SGLT2 Inhibitors and Sacubitril-Valsartan: How Trial Results will Revolutionize the Treatment of Heart Failure with Mildly Reduced Ejection Fraction

Miguel Morita Fernandes-Silva[1,2]
Universidade Federal do Paraná,[1] *Curitiba, PR – Brazil*
Quanta Diagnóstico por Imagem,[2] *Curitiba, PR – Brazil*

Left ventricular ejection fraction (EF) is a key parameter in the management of heart failure (HF) and a crucial biomarker for prognostic evaluation and therapeutic decision.[1] Patients with HF are classified into different categories according to EF. Although the concept of "normal" EF was introduced four decades ago, the cutoff values for normal and abnormal EF have considerably varied over time. In 2016, the European Society of Cardiology HF guidelines defined HF with reduced EF (HFrEF) as patients with EF below 40%, while HF with preserved EF (HFpEF) was the category for patients with EF equal to 50% or above.[2] To fill in the gap between the two categories, the term HF with mid-range EF was introduced. More recently, the guidelines considered more appropriate to rename this category to HF with mildly reduced EF (HFmrEF).[3,4] Why has the EF-based classification changed in recent years and how may this affect HF treatment?

In the 1980s, the first HF trials used in their design EF cutoffs to select patients with worse prognosis as an enrichment strategy, ie, they included patients based on a biomarker that improves design efficiency. Because patients with lower EF have worse prognosis and, therefore, higher rates of events, a relatively smaller sample size would be required to detect an effect. These trials used cutoff values for EF that ranged from < 45% to < 25% (Table) and were highly successful in finding effective therapies. In general, trials using a cutoff EF of < 40% consistently found drugs and devices for the treatment of HF that improved outcomes.

HF trials started including patients with EF above 40% in the early 2000s, covering the full EF range. Eligibility criteria for these trials varied from EF ≥ 40% to ≥ 50% (Table). Although the term "preserved EF" was used for these cutoff points, they differed from the cutoff values for normal EF established in the recommendations from echocardiographic reporting guidelines, which were based on the mean and 2 standard deviations for a healthy population: 52 to 72% for men and 54 to 74% for women.[5,6]

Current guidelines recommend treating all symptomatic patients with HFrEF with an angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor-neprylisin inhibitor (ARNi), a beta-blocker, a mineralocorticoid receptor antagonist (MRA), and a sodium-glucose cotransporter 2 inhibitor (SGLT2i) based on well-established evidence of their effect on reducing mortality. The success of these drugs in HFrEF was attempted to be reproduced in patients with HFpEF. ACEi, angiotensin receptor blocker (ARB), MRA, and ARNi have all been tested in HFpEF but have failed to show overall superiority for the primary endpoint (Table). This discrepancy suggests that HF is rather a heterogeneous disease with different mechanisms of progression depending on the phenotype.

Because no interventional trial was specifically dedicated to patients with HFmrEF, treatment of HFmrEF has been based on subanalysis of HFpEF trials, whose EF cutoff points included patients in this category. An analysis of the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM) program, combining the CHARM-added, CHARM- alternative and CHARM-preserved trials, showed that the benefit of candesartan on reducing the primary endpoint was observed in the EF range between 40 and 50%, but not above 50%.[7] A similar pattern was observed with spironolactone in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial,[8] with beta-blockers in patients in sinus rhythm in a meta-analysis,[9] and with sacubitril-valsartan.[10] In a subgroup analysis of the Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial, sacubitril-valsartan reduced the primary endpoint in the EF equal or below median (≤ 57%) but not above this cutoff point.[11] In a combined analysis of the PARADIGM-HF and PARAGON-HF trials across the continuum of EF, the treatment effect favoring sacubitril/valsartan appeared to extend to higher EF values (Figure).[10] In the past two years, regulatory agencies, including the United States Food and Drug Administration and the Brazilian National Health Surveillance Agency, have expanded the indication of sacubitril-valsartan for patients with HF, stating that the benefit is more clearly evident when EF is below normal.

Collectively, these data suggest that not only sacubitril-valsartan but also renin–angiotensin–aldosterone system and

Keywords

Heart Failure; Ejection Fraction; Angiotensin-converting Enzyme Inhibitor; Angiotensin receptor-neprylisin Inhibitor; Beta-blocker; Mineralocorticoid Receptor Antagonist; Sodium-glucose Cotransporter 2 Inhibitor.

