Acta Cardiologia Indonesiana
pISSN:2460-5700
eISSN:2579-4345
Web page: jurnal.ugm.ac.id/v3/jaci

Management of Heart Failure with Reduced Ejection Fraction (HFrEF) Based on Current International Guidelines

Fera Hidayati*

Department of Cardiology and Vascular Medicine, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada /Dr. Sardjito Hospital, Yogyakarta, Indonesia

ARTICLE INFO

*Corresponding author
Email:
fera.hidayati@mail.ugm.ac.id

Address:
Jalan Farmako Sekip Utara, Yogyakarta 55281 Indonesia

Manuscript submitted: Desember 28, 2022

Keywords:
HFrEF; Pharmacological Treatment; ARNI; SGLT2 Inhibitor

ABSTRACT

Heart failure (HF) is a clinical syndrome that consists of cardinal symptoms and the accompanying signs. HF poses a significant health and economic burden as it affects approximately 38 million people worldwide. Pharmacological therapies that target the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, and neurohormones have been developed to reduce mortality and morbidity in patients with heart failure reduced ejection fraction (HFrEF).

The triad of angiotensin-converting enzyme inhibitors (ACE-i) or an angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers, and mineralocorticoid receptor antagonists (MRA) has been proven to improve survival, reduce the risk of rehospitalizations, and reduce symptoms in patients with HFrEF. In the latest international guidelines both European and American, sodium-glucose cotransporter 2 (SGLT2) inhibitors, dapagliflozin and empagliflozin, has just been included as standard therapy for patients with HFrEF with class I recommendation.

INTISARI

Gagal jantung adalah sindrom klinis yang terdiri dari gejala utama dan tanda-tanda yang menyertainya. Gagal jantung menimbulkan beban kesehatan dan ekonomi yang signifikan karena mempengaruhi sekitar 38 juta orang di seluruh dunia. Terapi farmakologis yang menargetkan sistem renin-angiotensin-aldosteron (RAAS), sistem saraf simpatis, dan neurohormon telah dikembangkan untuk menurunkan angka mortalitas dan morbiditas pada pasien dengan gagal jantung dengan fraksi ejeksi rendah atau heart failure with reduced ejection fraction (HFrEF).

Triad angiotensin-converting enzyme inhibitor (ACE-i) atau angiotensin receptor-neprilysin inhibitor (ARNI), beta-blocker, dan mineralocorticoid receptor antagonists (MRA) telah terbukti meningkatkan kelangsungan hidup, mengurangi risiko rehospitalisasi, dan mengurangi gejala pada pasien dengan HFrEF. Dalam pedoman gagal jantung internasional terkini, baik dari Eropa maupun Amerika Serikat, sodium-glucose cotransporter 2 inhibitors (SGLT2i), dapagliflozin dan empagliflozin mulai disebutkan sebagai terapi standar untuk pasien HFrEF dengan kelas rekomendasi I.

Introduction

Heart failure (HF) is a clinical syndrome that consists of cardinal symptoms (shortness of breath, ankle swelling, and fatigue) and the accompanying signs (elevated jugular venous pressure, rales, and peripheral edema)[1]. HF poses a significant health and economic burden as it affects approximately 38 million people, with a prevalence of 1-2% of adults worldwide[1,2]. The incidence of HF in Europe is about 5/1000 person-years in adults[1]. The prevalence of HF in Asia is also 1-3% with the average cost of each HF hospitalization ranging from 813 USD in Indonesia to approximately 9000 USD in South Korea. The economic burden of HF is expected to rise dramatically in the coming years due to the increased aging population worldwide[3].

