Hội Tim Mạch Học Việt Nam
Vietnam National Heart Association

Tạp chí

Tim Mạch Học Việt Nam

JOURNAL OF VIETNAMESE CARDIOLOGY

(Xuất bản định kỳ 3 tháng 1 lần)
(Published quarterly)

Issue 107E (November, 2023)

JOURNAL OF VIETNAMESE CARDIOLOGY

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Publishing License No.: 472/GP-BTTTT issued on: 22-7-2021

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▶ Received: 25 October 2023
Accepted: 21 November 2023
Published online: 30 November 2023

To cite: Vu HV, Nguyen CT, Pham DDQ, *et al. J Vietnam Cardiol 2023*;**107E**:4-17

ABSTRACT

Heart failure is a growing public health issue with high mortality and hospitalization rates. Comprehensive management programs are needed to improve outcomes and reduce costs.

In Vietnam, there are gaps in guideline-directed medical therapy, lack of a multidisciplinary approach, inadequate patient education, and poor continuity from inpatient to outpatient care. However, management programs are evolving with 29 hospitals having established programs.

Initial results show improved use of medications, reduced hospitalizations and mortality, and better quality of life in some programs. Challenges remain around resources, costs, patient diversity, and lack of standardization.

Standardization initiatives like EuroHeart are working to define common data sets and care standards internationally. Effective programs require optimized hospital treatment, comprehensive discharge planning, structured follow up, and patient self-management support.

Further government support, healthcare professional training, public education, research, and regional collaborations are needed to advance heart failure care in Vietnam.

THE SIGNIFICANCE OF COMPREHENSIVE MANAGEMENT OF HEART FAILURE

Along with the development of the healthcare system, both in primary care and advances in disease management, human life expectancy is increasing. Concurrently, the prevalence of chronic diseases, such as heart failure, is on the rise across the globe. The estimated frequency of chronic heart failure accounts for 1-2% of the adult population in developed countries, and up to over 10% in the group older than 70 years[1-4]. The prognosis of patients with chronic heart failure is worse than most cancers[5,6]. Despite advances in medication therapy, the 5-year mortality rate remains between 40 and 50%[5,6]. Notably, the mortality rate in heart failure patients with preserved ejection fraction is only slightly lower than the reduced ejection fraction heart failure group[7]. These factors have led to an increasing burden on healthcare costs [8], raising the issue of the need to restructure the approach to caring for patients to achieve the best results at the most reasonable costs.

The primary goal of heart failure patient management is to reduce the rate of rehospitalization and mortality. Western countries have reported extensively on this issue in single and multi-country registry studies; at the same time, more and more individual countries in Asia have also provided data from their nations. In the West, the ESC HF Long-Term Registry, an observational, multicenter,

prospective registry enrolling 12,440 heart failure patients and following them for 1 year [9], must be mentioned. This study recorded a high all-cause mortality rate in the acute heart failure population, at 4.9% during hospitalization and 23.6% within 1 year. Over half of the deaths were due to cardiovascular causes. Considering the rehospitalization rate, this study recorded an average figure of 22.2% in 1 year. In one year, the percentage increased to 40.1% when death and rehospitalization caused by heart failure events were combined. This gives rise to concerns regarding the stringent management of patients with heart failure, particularly those who have been hospitalized for acute heart failure. Turning back to Asia, registry studies on heart failure have been emphasized for many years. In 2009, the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) registry study reported follow-up results of heart failure patients with both reduced and preserved EF [10]. Of the 1,692 patients enrolled in the study, 985 patients (58%) had EF <40%. At 1 year after discharge, the all-cause mortality rate was 8.9%, of which 66% were due to cardiovascular causes. Regarding rehospitalization, this figure was 23.7%. After that, 8 years later, we have registry studies from 2 other Asian countries: India and Taiwan. The Trivandrum Heart Failure Registry (THFR) study enrolled 1,205 patients hospitalized with acute heart failure from 18 hospitals in Trivandrum district of India [11] and followed them for 1 year after discharge. The rehospitalization rate recorded was even higher than previous studies, at 30.2%; of those, up to 64 patients (5.8%) were rehospitalized more than once. The cumulative 1-year mortality rate was 30.8%, and highest in the first 3 months after discharge, reaching up to 18.1% - an extremely worrying number. At the same time, Taiwan also reported its data [12]. 1509 patients with reduced EF heart failure admitted for acute episodes at 21 hospitals in Taiwan were enrolled in the study and followed up for 1 year. The rehospitalization rates in this study at 6 months and 12 months after discharge were 31.9% and 38.5%, respectively. Of those, up to 9.7% were rehospitalized more than once. 15.9% of patients died from all causes after 12 months from discharge, and cardiovascular deaths accounted for 10.5%. Most recently, the ASIAN-HF study is the first prospective, multi-country registry study to report heart failure data from Asian countries with regional classification [13]. This study enrolled 6,480 heart failure patients from 46 centers in 11 Asian countries. Of those, Southeast Asia had 5 participating countries: Thailand, Malaysia, Philippines, Indonesia and Singapore. The all-cause mortality rate within 1 year after discharge in the entire population and in the reduced EF heart failure population were 9.6% and 10.6%, respectively. Among reduced EF heart failure patients, Southeast Asia had the highest all-cause mortality rate, at 13.6% compared to 8.9% in Northeast Asia and 8.3% in South Asia. These figures show a worrying fact that, despite much progress in non-pharmacological and pharmacological treatments, as well as research efforts to incorporate into clinical practice new drugs proven to have good impacts on outcomes, mortality and rehospitalization rates remain unchanged.

Over the past decades, many groundbreaking new studies have emerged; from there, associations in countries have developed heart failure patient management programs to improve quality of life while also helping reduce the burden on healthcare costs [8]. In fact, there have been randomized controlled studies comparing multidisciplinary heart failure management with conventional management; the results show reduced rates of rehospitalization and mortality as well as optimized cost-effectiveness in the multidisciplinary group [14-17].

The natural progression of chronic diseases is accompanied by an increase in healthcare services, such as monthly outpatient visits and prescriptions [18]. However, current studies on the impact of management programs on healthcare costs still show inconsistent results (Table 1). Recently, a meta-analysis on the impact on outcomes as well as healthcare costs of an advanced heart failure management program involving 25 primary care centers provided an overview as follows: In terms of cost-effectiveness, management programs involving nurses may be cost-beneficial,

mainly from reduced rehospitalizations [19]. When considering quality-adjusted life years (QALYs), Fergenbaum et al. concluded that nurse-led care would improve QALYs by 11% and help reduce costs[20]. For patients with advanced heart failure, they need more support to improve QALYs, thus increasing costs more. This special patient group may need to be studied independently from the general heart failure population due to unique characteristics and needs.

***Table 1**. Randomized trials assessing the effectiveness of management programs on rehospitalization in elderly heart failure patients*

Author, Year	AHA Heart Failure Stages (Follow-up time)	Key outcomes comparing heart failure management program intervention vs usual care
Douglas, 2005 [21]	A, B, C (1,2 years)	Intervention reduced relative risk of composite outcome (heart failure rehospitalization or death) by 20%, 26.3% vs 31%, P=0.02. Intervention reduced heart failure rehospitalizations.
Laramee, 2003 [22]	A, B (3 months)	Rehospitalization rates were similar in both groups (37%). Mean total inpatient and outpatient costs and mean rehospitalization costs were reduced by 14% and 26% respectively in intervention group. Subgroup analysis of local patients seen by cardiologists showed significant reduction in heart failure rehospitalizations with intervention.
Stromberg, 2003 [23]	B, C (3 & 2 months)	Patients in intervention group had fewer composite outcomes (rehospitalization or death) after 12 months compared to control. Intervention group had fewer rehospitalizations (33 vs 56, P=0.047) and inpatient days (350 vs 592, P=0.045) in first 3 months. At 12 months, intervention was associated with 55% lower hospitalization rate/patient/month and fewer inpatient days/patient/month.
Doughty, 2002 [24]	A, B, C (1 year)	Intervention reduced total hospitalizations and inpatient days. Main intervention effect was due to preventing multiple rehospitalizations. Intervention improved quality of life.
Harrison, 2002 [25]	B (3 months)	In intervention group 23 patients were rehospitalized compared to 31 in usual care, with 35 patients not completing the 3-month study.
Kasper, 2002 [26]	A, B, C (6 months)	Intervention reduced composite outcome (heart failure rehospitalization or death): 43 rehospitalizations and 7 deaths vs 59 and 13, quality of life scores, use of vasodilator therapy and dietary recommendation compliance significantly better in intervention group.
Krumholz, 2002 [27]	A, B, C (1 year)	Intervention reduced composite outcome (rehospitalization or death) 25 vs 36. Intervention reduced total rehospitalizations by 39%. After adjusting for clinical and demographic characteristics, intervention group had significantly lower risk of rehospitalization.
McDonald, 2002 [28]	A, C (3 months)	Intervention reduced composite outcome (heart failure rehospitalization or heart failure death). Heart failure rehospitalizations less frequent in intervention group (25.5% vs 3.9%).
Riegel, 2002 [29]	A, B (3 and 6 months)	Heart failure rehospitalization rates 47.5% lower in intervention group after 3 months and 47.8% lower after 6 months. Significantly fewer heart failure inpatient days in intervention group at 6 months. Cost savings achieved even after deducting intervention costs. No evidence of cost-shifting to outpatient care. Patient satisfaction with care higher in intervention group.
Stewart, 2002 [30]	B, C (4, 2 years)	Significantly fewer unplanned rehospitalizations and composite outcomes (unplanned rehospitalization or death): mean 0.21 vs 0.37 events per patient-month. Mean event-free survival time longer (7 vs 3 months).
Blue, 2001 [18]	A, B, C (1 year)	Intervention reduced composite outcome (heart failure admission or death), fewer all-cause rehospitalizations (86 vs 114, P=0.018), fewer heart failure admissions (19 vs 45, P<0.001) and fewer heart failure inpatient days (mean 3.43 vs 7.46 days).

A review of 47 studies identified common key features of heart failure management programs across different studies: heart failure clinics, non-clinic follow-up, telephone contact, primary care follow-up, and promotion of self-care [31]. Both home visit programs and multidisciplinary clinic programs helped reduce all-cause rehospitalization rates at 3-6 months by 25% and 30%, respectively. Mortality rates during this period were also reduced by 23% and 44%, respectively. Also according to this analysis, telephone support helped reduce mortality by 31%. Based on this evidence, the European Society of Cardiology (ESC) strongly recommends (Class I, Level A evidence) that heart failure management programs should be multidisciplinary (Table 2).

***Table 2**. Current recommendations on heart failure management programs by the European Society of Cardiology 2021, American College of Cardiology 2022, and Vietnam National Heart Association 2022*

	Recommendation Contents	Level of Recommendation and Evidence
ESC 2021[1]	Patients with heart failure are recommended to enroll in multidisciplinary heart failure management programs to reduce the risk of heart failure hospitalization and mortality.	I A
	Both home-based and clinic-based management programs improve outcomes and are recommended to reduce the risk of heart failure hospitalization and mortality.	I A
AHA/ACC/HFSA 2022[32]	For high-risk heart failure patients, especially those with reduced EF and recurrent admissions, referral to multidisciplinary heart failure management programs is recommended to reduce hospitalization risk.	1
Vietnam National Heart Association 2022	Patient-centered, multidisciplinary, multifaceted heart failure management programs help prevent recurrent and advanced heart failure.	

CURRENT STATUS OF HEART FAILURE MANAGEMENT IN VIETNAM

Gaps in heart failure patient management

As of now, comprehensive epidemiological data on heart failure in Vietnam is lacking. However, based on analysis of the heart failure situation in Southeast Asian countries, the number of heart failure patients is rapidly increasing, particularly with a trend towards earlier onset and worse outcomes compared to other regions globally [33]. If calculated based on the global incidence of heart failure, it is estimated that in Vietnam there are between 320,000 and 1.6 million people currently facing heart failure. Despite progress in diagnosis and treatment, the reality shows that we still encounterlimitations in the process of managing heart failure patients.

Suboptimal medical treatment compared to current Guidelines

Medical treatment is considered the cornerstone for all heart failure patients, especially those with reduced ejection fraction. The main goals of medical treatment include: (1) reducing mortality, (2) decreasing rehospitalization due to acute decompensated heart failure, (3) improving symptoms and enhancing quality of life. Recommended drugs in heart failure treatment include: angiotensin-converting enzyme inhibitors (ACE-i), beta-blockers (BB), angiotensin receptor-neprilysin inhibitors (ARNI), mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter 2 inhibitors (SGLT2-i). However, there exists a significant gap between recommendations and reality in the utilization of these drugs.

An analysis of 302 outpatient heart failure patients being treated at three hospitals in Ho Chi Minh City (2020) found that the rates of using ACE-i/ARB, BB,

MRA and ARNI were 86.5%, 65.2%, 53% and 4.6%, respectively. Of those, 43.3% of patients were treated with all three foundation drugs. The rates of patients achieving target doses as recommended by the European Society of Cardiology (2016) for ACE-i/ARB, BB and MRA were 12.5%, 6.3%, 53.0%, respectively[34]. Another study at Hanoi Heart Hospital (2018) with 134 outpatient heart failure patients showed that no patient achieved target doses of ACE-i/ARB or BB after 12 months of treatment, although >80% of cases met dose escalation criteria [35]. At An Giang Cardiovascular Hospital, only 15.4% of heart failure patients were treated with allfour foundation drugs, and no patients achieved >50% of target BB dose [36].

Similar to many other Asian countries, the use of devices like implantable cardioverter defibrillators (ICD) and cardiac resynchronization therapy (CRT) in heart failure treatment in Vietnam is still very limited[37]. A report on 500 heart failure patients followed at University Medical Center Ho Chi Minh City recorded only 5 cases with ICD and 2 cases with CRT implantation.

These studies were conducted at leading healthcare facilities with adequate human resources and infrastructure. Therefore, considering lower-level facilities, the proportion of patients accessing proper treatment according to recommendations may be even lower. Figure 1 shows the barriers we are facing in managing heart failure and feasible solutions to these issues.

