

INDIVIDUALIZED TREATMENT STRATEGY FOR ACUTE EXACERBATION OF CHRONIC HEART FAILURE IN PATIENT WITH DILATED CARDIOMYOPATHY: WHAT IS THE OPTIMAL TREATMENT?

Si Dung Chu^{1,2,4}, Huy Quang Doan^{2,3}, Minh Thi Tran², Linh Tran Pham⁴, Khanh Quoc Pham⁴

¹Training and Direction of Healthcare Activities Center, Bach Mai Hospital

²Department of Internal Medicine, Vietnam University of Medicine, Hanoi.

³Directorate, Vietnam University of Medicine, Hanoi, Vietnam

⁴Vietnam National Heart Institute, Bach Mai Hospital, Hanoi, Vietnam.

Objective: To study clinical cases of acute heart failure based on dilated cardiomyopathy to clearly see what is the most optimal treatment in each clinical case.

Research method: Clinical case report and review of the literature. Research on a clinical case of acute heart failure in a patient with chronic heart failure with dilated cardiomyopathy at the Vietnam National Heart Institute, Bach Mai Hospital. Optimal medical treatment of heart failure while treating the underlying disease well helps improve heart function and clinical improvement.

Case report: The 59-year-old male patient was admitted to the Vietnam National Heart Institute - Bach Mai Hospital because of New York Heart Association (NYHA) III-IV dyspnea and bilateral lower extremity edema, with less urine about 700 - 800 ml/24 hours, Ejection Fraction (EF) 18%. History of type 2 diabetes, hypertension, old pulmonary tuberculosis, newly discovered dilated cardiomyopathy 6 months ago, and hospitalized without any treatment. Do not smoke and use alcohol. Patients were treated aggressively during the acute decompensated heart failure episode as well as optimized with foundational medications such as Angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, aldosterone antagonists, and digitalis (Digoxin) to help stabilize treatment of NYHA II, and EF 45% before discharge, and myocardial resynchronization therapy with CRT implantation was prescribed.

Conclusion: The treatment strategy for this patient is to first treat acute decompensated heart failure, then stabilize medical treatment with foundational drugs at the target or optimal dose for the patient. The addition of 2 therapies, Ivabradine and cardiac resynchronization, is a very reasonable indication that will improve functional status and quality of life while reducing the patient's risk of hospitalization and death; However, while waiting for the decision to intervene in CRT implantation from the patient's family, optimal medical treatment is needed. Current clinical evidence has shown that optimal medical treatment is individualized. Chemotherapy helped improve and stabilize this patient's clinical condition, helping to improve the prognosis.

Keywords: Chronic heart failure, Acute exacerbation of chronic heart failure, Dilated Cardiomyopathy, Optimal treatment.

INTRODUCTION

Heart failure is a pathological syndrome in which the heart's supply is insufficient to meet the body's oxygen needs in situations during the patient's life, it is a very common pathological syndrome and is a consequence of many cardiovascular diseases such as hypertension, coronary artery disease, heart valve disease, myocardial disease, congenital heart disease, rhythm disorders [1-3]. Many factors can exacerbate heart failure, leading to the decompensation of heart failures or the acute onset of chronic cardiac failure [4-8]. Since there has been a consensus on the classification of heart failure bodies by the European Heart Association in 2016 (ESC 2016), it really has high practical value and is widely applied today [2].

Among the causes of heart failure, Dilated Cardiomyopathy (DCM) is a heart disease characterized by two-ventricular dilatation and disorder of the whole cardiomyocytes (blood discharge rate < 40%). The majority of the disease has no clear cause, but there are three groups of factors that suggest cardiomyopathy is previous, autoimmune, and genetic [4], [9-12]. The natural course of the disease will lead to increased heart failure, open heart valves, vascular blockade, and heart arrhythmia, if not detected and treated promptly that can cause dangerous and potentially fatal complications in heart shock or rhythmic disorders such as ventricular arrhythmia symptoms [4-22]

Therefore, the optimum life expectancy for the patient can be extended, life quality improved, and unexpected

death in the sick prevented by early detection and effective treatment administered in the most tailored and optimal manner [4], [5], [14-19], [24], [25]. So we report a clinical case of acute heart failure in a person with chronic cardiomyopathy at the National Institute of Cardiovascular Diseases, Bach Mai Hospital, to see what is the best treatment for each clinical case.