HF is due to a structural and/or functional abnormality that must be identified to determine the most appropriate treatment. The common causes of HF are ischemic heart disease, myocardial infarction (MI), hypertension, and valvular heart disease (VHD)[4]. However, arrhythmia (tachycardia-mediated, premature ventricular contractions, and right ventricular pacing), cardiomyopathy (dilated, hypertrophic, restrictive, arrhythmogenic right ventricular cardiomyopathy/ARVC, peripartum, and takotsubo syndrome), congenital heart disease, infective heart disease, infiltrative cardiac disease, cardiotoxic medications, metabolic disease (thyroid, pheochromocytoma, autoimmune disease, diabetes, and obesity), substance abuse (alcohol, cocaine, methamphetamine), and pathology of the pericardium and endocardium can also cause or worsen HF[1,4].

After a cardiac injury (MI, increased preload, or increased afterload), cellular, structural, and neurohormonal modulation occurs[5]. Compensatory mechanisms including the Frank-Starling mechanism to increase cardiac output (CO), ventricular remodeling and development of ventricular hypertrophy, activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) to maintain tissue perfusion through augmented mean arterial pressure, and activation of other neurohormones (natriuretic peptide, nitric oxide, bradykinin, and prostacyclin) take place to maintain heart's adequate function. While the compensatory mechanisms are beneficial in the early stage of heart failure, the long-term effects are deleterious and will worsen HF[5,6]. Management strategies that target these mechanisms have been developed to reduce the mortality and morbidity of HF.

Discussion

Stages of Heart Failure

The American Heart Association (AHA)/The American College of Cardiology (ACC)/The Heart Failure Society of America (HFSA) stages of HF emphasize the development and progression of the disease. Stage A (At-Risk for HF) is defined as patients at risk for HF (patients with hypertension, cardiovascular disease, diabetes, obesity, exposure to cardiotoxic agents, genetic variant for cardiomyopathy, or family history of cardiomyopathy) but without symptoms, structural heart disease (SHD), or cardiac biomarkers. Stage B (Pre-HF) is defined as patients without current or previous symptoms/signs of HF but has 1 of the following 1) SHD, 2) evidence of increased filling pressures, or 3) risk factors and increased natriuretic peptide levels or persistently elevated cardiac troponin in the absence of competing diagnoses. Stage C (Symptomatic HF) is defined as patients with current or previous symptoms/signs of HF. Stage D (Advanced HF) is defined as severe HF symptoms that interfere with daily activities and with recurrent hospital admission despite optimal guideline-directed medical therapy (GDMT)[4].

Diagnostic Algorithm of Heart Failure

The diagnosis of HF requires the presence of symptoms (dyspnea on effort, orthopnea, paroxysmal nocturnal dyspnea, reduced exercise tolerance, ankle swelling, fatigue, and tiredness) and/or signs (jugular venous distention, pulmonary crackles, hepatojugular reflux, gallop rhythm, and peripheral edema) and evidence of cardiac dysfunction. The history-taking and physical examination remain fundamental in the evaluation of patients with HF. A thorough history-taking to determine clinical factors, family history of cardiomyopathy (CMP), cardiac and noncardiac disorder, lifestyle and behavioral factors, and social determinants of health should be obtained. Vital signs and evidence of clinical congestion (jugular venous distention, orthopnea, bendopnea, a square-wave response to the Valsalva maneuver, and peripheral edema) should be examined to guide overall management and adjustment of drug doses. Both history-taking and physical examination is essential in directing diagnostic strategies to uncover specific etiologies that need disease-specific management[4].