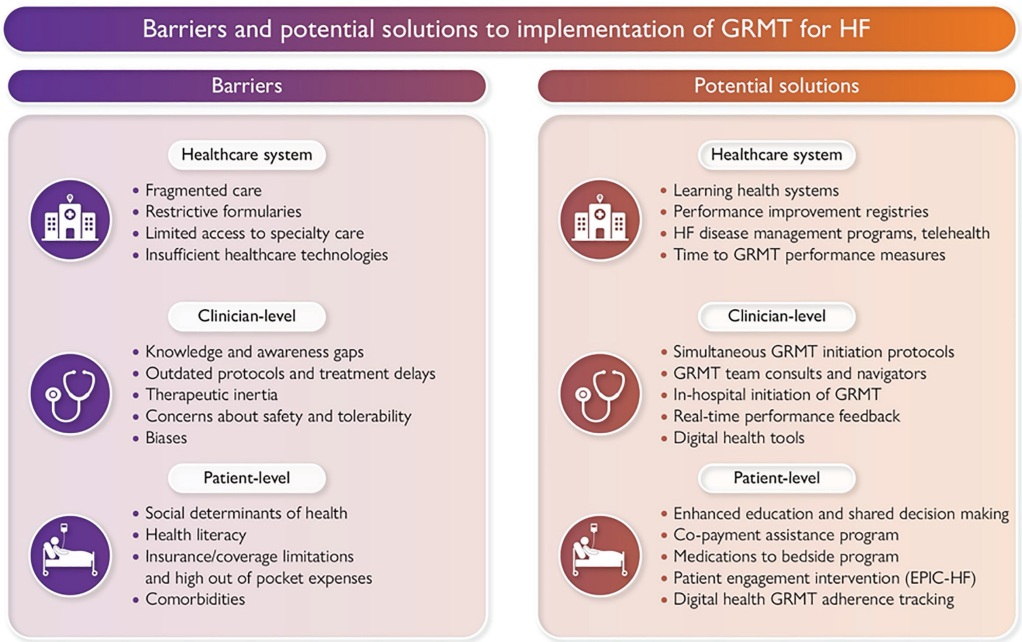


***Figure 1**. Challenges and solutions to guidelined-directed medical therapy for heart failure in clinical practice[38]*

Multidisciplinary approach in heart failure patient management in Vietnam

The multidisciplinary approach in heart failure patient management is still in its infancy and has not yet gained widespread adoption in Vietnam. In this model, the patient is at the center and receives care from healthcare professionals and experts from various disciplines, including general cardiology, interventional cardiology, cardiac arrhythmia, cardiovascular surgery, nutrition, rehabilitation, palliative care, psychological, social and spiritual support, etc. However, the traditional model of one doctor caring for one patient persists in many places. Especially for leading cardiovascular institutes like Ho Chi Minh City Heart Institute or Hanoi Heart Hospital, the coordination of different specialties in

heart failure patient management still encounters numerouschallenges. Specific areas like palliative care, cardiovascular rehabilitation, psychological, social and spiritual support are face shortages in human resources and lack full recognition.

Lack of counseling and health education

Treatment outcomes in heart failure heavily rely on patients' knowledge and self-care skills [39]. Numerous studies show that a majority heart failure patients do not fully comprehend their disease. An analysis of 143 heart failure patients at Vinmec Times City Hospital revealed that only 2.1% of patients correctly understood and properly used medications, while only 9.8% of patients had adequate knowledge of self-care [40]. Another study at An Giang Cardiovascular Hospital demonstrated that even with counseling and education, only 11.1% of heart failure patients fully grasped all knowledge of self-care at home[41]. These studies underscore the importance of effective patient counseling, as it correlates with better behaviors and lower rehospitalization rates[41,42]. Therefore, the development ofcommunity health information networks and enhancement ofhealthcare professionals' awareness and skills in patient education is imperative.

Disruption in outpatient heart failure management

Efforts in heart failure treatment mainly focus on the inpatient stage, with continuous developments in new therapies such as intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO), percutaneous coronary intervention, cardiovascular surgery, continuous renal replacement therapy (CRRT), contributing to reduced in-hospital mortality.. However, a significant challenge lies in the lack of close follow-up or the loss of patients after discharge. Factors contributing to this disconnect between inpatient and outpatient care include an uneven distribution of human resources and medical infrastructure, high outpatient treatment costs, mobility limitations in heart failure patients, epidemic situation, etc. The lost to follow-up rate after 12 months at University Medical Center Ho Chi Minh City is around 30%, a trend observed in many other leading hospitals.

Limited scientific research

It is essential to acknowledge the severe shortage of epidemiological to clinical research on heart failure management and treatment. This information is crucial to assess the burden of heart failure on the community, develop policies, strategies and effective interventions to mitigate the impacts of heart failure on patients and society.

From the above analysis, we clearly see the gaps in heart failure patient management and treatment in Vietnam, significantly affecting treatment outcomes. The rates of rehospitalization or mortality within 30 days after discharge remain quite high, from 23.4% to 34.9% [43,44]. Therefore, the development ofa comprehensive management program to address these challenges is extremely necessary and inevitable in the development process.

Evolution of heart failure management programs

In response topractical needs, many healthcare facilities in Vietnam have initiated the development and implementation of heart failure management programs. Initially, these models were rudimentary and spontaneous, then developed into sophisticated and unique models for each hospital. Collaboration among healthcare facilities has been instrumental in supporting and exchanging experiences, fostering the creation of management networks at both central and local levels. The establishment of the Vietnam Heart Failure Society – Vietnam National Heart Association has played a crucial role in fostering connections and advancing cohesive, professional, and effective national heart failure management programs.

The first heart failure management program in Vietnam was established at Ho Chi Minh City Heart Institute in 2016. Initially, the program focused on outpatient visits with the primary aim of increasing the utilization of guideline-directed medical therapy. An international publication in 2019 on 257 heart failure patients with EF <50% in the heart failure management program at Ho Chi Minh City Heart Institute reported over 85% of patients received health education and over 45% had adequate knowledge and adherence to self-care measures.

The rehospitalization rates after 30 and 60 days were 8.3% and 12.5%, and mortality rates after 30 days and 6 months were 1.2% and 6.4% [45]. However, the model had many limitations, including (1) lack of continuity between inpatient and outpatient care, (2) lack of a multidisciplinary approach, (3) lack of standardized management tools, (4) lack of information technology application. The heart failure management program at Ho Chi Minh City Heart Institute was temporarily suspended in 2021 and is currently undergoing a restart.

Hanoi Heart Hospital was the first to implement a heart failure management program in the North in 2017 and finalized the model in 2019. Initially, the program enrolled outpatients then expanded to include inpatients before discharge. Currently, Hanoi Heart Hospital has made further progress in connecting with hospitals in the region and nationwide, becoming a pioneer in supporting the deployment and scaling up of the model for local healthcare facilities.

The heart failure management model at University Medical Center Ho Chi Minh City commenced in 2018 and reached its finalization in 2020. With the advantages of a multi-specialty hospital with qualified human resources and infrastructure, the management model made breakthroughs to become one of the "exemplary" models. For the first time in Vietnam, some concepts in heart failure management were applied such as "management of heart failure patients from inpatient to outpatient", "multidisciplinary approach in heart failure management" and emphasizing the pivotal role of nurses in the model. In addition, it is also the pioneer in applying information technology to patient management, including the Heart Failure Management app for healthcare professionals, the Heart Failure Management app for patients, and using the REDCap (Research Electronic Data Capture) platform to collect digital data. The hospital also organized regular training courses for nurses nationwide to provide knowledge and skills in heart failure management. In the South, University Medical Center Ho Chi Minh City took the lead in connecting and supporting lower-level healthcare facilities to develop a network for heart failure management. Aiming for international integration, the variables, forms and management tools of the program were built according to European standards (2022) (Data standards for heart failure: the European Unified Registries for Heart Care Evaluation and Randomized Trials (EuroHeart)) [46].

At the National Cardiology Congress in October, 2020, for the first time, the heart failure management program was discussed and attracted attention from many healthcare facilities nationwide. Following the initial successes, many units learned, developed and participated in reporting at subsequent Conferences and Seminars. Sessions on heart failure management programs have become regular at most major Cardiology events of the Vietnam National Heart Association, Vietnam Interventional Cardiology Society, Vietnam Society of Hypertension, Ho Chi Minh City Society of Interventional Cardiology, Ho Chi Minh City Society of Geriatrics, etc.

The Covid-19 pandemic has created unprecedented challenges for heart failure management programs, especially the consequences of disruption and changes in healthcare services. However, the program has provided timely solutions to ensure heart failure patients still receive the best care, including telemedicine, enhancing self-care skills through health education, participating in the vaccination program and assisting patients in accessing healthcare services when needed.

In 2023, the Vietnam Heart Failure Society was established, opening a new chapter for heart failure management programs in Vietnam. The Summit "Comprehensive approaches in heart failure management" organized by the Vietnam Heart Failure Society discussed important issues in heart failure management nationwide, with the participation of international speakers. Many hospitals also sent officials to learn from management models worldwide such as those in Singapore, Thailand, Malaysia, South Korea.

Characteristics of heart failure management programs	**Workflow** Most models adopt a patient-centered approach, providing continuous management from inpatient to outpatient. Initially, the main participants were patients with reduced EF heart failure, then expanded to include mildly reduced EF and preserved EF heart failure.		**Key components in the model**	
			Human resources	**Management tools:**
Currently, there is no universal management model that can be uniformly applied across all healthcare facilities. Therefore, based on specific conditions and characteristics, each hospital can develop a heart failure management program at different levels, ranging from basic to advanced. However, most models share some key common features.	*Inpatient treatment phase* - Diagnose, treat acute heart failure and precipitating factors. Efforts to optimize guideline-directed medical therapy before discharge. - Counsel patients to participate in the heart failure management program. - Multidisciplinary approach: Cardiology, Interventional cardiology, Cardiovascular surgery, Cardiac electrophysiology, Nutrition, Rehabilitation, Palliative care, Psychological support and many other specialties. - Health education for patients: diet, exercise regimen, lifestyle changes, self-monitoring at home and recognizing signs of deterioration. - Develop specific treatment plans and schedule follow-up visits.	*Outpatient treatment phase* - Remind patients about follow-up appointments, continue health education counseling. - Counseling, examining and treating remotely (Telemedicine). - Monitor clinical status and optimize guideline-directed medical therapy.	Mainly comprised of doctors and nurses from Cardiology departments (General Cardiology, Interventional Cardiology, Geriatric Cardiology). Nurses play a pivotal role in connecting patients, families and healthcare professionals, requiring training in counseling and health education skills. In some hospitals, the program collaborates with many other Departments/Units such as Nutrition, Rehabilitation, Palliative Care, Clinical Pharmacy, Social Work, etc.	- Heart failure handbook for patients: Almost all hospitals have a handbook specifically for patients. It contains comprehensive knowledge about heart failure, guidance on self-care at home, and tables to record important parameters (weight, heart rate, blood pressure). This handbook also helps clinic doctors adjust medication doses accordingly. - Management forms: Include important variables that need to be collected to monitor treatment and perform statistics. Currently, University Medical Center Ho Chi Minh City has standardized the variable set according to European Society of Cardiology standards (2022). - Information technology application: Enables faster, more accurate management and easy data extraction when needed. University Medical Center Ho Chi Minh City pioneered the development of a heart failure management app for healthcare professionals in 2020, directly connecting to the hospital's electronic medical record system. Currently, to gain international recognition and enhance connectivity, University Medical Center Ho Chi Minh City has utilized the REDCap (Research Electronic Data Capture) digital data collection platform and expanded it to Thong Nhat Hospital, An Giang Cardiovascular Hospital. In addition, some other units also use the management software developed and sponsored by Novartis, including Gia Dinh People's Hospital, Cho Ray Hospital, Xuyen A General Hospital - Ho Chi Minh City, and Dong Do General Hospital. - Heart failure clinic, telemedicine. - Patient clubs, scientific activities for healthcare professionals.

Challenges in heart failure patient management

Challenges from the healthcare system

- Resource scarcity: This is the biggest challenge in heart failure management, including both human resources and medical equipment, especially at lower levels. The uneven distribution in quantity and quality of resources makes it difficult to build management networks from central to local levels. Healthcare professionals lack comprehensive knowledge and skills in patient management. Weak infrastructure affects outpatient management.

- Costs and financing: Developing and maintaining a heart failure management program requires financial resources, a difficult issue for most hospitals, even large hospitals or private hospitals.

- Lack of guidance and specific procedures on developing a heart failure management program.

- Disagreements between leaders and department heads or between department heads and staff.

- Lack of cooperation from other specialties and fields to implement a multidisciplinary approach.

- Health insurance referral system without connectivity between levels leading to "loss to follow-up" of patients at higher level facilities.

- Lack of heart failure clinics.

Challenges from patients

- Disease diversity: Patients have different causes and degrees of heart failure. This requires a flexible program to suit each specific group.

- Disease complexity: Heart failure is often accompanied by various other clinical issues, requiring coordination of different experts. Heart failure patients have many functional limitations affecting treatment adherence.

- Poor public awareness and cultural/religious differences.

- High costs of heart failure treatment compared to average income per capita.

Therefore, to sustain and develop heart failure management programs, it is necessary to adjust the organizational structure suitable for the healthcare system, available resources, laws and policies, and meet the needs of patients in each locality.

Initial results achieved

As of August 2023, 29 healthcare facilities nationwide have established heart failure management programs, operating in an increasingly professional and connected manner (Table 3). Over 800 nurses have participated in training courses on knowledge and skills for heart failure patient education. It is estimated that over 12,000 heart failure patients have participated in management programs across the country.

In November 2022, Vinmec Central Park Hospital (HCMC) and Vinmec Times City (Hanoi) received certification from ACC (American College of Cardiology) on standardization in heart failure management and treatment. The successful program achieved "2 decreases - 1 increase": decreased rehospitalization rate from 18% to nearly 0%, decreased average length of stay from 8 days to 4 days, and improved patients' quality of life. This accomplishment marked Vinmec as the first healthcare system in Asia with two certified hospitals.

Some hospitals have been honored with the Get with The Guidelines – Heart Failure Award from AHA (American Heart Association): Hanoi Heart Hospital (Silver Plus), Gia Dinh People's Hospital, Hue Central Hospital, Hue University Medical Center, Tam Anh Hospital (Bronze Plus).

Many hospitals have reported initial results after implementing the heart failure management program.