CASE REPRESENTATION

The 59-year-old male was admitted to the National Heart Institute of Vietnam – BachMai Hospital because of shortness of breath and edema of the lower limbs. Patient with type 2 diabetes, hypertension, and long-term lung tuberculosis, diagnosed with cardiomyopathy six months ago, was admitted to the hospital without any treatment. This person doesn't smoke and drink. About a month after entering the hospital, the patient showed symptoms of shortness of breath, increased swelling of the two legs, high swelling, soft swell, press concave,

small urine, urine 2-3 times a day, each time about 200 ml, accompanied by difficulty breathing a lot at night, no chest pain, no cough, no fever, normal discomfort. The patient at the entrance to the hospital had difficulty breathing NYHA III-IV, swelling of two legs, small urine about 700 – 800 ml/24 h, internal urine, and no chest pain.

The Blood test results showed the Glucose 24.7 mmol/l, HbA1C 13.8%, Ure/Creatine: 7.0/86.6 umol/L, GOT/GPT/GGT: 31.3/30.0/256.8 U/L, Uric Acid 314 U/L, Cholesterol/Triglyceride/HDL-C/LDL-C: 4.0/1.12/0.65/2.84 mmol/L, Albumin/Protein: 27.6/58.5 g/L, NT-ProBNP: 1473 pmol/L. Na / K / Cl: 135.0/4.64/97.5 mmol/L. The Serum protein electrophoresis results showed a non-monoclonal increase (All 3 A2, B, and G Globulin indexes increased).

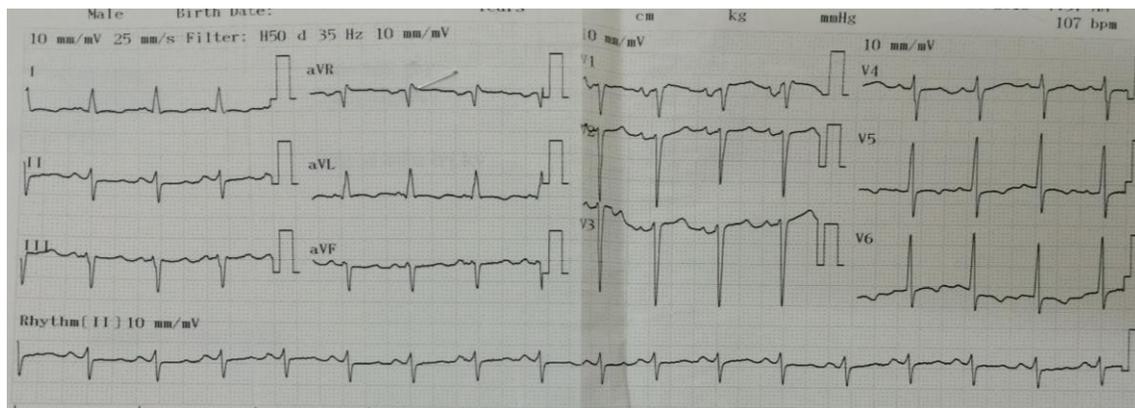


Figure 1: Electrocardiogram image at hospital admission

Electrocardiogram (ECG) showed Sinus rhythm 107 cycles/minute; P waves are positive in the aVL, P waves are broad and biphasic in V1 lead with lengthening the end of the terminal part of the P wave in V1 lead; S waves predominate in V1 to V4 lead; Left anterior bundle branch block – LBBB, ischemic heart disease, left axis deviation.

Figure 2: Echocardiogram image at hospital admission

Doppler cardiac ultrasound showed: low left ventricular function (EF: 18%), moderate two-leaf valve opening, multi-leaved three-left valve opening, dilated left ventral chamber, prolonged artery, and high pulmonary arterial pressure (68 mmHg).