Recommended diagnostic tests in all patients with HF include an electrocardiogram (ECG), laboratory evaluation if available (complete blood count, blood urea nitrogen, serum creatinine, serum electrolytes, thyroid function, liver function, lipid profile, fasting glucose and HbA1c, iron status, B-type natriuretic peptide/N-terminal pro-B-type natriuretic peptide (BNP/NTproBNP)), chest X-ray (CXR), and echocardiography[1,4]. ECG is a routine evaluation for patients with HF. A normal ECG indicates that the diagnosis of HF is unlikely. Atrial fibrillation, Q waves, left ventricular hypertrophy (LVH), and widened QRS complex are usually observed and increase the probability of a diagnosis of HF. Laboratory evaluations are recommended to distinguish HF from other diseases, to provide prognostic information, and to guide medical therapy. A plasma concentration of BNP ⍰ 35 pg/mL or NT-proBNP 125 pg/mL increases the likelihood of a diagnosis of HF. A CXR may show pulmonary congestion or cardiomegaly. Echocardiography is the key investigator of cardiac function as it determines left ventricle ejection fraction (LVEF) and other parameters (chamber size, eccentric or concentric LVH, regional wall motion abnormalities, and markers of diastolic dysfunction). If abnormal findings are present, HF is confirmed and HF is classified based on LVEF to determine the most appropriate management[1].

Classification of Heart Failure

Left ventricular ejection fraction is utilized to classify HF into distinct phenotypes due to differing prognoses and responses to treatments. HFrEF is defined as LVEF ≤ 40% and the presence of symptoms and/or signs of HF. HFimpEF (HF with improved EF) is defined as previous LVEF ≤ 40% and a follow-up measurement of LVEF > 40%. HFmrEF (HF with mildly reduced EF) is defined as LVEF 41%-49% with evidence of spontaneous or provokable increased LV filling pressures (increased natriuretic peptide levels, noninvasive and invasive hemodynamic measurement) and the presence of symptoms and/or signs of HF. HFpEF (HF with preserved EF) is defined as LVEF ≥ 50% with evidence of spontaneous or provokable increased LV filling pressures and the presence of symptoms and/or signs of HF.[1,4]

Pharmacological Treatment According to HF Phenotypes

The latest European Society of Cardiology (ESC) and AHA/ACC/HFSA guidelines recommended the use of simultaneous initiation of the quadruple therapy that includes ACE-i or ARNI, beta-blockers, MRA, and SGLT2 inhibitor in patients with HFrEF[1,4]. According to the current AHA/ACC/HFSA guidelines, in patients with HFmrEF, SGLT2 inhibitors can be beneficial in reducing HF hospitalization and cardiovascular (CV) mortality. The use of beta-blockers, ARNI/ACE-I/ ARB, and MRAs may be considered, particularly in patients with HFmrEF with LVEF in the lower end of the spectrum. Patients with HFmrEF should undergo repeat LVEF assessment to determine the disease trajectory. In patients with HFimpEF, GDMT should be continued to prevent relapse of HF and LV dysfunction even if the patients are asymptomatic.

HFpEF affects 50% of all patients with HF and has significant morbidity and mortality. In patients with HFpEF, SGLT2 inhibitors can be beneficial in reducing HF hospitalization and CV mortality. Patients with HFpEF and hypertension should have medications titrated to reduce blood pressure (BP) until BP target is achieved. In selected patients, the use of MRAs, ARBs, or ARNI may be considered, particularly in patients with HFpEF with LVEF in the lower end of the spectrum. Diuretics is also used to relieve congestion and alleviate symptoms in patients with HFmrEF and HFpEF[4].

Guideline-Directed Medical Therapy (GDMT) for HFrEF – The Fantastic Four

Pharmacotherapy is the foundation of HFrEF management and should be given before considering device therapy. The three main goals of treatment for patients with HFrEF include 1) reduction in mortality, 2) prevention of recurrent hospitalizations due to worsening HF, and 3) improvement in clinical status, functional capacity, and quality of life (QoL). Inhibition of RAAS and sympathetic nervous system with the triad of ACE-i or an ARNI, beta-blockers, and MRA has been proven to improve survival, reduce the risk of rehospitalizations, and reduce symptoms in patients with HFrEF[1].

