ≤40% remains HF with reduced EF (HFrEF), and HF with LVEF ≥50% remains HF with preserved EF (HFpEF).

Table 1. Heart failure (HF) nomenclature from ESC guideline 2021

| Type of HF | | HFrEF | HFmrEF | HFpEF |
|---|---|---|---|---|
| CRITERIA | 1 | Symptoms ± Signs[a] | Symptoms ± Signs[a] | Symptoms ± Signs[a] |
| | 2 | LVEF ≤40% | LVEF 41–49%[b] | LVEF ≥50% |
| | 3 | - | - | Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c] |

All patients with suspected HF should have: electrocardiogram, transthoracic echocardiogram, X-ray of thorax (lung and heart), complete blood count, urea, creatinine, electrolytes, thyroid hormones, glycosylated hemoglobin (HbA1c), lipid status, iron analysis, peptide (BNP / NT-proBNP). Magnetic resonance imaging of the heart is recommended in patients with poor acoustic window for ultrasound of the heart or in patients with suspected infiltrative cardiomyopathy, amyloidosis , hemochromatosis, dilated non-compaction cardiomyopathy or myocarditis [1]. The new diagnostic algorithm for heart failure (HF) is shown in Figure 1.

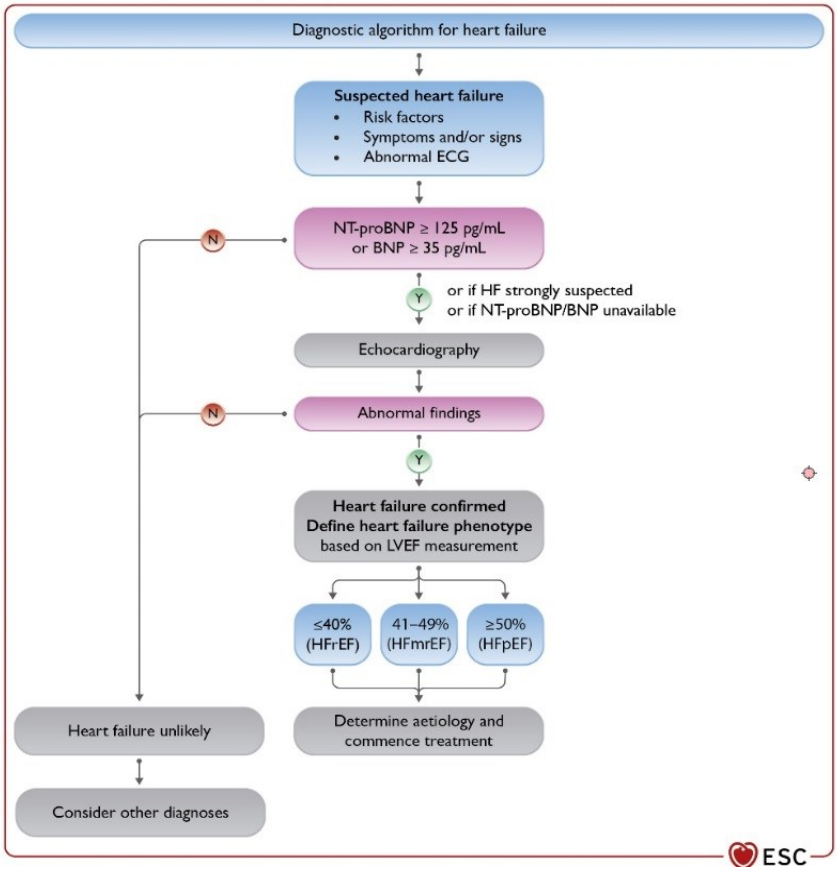



FIGURE 1. DIAGNOSTIC ALGORITHM FOR HEART INSUFFICIENCY (HF) ACCORDING TO THE NEW ESC GUIDE 2021.