Mailing Address: Miguel Morita Fernandes da Silva •
Departamento de Clínica Médica - Hospital de Clínicas da Universidade Federal do Paraná, 181 General Carneiro street, 10th floor. Postal Code 80060-900, Curitiba, PR - Brazil
E-mail: miguelmorita@ufpr.br
Manuscript received January 30, 2022, revised manuscript February 01, 2022, accpted February 16, 2022

DOI: https://doi.org/10.36660/abchf.20220013

Table 1 – Ejection fraction inclusion criteria for key phase III drug trials in heart failure

Treatment	HFrEF		HFpEF	
	Trial	EF cutoff (%)	Trial	EF cutoff (%)
ACEi	SOLVD[19]	≤ 35	PEP-CHF[20]	≥ 40
ARB	CHARM-Alternative[21]	≤ 40	CHARM-Preserved[22] I-PRESERVED[23]	> 40 ≥ 45
Beta-blocker	MERIT-HF[24] CIBIS-II[25] U.S. Carvedilol[26] COPERNICUS[27]	≤ 40 ≤ 35 ≤ 35 ≤ 25	J-DHF[28]	> 40
MRA	RALES[29] EMPHASIS-HF[30]	≤ 35 ≤ 35	TOPCAT[31] SPIRRIT-HFpEF[32] SPIRIT-HF[33] FINEARTS-HF[34]	≥ 45 ≥ 40 ≥ 40 ≥ 40
ARNi	PARADIGM-HF[35]	≤ 40	PARAGON-HF[11]	≥ 45
SGLT2i	DAPA-HF[37] EMPEROR-Reduced[38]	≤ 40 ≤ 40	DELIVER[39] EMPEROR-Preserved[40]	>40 >40

ACEi: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist; ARNi: angiotensin receptor-neprylisin inhibitor; CHARM: Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity; CIBIS-II: The Cardiac Insufficiency Bisoprolol Study II; COPERNICUS: Carvedilol Prospective Randomized Cumulative Survival Trial; DAPA-HF: Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DELIVER: Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; EMPEROR-Preserved: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction; EMPEROR-Reduced: Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction; EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; FINEARTS-HF: Finerenone Trial to Investigate Efficacy and Safety Superior to Placebo in Patients With Heart Failure; I-PRESERVED: Irbesartan in Heart Failure with Preserved Ejection Fraction Study; MERIT-HF: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; PARADIGM-HF: Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial; PARAGON-HF: Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction; PEP-CHF: Perindopril for Elderly People With Chronic Heart Failure Study; RALES: Randomized Aldactone Evaluation Study; SLGT2: sodium-glucose cotransporter 2 inhibitor; SOLVD: Studies of Left Ventricular Dysfunction; SPIRIT-HF: Spironolactone In The Treatment of Heart Failure; SPIRRIT-HFpEF: Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure With Preserved Ejection Fraction; TOPCAT: Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist.

sympathetic nervous system inhibitors have beneficial effects for HF in the "intermediate" EF range of 41 to 49%. These analyses provide insights that go beyond the treatment effect by indicating a role of these systems on disease progression in this category and helping understand part of the EF-related heterogeneity in HF. For instance, the contribution of noncardiac comorbidities on mortality is proportionally higher with increasing values of EF, particularly in the normal range.[12,13] This may explain why an intervention targeting the cardiovascular system is less likely to change the course of the disease in patients with normal EF. Patients with HFmrEF have intermediate features between HFrEF and HFpEF, but analyses from registries and clinical trials have shown that they display clinical characteristics that share more similarities with HFrEF than with HFpEF.[14] Accordingly, the recently published universal definition and classification of HF properly renamed the old "mid-range EF" category to "mildly reduced EF."[15]

Finally, the novel sodium-glucose cotransporter 2 (SGLT2) inhibitors have proven to be successful in HFrEF and paved the way for a new treatment target in HF. The question of whether this new drug class would also benefit patients with HFmrEF and HFpEF remained until the publication of the highly expected Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-preserved) trial in August 2021.[16] The EMPEROR-preserved trial included patients with HF and EF above 40% and showed that empagliflozin significantly reduced the primary outcome of cardiovascular death or HF hospitalization. Although this was mostly driven by a reduction in HF hospitalization, it was the first time that a HFpEF trial showed positive results for the primary outcome. A further analysis with data from the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-reduced) and EMPEROR-preserved trials was performed to evaluate whether the treatment effect differs across the EF categories. Similarly, the treatment effect of empagliflozin appeared to attenuate with higher EF values, but it remained consistent in patients with EF below 65%.[17] The results of the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial, which tested the SGLT2 inhibitor dapagliflozin and is expected to be presented soon, will help understand whether there is a class effect. A trial of a slightly different class, the SGLT2-SGLT1 inhibitor sotagliflozin, included patients with diabetes and worsening HF and showed a significant reduction in the primary endpoint of cardiovascular death, hospitalization, and urgent visits for HF across all spectrum of EF.[18]