Previous AHA and ESC guidelines emphasized the use of ACE-i and beta-blockers for patient with HFrEF in NYHA Class I-IV to reduce the risk of HF hospitalization and mortality[7,8]. Those ESC guidelines stated that MRAs should be given for patients with HFrEF who remained symptomatic despite treatment with ACE-i and beta-blockers to reduce the risk of HF hospitalization and death[8]. The latest ESC recommendations stated that SGLT2 inhibitor dapagliflozin and empagliflozin added to therapy with ACE-i/ARNI/beta-blocker/MRA reduced the risk of HF hospitalization and CV death in patients with HFrEF[1,9,10]. AHA/ACC/HFSA also recommended the use of 4 medication classes which also include SGLT2 inhibitors for patients with HFrEF[4]. The simultaneous initiation of the quadruple therapy may reduce mortality risk by 73% in the span of 2 years[11]. The initiation of GDMT before advanced HF or stage D HF ensues may improve QoL and reduce risk of sudden death[12].

Many physicians are still reluctant to prescribe the GDMT simultaneously due to the overlapping side effects profiles of hypotension, worsening renal function, and hyperkalemia[13]. However, the two newest additions to the quadruple therapy, ARNI and SGLT2 inhibitors, may improve tolerability of GDMT. The outcome of three large trials suggested that both ARNI and SGLT2 inhibitors reduce the risk of hyperkalemia as compared with ACE-i and placebo in the setting of concurrent MRAs therapy[9,10,14]. SGLT2 inhibitors also has minimal to no effect on BP and slows progression of renal dysfunction[9,10,13]. Tolerability of simultaneous or rapid sequence initiation of the 4 drugs can be augmented by initiating the drugs at lower doses and up-titrating every 1 to 2 weeks to achieve the maximally tolerated recommended dose[4,11]. Continuation of GDMT through hospitalization or before discharge is associated with improved outcome because of the benefit of the therapies and the better prognostic profile of patients who can tolerate them. Introduction of GDMT during hospitalization for patients with HFrEF is a key target to reduce HF risks as it frequently reverses disease progression[15]. Delaying the initiation of quadruple therapy increases the risk of a medication not being prescribed and the risk of HF worsening and mortality[4,11].

ACE inhibitors were the first class of drugs shown to reduce mortality and morbidity in patients with HFrEF since two major trials showed that enalapril reduced the risk of death in patients with HFrEF in NYHA class II-IV[1,4,16,17]. ACE-i are recommended in patients with HFrEF unless contraindicated or not tolerated[1]. They can produce angioedema and should be used in precaution on patients with low BP, renal insufficiency, or serum K^+ >5mEq/L. ARBs are recommended for patients who cannot tolerate ACE-i or ARNI due to angioedema or intolerable cough. In patients with chronic HFrEF and NYHA Class II-III who tolerate ACE-i or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality. If there is a switch from ACE-i to ARNI or vice versa, there should be a wash-out period of at least 36 hours between ACE-i and ARNI doses[4].

Angiotensin receptor-neprilysin inhibitor has a unique mechanism that targets both RAAS and natriuretic peptide (NP) systems[18]. One of the essential components of NP system is neprilysin which catalyzes the degradation of NP, bradykinin, and adrenomedullin. Inhibition of neprilysin increases the levels of NP which results in vasodilatation and decreased extracellular fluid volume.[14,18] Sacubitril/valsartan was observed to be superior to enalapril in the PARADIGM-HF Trial. Compared to enalapril, sacubitril/valsartan reduced the risk of HF hospitalization by 21%, reduced the risk of CV death and all-cause mortality, and decreased symptoms and physical limitations of HF in patients with ambulatory HFrEF[14]. Thus, AHA/ACC/HFSA Guidelines stated that in patients with HFrEF and NYHA Class II-III symptoms, the use of ARNI is recommended to reduce morbidity and mortality. An ARNI should be initiated de novo in patients hospitalized with acute HFrEF before discharge in the absence of contraindications due to clinical status improvement, NT-proBNP reduction, and LV remodeling parameters improvement. However, when the use of ARNI is not feasible, the use of ACE-i is beneficial to reduce morbidity and mortality in patients with previous/current symptoms of HFrEF[4].