LEGEND: Heart failure with reduced left ventricular ejection fraction (HFrEF)
Heart failure with mildly reduced left ventricular ejection fraction (HFmrEF)
Heart failure with preserved left ventricular ejection fraction (HFpEF)

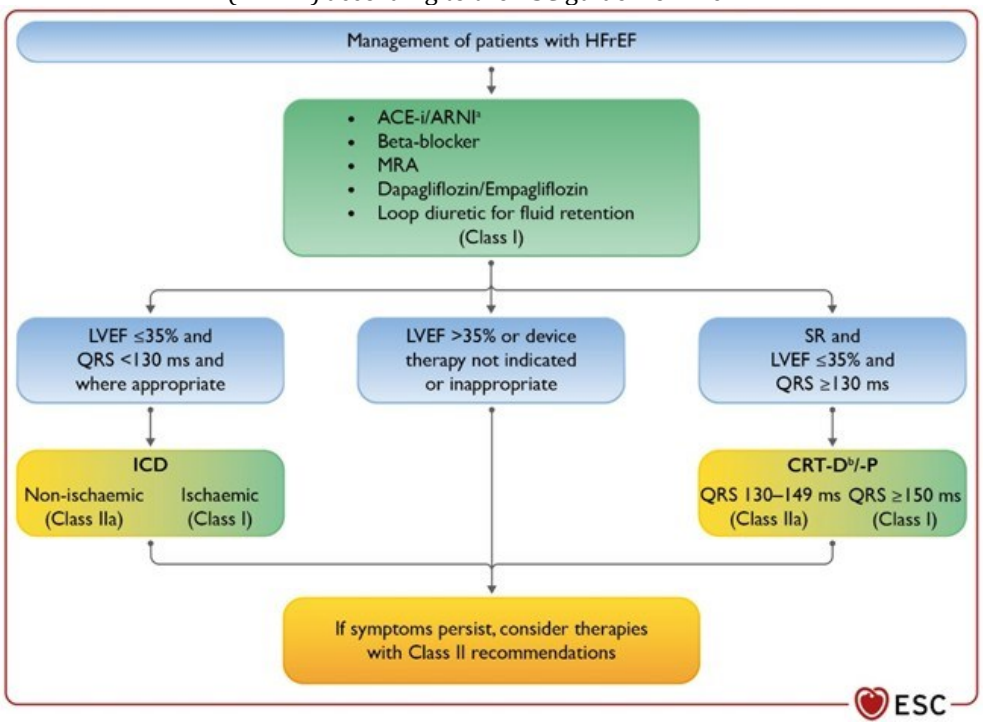
Available at www.escardio.org/guidelines (doi: 10.1093/eurheartj/ehab368)

*Medical, primarily drug therapy directed by the New ESC Guide, ie guidelines for patients with heart failure (HF) with reduced ejection fraction (HFrEF) brings significant innovations and changes in the treatment paradigm, from the gradual introduction of drugs to the simultaneous introduction of 5 main classes of drugs.*

Treatment of heart failure with reduced left ventricular ejection fraction (HFrEF) and symptoms of class II-New York Heart Association (NYHA) -dispnea at higher exertion and higher classes, now includes angiotensin receptor inhibitor neprilysin (ARNI) as a substitute for angiotenzin convertase enzyme inhibitor( ACEI). Another significant innovation is the addition of SGLT-2 (Sodium Glucose channels Cotransporter-2) inhibitors, dapagliflozin or empagliflozin in first-line therapy for heart failure, simultaneously with the introduction of beta-blockers, ACEI or ARNI,

mineralocorticoid receptor inhibitors and diuretics. class I. (picture 2)

Figure 2. Treatment of patients with HEART INSUFFICIENCY WITH REDUCED EJECTION FRAGMENT (HFrEF) according to the ESC guide from 2021




Legend ACE-I = angiotensin converting enzyme inhibitor; ARNI = angiotensin receptor-neprilysin inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; CRT-D = pacemaker for cardiac resynchronization with a defibrillator; CRT-P = pacemaker for cardiac resynchronization; Available at www.escardio.org/guidelines (doi: 10.1093/eurheartj/ehab368)

Excessive neurohumoral activation antagonists, beta-adrenergic receptor blockers, and renin-angiotensin-aldosterone system antagonists have shown a reduction in CV mortality in HFrEF in a number of clinical randomized studies and have been the primary therapy for heart failure for some time. These drugs achieved the following beneficial effects: slowing the progression of left ventricular remodeling, reducing discomfort, improving endurance and quality of life in all symptomatic categories from NYHA class II to NYHA class IV. Eplerenone as a selective mineralocorticoid aldosterone receptor antagonist is recommended for NYHA class II, while for severe class III-IV patients with beta-blockers and ACEIs or sartans, a non-selective mineralocorticoid aldosterone receptor antagonist beparon (beta blocker) should be added with . In decompensated patients with severe congestion, Henle's loop diuretics remain a pillar of therapy.