Multi-Slice Computerized Tomography (MSCT) scan of 256 rows of the coronary artery system shows the image of atherosclerosis causing 50-60% RCA stenosis, 40% LAD2 stenosis, and 60-70% LAD2 stenosis.

The patient was diagnosed with heart failure of the left ventricle (EF: 18%), the moderate opening of the two-leaf valves, the multi-left opening of the three-leaved valve, dilated left ventral vessels, prolonged vertebrae, increased pulmonary arterial pressure, cardiomyopathy, kidney malformation, type 2 diabetes mellitus.

In this clinical case, we firstly individualize medical treatment, according to the patient's condition with the main groups of drugs such as diuretics Furosemide 20mg/2ml administered intravenously in a daily dose of

two tubes divided into two in the morning and in the afternoon. The Aldosterone group of diuretics in this case is used at the start dose (Spironolactone 25 mg x 2 tablets per day) of two tablets divided into two in the morning and in the afternoon. ACE inhibitor Zestril 5 mg x 1 tablet/day, Procoralan 7.5 mg x 2 tablets/day, Nitralmyl 2.6 mg x 2 tablets/day, Dilatrend 6.25 mg x 1 tablet, taken in the morning. In addition, we also use drugs to treat diabetes including Humulin R 1000 UI/10 ml x subcutaneous injection of 30 IU/day divided into 3 times of 10 IU each time (6 AM-11 AM-5 PM) along with Lantus 1000 IU/day. 10 ml x subcutaneous injection of 8 IU/day at 9.00 PM, of course blood sugar is monitored Test blood sugar before injection to adjust dose. The patient with edema this time had a decreased Albumin and Protein index, so he was prescribed an infusion of Albumin 25% - 50 ml x 2 vials of slow intravenous infusion in the morning and afternoon.

During the course of treatment, the patient's symptoms of difficulty breathing gradually decreased, the edema of the lower limbs gradually declined, the lungs no longer rales, soft stomach, and urine of about 2 liters/24 hours.

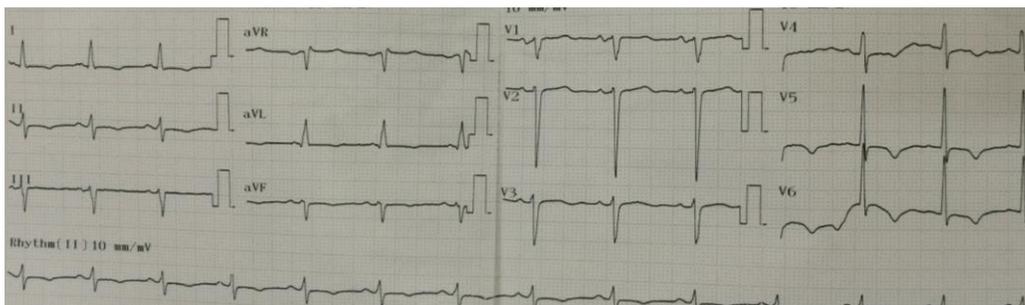


Figure 3: Electrocardiogram image after stable treatment

ECG after stable treatment showed Sinus rhythm 81 cycles/minute; P waves are negative in the V4-V6 lead,

ischemic heart disease, left axis deviation.

Figure 4: Echocardiogram image after stable treatment

After 10 days, the patient received stable treatment, good contact alertness, no chest pain, and breathing difficulties - NYHA II breathing difficulty, lungs no rale, Heart rate is 79/minute, blood pressure is 120/80 mmHg, edema is low, the lower limbs are slightly swollen, the urine is 2 liters/24h: The Doppler cardiac ultrasound showed a significant improvement in the contraction of the heart muscle compared to the new hospital (EF 45%). The result of the blood test showed Glucose 10.1 mmol/L, Albumin/Protein: 34.2/65.6 g/L, and NT-ProBNP 500.8 pmol/L.

DISCUSSION

In this clinical case, the patient was diagnosed with acute of chronic heart failure of the low Ejection Fraction (EF: 18%) based on the moderate opening of the two-leaf valves, the multi-left opening of the three-leaved valve, dilated left ventral vessels, prolonged vertebrae, increased pulmonary arterial pressure, dilated cardiomyopathy, kidney malformation, type 2 diabetes mellitus; Therefore, we firstly individualize medical treatment [5], [11-23].