Beta-blockers reduce mortality and morbidity in patients with HFrEF, in addition to treatment with an ACE-i and diuretic[19–22]. In patients with HFrEF, the use of 1 of 3 beta-blockers that has been proven to reduce mortality (bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended to reduce mortality and HF hospitalizations[4]. Even when patients are asymptomatic, have mild symptoms, or symptoms improve due to other therapies; beta-blocker should not be delayed. Long-term treatment with beta-blockers in patients whose symptoms or LVEF improves and those whose symptoms do not improve should be maintained to reduce the risk of progression of LV dysfunction or major cardiovascular events[4].

Mineralocorticoid receptor antagonists (also referred to as aldosterone antagonists or anti-mineralocorticoids) block receptors that bind aldosterone and, with different degrees of affinity, other steroid hormones receptor[1]. RALES trials showed that in addition to the standard therapy; spironolactone, as compared with placebo, reduced the risk of mortality from progressive HF and sudden cardiac death by 30%, reduced HF hospitalization by 35%, and improved symptoms of HF in patients with HFrEF.[23] EMPHASIS HF showed that in addition to the standard therapy; eplerenone, as compared with placebo, reduced the risk of CV death and HF hospitalizations in patients with HFrEF and mild symptoms[24]. Thus, AHA/ACC/HFSA guidelines stated that in patients with HFrEF and NYHA Class II-IV symptoms, an MRA is recommended to reduce morbidity and mortality if eGFR is >30 mL/min/1.73 m^2 and serum K^+ < 5 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be implemented to lessen the risk of hyperkalemia and renal insufficiency. The initial dose of spironolactone or eplerenone is 25 mg daily per oral which should be increased to 50 mg daily per oral in one month. However, if eGFR is 31-49 mL/min/1.73 m^2, the doses should be reduced by half[4].

Sodium-glucose cotransporter 2 (SGLT2) inhibitors act primarily in the proximal tubules of the kidney by colocalizing and interacting with sodium hydrogen exchanger (NHE) 3 that is responsible for the majority of sodium tubular reuptake after filtration[25]. The inhibition of sodium-hydrogen exchange promotes natriuresis and osmotic diuresis which results in the contraction of plasma volume and reduced preload[26]. Inhibition of SGLT2 also reduces the development and progression of ventricular hypertrophy by decreasing BP, arterial stiffness, and afterload[25,26]. The current ESC guideline and AHA/ACC/HFSA guidelines recommended the use of SGLT2 inhibitors in addition to the standard therapy to reduce the risk of HF hospitalization and CV death among patients with HFrEF[1,4]. EMPEROR-Reduced Trial and DAPA-HF Trial showed that in addition to the standard therapy; empagliflozin and dapagliflozin, as compared with placebo, reduced the composite of CV mortality or HF hospitalization by approximately 25% among patients with HFrEF in NYHA Class II-IV, regardless of the presence or absence of diabetes mellitus. The significant difference in both trials was primarily related to a 30% lower risk of HF hospitalization. The risk of CV death was 18% lower with dapagliflozin; while only 8% lower with empagliflozin[9,10]. In a meta-analysis of EMPEROR-Reduced Trial and DAPA-HF Trial, SGLT2 inhibitor was associated with a 13% reduction in all-cause mortality and a 14% reduction in CV mortality[27]. Dapagliflozin also alleviated HF symptoms and improved physical function and QoL[9]. Empagliflozin also reduced the risk of serious renal outcomes, reduced the rate of eGFR decline, and improved QoL[10]. Patients with HFrEF in Asia exhibits many differences compared to patients from other parts of the world as patients develop HF and type 2 diabetes at an earlier age and tend to have a lower BP and BMI compared to those in Europe and North America. Salt-sensitive hypertension that indicates a reduced ability to excrete sodium load is also reported in Asia. DAPA-HF Trial enrolled 23.1% patients from Asia and dapagliflozin reduced the composite of CV mortality or HF hospitalization to the same extent in Asian patients as elsewhere[28]. Indonesian Heart Association has also recommended the use of SGLT2i in addition to other standard therapy for patients with HFrEF in Indonesia[29]. In patients with HFrEF; up-titrating GDMT every 1 to 2 weeks, depending on patient's clinical status and laboratory results, to achieve the maximally tolerated recommended dose are beneficial in reducing CV mortality and HF hospitalization[4].