In the treatment of heart failure with reduced LVEF (HFrEF), sacubitril-valsartan, a combined neprilysin and angiotensin inhibitor (ARNI), was introduced in previous 2016 ESC guidelines, which showed an additional reduction in CV mortality and hospitalizations due to HFrEF compared to the ACE inhibitor enala .

Dapagliflozin and empagliflozin reduce the risk of cardiovascular mortality or hospitalization due to HF in patients with HF and reduced left ventricular ejection fraction <40% (HFrEF) [1] but empagliflozin has also recently shown an effect in HFpEF [65% ejection] .
In patients with HFrEF and NYHA class II to III symptoms, ARNi is recommended to reduce morbidity and mortality (class 1A) [3-7].
In patients with previous or current symptoms of chronic HFrEF, the use of ACEi is useful in reducing morbidity and mortality when ARNi is not feasible (class 1A) [8-15].

In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACEi due to cough or angioedema and when the use of ARNi is not feasible, the use of ARBs is recommended to reduce morbidity and mortality [16-20].
In patients with previous or current symptoms of chronic HFrEF, in whom the introduction of ARNi is not feasible, treatment with ACEi or ARB gives high economic viability [2,21-27].
ARNi is contraindicated in concomitant ACEi or within 36 hours of the last dose of ACEi, or in patients with a history of angioedema.

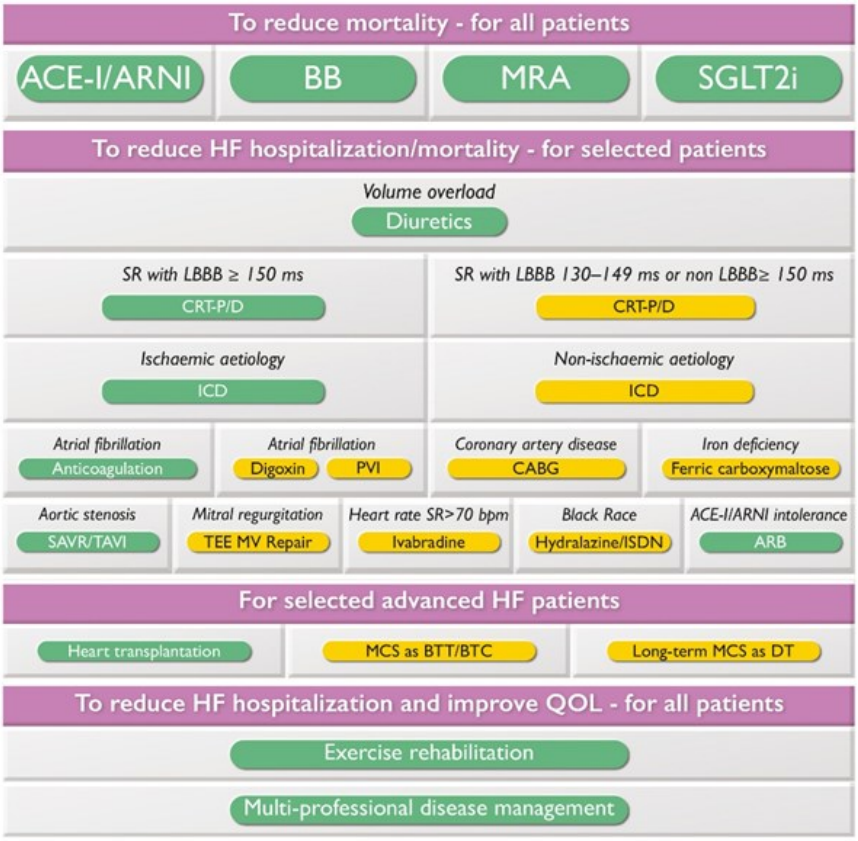
**Recommendations for the administration of empagliflozin and dapagliflozin that reduce cardiovascular mortality or hospitalization due to HF in patients with HF and reduced left ventricular ejection fraction <40% (HFrEF)**
In patients with symptomatic chronic HFrEF, SGLT2i is recommended to reduce hospitalization due to HF and cardiovascular mortality, regardless of the presence of type 2 diabetes [28,29] and thus introduced SGLT2i therapy has good economic justification [30,31].