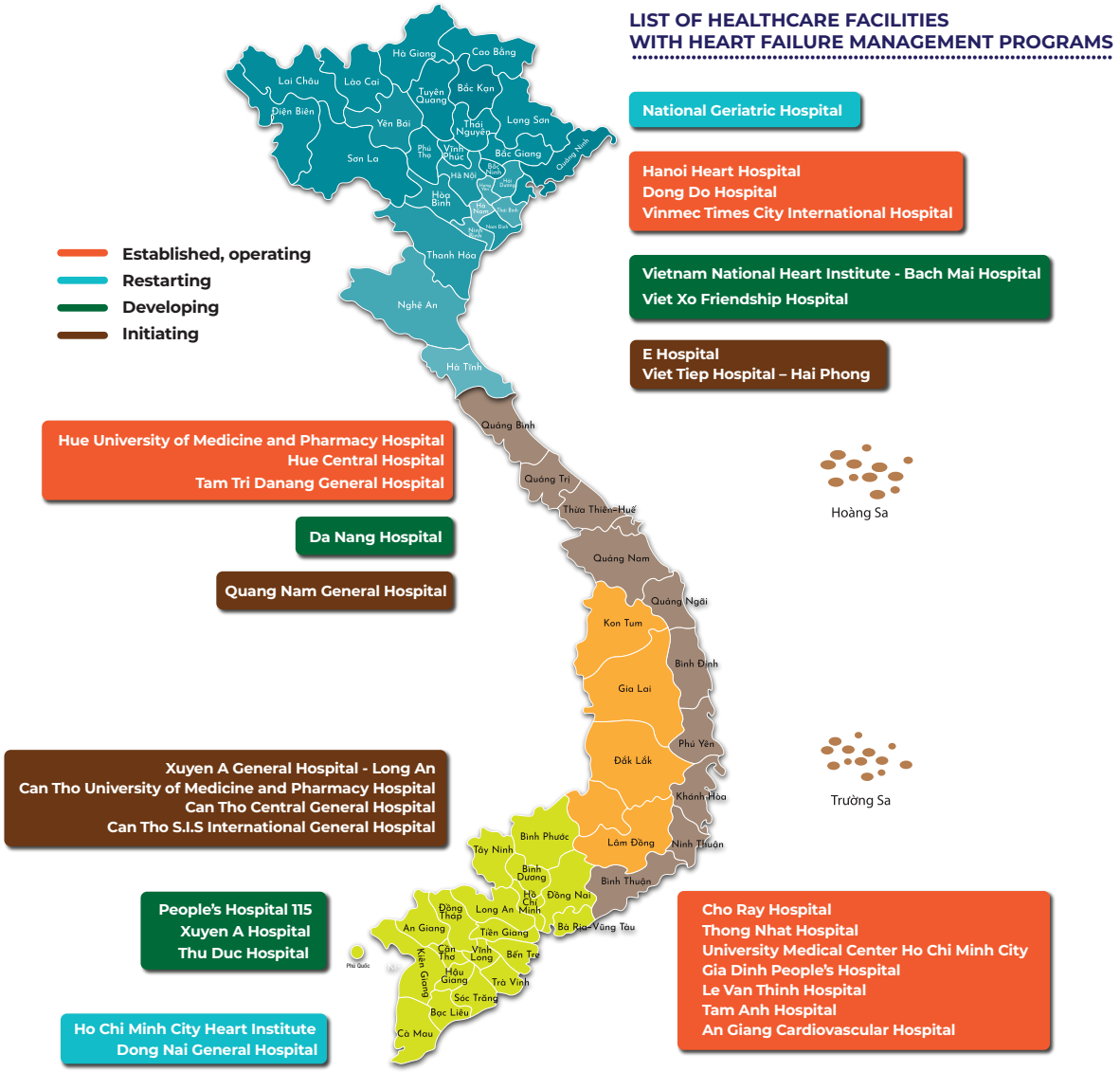
- Hanoi Heart Hospital: From September, 2019 to March, 2021, 1131 patients participated in the heart failure management program. The use rates of BB, ACE-i/ARB/ARNI and MRA were 74.3%, 80.9% and 69.5%, respectively. After an average follow-up of 10.59 months, the medication use rates were 86.7%, 86.5% and 68.9%, respectively. Rehospitalization and mortality rates were 17.8% and 1.9% [47].

- University Medical Center HCMC: As of 08/2023, the total number of patients in the heart failure management program was 918, with 100% of patients counseled and provided health education before discharge. The use rates of ACE-i/ARB/ARNI, ARNI, BB, MRA and SGLT2-I before discharge were 87%, 66%, 74% and 78%, respectively. Of those, the rate of

patients treated with 4 foundation medications before discharge was 50%. The 30-day rehospitalization and mortality rates were 9.6% and 0.5%.

- Gia Dinh People's Hospital: The effectiveness of the heart failure management program is evident through increased use of heart failure medications at discharge and after 3 months: BB (94.2% and 96.1%), ACEI-i/ARB (65.4% and 51.9%), ARNI (21.1% and 44.2%), MRA (82.7% and 86.6%), SGLT2-i (5.8% and 51.9%). The rates of achieving 100% target doses after 3 months for BB, ACE-i/ARB, ARNI and MRA were 23.8%, 26.9%, 5.8% and 57.7%, respectively. NT-proBNP levels decreased significantly (5555 ng/L vs 1983 ng/L, p<0.01), left ventricular ejection fraction improved (29.4% vs 38.1%, p<0.01). The 3-month rehospitalization rate was 21.5%, including non-cardiovascular causes and elective admissions for angiography and PCI.

- An Giang Cardiovascular Hospital: After 4 months, 195 patients participated in the program, mostly mildly reduced EF heart failure. The use rates of ACE-i/ARB/ARNI, BB, MRA and SGLT2-I at discharge were 96%, 5%, 80% and 76%, respectively. The 30-day rehospitalization and mortality rates were 7.1% and 1.4%.



STANDARDIZING THE HEART FAILURE MANAGEMENT MODEL AND FUTURE DEVELOPMENT DIRECTIONS

What actions have been, are being, and will continue to be taken in the world?

The world's real knowledge and data on the importance and impact of heart failure on individual patients and the entire population are key things every country needs to recognize. Despite housing the majority of the world's population in Asia, the majority of the heart failure data at present originates from Europe and North America [48].

In Asia, some of the first registry studies came from Japan [49] and South Korea [50]. The CHART-1 study in Japan enrolled 1,278 heart failure patients with left ventricular ejection fraction <50% or left ventricular end-diastolic diameter >55mm, or at least 1 episode of acute decompensated heart failure. This study recorded 1-year all-cause mortality of 13% in the group with NYHA II-IV and LVEF ≤40%, and 21% in the group with NYHA III-IV and LVEF ≤35%. The study also showed the status of guideline-directed medical therapy use, with 70% and 28% of patients taking ACEI/ARB or BB, respectively [49]. The KorAHF study in South Korea with 2,066 patients after 1 year also showed high in-hospital mortality at 6.1%. For discharged alive patients, all-cause mortality rates at 30 days and 180 days were 1.2% and 9.2%, respectively. Rates of rehospitalization for worsening heart failure at 30 days and 180 days were 6.4% and 24%, respectively [50]. In addition to these registry studies, there is also the multinational ASIAN-HF study enrolling both heart failure patients with reduced and preserved ejection fraction [51]. At the same time, many regions (such as Central Asia and East Asia) as well as many countries (Malaysia, Thailand) have also reported long-term follow-up data on heart failure patients, which are important for us to have a clearer view of current trends and risk factors for heart failure [52, 45].

As previously mentioned, the majority of heart failure management programs continue to be fragmented, inconsistent, and devoid of well-defined strategies. In July 2019, the European Society of Cardiology approved the initial 2-year phase of the EuroHeart program [46]. This is a collaboration between national registry studies and an effort between Cardiology Societies to enable continuous patient care monitoring that benefits patients and the healthcare system of each country. The program starts with standardizing a core data set for the most common diseases, including heart failure. The standardized heart failure core data set was drafted quite meticulously, starting from reviewing 1,715 papers to select 372 eligible ones, from which 189 initial variables were extracted, including 107 from meta-analyses and 82 from clinical practice guidelines. These variables were further analyzed using the Delphi method to finally agree on 84 variables for Level 1 and 79 for Level 2. All these variables are divided into main sections: (i) demographics, (ii) characteristics and comorbidities, (iii) status on admission, (iv) pre-admission medications, (v) health-related quality of life, (vi) clinical and laboratory measures, (vii) in-hospital management, (viii) discharge characteristics, (ix) discharge medications. After the initial 2-year phase, this program attracted 194 centers from 9 countries, including Singapore. The next 2-year phase is underway and expected to expand to a total of 15 countries, forming a large enough network to initiate robust clinical research projects capable of impacting current recommendations.

Determining the effectiveness of the program also requires the implementation of a practical patient follow-up strategy, in addition to the development of a standardized data system. For hospitalized heart failure patients, the transition from inpatient to outpatient is a sensitive period due to the highest risk of heart failure rehospitalization during this time [32]. Having an optimal plan will help reduce rehospitalization and improve quality of life. Higher risk patients should receive follow-up via phone, home visits or clinic visits, or remote monitoring within 72 hours after discharge. After a heart failure hospitalization, patients should have a follow-up appointment within 7-10 days after discharge. At the same time, patients themselves or their families also need thorough counseling on management

plans if any sudden health changes occur [53]. Table 3 summarizes the important components of a care transition plan.

***Table 3**. Important components of a care plan during the pre- and immediate post-discharge period*

A care plan should specifically address the following:
Review precipitating factors causing worsening heart failure requiring hospitalization
Adjust diuretic therapy based on volume status (including weight assessment) and electrolytes
Check safety labs pertinent to medications (like electrolytes after initiation or uptitration of guideline-directed medical therapy)
Optimize guideline-directed medical therapies, including: **- Having a plan to restart medications held during hospitalization** **- Having a plan to initiate remaining medications** - Having an uptitration plan to reach target or maximally tolerated doses
Reassess heart failure knowledge and evaluate adherence to pharmacological and non-pharmacological therapies, including diet and physical activity
Reevaluate high risk factors that may affect post-discharge outcomes such as: **- Comorbidities (kidney disease, lung disease, diabetes, psychological and substance use disorders)** **- Limitations in social support** - Cognitive impairment
Necessity of surgery or device-based therapies; and refer for cardiovascular rehabilitation when appropriate
Transition appropriate patients to palliative care specialists

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Results of the Heart Failure Management Program at Hue Central Hospital after 1 year of implementation

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▶ Received: 26 October 2023
Accepted: 28 November 2023
Published online: 30 November 2023

To cite: Nguyen TD, Tran TN, Pham QT, *et al. J Vietnam Cardiol 2023*;**107E**:18-24

ABSTRACT

Background: Heart failure is the consequence of many diseases that cause structural and/or functional disorders of the heart. Having a heart failure management program is essential to ensure patients receive optimal care and can improve clinical prognosis.

Objectives: 1. Describing real-world results of the Heart Failure Management Program at Hue Central Hospital; 2. Surveying the current status of prescribing drugs according to guidelines to treat heart failure in the program.

Studying methods: Implementation time is from July 2022 to September 2023 at Hue Central Hospital. The study design is a cross-sectional descriptive study with short-term longitudinal follow-up for at least 6 months.

Results: There were 734 patients including 445 men (60.6%) and 289 women (39.4%) with a mean age of 65.6 ± 15.4 years. The average follow-up time was 5.16 ± 3.53 months (the longest was 14 months). The prescription rates of ARNi, BB, MRA, SGLT2i were 55.9%, 77.9%, 78.7% và 76.5% respectively. After 6 months of management, these rates are 58.8%, 86.8%, 83.8%, 83.1% respectively. The average initial ejection fraction of the group of patients followed over 6 months was 34.5 ± 6.9%, after 6 months of management this rate increased to 39.9 ± 11.9%. The rate of rehospitalization due to heart failure decreased by 27.2% in the group of patients followed for more than 6 months. The mortality rate gradually decreased over time, from 4.4% to 1.7% after 6 months of follow-up.

Conclusion: The rate of optimal drug use in heart failure treatment improves over time, the death rate gradually decreases with each stage, but a lot of management measures need to be strengthened to avoid losing track of patients.

Keywords: Heart failure, management, treatment.

INTRODUCTION

Heart failure is an increasingly common condition globally. About 1-4% of hospital admissions for all causes in developed countries are initially diagnosed as heart failure. The average hospital stay for heart failure worldwide is about 5-10 days. Heart failure patients have a high risk of rehospitalization. About 1 in 4 patients over 65 years old need to be rehospitalized within 30 days[5] and about 44% of patients need to be rehospitalized at least once within 1 year [17]. There are many reasons why

heart failure patients need to be rehospitalized, of which 2/3 are potentially modifiable [2]. There are still gaps in clinical practice that affect the efficacy of treatment and quality of life of patients. Therefore, a heart failure management program will be an opportunity to optimize treatment for patients, as well as make the patient journey less fragmented, helping to monitor patients more closely. The efficacy of heart failure management programs has been demonstrated by pooled data from 29 clinical trials showing that heart failure hospitalization rates decreased by 27%, all-cause mortality decreased by 25%, and all-cause hospitalization decreased by 20%[7]. Based on this scientific basis, we conduct this topic with the following objectives:

1. Describe the real-world results of the Heart Failure Management Program at Hue Central Hospital.

2. Survey the status of heart failure treatment prescription according to recommendations in the program.

OBJECTIVES AND METHODS

Patient selection criteria: Heart failure patients ≥ 18 years old being managed in the inpatient and outpatient heart failure management program, with left ventricular ejection fraction ≤ 50%.

Exclusion criteria: Patients lost to follow-up in the management program for ≥ 6 months.

Time and place: From July 2022 to September 2023 at the Cardiovascular Center - Hue Central Hospital.

Study design: Cross-sectional descriptive study with short-term longitudinal follow-up for at least 6 months.

Variables: Variables collected using a unified form for outpatients in the heart failure management program diagnosed with heart failure, retrospectively retrieving data from patients' outpatient records. Research variables include:

- Clinical symptoms of heart failure according to NYHA classification, systolic blood pressure, diastolic blood pressure, heart rate, heart rhythm at follow-up visits.

- Echocardiographic measurements of left ventricular end-systolic diameter (Dd, Ds), ejection fraction (EF) calculation, and estimated pulmonary artery systolic pressure.

- Data on medication use: drug name, dosage, combination of heart failure treatment drugs for each patient at timepoints: after 1 month, after 3 months, after 6 months of treatment in the heart failure program.

- Data on causes of hospitalization, triggering factors for acute heart failure exacerbations in patients (if any).

- For patients lost to follow-up after a period of treatment in the program, contact them by phone to ask about the reason for dropout and current treatment status.

Data analysis and processing: Qualitative variable data are described as percentage, quantitative variables are expressed as mean ± standard deviation. Data analysis uses SPSS 26.0 software. Mann-Whitney U test and Kruskal-Wallis ANOVA are used for non-parametric tests, with p <0.05 considered statistically significant.