The Aldosterone group of diuretics in this case used at the start dose (Spironolactone 25 mg x 2 tablets per day) is also the optimal dose for the patient, it not only has diuretic effect but also has particular benefits in reducing the overcompensation processes of the increase of Aldosterone in severe heart failure, thereby reducing vascular contractions, retention of salt and water, cardiomyopathy, kidney failure, and endothelial dysfunction, it also helps to reduce the rate of mortality and hospitalization in patients who are suffering from severe cardiac failure. However, due to acute heart failure, it is important to give priority to the

prescription of diuretics, the most common one is Furosemide, so far, a diuretic is still the most potent and the basic treatment for acute cardiac failure. It helps to decrease blood supply due to dropped water retention, and reduced preload. Diuretic drugs can relieve symptoms immediately, the vasodilator effect appears soon after 10-15 minutes, diuretics effect occurs after 30-60 minutes and lasts for 4 – 6 hours. The guidelines suggest that the use of intravenous diuretics to empty sodium discharge doses is faster and more effective in poorly progressed chronic heart failure cases, where the usual bolus dose is 40-80 mg, should be started with 20 mg per vein in patients who have never used diuretic, followed response after 30-60 minutes, doubled dose if not responding. Dividing the dose with a responsive dose multiple times a day instead of a high dose to reduce reabsorption of sodium after diuretics is effective. The patient is re-tested for kidney function, and electrolytes to detect complications of diarrhea, and monitoring of the creatinine background is also predictive for people with acute heart failure [1], [26], [27]. [28], [29].

Today, ACEI drugs are still considered the top choice in the treatment of heart failure, the mechanism of this group of drugs which inhibits the enzyme that converts Angiotensin I into Angiotensin II catalyst, resulting in a decrease in Angiotensin II levels, while increasing Bradykinin, a substance that has an almost inverse effect to Angiotensin II. Through this, the enzyme inhibitors will regulate the nervous system (Renin-Angiotensin-Aldosterone), and dilate the blood vessels (both the arteries and veins), resulting in reducing both the post- and pre-load as well as the restructuring of the heart muscle cells, thereby reducing the burden on

the heart will help improve and reduce heart failure. Many studies have shown that the ACEI group improves endometrial function, improves left-handed function, and not only reduces symptoms, but also significantly improves prognosis. In this case, we use Zestril (Lisinopril) at a dose of 5 mg/day. After taking the initial dose, the blood pressure is well controlled and at 100/64 mmHg, it is not recommended to increase the dose as it may lead to low blood pressure while there are signs of symptomatic improvement [1], [26], [30], [31].

In recent years, beta-blockers have become an important choice in the treatment of heart failure, especially cardiac failure caused by myocardial dysfunction, it is considered one of the fundamental medicines in the treatments for chronic cardiovascular failure with decreased Ejection Fraction. The mechanism of action of the drug is to prevent the strong stimulating effect of the sympathetic nervous system in chronic cardiovascular failure, the drug reduces the need for oxygen in the heart muscle, reduces catecholamine toxicity to the heart's muscle cells, inhibits the vascular contraction of the sympathetic system, helps improve the symptoms and frequency of left arterial hemorrhage, reduce the risk of death from arthritis disorders. However, this group of drugs is also contraindicated in patients with heart failure in the decompression phase, slow rhythm, and bronchial asthma, and is relatively contraindicated in chronic obstructive pulmonary disease (COPD), so monitoring during treatment is necessary as it can exacerbate heart failures in the period of decompression as well as trigger asthmatic attacks in people with a history of asthma, COPD. In this case, because a person with heart failure has symptoms of NYHA III-IV with a significantly reduced Ejection Fraction (EF: 18%) we did not use an initial beta-blocker and instead, we used Procoralan (Ivabradine) at a dose of 15 mg/day, this is a drug in the If the cluster that also reduces the sinus rhythm, which has been shown to improve symptoms and reduce mortality for the patient; it is worth noting that this If channel blockers group has been recommended for people with cardiac failure even if they have symptoms (NYHA II-IV), EF < 35%, and sinuses at a rate of > 70 per minute [1], [26], [32-35].

