

Achieving optimal doses in treatment of heart failure with reduced ejection fraction at Nhan dan Gia Dinh Hospital

Pham Truong My Dung , Nguyen Hoang Hai

Nhan dan Gia Dinh Hospital

► **Correspondence to**

Dr. Pham Truong My Dung
Nhan dan Gia Dinh Hospital
Email: ptmydungdr@yahoo.com

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INTRODUCTION

Heart failure (HF) with reduced ejection fraction (HFrEF) is a complex clinical syndrome associated with high mortality, long hospital length of stay, high readmission rates, reduced exercise tolerance, and decreased quality of life, as well as requiring significant resources to support treatment and care¹. Currently, it is reported that approximately 50% of all heart failure cases are HFrEF. However, due to recent advancements in cardiovascular diagnostic imaging, earlier, and possibly more precise, detection of HFrEF is greatly enabled. Not only does this seemingly increase the incidence rate of HFrEF in the general population, but it also gives treatment facilities an advantage in improving the prognosis and average life expectancy for these newly rising cases of HFrEF². According to heart failure treatment guidelines by Heart Associations around the world, an effective, interdisciplinary, and coordinated care system needs to be applied to all heart failure patients, including the reduced ejection fraction heart failure group, in order to achieve optimal guideline-recommended therapy, reduce mortality and readmission. In addition, each patient needs to be provided with a detailed treatment plan, which comprises treatment goals, effective

management of comorbidities, follow-up time, diet, and physical activity⁶. Therefore, the critical role of HF management programs in improving symptoms and quality of life in both inpatient and outpatient settings has been well recognized and paid continuous attention for the last two decades, with regular updates on team-based healthcare systems and home-based patient care^{8,9,10}.

Recent updates in treatment guidelines have highlighted the role of the treating physician in customizing and adjusting the therapeutic drugs' doses, to match those recommended as target or optimal, which must also be well-tolerated by the patients, with the aim of improving clinical outcomes.¹² Therefore, it could be deduced that not only the sheer application of the four evidence-based foundational treatment but also dose adjustment over time of each one, should be collectively recognized as the basis of treating patients with HFrEF.

The operation of a highly-specialized unit, solely dedicated to the management of HF, known as 'Heart Failure Unit', has proven its effectiveness, by means of optimization of medical therapy, irrespective of baseline EF, but most notably reduced EF. Therefore, patients' symptoms and readmission rate in facilities with "Heart Failure

Unit" has witnessed a noticeable reduction.

In today's Vietnam, many tertiary medical facilities have implemented such centralized heart failure care models, and the Cardiology Department of Nhan dan Gia Dinh Hospital is definitely not an exception. The Heart Failure Unit in our department has been established and operating with a soulful dedication to providing HF patients with utmost comprehensive care and guideline-recommended therapy.

EFFICACY OF FOUR FOUNDATIONAL DRUG GROUPS IN IMPROVING PROGNOSIS IN REDUCED EJECTION FRACTION HEART FAILURE PATIENTS

Medical therapy has been recommended to be the foundation of HFrEF treatment, and thus must be attempted before resorting to device-based therapy and non-pharmaceutical therapy. The management of HFrEF consists of three goals: reduction of mortality, reduction of HF-associated hospitalizations, improvement of clinical symptoms, exercise capacity and quality of life.

In light of the most updated guidelines, optimal treatment of HFrEF is recommended to include ACEI/ARB/ARNI, beta-blockers, aldosterone antagonists and empagliflozin/dapagliflozin. It should be kept in mind that not the drugs per se, but the proper adjustment of the dosage of each pharmaceutical agent to match those proposed in the guidelines and those well-tolerated by patients is also of key importance¹³.

Angiotensin Converting Enzyme Inhibitors (ACEIs)

ACEI drugs have been shown to reduce mortality and complications and alleviate symptoms in HFrEF patients. ACEIs are one of the foundational drug groups recommended for first-line treatment except in cases with contraindications or drug intolerance¹⁴. ACEIs can be titrated up to the optimal dose or maximal dose that patients can tolerate, to achieve the highest possible inhibition of the RA system. ACEIs are also recommended in patients with asymptomatic left ventricular dysfunction to reduce the risk of progression to overt heart failure, rehospitalization, and HF-related death. However, several studies have reported that the majority of patients treated with

ACEIs do not reach the optimal or maximal doses they can tolerate¹⁵.