RESULTS

***Table 1**. General characteristics of study subjects*

Characteristics	Reduced EF		Mildly reduced EF		Total		p
	n	%	n	%	n	%	
Male	309	42.1	136	18.5	445	60.6	**0.028**
Female	178	24.3	111	15.1	289	39.4	
Total	487	66.3	322	39.4	734	100.0	
Age (years)	65.1 ± 15.6		66.7 ± 15.0		65.6 ± 15.4		0.186

Characteristics	Reduced EF		Mildly reduced EF		Total		p
	n	%	n	%	n	%	
Systolic BP (mmHg)	122.01 ± 23.3		124.42 ± 25.4		122.9 ± 24.1		0.402
Diastolic BP (mmHg)	73.2 ± 12.4		72.4 ± 11.6		72.9 ± 12.1		0.576
Heart rate (bpm)	90.9 ± 17.8		84.9 ± 16.5		88.6 ± 17.6		**0.004**
Ejection fraction (%)	31.7 ± 6.09		45.82 ± 2.8		36.4 ± 8.5		**< 0.001**
Creatinine (µmol/L)	174.8 (103.8)		135.4 (90)		161.5 (100.4)		0.084
NT-proBNP (pg/mL)	10882.1 (5416)		6661.6 (2301)		9560.7 (4669)		**0.005**

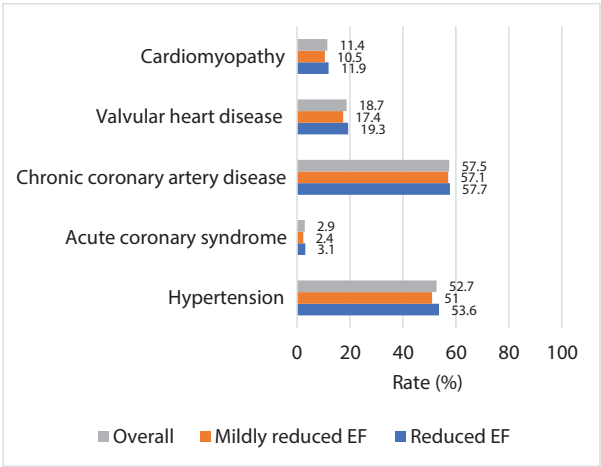

***Figure 1**. Causes of heart failure*

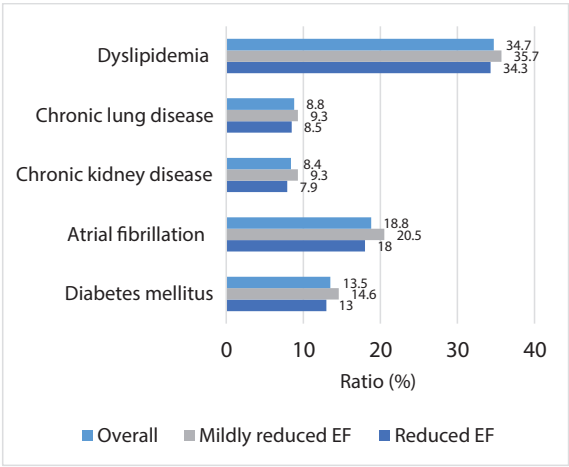

***Figure 2**. Comorbidities*

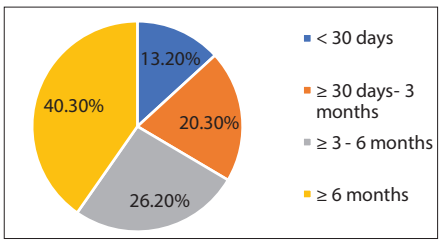

***Figure 3**. Patient statistics by follow-up time*

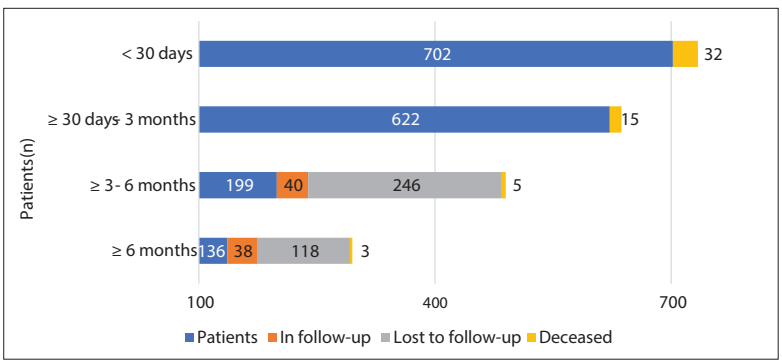

***Figure 4**. Patient follow-up statistics at different timepoints*

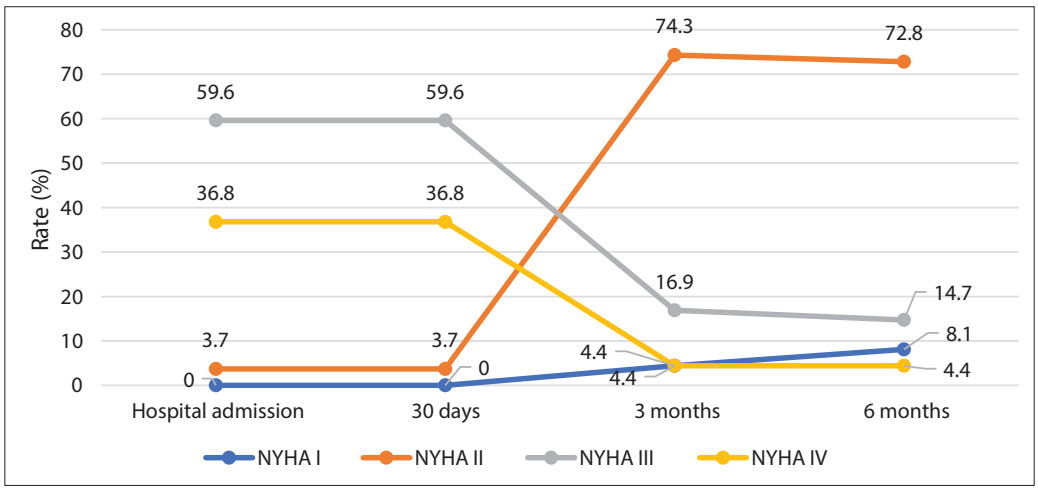

***Figure 5**. NYHA class distribution in ≥6 month group by stage*

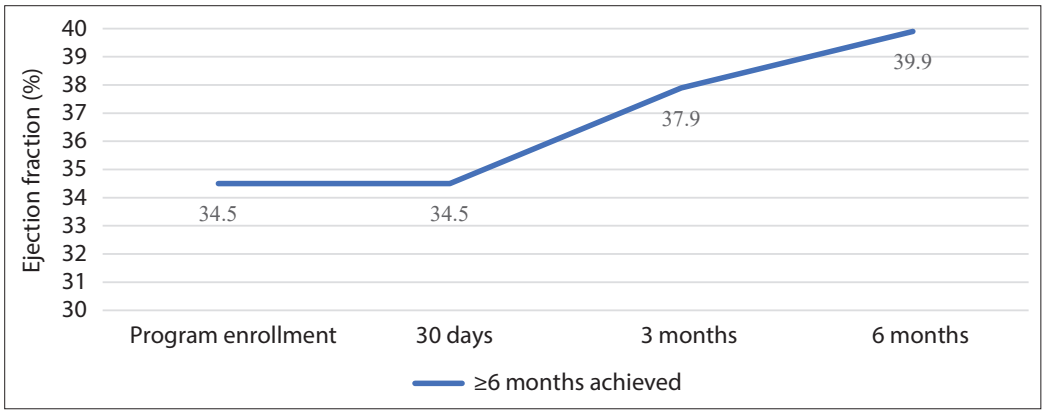

***Figure 6**. Ejection fraction by stage in ≥6 month group*

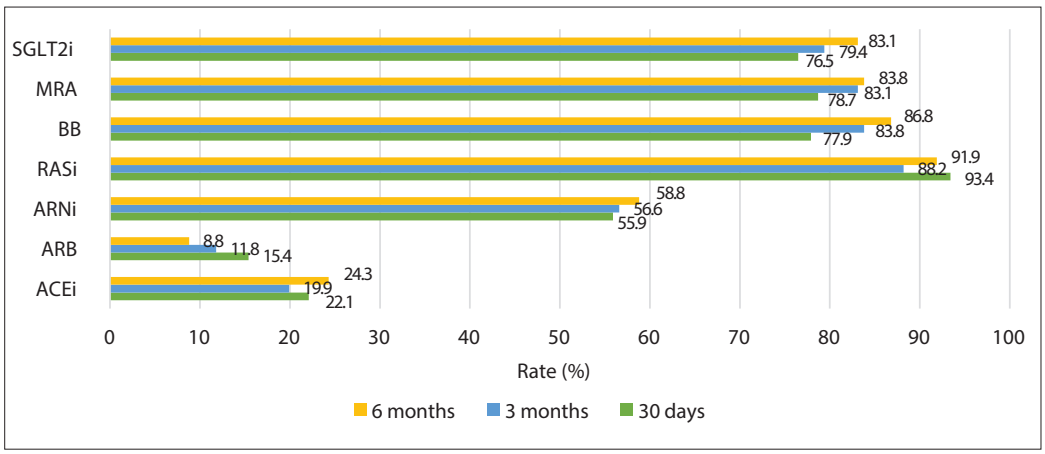

***Figure 7**. Medication usage rates in ≥6 month group*

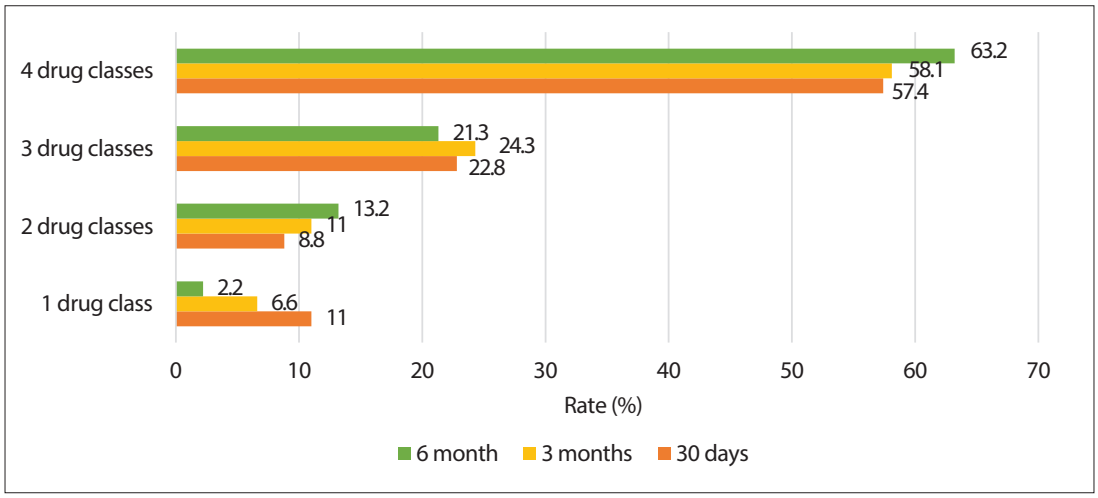

***Figure 8**. Proportion using number of drug classes in ≥6 month group*

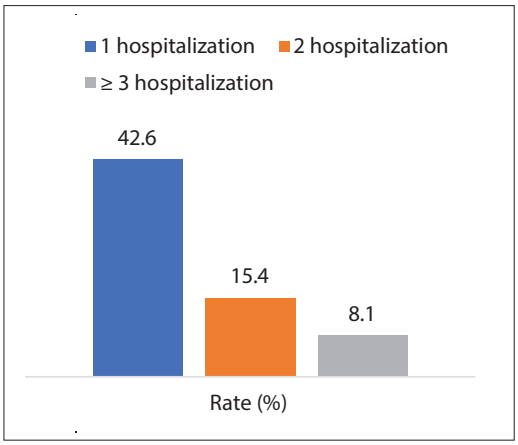

***Figure 9**. Heart failure rehospitalization rates in ≥6 month group*

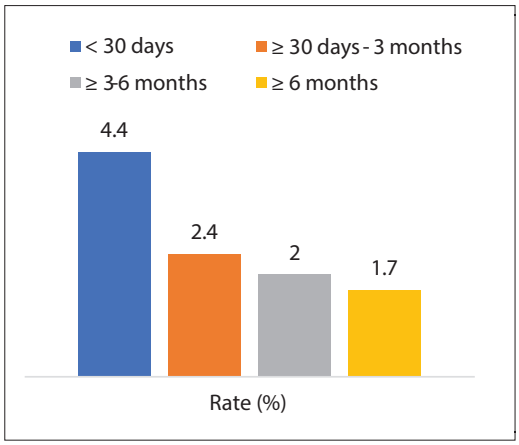

***Figure 10**. Overall mortality rates by stage*

DISCUSSION

Clinical and paraclinical characteristics

The mean systolic blood pressure in our study was 122.9 ± 24.1 mmHg, lower compared to the EFICA study (126 ± 29 mmHg) [16]. High or low blood pressure compared to normal levels is also a factor considered in heart failure treatment and can affect prognosis.

At program enrollment, in the ≥6 month group, the initial EF was 34.5 ± 6.9%. After 3 and 6 months of treatment, EF was 37.9 ± 12.1% and 39.9 ± 11.9% respectively, with statistically significant changes, compared to Vu Quynh Nga et al. where initial EF and after 1 year follow-up were 37.93 ± 8.58% and 40.26 ± 9.44% respectively[14].

The mean follow-up time in our study was 5.16 ± 3.53 months (maximum 14 months). In reality, good or poor treatment adherence depends on prescription of ACEi/ARB/ARNi, BB, MRA and SGLT2i [1].

Prescription rates of drug classes

The STRONG-HF study showed that early combination of all drug classes along with close monitoring and rapid up-titration over a short time was proven safe and helped improve patients' quality of life, as well as reduced rehospitalization and all-cause mortality rates [9]. Therefore, complete combination of all

4 drug classes from the beginning if no contraindications is necessary and beneficial for patients.

The TOPCAT study in patients with EF ≥ 45% showed spironolactone reduced heart failure hospitalizations in the EF < 55% group, while cardiovascular mortality was equivalent (not including all-cause mortality)[13]. The mineralocorticoid receptor antagonist prescription rate in our study was 78.7% initially, increasing to 83.8% after 6 months, higher than the THAI ADHERE study (17.1% and 12.5% respectively), and higher than Vu Quynh Nga et al. at 68.9%[14].

Results from the PARADIGM-HF study showed the ARNi group was superior in reducing cardiovascular mortality and heart failure hospitalizations compared to ACEi[8]. Therefore, ARNi is preferred over ACEi and ARB. In our study, the proportion of patients taking ARNi at 30 days was 55.9%, much higher than ACEi (22.1%) and ARB (15.4%). After 6 months, ARNi prescription reached 58.8%, while only 8.8% and 24.3% of patients used ARB and ACEi. Additionally, overall ACEi/ARB/ARNi use at baseline was 93.4%, and 91.9% after 6 months, much higher than the THAI ADHERE study (25.7% and 28.1% respectively) and Vu Quynh Nga et al. at 86.52%[10, 14].