**Recommendations for HF with MILDLY reduced EF (HFmrEF)**
In patients with HFmrEF, SGLT2i may be helpful in reducing hospitalizations for HF and cardiovascular mortality [32]. Among patients with current or previous symptomatic HFmrEF (LVEF, 41% –49%), the use of ARNi, ACEi or ARB and MRA and evidence-based beta blockers for HFrEF may be considered adequate for use to reduce the risk of hospitalization for HF and cardiovascular mortality , especially among patients with LVEF at the lower end of this spectrum [33-40].
Recommendations for HF with preserved EF (HFpEF) according to the ACC / AHA guide from 2022 (ref 2)

1. Patients with HFpEF and hypertension should be titrated with antihypertensive drugs in order to achieve the target blood pressure in accordance with published guidelines of clinical practice for the prevention of morbidity [41-43].
2. In patients with HFpEF, SGLT2 inhibitors may be useful in reducing HF hospitalizations and cardiovascular mortality [44].
3. In patients with HFpEF, treatment of atrial fibrillation (AF) may be helpful in improving symptoms.
4. In selected patients with HFpEF, mineralocorticoid receptor (MRA) antagonists may be considered effective in reducing hospitalizations, especially among patients with LVEF at the lower end of this spectrum [45-47].
5. In selected patients with HFpEF, the use of ARBs may be considered to reduce hospitalizations, especially among patients with LVEF at the lower end of this spectrum [48,49].

Implantable cardioverter-defibrillators (ICDs) are recommended for the primary prevention of sudden cardiac death in symptomatic ischemic or non-ischemic cardiomyopathy with LVEF ≤35% despite 3 months of optimal targeted therapy (GDMT) if 1-year survival is expected. ICD is not recommended within 40 days of myocardial infarction (MI) or for patients with NIHA class IV symptoms who are not candidates for advanced therapy.
Cardiac pacemaker resinchronization (CRT) therapy is recommended for symptomatic HFrEF with EF <35% in sinus rhythm with left bundle branch block (LBBB) for 150 ms despite GDMT. It is also recommended for HFrEF with EF <35% regardless of the symptoms or duration of heart failure if there is a high degree of atrioventricular (AV) block with the need for a pacemaker. (FIGURE 3)

FIGURE 3. Strategic review of care for patients with heart failure and reduced left ventricular ejection fraction (HFrEF)




LEGEND: b.p.m = beats per minute; BTC = bridge to transplant candidate; BTT = bridge to heart transplant; CABG = surgical coronary artery bypass grafting; CRT-D = defibrillator pacemaker resynchronization; CRT-P = pacemaker for cardiac resynchronization; DT = definitive therapy; ICD = implantable cardioverter-defibrillator; ISDN = isosorbide dinitrate; LBBB = block of the left branch of the His bundle; MCS = mechanical circulation support; MV = mitral valve; PVI = radiofrequency isolation of pulmonary veins; SAVR = surgical replacement of the aortic valve; SR = sinus rhythm; TAVI = transcatheter replacement of the aortic valve; TEE MV repair = transcatheter MV reconstruction from edge to edge.
Color code for recommendation class: green for recommendation class I; Yellow for recommendation class IIa. The figure shows the management options with Class I and IIa recommendations. See special tables for those with Class IIb recommendations.
Available at www.escardio.org/guidelines (doi: 10.1093/eurheartj/ehab368)

For HFmEF, diuretics are recommended to alleviate or eliminate congestion. ACE inhibitors / angiotensin receptor blockers / ARNI / beta-blockers / mineralocorticoid receptor antagonists may be considered as adjunctive therapy to reduce mortality and hospitalization (Class IIa recommendation).