ARNI

Neprilysin is a zinc-dependent metalloprotease enzyme, that inactivates vasodilator peptides including natriuretic peptides, adrenomedullin, bradykinin, and substance P, which all play important roles in the pathophysiology and progression of heart failure². As angiotensin II is a substrate for neprilysin, neprilysin inhibitors also increase angiotensin levels, which explains the synergistic effect when combined with ARB. Neprilysin inhibitors (sacubitril) are not to be combined with ACEIs due to the increased risk of angioedema.

In the PARADIGM-HF study, sacubitril/valsartan was tested on HFrEF patients. The inclusion criteria were NYHA II-IV heart failure patients with EF \leq 40% (amended to EF < 35% after 1 year) who had already been started on ACEIs/ARBs and other guideline-directed medical therapies for heart failure. Exclusion criteria were estimated glomerular filtration rate < 30 mL/min/1.73 m², symptomatic hypotension, systolic blood pressure < 100 mmHg, or acute decompensated heart failure. Results showed the risk of cardiovascular death or HF-related hospitalization was reduced by 21% (HR 0.80, $p < 0.001$) in the sacubitril/valsartan group compared to enalapril, with a number needed to treat (NNT) of 21. In addition to the proven benefits in the trial, symptomatic hypotension was more common in the sacubitril/valsartan group than with enalapril (14% vs 9.2%, $p < 0.001$) but was not accompanied by worsening renal function. In addition, the rate of angioedema in the sacubitril/valsartan treatment arm was higher but not significantly and statistically different from the enalapril arm¹⁷.

Beta-blockers

Beta-blockers have been shown to reduce mortality and severe morbidity in symptomatic HFrEF patients already treated with ACE inhibitors and diuretics. Notably, when initiated, beta-blockers should be started in clinically stable patients with balanced fluid input and output, at low starting

doses, then gradually increased to target or maximally tolerated doses. For patients hospitalized with acute heart failure, careful in-hospital initiation of beta-blockers should be attempted once the patient is hemodynamically and clinically stable¹⁴. For HFrEF patients with atrial fibrillation, beta-blockers should be considered to control ventricular rate, especially with rapid ventricular response. Additionally, beta-blockers are recommended for patients with prior myocardial infarction and asymptomatic left ventricular dysfunction to reduce mortality risk.

Aldosterone antagonists

Aldosterone antagonist drugs (spironolactone and eplerenone) act by blocking aldosterone and other steroid hormones from binding to their receptors. According to the 2022 ACC/AHA guidelines, spironolactone and eplerenone are recommended in symptomatic HFrEF patients with ejection fraction $\leq 35\%$ to reduce cardiovascular mortality and hospital readmission rates. However, caution is advised in patients with impaired renal function and serum potassium levels >5.0 mmol/L. In this group of patients, serum potassium levels and renal function should be monitored regularly, depending on clinical status.

SGLT2 Inhibitors

SGLT2 inhibitor drugs have been shown to improve prognosis, including severe complications and death, in HFrEF patients, regardless of diabetes status. Studies show these drugs increase osmotic diuresis, reduce arterial pressure, vascular stiffness, and shift the metabolic mechanism of cardiomyocytes towards ketones. In addition, SGLT2 inhibitors also reduce the impact on the preload and afterload, thereby reducing “stress”, hypertrophy, and fibrosis damage, thus slowing cardiac remodeling.

Table 1. Foundational drug classes for the treatment of HFrEF and recommended doses

Drug agent	Starting Dose (mg)	Target Dose (mg)
ACEIs		
Captopril	6.25; t.i.d.	50; t.i.d.