The baseline beta-blocker prescription rate in our study was 77.9% in the ≥6 month group, increasing to 86.8% after 6 months, higher than the THAI ADHERE study (26.1% and 24% respectively), the US ADHERE trial (56%; 64%) and EHFSII (43.2%; 61.4%)[10, 11].

Data from the EMPEROR-Reduced and DAPA-HF studies demonstrate that SGLT2i are effective in improving symptoms and prognosis in heart failure patients with reduced and mildly reduced ejection fraction[6, 12]. The proportion of patients taking SGLT2i within 30 days in our study was 76.5%, increasing to 83.1% after 6 months. However, as these drugs are only partially covered by insurance and have high costs compared to average income, they are not easily accessible for most patients.

To achieve treatment goals in heart failure, treatment optimization is very important[4]. Compared to other studies like QUALIFY, a multinational study of 6669 patients over 36 countries within 15 months post-discharge evaluating guideline-directed medical therapy adherence, results showed 22% of patients were not prescribed ACEi/ARB, beta-blockers, or MRA without any contraindications. Only 55% of patients achieved ≥50% of target doses of ACEi/ARB and beta-blockers. Just 23% of reduced ejection fraction heart failure patients reached target doses of ACEi/ARB and beta-blockers[3].

Heart failure rehospitalization and mortality rates and patient adherence

Earlier combination of more drug classes in heart failure treatment reduces mortality and rehospitalization compared to incomplete regimens[15]. For heart failure rehospitalizations, in our ≥6 month group, the proportion with 1 hospitalization was 42.6%, decreasing to 15.4% for 2 hospitalizations, and 8.1% for ≥3 hospitalizations. Our study also showed 57.4% of patients received complete combination of 4 drug classes within 30 days of enrollment, increasing to 63.2% after 6 months. Additionally, in our study, mortality rate was 4.4% in the <30 day group, declining over stages to 2.0% in the 3-6 month group, and only 1.7% in the ≥6 month group, demonstrating the management program's effectiveness. Pooled data from 29 global clinical trials showed a 27% reduction in heart failure hospitalizations, 25% reduction in all-cause mortality with a multidisciplinary team-based heart failure program[7].

Our study indicates the highest lost to follow-up rate was in the 3-6 month period, with 246 patients (50.2%). High loss to follow-up is due to patients returning to primary care without referral back to higher levels per insurance, low health awareness in patients, geographical barriers, etc. causing fragmentation after referral to outpatient management.

CONCLUSION

The optimal medication usage rate in heart failure treatment improved over time, mortality rates declined in each stage, however more management measures are needed to prevent patient loss to follow-up.

Lessons learned:

- The program succeeded in patient management, helping to optimize treatment as well as reducing mortality and rehospitalization rates after implementation.

- The management network should be expanded to provincial and district levels to avoid patient loss to follow-up and fragmentation.

- Promote education and training of healthcare staff in the program, enhance monitoring, supervision and experience learning during program implementation.

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Treatment characteristics and factors associated with heart failure with improved ejection fraction in the heart failure patient management program at Hanoi Heart Hospital

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▶ Received: 27 October 2023
Accepted: 28 November 2023
Published online: 30 November 2023

To cite: Vu QN, Tran TH, Nguyen TQT. *J Vietnam Cardiol 2023*;**107E**:25-36

ABSTRACT

Background: Many patients with heart failure (HF) with reduced ejection fraction (HFrEF) have improved or restored left ventricular ejection fraction (LVEF). Within context heart failure with recovered or improved ejection fraction (HFiEF) has been proposed as a new category of HF. Data on clinical characteristics, outcomes, and medical, interventional, surgical, or related factors in patients with heart failure with improved ejection fraction (HFiEF) are scarce.

Methods: Descriptive analysis study, the period from May 2021 to November 2022 satisfies the criteria for heart failure with reduced or slightly reduced ejection fraction and is hospitalized for inpatient treatment, discharged from the hospital to participate in the patient management program heart failure for at least 3 months.

Results: 488 patients were included in the study, the average age of the improved group and the remaining group were 64.35±13.74 and 64.39±13.55, the proportion of women in the improvement group and the remaining group are 50% and 41.6%. The rate of use of RAS system drugs and beta blockers improved by 96.4% and 89.3%, respectively, higher than the other group's 86.1% and 74.5%, which is statistically significant. The rate of MRA, SGLT2-i in the improved group and the remaining group was 63.1%; 59.5% and 64.9%; 61.9%. The rate of using 2 drugs including RAS and beta blockers in the improvement group (85.7%) was statistically significantly higher than the other group (67.6%). The area under the ROC curve of admission EF, LVEDVi, LVESVi in predicting improvement was 0.687 (95% CI 0.640-0.730; p< 0.001), respectively; 0.531(95% CI 0.462-0.599; p=0.378); 0.543 (95% CI 0.467-0.611; p=0.211). If only calculated on the total number of patients with EF ≤ 40%, the Kaplan Meier chart of CABG, heart valve surgery and percutaneous coronary intervention predicting improvement in heart failure after 3 months are all statistically significant.

Conclusion: The rate of heart failure improved in the program was 17.2%. EF at admission, rate of use of RAS system drugs, beta blockers, rate of use of 2 RAS system drugs and beta blockers, percutaneous

coronary intervention, CABG surgery or Heart valve surgery is significant in predicting improved heart failure in the heart failure program at Hanoi Heart Hospital.

Keywords: heart failure, guidelines, heart failure outpatient program, heart failure improved ejection fraction.

INTRODUCTION

Heart failure is characterized by multiple relapses, with an expected one-year hospital readmission rate of over 50% and a one-year mortality rate of over 30%[1,2]. Outpatient management for heart failure patients is multimodal and includes several steps listed in the American College of Cardiology/ American Heart Association (ACC/AHA) Heart Failure Management Guidelines[3].

Many patients with reduced ejection fraction heart failure (HFrEF) have improved or recovered left ventricular ejection fraction (LVEF). In the context of improved ejection fraction, it has been proposed as a new type of heart failure. Data on clinical characteristics, outcomes and medical, interventional, surgical treatment or related factors in patients with improved ejection fraction heart failure (HFiEF) are still scarce. We conducted a study with the goal of:

Determining the clinical, subclinical characteristics and treatment characteristics of patients with improved ejection fraction heart failure in the Hanoi Heart Hospital heart failure patient management program.

SUBJECTS AND METHODS

Inclusion criteria: Patients with reduced or mildly reduced ejection fraction heart failure who were hospitalized for inpatient treatment, discharged and participated in the Hanoi Heart Hospital heart failure management program continuously for at least 3 months.

Study period: From May 2021 to November 2022.

Method: Cross-sectional, prospective analysis.

Variables:

Collecting data according to a unified sample of eligible patients who underwent inpatient treatment and data on participation in the outpatient heart failure management program.

Patients enrolled in the Heart Failure Management Program from May 2021 to November 2022, the time of enrollment in the study did not start at the same time, however at the time the patient was admitted was considered the initial follow-up time. Excluding patients who were not followed up for at least 3 months in the Heart Failure Management Program.

Clinical symptoms of heart failure according to NYHA classification, HA parameters, heart rate at each follow-up.

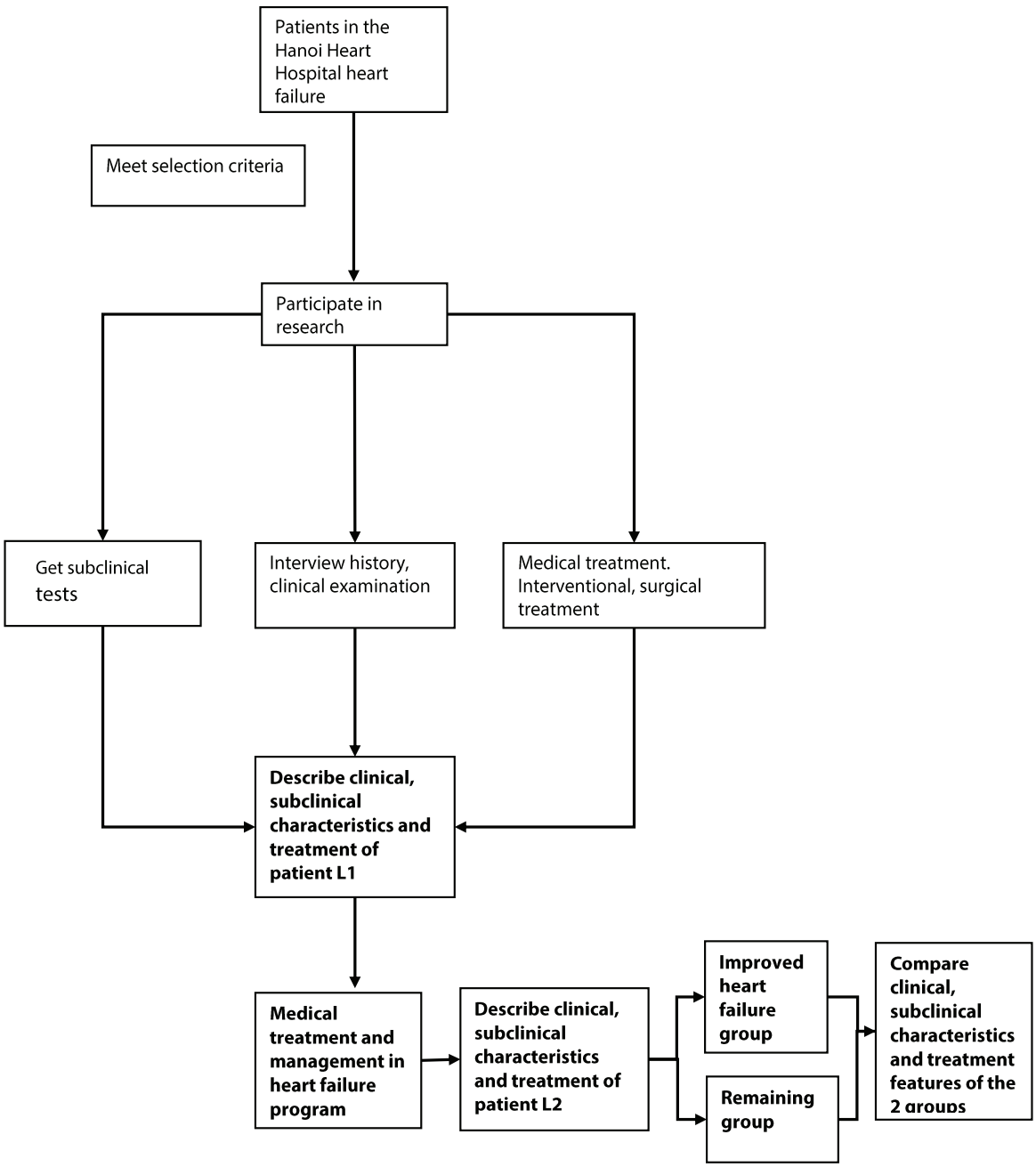
Investigating comorbidities or medical history (localized ischemic heart disease, hypertension, atrial fibrillation, stroke history, diabetes,, heart valve disease, chronic lung disease, dilated cardiomyopathy, hypertrophic cardiomyopathy, congenital heart disease, pacemaker implantation, heart surgery), current medications (digoxin, diuretics, ACE inhibitors, ARBs, beta-blockers, aldosterone antagonists, SGLT2 inhibitors, etc.), medication compliance (regular, irregular, non-adherent), changes in medications at each follow-up timepoint.

Recording echocardiogram results assessing left ventricular end-diastolic diameter (Dd), end-systolic diameter (Ds), calculating ejection fraction (EF), estimating pulmonary artery systolic pressure. Recording electrocardiogram results and blood tests during follow-up.

Collecting data on medication use: drug name, dosage, combination of heart failure drugs for each patient within 12 months at timepoints: initial follow-up, 1 week, 1 month, 3 months, 6 months, 12 months of treatment in the heart failure program.

Collecting data on causes of hospitalization, triggering factors for acute heart failure exacerbations in patients (if any).

Study schema:



L1: Timepoint of inpatient treatment, initial study timepoint.

L2: Timepoint after 3 months since discharge.

Statistical Analysis: Described as percentage for categorical variables, mean ±SD for quantitative variables; All collected data were stored and analyzed using SPSS 24.0 statistical software; The collected data of the study were processed according to medical statistical algorithms using STATA 12.0 software; Mann–Whitney U tests and Kruskal-Wallis analysis of variance (ANOVA) tests were used as appropriate nonparametric parameter tests and a p value <0.05 was considered significant.

Research Ethics: Obtained patient consent,

patient information was kept confidential and study results were for scientific research purposes.

Here is my translation of the Vietnamese results section into English:

RESULTS

From May 2021 to November 2022, 488 patients were included in the study, of which 84 patients had improved ejection fraction heart failure after 3 months, accounting for 17.2%. The average age of the improved group and remaining group was 64.35±13.74 and 64.39±13.55, respectively; the proportion of females in the improved group and remaining group was 50% and 41.6%, respectively. The patients were divided into 2 groups for comparison: improved group and remaining group. We have the following observations:

***Table 3.1**. Epidemiological characteristics and causes of heart failure*

	Improved heart failure group		Remaining group		p
	n	%	n	%	
Epidemiological, clinical characteristics					
Female	42 (50.0)		168(41.6)		0.098
Male	42 (50.0)		236(58.4)		
Age (M±SD)	64.35±13.74		64.39±13.55		0.551
Comorbidities					
Hypertension	45	54.2	222	55.0	0.498
Type 2 diabetes	24	28.6	117	29.0	0.529
Chronic kidney disease	11	13.1	75	18.6	0.149
COPD or asthma	**2**	**5.9**	**24**	**2.4**	**0.043**
Main causes of heart failure					
Ischemic heart disease	**40**	**47.6**	**203**	**50.4**	**0.046**
Dilated cardiomyopathy	23	27.4	102	25.2	0.956
Valvular heart disease	21	25.0	97	24.0	
Chemotherapy-induced cardiomyopathy	0	0	1	0.2	
Hypertrophic cardiomyopathy	0	0	1	0.2	

Observations: There was no difference in gender, age, risk factors of alcohol drinking or smoking between the two groups; comorbidities such as hypertension, type 2 diabetes, chronic kidney disease were higher in the remaining group but without statistical significance compared to the improved group; the common causes of heart failure were ischemic heart disease, dilated cardiomyopathy and then valvular heart disease.

***Table 3.2**. Characteristics of rehospitalization*

	Improved heart failure group		Remaining group		p
	n	%	n	%	
Rehospitalization within 1 year	**8**	**9.5**	**82**	**20.3**	**0.012**
Number of rehospitalizations within 30 days (M±SD) (min-max)	0.01±0.11		0.06±0.29		0.177
Number of rehospitalizations within 1 year (M±SD) (min-max)	**0.14±0.49**		**0.29±0.74**		**0.043**

Observations: The improved group had a statistically significantly lower rate of rehospitalization and number of rehospitalizations within 1 year compared to the remaining group.