After optimum and appropriate dosage adjustment of the Digitalis diuretics and enzyme inhibitors continued to be administered with the Dilatrend 6.25 mg group, the main ingredient being Carvedilol of the beta-blockers with a starting dose of 3.215 mg x 2 tablets per day [1]. The mechanism of action by expanding and opening the blood vessels, helping to reduce the burden on the heart, helping the heart to pump blood into the circulatory

system more easily, thereby reducing the risk of coronary artery disease, it is actually a drug that is also quite useful in the treatment of hypertension, cardiovascular disease, chronic heart failure and left-hand failure after acute myocardial infarction. Patients who have been screened for coronary MSCT 25 series have been found to have fibrosis that narrows the coronal vessels (50-60% narrow RCA and RCA1, 40% narrow LAD, and 60-70% narrow LAD) with chronic heart failure so the use of Carvedilol is very useful in this case.

In addition, in heart failure on the background of a low supply of cardiomyopathy and guaranteed heart rate, the prescription of Glycoside cardiac aid (Digoxin) medication as in this case is perfectly reasonable, it helps to improve the contraction of the heart muscle, decreases the heart rhythm, reduces the stimulation of the sympathy in chronic heart failures, increases the cardiac muscle contraction, effectively reduces symptoms and reduces re-hospitalization rates for people with chronic cardiac failure. We used the low starting dose (Digoxin 0.25 mg x ½ tablet/day) and this is also the common dose used in the treatment of heart failure with cardiac Glycoside although the maximum recommended allowable dose for Digoxin is < 0.375 mg/day [1], [23], [28], with the usual dose of 0.125 mg/day contributing to significant symptomatic improvement, after 10 days of treatment improved the transfusion rate (EF) from 18% to 45%. Moreover, the patient is prescribed vasodilator nitroglycerin 2.6 mg with a dosage of x 2 tablets per day in this case, it has an arterial dilator effect that reduces rectum, helps to make better heart supply, varicose veins reduces preload, enhances pulmonary edema and renal vasoconstriction, when the prescription note must ensure systolic blood pressure > 110 mmHg before use [1], [23], [28], [30], [31].

Nowadays, for patients with Dilated Cardiomyopathy who do not respond to medical treatment, some of the extracurricular interventions that have been applied, such as cardiac transplant surgery, are considered to be the latest best treatment for cardiomyopathy, but it has limited influence factors for this method: Proper donor, post-transplant rejection and long-term use of immunosuppressants, with a survival rate of 92% after 5 years and 53% after 25 years; Or maybe a temporary surgery to remove a large portion of the epithelial muscle and repair or replace the double-leaf valve has also shown an improvement in symptoms, but it does not change the nature of the disease. Cardiac resynchronization therapy (CRT) is a two-ventricular rhythm generator that is effective for adults, while the CRT is used for people with slow rhythmic disorders that do not fall into this clinical condition. A promising new method is stem cell transplantation; stem cells, especially

the heart muscle stem cell, are transplanted as a substitute for degenerated cardiac muscle cells. However, this technique is now more research than clinical application [1], [2], [26], [36], [37].

Internal case is still considered the basic treatment for all cases of reduced ventricular failure and needs to be optimized before discharge or after each cardiac failure. Effects on the renin-angiotensin-aldosterone system (RAAS) and other organic nervous systems with enzyme inhibitors (ACE-I) or neprilysin angiotensin receptor inhibitor (ARNI) [30], [31], [34], [36], beta-sympathetic blockers and aldosterone antagonists (MRAs) help lower mortality, reduce the risk of hospitalization for heart failure, and decrease the symptoms of cardiac failure [1], [23], [25], [26], [35], [36]. These groups of drugs are considered to be fundamental in internal medical treatment, with the combination of three ACE-I or ARNI groups with sympathetic beta-blocking and MRA recommended, except in cases where contraindications or patients are intolerant drugs. In clinical practice, clinicians need to adjust the dosage of these groups of drugs to the maximum dose that the patient can tolerate. In the latest recommendation, ARNI is given priority over ACE-I, especially in cases where ACE-I, especially in cases where ACE-I, sympathetic beta-blocking and MRA have been used but still have symptoms. However, ARNIs can completely be prescribed to initiate heart failure replacing the ACE-I group, Angiotensin Receptor Inhibitors (ARBs) still play a certain role in cases where the patient is intolerant to ACEI or ARNI [30], [31], [34], [36].