Drug agent	Starting Dose (mg)	Target Dose (mg)
Enalapril	2.5; b.i.d.	10-20; b.i.d
Lisinopril	2.5 – 5; o.d.	20-40; o.d.
Ramipril	1.25; o.d.	10, o.d.
Beta-blockers		
Bisoprolol	1.25; o.d.	10; o.d.
Carvedilol	3.125; b.i.d.	25 mg, b.i.d. (body weight < 85kg), and 50 mg, b.i.d. (body weight \geq 85 kg)
Metoprolol succinate	12.5-25; o.d.	200; o.d.
ARBs		
Candesartan	4-8; o.d.	32; o.d.
Valsartan	40; b.i.d.	160; b.i.d.
Losartan	25-50; o.d.	150; o.d.
Aldosterone antagonists		
Eplerenone	25, o.d.	50; o.d.
Spironolactone	12.5-25; o.d.	25-50; o.d.
ARNIs		
Sacubitril/valsartan	24/26-49/51; b.i.d.	97/103; b.i.d.
SGLT2 Inhibitors		
Dapagliflozin	10; o.d.	10; o.d.
Empagliflozin	10; o.d.	10; o.d.

t.i.d: three times a day; b.i.d: twice a day; o.d.: once a day

The first study demonstrating the efficacy of SGLT2 inhibitors in HFrEF was the DAPA-HF trial. The study was conducted on 4744 HFrEF patients and showed the dapagliflozin treatment group had lower rates of cardiovascular death or worsening heart failure compared to placebo, regardless of type 2 diabetes status. Moreover, the DEFINE-HF study showed dapagliflozin improved clinical symptoms and BNP levels in HFrEF patients with or without type 2 diabetes¹⁸. The EMPEROR-Reduced study included 3730 patients with chronic heart failure, randomly

assigned to empagliflozin treatment or placebo. The study demonstrated empagliflozin reduced the risk of cardiovascular death and heart failure hospitalizations in patients with or without type 2 diabetes (19.4% in the empagliflozin group vs. 24.7% in placebo; HR = 0.75). In the EMPEROR-Reduced study, results also showed empagliflozin slowed the decline in renal function over time. Moreover, a pooled analysis of the DAPA-HF and EMPEROR-Reduced studies also reported the efficacy of dapagliflozin and empagliflozin in reducing all-cause mortality, cardiovascular death, and improving renal function in hospitalized HFrEF patients¹⁹.

GAPS IN CLINICAL PRACTICE IN OPTIMIZING DOSING

According to a 2020 survey in Canada, 73.6% of HFrEF patients had no contraindications to RAS inhibitors, 94.9% to beta-blockers, 84.4% to mineralocorticoid receptor antagonists (MRAs), and 81.1% to sodium-glucose co-transporter-2 inhibitors. Up to 71.6% of HFrEF patients (75.5% new onset, 69.5% chronic HF) were eligible to be initiated all four foundational drug classes.

However, real-world data shows that the rates of foundational medications being prescribed at target or optimal doses for HFrEF treatment are still low. Uptitration of GDMT has been a challenge and many patients do not receive optimal doses. Data from the CHAMP-HF study, including 2588 outpatients with HFrEF in the United States, reported that the percentage of patients who received mineralocorticoid receptor antagonist (MRA) antagonists, beta-blockers, ACEIs/ARBs, angiotensin receptor-neprilysin inhibitor (ARNI) at target doses after a 12-month follow-up were 27%, 22%, 10% and 3%, respectively. With data from the CHECK-HF cross-section of 34 HF outpatient clinics in the Netherlands, the average achieved dose was 50% of the target dose for renin-angiotensin system (RAS) inhibition, 25% of the target dose for beta-blockers, and 25% of the target dose for MRAs.

Several explanations for suboptimal uptitration could be fathomed, namely limited resources of

local healthcare system, comorbidities and/or misconceptions of patients, unwanted side effects of the prescribed drugs. Common side effects such as fatigue, hypotension, renal dysfunction and hyperkalemia can overlap with heart failure syndromes, thus, pose further challenge to treatment decisions. However, studies have also shown that if efforts are made to establish a patient-centered and optimal heart failure management models, achieving target or maximally-tolerated doses, and educating patients on heart failure plus beneficial practices, are still highly-possible goals¹¹.