***Table 3.3**. Clinical and subclinical characteristics*

		Improved heart failure group	Remaining group	p
Clinical characteristics				
Heart rate_1 (M±SD)		77.62±11.75	78.84±16.69	0.605
SBP_1 (M±SD)		**88.52±18.96**	**90.27±21.57**	**0.035**
Subclinical characteristics				
NT proBNP 1 (M±SD)		6929.80±8756.24	5413.12±6996.60	0.294
Troponin Ths 1(M±SD)		271.28±941.08	499.09±1245.66	0.208
Creatinine 1(M±SD)		88.97±31.68	105.13±51.51	0.115
Hb 1(M±SD)		136.54±19.15	133.534±20.47	0.221
LDL 1(M±SD)		**1.57±0.84**	**1.405±0.74**	**< 0.001**
Echocardiogram characteristics				
EF_1(M±SD)	**EF(M±SD) (min-max)**	**32.23±5.55**	**37.62±8.73**	**< 0.001**
	EF ≤ 30%	**32(38.1)**	**122 (27.7)**	**< 0.001**
	30%< EF ≤ 40%	**52(61.9)**	**128 (31.7)**	
	EF > 40%	**0**	**164 (40.6)**	
LVEDVi_1(M±SD)		141.12±41.73	146.78±49.69	0.469
LVESVi_1(M±SD)		75.31±36.27	82.84±45.64	0.302

Observations: Systolic blood pressure was lower and LDL was higher with statistical significance in the improved heart failure group compared to the remaining group.

***Table 3.4**. Characteristics of guideline-directed medical therapy*

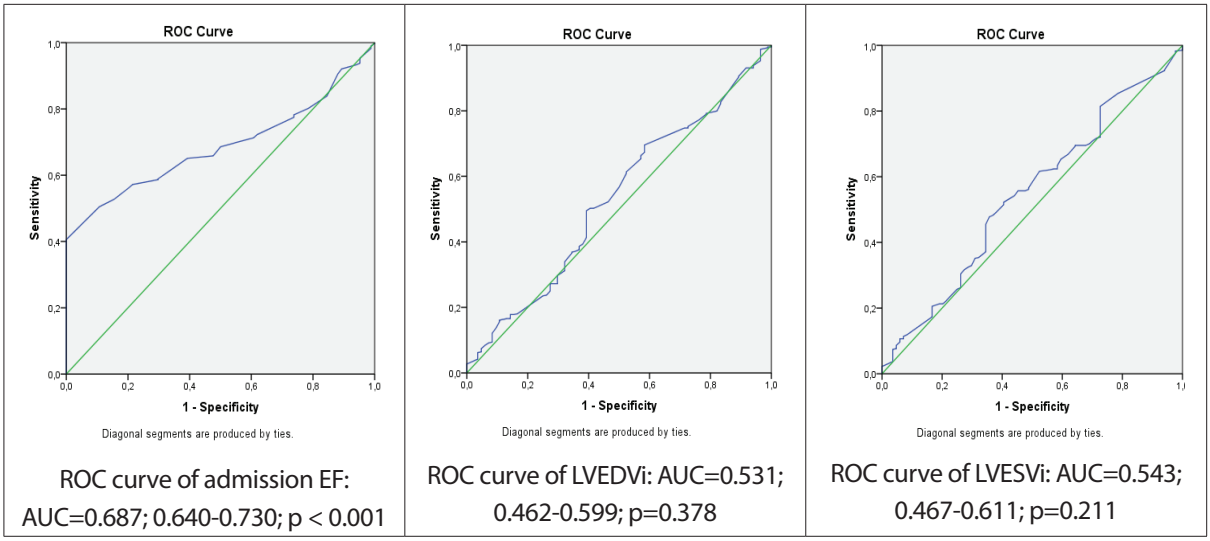
	Improved heart failure group		Remaining group		p
	N=84	%	N=404	%	
1-drug therapy					
ARNI/ARB/ACEI	**81**	**96.4**	**348**	**86.1**	**0.004**
Beta-blocker	**75**	**89.3**	**301**	**74.5**	**0.004**
MRA	53	63.1	262	64.9	0.279
SGLT2i	50	59.5	250	61.9	0.354
2-drug therapy					
ARNI/ARB/ACEI + beta-blocker	**72**	**85.7**	**273**	**67.6**	**< 0.001**
ARNI/ARB/ACEI + MRA	50	59.5	234	57.9	0.442
ARNI/ARB/ACEI + SGLT2i	49	58.3	236	58.4	0.541
MRA + beta-blocker	47	56.0	215	53.2	0.369
MRA + SGLT2i	36	42.9	187	46.3	0.326
Beta-blocker + SGLT2i	46	54.8	195	48.3	0.168
3-drug therapy					
ARNI/ARB/ACEI + beta-blocker + MRA	44	52.4	199	49.3	0.344
ARNI/ARB/ACEI + beta-blocker + SGLT2i	45	53.6	189	46.8	0.155
Beta-blocker + MRA + SGLT2i	47	56.0	215	53.2	0.369
4-drug therapy					
ARNI/ARB/ACEI + beta-blocker + MRA + SGLT2i	32	38.1	153	37.9	0.531

Observations: The rates of using RAS system and beta-blocker drugs, or the rate of using both drugs, were statistically significantly higher in the improved group compared to the remaining group.

***Table 3.5**. Characteristics of achieving half target dose of guideline-directed medical therapy*

		Improved heart failure group (%)	Remaining group (%)	p
RAS inhibitors	ARNI	15.4	24.6	0.002
	AECI	**7.2**	**1.4**	**0.02**
	ARB	**40.4**	**23.7**	**0.04**
	Total	**63**	**49.7**	**0.032**
Beta-blocker		34.5	31.9	0.505
MRA		**30.9**	**39.3**	**0.001**

Observations: The rate of achieving half the target dose for RAS system drugs was statistically significantly higher in the improved group compared to the remaining group.



ROC curve of admission EF: AUC=0.687; 0.640-0.730; p < 0.001

ROC curve of LVEDVi: AUC=0.531; 0.462-0.599; p=0.378

ROC curve of LVESVi: AUC=0.543; 0.467-0.611; p=0.211

***Figure 3.1**. Area under the ROC curve (AUC) to predict improved ejection fraction heart failure of EF, LVEDVi, LVESVi*

Observations: The AUC of EF had statistical significance in predicting improved ejection fraction heart failure.

***Table 3.6**. Univariate and multivariate analysis to predict improved ejection fraction heart failure*

	HR	95% CI	p	HR	95%CI	p
	Univariate model			Multivariate model		
Admission SBP	**1.016**	**1.006-1.026**	**0.001**	**1.014**	**1.004-1.024**	**0.007**
Admission EF	**0.936**	**0.913-0.960**	**< 0.001**	**0.936**	**0.909-0.963**	**< 0.001**
PCI performed	0.729	0.426-1.249	0.250			
AF ablation performed	1.358	0.763-2.417	0.298			
ICD implanted	0.340	0.047-2.463	0.286			

	HR	95% CI	p	HR	95%CI	p
	Univariate model			Multivariate model		
Surgery performed	**2.403**	**1.330-4.334**	**0.004**	**0.695**	**0.344-1.404**	**0.031**
Rehospitalization within 1 year	**2.493**	**1.202-5.172**	**0.014**	0.503	0.233-1.083	0.079
Ventilated	**0.398**	**0.232-0.683**	**0.001**	**0.675**	**0.361-1.262**	**0.021**

Observations: In univariate models for predicting improved heart failure, admission systolic blood pressure, admission EF, surgery, rehospitalization within 1 year, and ventilation during first admission had statistical significance. In multivariate models, only admission EF, surgery, and ventilation remained statistically significant.

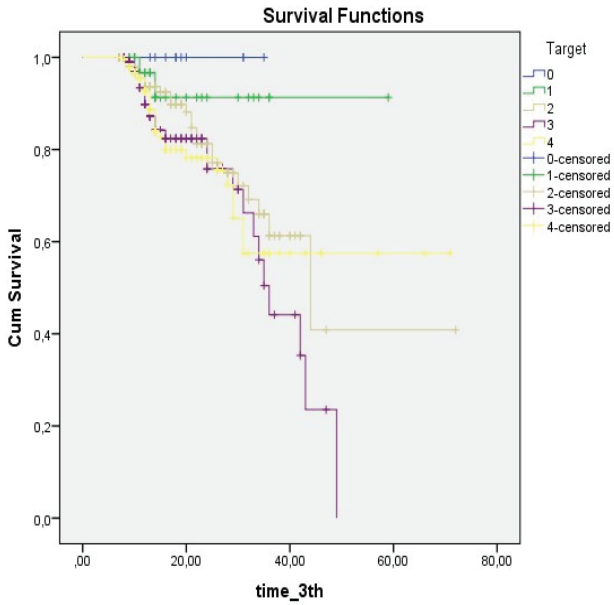


***Figure 3.2**. Kaplan-Meier curves for use of 1, 2, 3, and 4 drugs in predicting improved ejection fraction heart failure*

Observations: Kaplan-Meier curves predicting improved heart failure after 3 months based on use of 2, 3, or 4 drugs had statistical significance (p 1 drug = 0.178; p 2 drugs = 0.01; p 3 drugs = 0.02; p 4 drugs = 0.01). There were significantly more patients with improvement when using 3 drugs.

***Table 3.7**. Characteristics of interventions and surgery in reduced ejection fraction heart failure patients*

	Improved heart failure group		Remaining group		p
	N	%	n	%	
Intervention characteristics					
Percutaneous coronary intervention (PCI)	18	21.4	47	19.6	0.32
Atrial fibrillation ablation	2	2.4	4	1.7	0.49
CRT device implantation	0	0	0	0	
ICD device implantation	1	1.2	2	0.8	0.43
Surgical treatment					
CABG	**9**	**10.7**	**12**	**5.0**	**0.049**

	Improved heart failure group		Remaining group		p
	N	%	n	%	
Mitral valve replacement	**6**	**7.1**	**12**	**5.0**	**0.03**
Aortic valve replacement	**3**	**3.6**	**4**	**1.7**	
Double valve (mitral + aortic) replacement	**4**	**4.8**	**4**	**1.7**	
Other treatments					
Hemodialysis	0	0	2	0.8	0.567
Mechanical ventilation	**18**	**21.4**	**34**	**14.2**	**0.008**

Observations: In patients with EF ≤ 40%, the rates of CABG, valve surgery were higher and ventilation was lower in the improved group, with statistical significance for all.

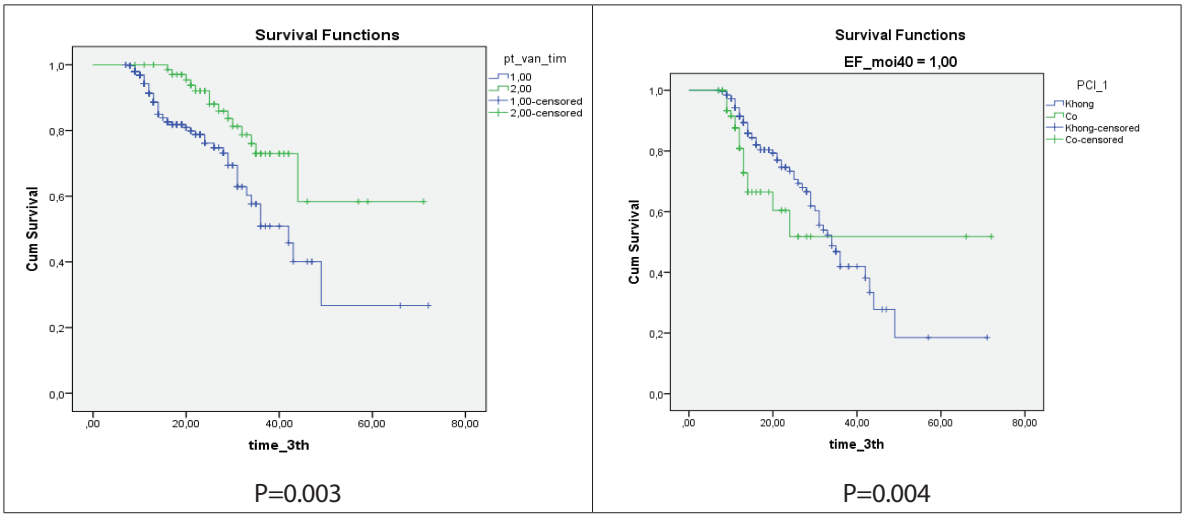


***Figure 3.3**. Kaplan-Meier curves for valve surgery and PCI in predicting improved ejection fraction heart failure.*

Observations: In patients with EF ≤ 40%, Kaplan-Meier curves predicting improved heart failure after 3 months for valve surgery and PCI both had statistical significance.

DISCUSSION

Epidemiological, clinical and subclinical characteristics

In our study, the mean age of the improved and remaining groups was 64.35±13.74 and 64.39±13.55 respectively; the proportion of females in the improved and remaining groups was 50% and 41.6% respectively. Compared to the study by Viorel et al. on a total of 3519 patients: the age of the improved and remaining groups was 61±11 and 62±11 respectively; females in the improved and remaining groups were 26% and 20% respectively; their age was lower than our study, and the proportion of females was also lower. Or when compared to Chan Soon Park et al. on 1509 patients: the age of the improved and remaining groups was 59.5±15.8 and 65.0±14.1 respectively; females in the improved and remaining groups were 41.5% and 34.6% respectively, noting that in the improved group, our age and proportion of females was higher.[4;5]

The rate of comorbidities in our study was highest for hypertension and type 2 diabetes, with rates in the improved and remaining groups of 54.2%; 28.6% and 55%; 29% respectively, with no statistically significant difference between the two groups. This rate is higher than in the study by Viorel et al: 12%; 24% and 6%; 25% respectively; meanwhile, the rate of hypertension was

lower in the study by Chan Soon Park et al: 48.3%; 51.8%; the rate of type 2 diabetes was higher in the improved group (24.4%) and lower in the remaining group (40.4%). [4;5]

The most common cause in both groups was ischemic heart disease, with rates in the improved and remaining groups of 47.6% and 50.4% respectively, significantly higher in the improved group. This was followed by high rates of dilated cardiomyopathy and valvular heart disease, with rates in the improved and remaining groups of 27.4%; 25% and 25.2%; 24% respectively. This once again shows the changing trend in heart failure, with lower rates of valvular disease and higher rates of coronary disease.