Loop diuretics (bumetanide, furosemide, and torsemide) inhibit sodium and chloride reabsorption at the loop of Henle, whereas thiazide-like diuretics work in the distal convoluting tubule. Loop diuretics are preferred due to their intense and shorter diuresis, as compared with thiazides. Diuretics are recommended in patients with HFrEF with signs and/or symptoms of congestion to relieve congestion, improve symptoms, improve exercise capacity, prevent worsening of HF, and HF hospitalization. The treatment goal of diuretics is to eliminate congestion with the lowest dose possible. In euvolemic or hypovolemic patients, the use of diuretics may be reduced or stopped[1,4].

Device and Interventional Therapies for HFrEF

GDMT should be optimized before the implantation of cardiac devices. Implantable cardioverter-defibrillator (ICD) implantation, as primary prevention of sudden cardiac death (SCD), is recommended in 1) patients with non-ischemic dilated cardiomyopathy (DCM) or ischemic heart disease at least 40 days post myocardial infarction with LVEF ≤ 35% with symptomatic NYHA class II-III HF despite ≥ 3 months of GDMT and have expectation of meaningful survival for >1 year and 2) patients of at least 40 days post myocardial infarction with LVEF ≤ 30% and NYHA class I while receiving GDMT and have expectation of meaningful survival for >1 year[1,4].

Cardiac resynchronization therapy (CRT) implantation; to reduce total mortality and HF hospitalization and to improve symptoms and QoL; is indicated in patients with LVEF ≤35%, sinus rhythm (SR), left bundle branch block (LBBB) with a QRS duration ≥ 150 ms, and NYHA class II-III or ambulatory IV symptoms on GDMT. CRT implantation can be useful in 1) patients LVEF ≤35%, SR, a non-LBBB pattern with a QRS duration ≥ 150 ms, and NYHA class II-III or ambulatory IV symptoms on GDMT, 2) patients with high-degree or complete heart block and LVEF 36-50%, and 3) patients with LVEF ≤35%, SR, LBBB with a QRS duration 120-149 ms, and

NYHA class II-III or ambulatory IV symptoms on GDMT. CRT implantation may be considered in 1) patients with LVEF ≤35%, SR, a non-LBBB pattern with a QRS duration 120-149 ms, and NYHA class III or ambulatory IV symptoms on GDMT and 2) patients with LVEF ≤30%, ischemic cause of HF, SR, LBBB with a QRS duration ≥ 150 ms, and NYHA class I symptoms on GDMT[4].

Conclusions

The four pillars of HFrEF therapy of ACE-i/ARNI, beta-blockers, MRAs, and SGLT2 inhibitors should be started simultaneously and have been proven to reduce cardiovascular mortality, reduce heart failure rehospitalization, and alleviate symptoms in patients with HFrEF. These guideline-directed medical therapy start at low dose and up-titrated to the maximally tolerated recommended dose.