CONCLUSION

Patients in this clinical case have been treated with almost all of the classic systolic heart failure treatments, which are optimally treated internally. The enzyme inhibitory dose that the patient is taking is not the target dose (5 mg Enalapril). Bisoprolol is not the target dose. The dose of spironolactone as well as the dose of digoxin that the patient is taking are the usual doses. If you increase the dosage of these drugs, the probability of actual clinical improvement is not high while the risk of side effects is real. The patient does not have any symptoms of pulmonary or systemic hemorrhage, so there is no indication of an increase in the dose of diuretics.

For this person, instead of increasing the doses of the medication they are taking, two therapies are adopted: Ivabradine and re-synchronization of the heart. Indeed, the clinical and subclinical characteristics of the patient are very suitable for ivabradine (based on disease selection criteria in the SHIFT study): NYHA III cardiac failure with stable symptoms for at least 4 weeks, sinus

and heart rate of 80/minute and 30% left-ventricular failure. Moreover, the patient's QRS complex is 140 ms long, so re-synchronization of the heart is a very reasonable indication. The clinical evidence available provides a basis for hope that ivabradine supplementation and cardiovascular re-synchronization will improve functionality and quality of life while reducing the risk of hospitalization and death.

REFERENCE

1. McDonagh TA, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: ESC Clinical Practice Guidelines. *European Heart Journal*. 2021; 42 (36): 3599 – 3726.
2. Ponikowski P, Voor AA, Anker SD, et al. 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 Fail. 2016; 18 (8): 891-975.
3. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. *Card Fail Rev*. 2017; 3 (1): 7-11.
4. Farmakis D, Parissis J, et al. Acute heart failure: epidemiology, classification, and pathophysiology. *The ESC Textbook of Intensive and Acute Cardiovascular Care*, Oxford 2015; 486-97.
5. Virani SS, Alonso A, Benjamin EJ, et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics – 2020 Update: A Report From the American Heart Association. *Circulation*. 2020; 141 (9): e139-3596.
6. Gheorghide M, Abraham TW, et al. Systolic Blood Pressure at Admission, Clinical Characteristics, and Outcomes in Patients Hospitalized With Acute Heart Failure. *JAMA*. 2006; 296: 2217-26.
7. Vedin O, Lam CSP, Koh AS, et al. Significance of Ischemic Heart Disease in Patients With Heart Failure and Preserved, Midrange, and Reduced Ejection Fraction: A Nationwide Cohort Study. *Circulation Heart Fail*. 2017; 10 (6).
8. Kellum AJ, Lameire N. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney International Supplements*. 2012; 2: 1-141.
9. Atherton JJ, Hayward SC. Patient Characteristics From a Regional Multicenter Database of Acute Decompensated Heart Failure in Asia Pacific (ADHERE InternationaleAsia Pacific). *Cardiac Fail*. 2012; 18: e82-e8.
10. Felker MG, Shaw KL. A Standardized Definition of Ischemic Cardiomyopathy for Use in Clinical Research. *J Am Coll Cardiol*. 2002; 39: 210-8.
11. Al-Makki, et al. Hypertension. *Hypertension Pharmacology Treatment in Adult: A World Health*