OPTIMAL DOSING IN REDUCED EJECTION FRACTION HEART FAILURE PATIENTS AT NHAN DAN GIA DINH HOSPITAL

In June 2020, the Cardiology Department of Nhan dan Gia Dinh Hospital established a heart failure unit to meet the demand for specialized management of heart failure patients. Our priority is to provide HF patients with, but not limited to, the followings:

- A holistic plan for treatment, care and health education.
- The most up-to-date treatment strategy, as recommended by specialized guidelines

Our data, with the inclusion of 412 inpatients and outpatients monitored and treated by the Heart Failure Unit of Nhan dan Gia Dinh Hospital, reported the following findings:

Demographic characteristics

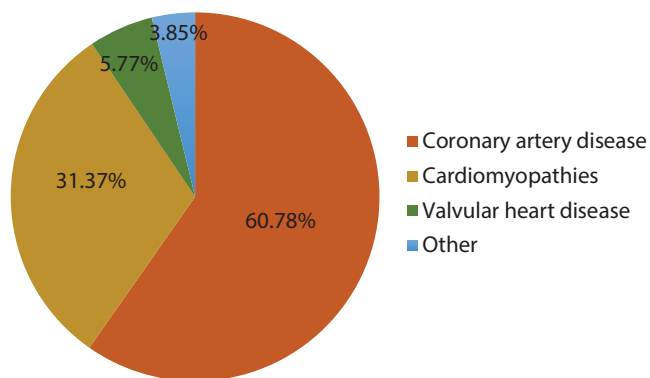
- The average age was 66.1 years old, youngest 18 years old and oldest 96 years old, with 20% of patients belong to the ≥ 80 -year-old group.
- Gender: female predominates, with 59.7%.

Etiologies of heart failure

Coronary artery disease is the leading cause of HF in our population, accounting for 60.7%. Other notable causes include cardiomyopathies and valvular heart disease.

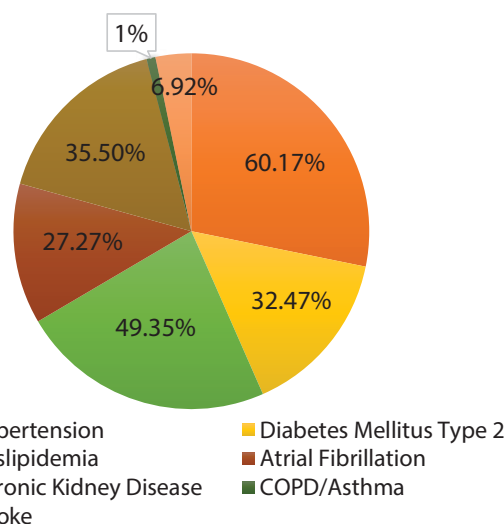
Comorbidities

Our survey recorded certain common comorbidities: hypertension (60.1%), dyslipidemia (49.35%), diabetes (32.47%), chronic kidney disease



Picture 1. Etiologies of heart failure in Nhan dan Gia Dinh Hospital

(35.5%), and atrial fibrillation (27.27%). Notably, chronic kidney disease, which could hinder efforts for optimal treatment for heart failure patients, accounts for a fairly high proportion. However, it should also be emphasized that most foundational drug groups for heart failure treatment have kidney-protective effects. Hence, appropriate indications, dosing, and monitoring should be considered if renal function is not an absolute contraindication.

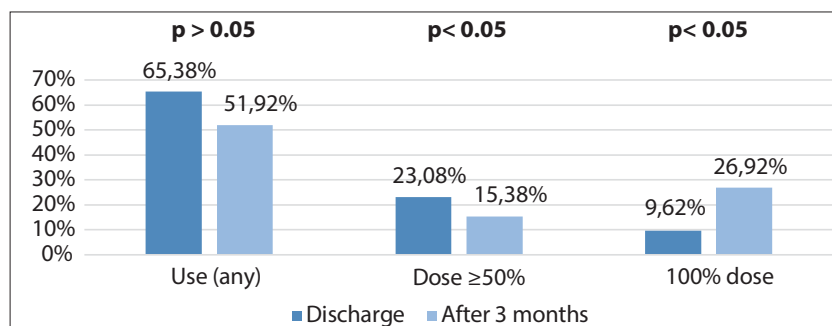


Picture 2. Comorbidities in HF patients at Nhan dan Gia Dinh Hospital

Rates of foundational medication use in HFrEF patients

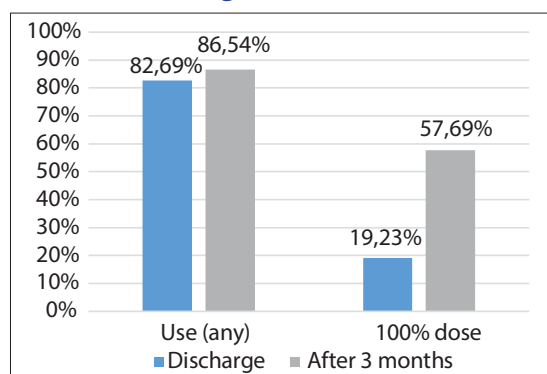
At time of discharge and after 3 months, we documented the rates at which foundational therapies are prescribed.