Diagnosis and treatment of factors that contribute to heart failure (hypertension, kidney disease, etc.) and the use of diuretics are recommended for patients with heart failure with preserved left ventricular ejection fraction (HFpEF). Specific therapies have not been shown to reduce mortality in HFpEF. However, after the release of the ESC guide (August 2021), a new registration study Emperor-preserved (2) appeared, where empagliflozin showed improvement in the clinical outcome of treatment in patients with heart failure and preserved LVEF> 40%. A pooled analysis of the effects of empagliflozin 10 mg daily with pre-existing drug therapy for heart failure was performed on 9,718 Emperor-reduced and Emperor-Preserved patients. These two studies were comparable so that a wide range of left ventricular ejection fraction from 25% to 65% was obtained. Studies have shown that empagliflozin reduces the risk of hospitalization due to heart failure in a wide range of ejection fraction values by up to 65%, and its efficiency is

reduced in patients with LVEF> 65%. There is also a beneficial effect of empagliflozin on symptoms and endurance effort consistently with an ejection fraction of less than 65%. Further analysis found that the size of the therapeutic response to empagliflozin did not depend on the size of LVEF in the range of 25% to 65%, with a similar reduction in HF hospitalization risk to LVEF size in subgroups <30% and 40-50%, and in the subgroup with preserved left ventricular ejection fraction> 50%. An important fact from these studies is that empagliflozin reduces the risk of worsening glomerular filtration (GFR) in HF along the entire spectrum of the ejection fraction of LVEF, both with reduced, slightly reduced and preserved LVEF from 25% to 65% (2).

For all patients with HF, enrollment in a multidisciplinary HF program, at home or at the clinic, is recommended. For the prevention of HF, Class I recommendations include: appropriate hypertension treatment, statin use, when indicated, SGLT2 inhibitors in diabetics at high risk for or with cardiovascular disease, and counseling to discontinue, consume alcohol and drugs, and treat obesity.
For acute decompensated HF, routine use of inotropic drugs is not recommended in the absence of cardiogenic shock, and routine use of opioid-morphine is also not recommended for cardiogenic pulmonary edema. Routine use of an intra-aortic balloon pump in cardiogenic shock after myocardial infarction is not recommended.
Additional Class I recommendations for hospitalized patients with acute HF include the introduction of targeted oral therapy and the careful elimination of pre-discharge volume overload (congestion) with early follow-up within 1-2 weeks of hospital discharge.

For patients with atrial fibrillation (AF), routine use of anticoagulants for CHA2DS2-VASc ≥2 in men and ≥3 in women is recommended, preferably with direct-acting oral anticoagulants (NOAC), except in the presence of a prosthetic mechanical valve or moderate or severe mitral stenosis. Recommended. Emergency cardioversion is recommended for patients with HF AF who are hemodynamically compromised. Rhythm control, including radiofrequency catheter ablation, should be considered in AF patients who have symptoms.

For patients with HF and severe aortic stenosis, transcatheter / surgical replacement of the aortic valve using the Heart Time approach is recommended. For patients with HF with secondary mitral regurgitation, percutaneous edge-to-edge mitral valve repair should be considered if severe symptoms persist despite appropriate guided therapy (GDMT). For patients with secondary mitral regurgitation and coronary artery disease requiring revascularization, coronary by-pass and mitral valve surgery should be considered.
Patients with cancer who are being considered for cardiotoxic chemotherapeutic drugs and who are at risk of cardiotoxicity should ideally be evaluated by a cardio-oncologist before starting therapy.
Tafamidis is a Class I recommendation in patients with TTR-type amyloidosis with symptoms of NIHA class I-II.
All patients with HF should be periodically examined for iron deficiency anemia. Administration of ferric carboxymaltose should be considered in symptomatic, outpatient patients with HF and anemia due to iron deficiency and EF ≤45% or hospitalized patients with HF with EF ≤50%.