Acknowledgements

-

Funding Sources

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosures

Declaration of Conflicting Interest: I have no conflict of interest

References

1. 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.
2. Braunwald E. The war against heart failure: The Lancet lecture. Lancet [Internet]. 2015;385(9970):812–24. Available from: http://dx.doi.org/10.1016/S0140-6736(14)61889-4
3. Reyes EB, Ha JW, Firdaus I, Ghazi AM, Phrommintikul A, Sim D, et al. Heart failure across Asia: Same healthcare burden but differences in organization of care. Int J Cardiol [Internet]. 2016;223:163–7. Available from: http://dx.doi.org/10.1016/j.ijcard.2016.07.256
4. 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. Vol. 145, Circulation. 2022. 895–1032 p.
5. Schwinger RHG. Pathophysiology of heart failure. Cardiovasc Diagn Ther. 2021;11(1):263–76.
6. Kemp CD, Conte J V. The pathophysiology of heart failure. Cardiovasc Pathol [Internet]. 2012;21(5):365–71. Available from: http://dx.doi.org/10.1016/j.carpath.2011.11.007
7. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. Circulation. 2013;128(16):240–327.
8. 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. Eur Heart J. 2016;37(27):2129-2200m.
9. McMurray JJ V, Solomon SD, Inzhucchi 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):195–2008.
10. 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.
11. Greene SJ, Butler J, Fonarow GC. Simultaneous or Rapid Sequence Initiation of Quadruple Medical Therapy for Heart Failure— Optimizing Therapy With the Need for Speed. J Am Med Assoc. 2021;6(7):743–4.
12. Allen LA, Stevenson LW, Grady KL, Goldstein NE, Matlock DD, Arnold RM, et al. Decision making in advanced heart failure: A scientific statement from the american heart association. Circulation. 2012;125(15):1928–52.
13. Greene SJ, Butler J, Metra M. Another reason to embrace quadruple medical therapy for heart failure: medications enabling tolerance of each other. Eur J Heart Fail. 2021;23(9):1525–8.
14. McMurray JJ V, 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.
15. Hollenberg SM, Warner Stevenson L, Ahmad T, Amin VJ, Bozkurt B, Butler J, et al. 2019 ACC Expert Consensus Decision Pathway on Risk Assessment, Management, and Clinical Trajectory of Patients Hospitalized With Heart Failure: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2019;74(15):1966–2011.
16. The 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;316:1429–35.
17. The SOLVD Investigators. Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fraction and Congestive Heart Failure. N Engl J Med. 1991;325(5):293–302.
18. Menendez JT. The Mechanism of Action of LCZ696. Card Fail Rev. 2016;2(1):40.
19. Packer M, Fowler MB, Roecker EB, Coats AJS, Katus HA, Krum H, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: Results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation. 2002;106(17):2194–9.
20. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): A randomised trial. Lancet. 1999;353:9–13.

21. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). Lancet. 1999;353:2001–7.
22. Flather MD, Shibata MC, Coats AJS, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005;26(3):215–25.
23. 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. N Engl J Med. 1999;341(10):709–17.
24. Zannad F, McMurray JJ V, 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.
25. Packer M, Anker SD, Butler J, Filippatos G, Zannad F. Effects of sodium-glucose cotransporter 2 inhibitors for the treatment of patients with heart failure - Proposal of a novel mechanism of action. JAMA Cardiol. 2017;2(9):1025–9.
26. Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZI. Sodium glucose cotransporter-2 inhibition in heart failure: Potential mechanisms, clinical applications, and summary of clinical trials. Circulation. 2017;136(17):1643–58.
27. Zannad F, Ferreira JP, Pocock SJ, Anker SD, Butler J, Filippatos G, et al. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. Lancet. 2020;396(10254):819–29.
28. Docherty KF, Anand IS, Chiang CE, Chopra VK, Desai AS, Kitakaze M, et al. Effects of Dapagliflozin in Asian Patients With Heart Failure and Reduced Ejection Fraction in DAPA-HF. JACC Asia. 2022;2(2):139–53.
29. Nauli SE, Putri VKP. Sodium Glucose Co-Transporter-2 Inhibitors (SGLT2-i): Dari Prevensi sampai Tatalaksana Gagal Jantung. 2021. Furtado RHM et al. Online ahead of print. *Circulation.* 2019.