RAS Inhibition



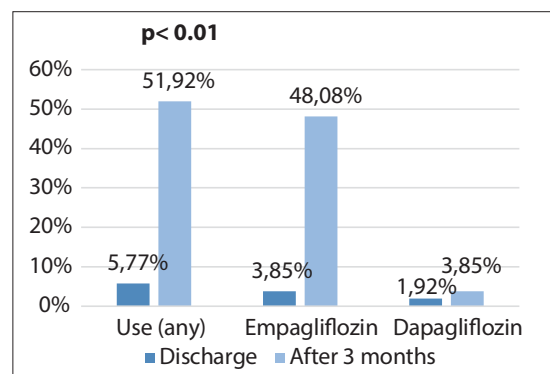
Picture 3. The prescription of RAS inhibitors at discharge and 3-month post-discharge

Aldosterone Antagonists



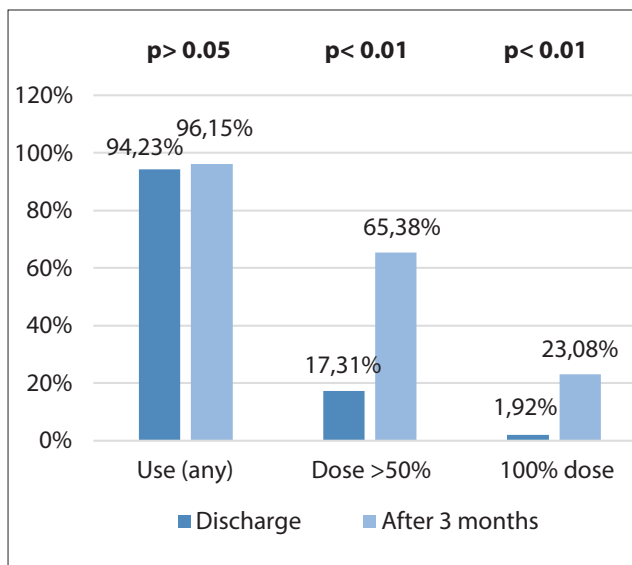
Picture 4. The prescription of Aldosterone antagonists at discharge and after 3 months

SGLT2 Inhibitors



Picture 5. The prescription of SGLT-2 inhibitors at discharge and 3-month post-discharge

Beta Blockers



Picture 6. The prescription of Beta-blockers at discharge and 3-month post-discharge

DISCUSSION

Effective heart failure management programs, as described in studies, use a consistent protocol to achieve target doses in most patients. If a systematic approach for heart failure reduced ejection fraction patients is not applied, treatment thresholds could be challenging to obtain. The COHERE study, whose selection criteria comprise of elderly patients with multiple comorbidities, proved that target doses of beta blockers could still be reached with an efficient and highly focused protocol.

With that in mind, we are striving to gradually perfect the standard GDMT protocol according to recommendations, but surely must tailor our approach to suit the economic-medical situation at the hospital. Hence, as demonstrated in our most recent data, the proportion of patients who did not complete the 3-month post-discharge follow-up program is still unneglectable. Several explanations could be provided, some of which are limitations in the reimbursement and distribution policy of the national health-care insurance, patient's financial status, and the dependence on health-care providers to make treatment-related decisions.

CONCLUSION

The heart failure patient care program is in charge of a long-term, continuous and comprehensive mission. The formation of a heart failure unit is indispensable to ensure quality treatment for patients. At the initial stage, the effectiveness of the heart failure unit could only be assessed by analyzing the data on medical treatment of heart failure, specifically in terms of classes and doses of drugs. In the long run, there will be more aspects which need to be evaluated and appropriately adjusted, in order to standardize the heart failure patient management, while still having to ensure the suitability with the actual situation at Nhan dan Gia Dinh Hospital.

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