Despite its essential role in the management of HF, EF is an imperfect measure that is influenced by several biological phenomena. Its wide availability in clinical practice is counterbalanced by limitations to accurate measurement of EF. The intra- and interobserver variability of

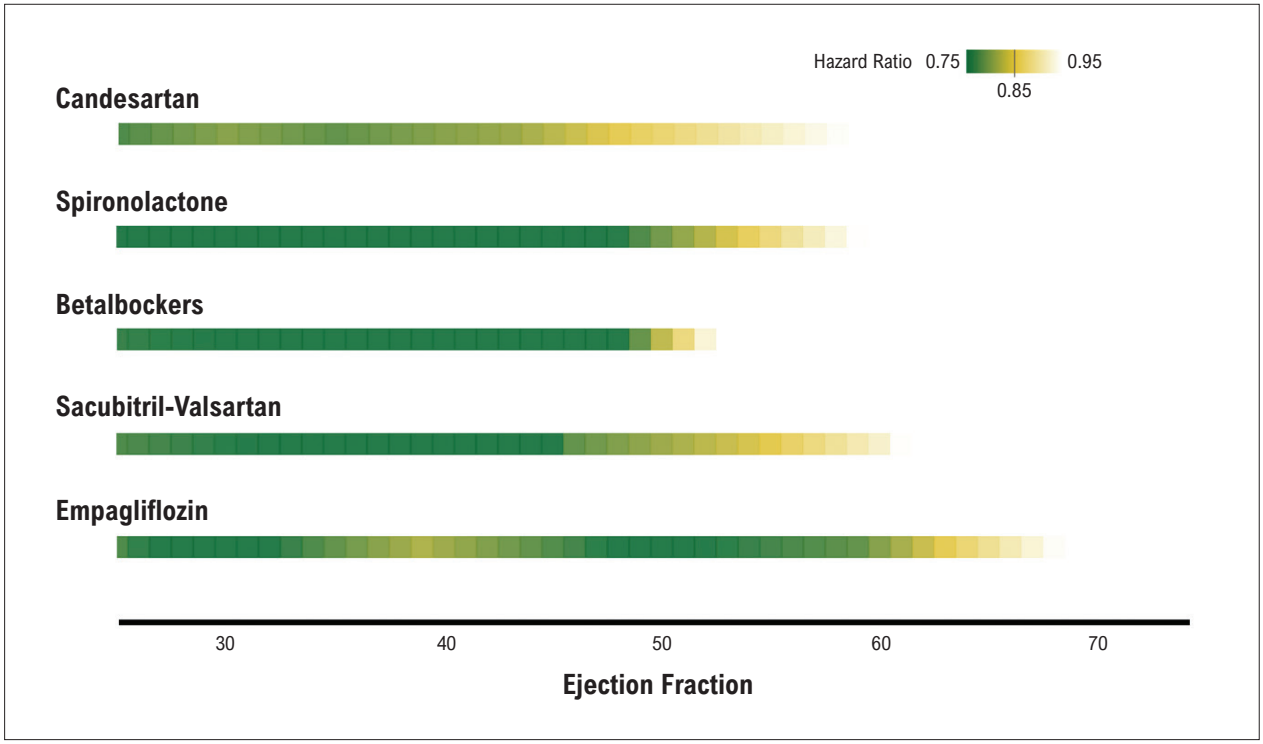

Figure 1 – *Treatment effect estimates of disease-modifying medications in heart failure across the spectrum of ejection fraction. Bar colors represent the reported estimated hazard ratios (HR) for each intervention according to ejection fraction. HR were extracted from respective published subanalysis from clinical trials:*
Candesartan: Lund et al.[7]
Spironolactone: Pitt et al.[29] and Solomon et al.[8]
Beta-blockers: Cleland et al.[9]
Sacubitril-valsartan: Solomon et al.[10]
Empagliflozin: Butler et al.[17]