- Organization Guideline Executive Summary. Clinical Statements And Guidelines January 2022; 79: 293-301.
12. Bogaev RC. Cost consideration in the treatment of heart failure. *Texas heart inst J*. 2010; 37: 557-558.
 13. Ambrossy AP, et al. The global health and economic burden of hospitalizations for heart failure. *J Am Coll Cardiol*. 2014; 63: 1123 – 1133.
 14. Kitzman DW, Whllan DJ, Duncan P, et al. Rehabilitation for Older Patients Hospitalized for Heart Failure. *N Engl J Med*. 2021.
 15. Felker MG, Linda KS. A standardized Definition of Ischemic Cardiomyopathy for Use in Clinical Research, *J Am Coll Cardiol*. 2002; 39: 210-8.
 16. Panduranga P, Sulaiman K. Demographics, Clinical Characteristics, Management, and Outcomes of Acute Heart Failure Patients: Observations from the Oman Acute Heart Failure Registry, *Oman Medical Journal*. 2016; 31: 188-95.
 17. Felker MG, Teerlink RJ. Diagnosis and Management of Acute Heart Failure, *Braunwald's Heart Disease A Textbook of Cardiovascular Medicine*. Elsevier 2018; 1228-88.
 18. Tsutsui H, Makaya TM, Kinugawa S. Clinical Characteristics and outcomes of heart failure with preserved ejection fraction: Lessons from epidemiological studies. *Journal of Cardiology*. 2009; 55 (1): 13-22.
 19. Borlaug AB. The pathophysiology of heart failure with preserved ejection fraction. *Nature Reviews Cardiology*. 2014; 11: 507-515.
 20. Naing P, Forrester D, Kangaharan N. Heart Failure with preserved ejection fraction: A growing global epidemic. *AJGP*. 2019; 48 (7): 465-471.
 21. Vaz-Salvador P, Adão R, Vasconcelos I, et al. Heart Failure with Preserved Ejection: a Pharmacotherapeutic Update. *Cardiovascular Drugs and Therapy*. 2021; 36 (1): 07306-8.
 22. McDonald M, Virani S, Chan M, et al. CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction. *Canadian Journal of Cardiology*. 2021; 37 (4): 531-546.
 23. Pfeffer AM, Shah MA and Borlaug AB. Heart Failure With Preserved Ejection Fraction In Perspective. *Circulation Research*. 2019; 124: 1598-1617.
 24. Vaz-Salvador P, Adão R, Vasconcelos I, et al. Heart Failure with Preserved Ejection: a Pharmacotherapeutic Update. *Cardiovascular Drugs and Therapy*. 2021; 36 (1): 07306-8.
 25. McDonald M, Virani S, Chan M, et al. CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction. *Canadian Journal of Cardiology*. 2021; 37 (4): 531-546.
 26. Heidenreich PA, Bozkurt B, Aguilar D, 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.
 27. Pfeffer AM, Shah MA and Borlaug AB. Heart Failure With Preserved Ejection Fraction In Perspective. *Circulation Research*. 2019; 124: 1598-1617.
 28. Yancy CW, Jessup M, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. *Circulation*. 2017; 136: e137-e61
 29. Rossignol P, Hernandez FA, et al. Heart failure drug treatment. *Lancet*. 2019; 393: 1034-44.
 30. McMurray JJ, Packer M, Desai AS, et al. Angiotensin neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014. 371 (11): 993-1004.
 31. Leong PD, McMurray JJV. From ACE Inhibitors/ARBs to ARNIs in Coronary Artery Disease and Heart Failure. *J Am Coll Cardiol*. 2019; 74: 683-98.
 32. Velazquez JE, Morrow AD. Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure, *N Engl J Med*. 2019; 380: 539-48.
 33. Solomon SD, Claggett B, Lewis EF. 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.
 34. McMurray JJV, Jackson AM, Lam CSP, et al. Effects of Sacubitril-Valsartan Versus Valsartan in Women Compared With Men With Heart Failure and Preserved Ejection Fraction: Insights From PARAGON-HF. *Circulation*. 2021; 141 (5): 338-51.
 35. Cleland JGF, Bunting KV, Flather MD, 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.
 36. 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): 1609-20
 37. Samsky DM, Patel BC, et al. Cardiohepatic Interactions in Heart Failure: An Overview and Clinical Implications, *J Am Coll Cardiol*. 2013; 61: 2397-405.