REFERENCE:

1. McDonagh TA, Metra M, Adamo M, et al.Citation: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 Heart J. 2021;42(36):3599-3726. doi: 10.1093/eurheartj/ehab368.
2. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022;79(17):e263-e421. doi: 10.1016/j.jacc.2021.12.012. Epub 2022 Apr 1.
3. McMurray JJ, Packer M, Desai AS, et al. Angiotensinneprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993–1004.
4. Wachter R, Senni M, Belohlavek J, et al. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. Eur J Heart Fail. 2019;21:998–1007.
5. Velazquez EJ, Morrow DA, DeVore AD, et al. Angiotensin-neprilysin inhibition in acute decompensated heart failure. N Engl J Med. 2019;380:539–548.

6. Desai AS, Solomon SD, Shah AM, et al. Effect of sacubitril-valsartan vs enalapril on aortic stiffness in patients with heart failure and reduced ejection fraction: a randomized clinical trial. JAMA. 2019;322:1077–1084.
7. Wang Y, Zhou R, Lu C, et al. Effects of the angiotensin-receptor neprilysin inhibitor on cardiac reverse remodeling: meta-analysis. J Am Heart Assoc. 2019;8:e012272.
8. Consensus Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987;316:1429–1435.
9. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325:293–302.
10. Packer M, Poole-Wilson PA, Armstrong PW, et al. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure. ATLAS Study Group. Circulation. 1999;100:2312–2318.
11. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. The SAVE Investigators. N Engl J Med. 1992;327:669–677.
12. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet. 1993;342:821–828.
13. Køber L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med. 1995;333:1670–1676.
14. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA. 1995;273:1450–1456.
15. Woodard-Grice AV, Lucisano AC, Byrd JB, et al. Sex-dependent and race-dependent association of XPNPEP2 C-2399A polymorphism with angiotensinconverting enzyme inhibitor-associated angioedema. Pharmacogenet Genomics. 2010;20:532–536.
16. Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensinreceptor blocker valsartan in chronic heart failure. N Engl J Med. 2001;345:1667–1675.
17. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both [published correction appears in N Engl J Med. 2004;350:203]. N Engl J Med. 2003;349:1893–1906.
18. Konstam MA, Neaton JD, Dickstein K, et al, HEAAL Investigators. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet. 2009;374:1840–1848.
19. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008;358:1547–1559.
20. Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators, Yusuf S, Teo K, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. Lancet. 2008;372:1174–1183.
21. Banka G, Heidenreich PA, Fonarow GC. Incremental cost-effectiveness of guideline-directed medical therapies for heart failure. J Am Coll Cardiol. 2013;61:1440–1446.
22. Dasbach EJ, Rich MW, Segal R, et al. The costeffectiveness of losartan versus captopril in patients with symptomatic heart failure. Cardiology. 1999;91:189–194.
23. Glick H, Cook J, Kinosian B, et al. Costs and effects of enalapril therapy in patients with symptomatic heart failure: an economic analysis of the Studies of Left Ventricular Dysfunction (SOLVD) Treatment Trial. J Card Fail. 1995;1:371–380.
24. Paul SD, Kuntz KM, Eagle KA, et al. Costs and effectiveness of angiotensin converting enzyme inhibition in patients with congestive heart failure. Arch Intern Med. 1994;154:1143–1149.
25. Reed SD, Friedman JY, Velazquez EJ, et al. Multinational economic evaluation of valsartan in patients with chronic heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). Am Heart J. 2004;148:122–128.
26. Shekelle P, Morton S, Atkinson S, et al. Pharmacologic management of heart failure and left ventricular systolic dysfunction: effect in female, black, and diabetic patients, and cost-effectiveness. Evid Rep Technol Assess (Summ). 2003:1–6.
27. Tsevat J, Duke D, Goldman L, et al. Cost-effectiveness of captopril therapy after myocardial infarction. J Am Coll Cardiol. 1995;26:914–919.
28. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995–2008. doi: 10.1056/NEJMoa1911303. Epub 2019 Sep 19.
29. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413–1424. doi: 10.1056/NEJMoa2022190. Epub 2020 Aug 28.
30. Parizo JT, Goldhaber-Fiebert JD, Salomon JA, et al. Cost-effectiveness of dapagliflozin for treatment of patients with heart failure with reduced ejection fraction. JAMA Cardiol. 2021;6(8):926–935. doi: 10.1001/jamacardio.2021.1437.
31. Isaza N, Calvachi P, Raber I, et al. Cost-effectiveness of dapagliflozin for the treatment of heart failure with reduced ejection fraction. JAMA Netw Open. 2021;4(7):e2114501. doi: 10.1001/jamanetworkopen.2021.14501.
32. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385(16):1451–1461. doi: 10.1056/NEJMoa2107038. Epub 2021 Aug 27.
33. Cleland JGF, Bunting KV, Flather MD, et al. Betablockers 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(1):26–35. doi: 10.1093/eurheartj/ehx564.
34. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med. 2019;381(17):1609–1620. doi: 10.1056/NEJMoa1908655. Epub 2019 Sep 1.
35. Halliday BP, Wassall R, Lota AS, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. Lancet. 2019; 393(10166):61-73. doi: 10.1016/S0140-6736(18)32484-X. Epub 2018 Nov 11.
36. Nilsson BB, Lunde P, Grogaard HK, et al. Long-term results of high-intensity exercise-based cardiac rehabilitation in revascularized patients for symptomatic coronary artery disease. Am J Cardiol. 2018;121(1):21–26. doi: 10.1016/j.amjcard.2017.09.011. Epub 2017 Oct 10.
37. Solomon SD, Claggett B, Desai AS, et al. Influence of ejection fraction on outcomes and efficacy of sacubitril/valsartan (lcz696) in heart failure with reduced ejection fraction: the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGMHF) trial. Circ Heart Fail. 2016;9(3):e002744. doi: 10.1161/CIRCHEARTFAILURE.115.002744.
38. Tsuji K, Sakata Y, Nochioka K, et al. Characterization of heart failure patients with mid-range left ventricular ejection fraction-a report from the CHART-2 Study. Eur J Heart Fail. 2017;19(10):1258–1269. doi: 10.1002/ejhf.807. Epub 2017 Mar 31.
39. Solomon SD, Vaduganathan M, Claggett BL, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. Circulation. 2020;141(5):352–361. doi: 10.1161/CIRCULATIONAHA.119.044586. Epub 2019 Nov 17.
40. Zheng SL, Chan FT, Nabeebaccus AA, et al. Drug treatment effects on outcomes in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Heart. 2018;104(5):407–415. doi: 10.1136/heartjnl-2017-311652. Epub 2017 Aug 5.
41. Thomopoulos C, Parati G, Zanchetti A. Effects of bloodpressure-lowering treatment in hypertension: 9. Discontinuations for adverse events attributed to different classes of antihypertensive drugs: meta-analyses of randomized trials. J Hypertens. 2016;34(10):1921–1932. doi: 10.1097/HJH.0000000000001052.
42. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years: A Randomized Clinical Trial. JAMA. 2016;315(24):2673–2682. doi: 10.1001/jama.2016.7050.
43. SPRINT Research Group, Wright JT Jr, Williamson JD, et al. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373(22):2103–2116. doi: 10.1056/NEJMoa1511939. Epub 2015 Nov 9.
44. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021;385(16):1451–1461. doi: 10.1056/NEJMoa2107038. Epub 2021 Aug 27.
45. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014;370(15):1383–1392. doi: 10.1056/NEJMoa1313731.
46. Pfeffer MA, Claggett B, Assmann SF, et al. Regional variation in patients and outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial. Circulation. 2015;131(1):34–42. doi: 10.1161/CIRCULATIONAHA.114.013255. Epub 2014 Nov 18.
47. Solomon SD, Claggett B, Desai AS, et al. Influence of Ejection Fraction on Outcomes and Efficacy of Sacubitril/Valsartan (LCZ696) in Heart Failure with Reduced Ejection Fraction: The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Trial. Circ Heart Fail. 2016;9(3):e002744. doi: 10.1161/CIRCHEARTFAILURE.115.002744.
48. Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003;362(9386):777–781. doi: 10.1016/S0140-6736(03)14285-7.
49. Lund LH, Claggett B, Liu J, 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(8):1230–1239. doi: 10.1002/ejhf.1149. Epub 2018 Feb 12.