EF measurements using echocardiogram has been reported as 8-21% and 6-13%, respectively, which limits the correct classification in categories with relatively narrow ranges of EF.[14] Some studies have evaluated the longitudinal changes of EF, showing considerable variation over time. In a Swedish registry, nearly 1/3 of patients switched to a lower EF category and 1/4 switched to a higher EF category over a median follow up duration of 1.4 years.[14] Because of the limitations of EF measurement, alternative methods have been suggested to better address the heterogeneity of HF, such as myocardial tissue characterization with magnetic resonance imaging, global longitudinal strain from speckle-tracking analysis with echocardiogram, multiple biomarker approaches, and proteomic characterization, but their use to guide the clinical management is still limited.[14]

Well-conducted trials are not only about finding effective therapies. They help understand the pathophysiology of a disease. HF classification has evolved together with the understanding of the disease. Despite the necessary strict and pragmatic criteria adopted in clinical trials, treatment effect of HF drugs has been consistently modified by EF as a continuous measure. Analysis from the latest HF trials of sacubitril-valsartan and SGLT2 inhibitor point to the same direction as those of renin–angiotensin–aldosterone system and sympathetic nervous system inhibitors, grouping together the categories of HF with EF below normal. I look forward to seeing what we will learn from the upcoming trials in HFpEF.

Author Contributions

Writing of the manuscript and Critical revision of the manuscript for intellectual content: Fernandes-Silva MM.

Potential Conflict of Interest

Received consulting and speaking fees from Novartis.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Savarese G, Stolfo D, Sinagra G, Lund LH. Heart Failure with Mid-range or Mildly Reduced Ejection Fraction. Nat Rev Cardiol. 2022;19(2):100-16. doi: 10.1038/s41569-021-00605-5.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) Developed with the Special Contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200. doi: 10.1093/eurheartj/ehw128.
3. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. Eur Heart J. 2021;42(36):3599-726. doi: 10.1093/eurheartj/ehab368.
4. Marcondes-Braga FG, Moura LAZ, Issa VS, Vieira JL, Rohde LE, Simões MV, et al. Emerging Topics Update of the Brazilian Heart Failure Guideline - 2021. Arq Bras Cardiol. 2021;116(6):1174-212. doi: 10.36660/abc.20210367.
5. 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(3):233-70. doi: 10.1093/ehjci/jev014.
6. Barberato SH, Romano MMD, Beck ALS, Rodrigues ACT, Almeida ALC, Assunção BMBL, et al. Position Statement on Indications of Echocardiography in Adults - 2019. Arq Bras Cardiol. 2019;113(1):135-81. doi: 10.5935/abc.20190129.
7. 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(8):1230-9. doi: 10.1002/ejhf.1149.
8. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, et al. Influence of Ejection Fraction on Outcomes and Efficacy of Spironolactone in Patients with Heart Failure with Preserved Ejection Fraction. Eur Heart J. 2016;37(5):455-62. doi: 10.1093/eurheartj/ehv464.
9. Cleland JGF, Bunting KV, Flather MD, Altman DG, Holmes J, Coats AJS, et al. 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(1):26-35. doi: 10.1093/eurheartj/ehx564.
10. Solomon SD, Vaduganathan M, L Claggett B, Packer M, Zile M, Swedberg K, et al. Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure. Circulation. 2020;141(5):352-61. doi: 10.1161/CIRCULATIONAHA.119.044586.
11. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2019;381(17):1609-20. doi: 10.1056/NEJMoa1908655.
12. Rohde LE, Claggett BL, Wolsk E, Packer M, Zile M, Swedberg K, et al. Cardiac and Noncardiac Disease Burden and Treatment Effect of Sacubitril/Valsartan: Insights from a Combined PARAGON-HF and PARADIGM-HF Analysis. Circ Heart Fail. 2021;14(3):e008052. doi: 10.1161/CIRCHEARTFAILURE.120.008052.
13. Wolsk E, Claggett B, Køber L, Pocock S, Yusuf S, Swedberg K, et al. Contribution of Cardiac and Extra-cardiac Disease Burden to Risk of Cardiovascular Outcomes Varies by Ejection Fraction in Heart Failure. Eur J Heart Fail. 2018;20(3):504-10. doi: 10.1002/ejhf.1073.
14. Savarese G, Stolfo D, Sinagra G, Lund LH. Heart Failure with Mid-range or Mildly Reduced Ejection Fraction. Nat Rev Cardiol. 2022;19(2):100-16. doi: 10.1038/s41569-021-00605-5.
15. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, 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. J Card Fail. 2021:S1071-9164(21)00050-6. doi: 10.1016/j.cardfail.2021.01.022.
16. Anker SD, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, et al. Evaluation of the Effects of Sodium-Glucose Co-Transporter 2 Inhibition with Empagliflozin on Morbidity and Mortality in Patients with Chronic Heart Failure and a Preserved Ejection Fraction: Rationale for and Design of the EMPEROR-Preserved Trial. Eur J Heart Fail. 2019;21(10):1279-87. doi: 10.1002/ejhf.1596.
17. Butler J, Packer M, Filippatos G, Ferreira JP, Zeller C, Schnee J, et al. Effect of Empagliflozin in Patients with Heart Failure Across the Spectrum of Left Ventricular Ejection Fraction. Eur Heart J. 2022;43(5):416-26. doi: 10.1093/eurheartj/ehab798.
18. Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. N Engl J Med. 2021;384(2):117-28. doi: 10.1056/NEJMoa2030183.
19. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure. N Engl J Med. 1991;325(5):293-302. doi: 10.1056/NEJM199108013250501.
20. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) Study. Eur Heart J. 2006;27(19):2338-45. doi: 10.1093/eurheartj/ehl250.
21. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al. Effects of Candesartan in Patients with Chronic Heart Failure and Reduced Left-Ventricular Systolic Function Intolerant to Angiotensin-Converting-Enzyme Inhibitors: The CHARM-Alternative Trial. Lancet. 2003;362(9386):772-6. doi: 10.1016/S0140-6736(03)14284-5.
22. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, 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):777-81. doi: 10.1016/S0140-6736(03)14285-7.
23. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction. N Engl J Med. 2008;359(23):2456-67. doi: 10.1056/NEJMoa0805450.
24. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, et al. Effect of Metoprolol CR/XL in Chronic Heart Failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353(9169):2001-7.
25. Dargie HJ, Lechat P. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A Randomised Trial. Lancet. 1999;353(9146):9-13.
26. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The Effect of Carvedilol on Morbidity and Mortality in Patients with Chronic Heart Failure. N Engl J Med. 1996;334(21):1349-55. doi: 10.1056/NEJM199605233342101.
27. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, et al. Effect of Carvedilol on Survival in Severe Chronic Heart Failure. N Engl J Med. 2001;344(22):1651-8. doi: 10.1056/NEJM200105313442201.
28. Yamamoto K, Origasa H, Hori M. Effects of Carvedilol on Heart Failure with Preserved Ejection Fraction: The Japanese Diastolic Heart Failure Study (J-DHF). Eur J Heart Fail. 2013;15(1):110-8. doi: 10.1093/eurjhf/hfs141.
29. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med. 1999;341(10):709-17. doi: 10.1056/NEJM199909023411001.
30. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms. N Engl J Med. 2011;364(1):11-21. doi: 10.1056/NEJMoa1009492.

31. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2014;370(15):1383-92. doi: 10.1056/NEJMoa1313731.

32. Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction [Internet]. Bethesda: ClinicalTrials.gov. 2017 [cited 2022 Jan 28]. Available from: https://clinicaltrials.gov/ct2/show/NCT02901184?cond=spirrit+heart+failure&draw=2&rank=1.

33. Clinical Trials Register - Search for Spirit Heart Failure [Internet]. Amsterdam: EU Clinical Trials Register. c2022 [cited 2022 Jan 28]. Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=spirit+heart+failure.

34. Study to Evaluate the Efficacy (Effect on Disease) and Safety of Finerenone on Morbidity (Events Indicating Disease Worsening) & Mortality (Death Rate) in Participants with Heart Failure and Left Ventricular Ejection Fraction (Proportion of Blood Expelled Per Heart Stroke) Greater or Equal to 40% [Internet]. Bethesda: ClinicalTrials.gov. 2020 [cited 2022 Jan 28]. Available from: https://clinicaltrials.gov/ct2/show/NCT04435626?cond=NCT04435626&draw=2&rank=1.

35. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-Neprilysin Inhibition Versus Enalapril in Heart Failure. N Engl J Med. 2014;371(11):993-1004. doi: 10.1056/NEJMoa1409077.

36. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, 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.

37. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020;383(15):1413-24. doi: 10.1056/NEJMoa2022190.

38. Dapagliflozin Evaluation to Improve the LIVEs of Patients with Preserved Ejection Fraction Heart Failure [Internet]. Bethesda: ClinicalTrials.gov. 2021 [cited 2022 Jan 28]. Available from: https://clinicaltrials.gov/ct2/show/NCT03619213?cond=nct03619213&draw=2&rank=1.

39. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021;385(16):1451-61. doi: 10.1056/NEJMoa2107038.