The mean SBP in the improved and remaining groups was 88.52±18.96 and 90.27±21.57 respectively, this difference was statistically significant, lower than in the EFICA study (126 ± 39 mmHg) [7], compared to Chan Soon Park et al. the mean SBP in the improved and remaining groups was also higher than our study, specifically 130.3 ± 30.5; 125.4 ± 25.7 respectively and also lower than Viorel et al. [4;5] Blood pressure higher or lower than normal is also a factor to consider in treating heart failure patients and can affect prognosis.

The mean heart rate in the improved and remaining groups was 77.62 ± 11.75 and 78.84 ± 16.69 respectively, with no statistically significant difference. The heart rate in our study is comparable to Viorel et al., with rates of 74 ± 13 and 73 ± 12 respectively; lower than Chan Soon Park et al. (97.1 ± 25.7 and 92.5 ± 23.5). [4;5]

The mean EF in our study in the improved and remaining groups was 32.23 ± 5.55 and 37.62 ± 8.73 respectively, the mean EF was significantly lower in the improved group; the rate of EF ≤ 30% was 38.1% and 27.7% respectively, higher in the improved group; the rate of 30%< EF ≤ 40% was 61.9% and 31.7% respectively, higher in the improved group. This can be explained by the improved heart failure group only including EF ≤ 40%, while the remaining group still includes mild reduced EF heart failure patients. The mean EF was lower in the study by Viorel et al. (28.7 ± 5.6 and 25.2 ± 6.2) and the study by Chan Soon Park et al. (27.3 ± 7.6 and 25.3 ± 7.1). [4;5]

Additionally, the mean NT-proBNP in our study in the improved and remaining groups was 6929.80 ± 8756.24 and 5413.12 ± 6996.60 respectively, higher than in the study by Chan Soon Park et al. (4453.0 (2336.0–9531.5) and 785.0 (2419.0–11 784.0)). [4] The mean creatinine in our study in the improved and remaining groups was 88.97 ± 31.68 and 105.13 ± 51.51 respectively, lower without statistical significance in the improved group than the remaining group; lower compared to Viorel et al. (107 ± 22 and 112 ± 26). [5]

Treatment characteristics

Looking at the drugs in the guideline-directed medical therapy for heart failure including: RAS system drugs, beta-blockers, MRAs, and SGLT2 inhibitors.

The usage rate of RAS system drugs in the improved and remaining groups was 96.4% and 86.1% respectively, significantly higher in the improved group (p<0.05). The usage rate of RAS drugs in the improved group was higher than Viorel et al. at 93%, the remaining group was lower (93%). [5] Meanwhile, these rates were much higher than author Chan Soon Park et al. (78.3% and 78.8%). [4] This rate is higher than some previous studies (80-86%). [8;9] Compared to a study conducted at Hanoi Heart Hospital, the rate of author Vu Quynh Nga et al. was 80.9% initially, after 12 months it was 86.52%, our rate was higher than theirs. [6]

The beta-blocker usage rate in our study was higher in the improved group than the remaining group, at 89.3% and 74.5% respectively, this difference was also statistically significant (p<0.05). Our rate was higher than Chan Soon Park et al. (62.9% and 57.4%); Viorel et al. (47% and 34%). [4;5] This rate when compared to other studies was also higher, for example THAI ADHERE (26.1%; after 12 months 24%), and EHFSII (43.2% after 12 months was 61.4%). [10;11] Compared to the previous study by Vu Quynh Nga conducted earlier, the proportion of patients using beta-blockers initially was 74.36%, after 12 months of treatment this rate reached 86.75%, clearly our

rate was higher. The increased rates of using RAS and beta-blocker drugs compared to Vu Quynh Nga once again confirms the role of the heart failure patient management program.[6]

The MRA usage rate in our study in the improved and remaining groups was 63.1% and 64.9% respectively, with no statistically significant difference between the two groups. The rate in our study was higher than Chan Soon Park et al. at 51.1% and 59.8%.[4] This rate was also higher than the THAI ADHERE study (17.1%; after 12 months 12.5%).[11]

Compared to other studies around the world, we saw in the QUALIFY study which was a multicenter study conducted on 6,669 heart failure patients in 36 countries over 15 months to assess adherence to reduced ejection fraction heart failure treatment guidelines. The results showed up to 22% of patients were not prescribed ACEI/ARB, beta-blocker or MRA without contraindications to these drugs.[12] The 2016 study by Reyes et al. showed around 90% of heart failure patients were prescribed ACEI/ARB, however the proportion prescribed beta-blockers was only 40%.[13]

One drug usage rate not mentioned in previous domestic and foreign studies was the SGLT2 inhibitor rate. Since SGLT2 inhibitors were only recently officially included as one of the four pillars of heart failure treatment, in our 2021 study the usage rate was still low, and in 4Q 2022 the rate was still low due to stock-outs in health insurance. However, the SGLT2 inhibitor usage rate in our study was quite positive, with rates in the improved and remaining groups of 59.5% and 61.9% respectively. Although the rate was lower in the improved group than the remaining group, it was not statistically significant. In fact, SGLT2 inhibitors are not only prescribed in the reduced ejection fraction heart failure group, but also in the mildly reduced or preserved ejection fraction heart failure groups.

The usage rate of 2 drugs - RAS and beta-blockers in the improved group was lower than the remaining group, at 85.7% and 67.6% respectively, significantly higher in the improved group than the remaining group ($p<0.05$). In addition, the use of 2, 3 or 4 drugs in the improved group was also higher than the remaining group, however there was no statistically significant difference. Perhaps our sample size was not large enough.

Looking at the rate of achieving half the target dose of drug groups in our study, the rate of using RAS drugs in our study was 63% in the improved group, significantly higher than the remaining group at 49.7% ($p<0.05$); the rate of achieving half the target dose when using beta-blockers in the improved group was 34.5%, also higher than the remaining group at 31.9%, although this difference was not statistically significant. Compared to other studies, the QUALIFY study showed the proportion of patients using ACEI/ARB and beta-blockers at ≥ 50% of target dose was 55.0%, and 23% of reduced ejection fraction heart failure patients achieved target doses of ACEI/ARB and beta-blockers in the study.[12] The TSOC – HFrEF study in Taiwan followed 1509 reduced ejection fraction heart failure patients, after 1 year follow-up the proportion achieving target doses for ACEI/ARB and Beta-blockers was 25.0% and 40% respectively.[14]

When assessing the issue of rehospitalization in our study groups, we noted that rehospitalization within 1 year occurred in 9.5% of the improved group, significantly lower than the remaining group at 20.3% ($p<0.05$). In addition, the average number of rehospitalizations within 1 year in the improved group was 0.14±0.49, also significantly lower than the remaining group 0.29±0.74($p<0.04$). This may also be a contributing factor in assessing ejection fraction improvement capabilities.

Factors related to predicting improved ejection fraction heart failure

Another way to describe the relationship between sensitivity and specificity is the ROC (receiver operating characteristic) curve. By connecting points on the ROC curve, we get a continuous ROC curve. But here we have two indicators (false positive rate and sensitivity), which vary inversely. Therefore, we need a "balanced indicator" of both indicators. The best

way to balance is to estimate the area under the ROC curve (also called AUC). The AUC index is very useful in comparing the accuracy of 2 or more diagnostic tests. Of course, the method with the higher AUC means that the method has higher accuracy. We used AUC to assess the ability to predict improved ejection fraction heart failure of parameters such as admission EF, LVEDVi, LVESVi. Our results were: area under the curve of admission EF, LVEDVi, LVESVi in predicting improvement were 0.687(95% CI 0.640-0.730; p< 0.001); 0.531 (95% CI 0.462-0.599; p=0.378); 0.543 (95% CI 0.467-0.611; p=0.211), so only the admission EF index was statistically significant in predicting the ability to improve (p<0.05).

In addition, we used univariate and multivariate models in predicting improved heart failure, we noted admission systolic blood pressure, admission EF, surgery, rehospitalization within 1 year, ventilation during first admission were statistically significant, but when included in the multivariate model only admission EF, surgery and ventilation remained statistically significant. Thus, admission EF, surgery and ventilation are very significant indicators in predicting improved ejection fraction.

The Kaplan Meier curve is a jagged, uneven staircase, with the y-axis being the rate and the x-axis being time. On the length there are vertical marks indicating the time a subject is censored, on the height if there are horizontal marks corresponding to that timepoint when an event occurred. Among survival analysis methods, the Kaplan Meier method is the most accurate. In our study we also used Kaplan-Meier curves to predict improved ejection fraction heart failure, by using 1, 2, 3 or 4 drugs. From Figure 3.2 we can clearly see greater improvement when using 2 or 3 drugs compared to 1 drug or no drug use. When using 4 drugs the improvement rate increased but not as much as with 3 drugs, this is not because 4 drugs is not as good as 3 drugs but because our sample size is small, and our rate of 4 drug use is not high yet. In addition, the Kaplan Meier curve predicting improved heart failure after 3 months based on use of 2, 3 and 4 drugs was statistically significant (p 1 drug = 0.178; p 2 drugs = 0.01; p 3 drugs = 0.02; p 4 drugs = 0.01; the chart shows each group of 1, 2, 3, 4 drugs p = 0.049).

Previous studies have not noted the use of AUC, Cox regression or Kaplan Meier for predicting improved ejection fraction in heart failure patients.

When looking at the total number of patients with reduced ejection fraction, we noted the rate of PCI and AF ablation and ICD implantation in the improved group was 21.4%; 2.4% and 1.2% respectively, higher than the remaining group (19.6%; 1.7% and 0.8%), however the difference was not statistically significant. Looking at the surgical treatment aspect, the rates of CABG and valve replacement in the improved group were 10.7% and 15.2% respectively, significantly higher than the remaining group (5% and 8.4%) (p<0.05). And we also used Kaplan Meier curves to assess the ability to predict improved ejection fraction heart failure in this patient group, showing valve surgery and PCI were both statistically significant (p<0.05).

CONCLUSION

The rate of improved ejection fraction heart failure in the program was 17.2%. Admission systolic blood pressure, admission EF, usage rates of RAS system drugs, beta-blockers, use of 2 RAS and beta-blocker drugs, PCI, AF ablation, and CABG or valve surgery were significant in predicting improved ejection fraction heart failure in the heart failure program at Hanoi Heart Hospital.

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12-month mortality and hospitalizations in patients with heart failure with preserved ejection fraction and comorbid hypertension and type 2 diabetes mellitus

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▶ Received: 10 October 2023
Accepted: 15 November 2023
Published online: 30 November 2023

To cite: Nguyen NTV, Truong QB, Chau NH. *J Vietnam Cardiol 2023*;**107E**:37-41

ABSTRACT

Background: Heart failure with preserved ejection fraction (HFpEF) carries a high risk of mortality and hospitalization, especially in patients with comorbid hypertension and type 2 diabetes mellitus. Little is known about the prognosis of hypertensive-diabetic HFpEF in Vietnam.

Objective: To examine the 12-month mortality, hospitalization, and combined outcome of all-cause mortality or heart failure hospitalization in hypertensive-diabetic HFpEF patients.

Methods and Materials: A 12-month prospective cohort study conducted in University Medical Center, HCMC and Nhan Dan Gia Dinh hospital. Recruiting period started in January 2021 and ended in April 2022.

Results: 233 patients were recruited. During 12-month, 6.9% died (n=16), in which 50% were due to cardiovascular cause. Hospital admission was reported in 62.2% of patients (n=145). 23.5% (n =55) were hospitalized at least 3 times. During the first hospitalization, 57.3% were due to cardiovascular reasons, most often heart failure (24.2%) and acute myocardial infarction (9%). Among non-cardiovascular admissions (42.7%), infection was the leading cause (22.1%). Combined outcome was observed in 24.9% (n=58).

Conclusions: Hypertensive-diabetic HFpEF patients experienced high rates of adverse events during a 12-month period, which were not restricted to cardiovascular causes, but also triggered by non-cardiovascular diseases. Comprehensive management should be taken into consideration to reduce both cardiovascular and non-cardiovascular events.

Keywords: Heart Failure with Preserved Ejection Fraction, Hypertension, Type 2 Diabetes Mellitus, All-cause Mortality, All-cause Hospitalization.

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) accounts for roughly 50% of heart failure population, with similar risk of all-cause mortality compared to those with reduced ejection fraction [1]. While heart failure with reduced ejection fraction had multiple foundational therapies to improve survival, SGLT2 inhibitor was the only treatment with proven cardiovascular protection in HFpEF [2]. Therefore, HFpEF is becoming

a research priority in recent years.

The last two decades have seen major advancement in both the diagnosis and management of HFpEF. The development and validation of scoring systems as well as practical guidelines on early detection of HFpEF contributed to an increasing prevalence of HFpEF. In fact, due to the high comorbidity burden, the first point of contact for many HFpEF patients were non-cardiovascular facilities. Even after HFpEF diagnosis, non-cardiovascular comorbidity remained to be an issue of top concern in HFpEF patients. Since the ARIC trial, an increasing trend in non-cardiovascular mortality and hospitalization were observed in many HFpEF population [3]. Regardless of etiologies, an episode of hospitalization increased the risk of all-cause mortality in HFpEF individuals [4].

Among HFpEF patients, those with diabetes were subject to higher rates of adverse events [5]. As hypertension was present in most HFpEF patients, diabetic HFpEF frequently had concurrent hypertension. Not only does the combination of hypertension and diabetes increased the risk of incident HFpEF, they also heightened the risk for other HFpEF comorbidities, such as cornary syndrome or chronic kidney disease. These comorbidities in turn predisposed patients to further adverse events. Therefore, the coprevalence of hypertension and diabetes in HFpEF was expected to be associated with worse prognosis.

Most HFpEF studies focused on cardiovascular outcomes rather than non-cardiovascular events. In Asia, cardiovascular causes accounted for roughly half of all-cause mortality and hospitalization[6]. However, this registry (ASIAN-HF) excluded Vietnam. As data in Vietnamese HFpEF patients were lacking, we conducted the first multicentered prospective cohort study to evaluate the 12-month cardiovascular and non-cardiovascular events, including mortality, hospitalization and combined endpoint of all-cause mortality or heart failure hospitalization in hypertensive-diabeteic HFpEF patients.

METHODS

A 12-month multicentered, prospective cohort study was conducted in University Medical Center, HCMC and Nhan Dan Gia Dinh hospital. Patient enrolment started in January 2021 and ended in April 2022. The study adhered to Declaration of Helsinski and received approval from Ethics Committee of Biomedical Research at the University of Medicine and Pharmacy at Ho Chi Minh city prior to initial patient recruitment. The study was registered in clinicaltrial.gov in 2021 (NCT: 04835194).

Inclusion criteria included hypertensive-diabetic adults with HFpEF. Exclusion criteria included prior cardiovascular admission within 30 days, acute heart failure, <1 year of life-expectancy due to other causes, unrepaired congenital heart disease, stage D primary valvular disease or prosthetic valve, severe pericardial diseases or cardiomyopathies (hypertrophic, restrictive, stress-induced, chemo-induced, amyloidosis, sarcoidosis), implantation with ICD, PM or CRT, Child C cirrhosis, end stage renal disease, severe COPD or asthma requiring home oxygen, pregnancy or lactation or active enrolment in interventional trial.

After giving informed consent, each patient was collected data on demographics, comorbidities, investigations and medications. For the next 12 months, data on all-cause hospitalization or mortality were collected at each follow-up and adjudicated by the main investigators.

For calculation of sample size, we employed the 12-month all-cause mortality or heart failure hospitalization rate from ASIAN-HF trial. The formula was as follow.

$$n = Z^2_{1-\alpha/2} \frac{p(1-p)}{d^2}$$

With α = 0.05, $Z_{0.975}$ = 1.96, d= 0.05, p=0.121, the minimal number of patients required was 162.

Python 3.11 was used for data analysis. Numerical variables were presented as mean (normal distribution) or median (skewed distribution). Categorial variables were presented as percentage. T-test or Wilcoxon range sum test was used to compare means of 2 groups. Chi square test was

performed to compare the difference between the categorial variables.

RESULTS

A total of 233 patients were recruited, 3.9% of which (n=9) were lost to follow-up. Mean age was 73. The ratio of women to men was 2.1. Apart from hypertension and diabetes, 82% had at least two other comorbidities. The proportion of patients with concurrent dyslipidemia, chronic coronary artery synfrom, anemia, chronic kidney disease and atrial fibrillation were 99.6%, 77.3%, 64%, 38.2% and 29.2% respectively. Prior myocardial infarction was documented in 38.2% of patients.

12-month Mortality

During a 12-month period, there were 16 dealths, 8 of which were attributed to cardiovascular causes. The remaining were due to non-cardiovascular etiologies.

12-month Hospitalization

62.2% of patients were admitted at least once (n=145). The proportion of patients with one, two, three and at least 4 admissions were 23.2%, 15.5%, 9.4% and 14.1% respectively (Figure 1).

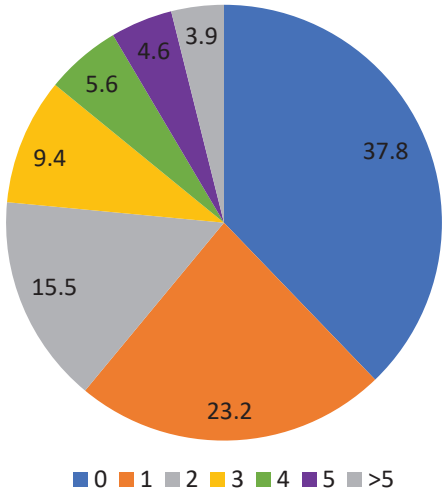

Figure 1. *Number of hospital admissions during 12 months*

For the first hospitalization, 57.3% of patients got admitted because of cardiovascular disease, with the two most common causes being heart failure (24.2%), and acute myocardial infarction (9%). For non-cardiovascular admissions (42.7%) of all hospitalizations), the most frequent trigger was infection, accounting for 22.1% of cases. Details on triggers of the first admission were demonstrated in Figure 2.

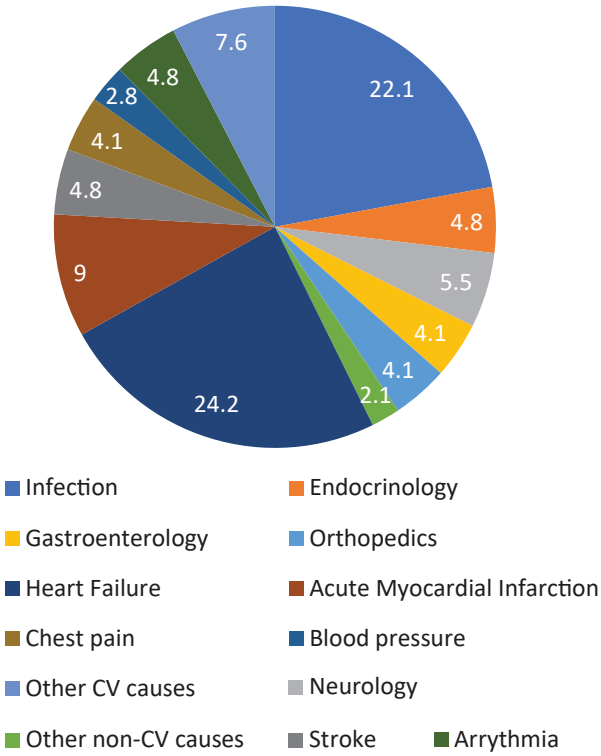

Figure 2. *Main causes of First Admission*

12-month combined outcome

Combined outcome of all-cause mortality or heart failure hospitalization was reported in 24.9% of patients (n=58). Specifically, 46 patients (19.7%) experienced heart failure hospitalization.

DISCUSSIONS

12-month Hospitalizations

The percentage of patients with at least one admission in our study was higher than that of I-PRESERVE trial (62.2% versus 55%), but the proportion of cardiovascular causes were similar (57.3% versus 53.8%) [4]. For the first admission, our study demonstrated higher rates of heart failure hospitalization or acute myocardial infarction

(24.2% and 9% respectively) compared to those of I-PRESERVE trial (17.6% and 3.3%).

The difference between our study and I-PRESERVE trial could be explained by the study population. All of our patients had concurrent hypertension and type 2 diabetes mellitus, whereas in the I-PRESERVE trial, hypertension and diabetes were presented in 88.4% and 25.1% of patients respectively. The combination of hypertension and diabetes increase the risk of acute myocardial infarction and heart failure hospitalization.

In HFpEF patients, apart from mortality and heart failure hospitalization, incident acute myocardial infarction is associated with prognosis. In a meta-analysis from CHARM-Preserved, I-PRESERVE and TOPCAT, 3.8% of patients had incident myocardial infarction [7]. In these patients, the risk of cardiovascular death was highest in the first 30 days (HR=31, 95% CI 22-44), then gradually decreased during the next 12 months (HR=3.6, 95% CI 2.6-5.1). This heightened risk persisted even after 12 months (HR=1.58, 95% CI 1.03-2.43). There was similar risk for cardiovascular death between first and recurrent myocardial infarction, highlighting the importance of primary and secondary prevention of myocardial infarction in HFpEF patients. In our study, 9% of patients reported incident myocardial infarction, almost trippled that of the meta-analysis of CHARM-Preserved, I-PRESERVE and TOPCAT (3.8%). Thus, our hypertensive-diabetic HFpEF patients with high rates myocardial infarction were at an increased risk for more adverse events compared to other HFpEF population.

In the first admission, there was striking similarity between our study and I-PRESERVE trial in terms of heart failure hospitalization (24.2% and 17.6%) and non-cardiovascular hospitalizations (42.7% and 43.8%) [4]. These findings were in contrast to studies on heart failure patients with reduced ejection fraction (HFrEF). In HFrEF patients, heart failure was the most common cause of hospitalization, accounting for 46% of all admissions in EVEREST trial and 56% in COPERNICUS trial. Taken together, these data illustrated the difference in causes of hospitalization across ejection fraction spectrum, with non-cardiovascular causes being more frequent in HFpEF patients. In a recent analysis from SwedeHF registry, an increasing trend in non-cardiovascular admission was noted in HFpEF population. When HFpEF is accompanied by diabetes, the most common non-cardiovascular etiology was infection [8]. The same pattern was observed in our study, with infection being the leadning cause of non-cardiovascular infection (22.1%).

Regardless of the cause, all-cause mortality significantly increased in HFpEF patients post hospitalization, especially in the first 30 days [4]. All-cause hospitalization was higher in our study (62.2%) compared to I-PRESERVE trial (55%), inferring a higher-risk population.

12-month Mortality

In regard to mortality, 6.9% (n=16) of the study population died within 12 months. Among these cases, 50% (n=8) was attributed to cardiovascular diseases. Our result was in accordance with other HFpEF registries, such as GWTG-HF (52%), ESC-HF-LT (47%), ASIAN-HF (53%) and Olmsted County (51%). However, our finding was lower than HFpEF randomized controlled trials (I-PRESERVE, TOPCAT, CHARM-Preserved, PEP-CHF, and ASCEND-HF), in which cardiovascular mortality accounted for roughly 60-70% of cases. In both registries and RCTs, HFpEF patients experienced more non-cardiovascular mortality as opposed to HFrEF counterparts [9]. High rates of non-cardiovascular causes may explain the difficulties in improving all-cause mortality of HFpEF population.

12-month combined outcome

During the 12-month follow-up, 24.9% of patients reported either mortality (6.9%) or first hospitalization for heart failure (19.7%). Compared to diabetic HFpEF population from ASIAN-HF registry, our patients experienced higher rates of combined endpoint (24.9% versus 14.8%) [5]. The difference was mostly attributed to heart failure hospitalization (19.7% versus 10.6%), rather than all-cause mortality (6.9% versus 5.7%). ASIAN-HF registry was conducted in 47 centers from 11 Asian nations. These representative

sites were carefully chosen, depending on the population size, geographic features, patient volume and standardized echocardiogram protocol. Due to their high-quality healthcare delivery, adverse events in ASIAN-HF registry was expected to be lower than the general population. Specifically, marked regional variation in combined endpoint was noted in the ASIAN-HF registry with highest events observed in South East Asian (25.4%). This was similar to our study at 24.9%.

CONCLUSION

We described a modern-day population of heart failure with preserved ejection fraction and concurrent hypertension, diabetes, who experienced high rates of mortality and admissions during a 12-month period. Non-cardiovascular causes was responsible for about half of all adverse events, including both mortality and hospitalization. Three most common causes of first hospital admission were heart failure, infection and acute myocardial infarction. These findings warrant the need for comprehensive risk management in hypertensive-diabetic HFpEF patients, taking into account other non-cardiovascular events in addition to hospitalization for heart failure.

Conflictcs of interest: The authors declared no conflicts of interest.

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Assessment of left ventricular systolic function in patients with chronic coronary syndrome and heart failure with reduced ejection fraction after percutaneous coronary intervention

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▶ Received: 15 October 2023
Accepted: 20 November 2023
Published online: 30 November 2023

To cite: Dao AT, Nguyen LH, Do TC, *et al. J Vietnam Cardiol 2023*;**107E**:42-46

ABSTRACT

Objective: Describe the characteristic and change of left ventricular systolic function after percutaneous coronary intervention in patients with chronic coronary syndrome and heart failure with reduced ejection fraction after percutaneous coronary intervention.

Methods: This prospective study involved the monitoring of 40 patients who had an ejection fraction of 40% or less and were diagnosed with chronic coronary artery disease. These patients underwent a successful percutaneous coronary intervention at the Vietnam National Heart Institute and Hanoi Medical University Hospital between September 2022 and August 2023. The main objective is to evaluate the left ventricular systolic function following the intervention using 2D echocardiography.

Results: A total of 40 patients (34 male and 6 females) with a mean age of 68.3 ± 10.2, were assessed for left ventricular systolic function using 2D echocardiography before and after the intervention. In paired assessment at 90-day follow-up, baseline LVEF improved significantly (before intervention: 32.8 ± 7.2% and after: 38,7 ± 7,3%, $p < 0.01$). Left ventricular longitudinal strain improved significantly on all cross-sections such as: 4-chamber GLS (before: -10.4 ± 3.97%, after: -13.6 ± 4.3%, $p < 0.01$), 2-chamber GLS (before: -10.6 ± 3.8%, after: -13.1 ± 4.2%, $p < 0.01$), 3-chamber GLS (before: -9.8 ± 3.7%, after: -12.3 ± 4.6%, $p < 0.01$), GLS Avg (before: -10.3 ± 3.6%, after: -13 ± 4.1%, $p< 0.01$), basal GLS (before: -11.2 ± 3.8%, after: -14 ± 4.5%, $p < 0.01$), middle GLS (before: -9.3 ± 4.4%, after: -11.8 ± 3.9%, $p < 0.01$), apical GLS (before: -11.5 ± 5.1%, after: -14.3 ± 5.9%, $p < 0.01$). In comparison with the incomplete-revascularization group, there was a significant improvement in left ventricular systolic function in the complete-revascularization group (OR= 22.17, $p < 0.01$).

Conclusions: In patients with chronic coronary syndrome and a reduced left ventricular ejection fraction, the systolic function of the left ventricle was enhanced following percutaneous coronary intervention, particularly in the group that underwent complete revascularization.

Keywords: Heart failure with reduced ejection fraction (HFrEF), Global longitudinal strain (GLS), Chronic coronary syndrome (CCS), Percutaneous coronary intervention (PCI).

INTRODUCTION

The most common cause of heart failure with a reduced ejection fraction is chronic coronary artery disease (CAD). Despite continuing advances in medical therapy of heart failure, a poor prognosis of CAD substantially reduces both life expectancy and quality of life.[1–3] T The efficacy of percutaneous coronary revascularization in this patient group is primarily dependent on observational data and extrapolation from surgical trials.[4–6] The lack of scientific evidence has led to confusion in clinical practice. Coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) might be used to revascularize the coronary arteries. The 10-year STICH study demonstrated that CABG improved the all-cause mortality rate compared with medical treatment.[7]a total of 1212 patients with an ejection fraction of 35% or less and coronary artery disease amenable to CABG were randomly assigned to medical therapy alone (602 patients Besides CABG, PCI is an minimally invasive intervention method and very developed in the current intervention era. However, the efficacy of PCI in patients with chronic coronary syndrome with a reduced left ventricular ejection fraction has been remained controversial. In 2022, the REVIVED BCIS-2 trial researched on chronic coronary syndrome subjects with severe coronary artery damage and a left ventricular ejection fraction of 35%. After an average follow-up period of 41 months, it was concluded that PCI did not improve the mortality rate and the hospitalization rate due to heart failure. In addition, PCI did not improve left ventricular ejection fraction compared with medical treatment. [2] However, the REVIVED BCIS-2 research had limitations as it did not reveal the proportion of patients who had full revascularization and simply examined left ventricular systolic function based on left ventricular ejection fraction (EF).

Speckle tracking echocardiography has demonstrated to be a non-invasive exploration technique that exhibits notable sensitivity and specificity when evaluating early-stage alterations in the function of the left ventricle and early-stage treatment efficacy[8,9] In Vietnam, there have been no studies evaluating changes in left ventricular systolic function after percutaneous coronary intervention in patients with chronic coronary syndrome with heart failure and reduced left ventricular ejection fraction.

METHODS

Study population

40 patients diagnosed with chronic coronary syndrome and heart failure with reduced left ventricular ejection fraction (biplane EF ≤ 40%) who received successful percutaneous coronary intervention at Vietnam Heart Institute and Hanoi Medical University Hospital from September 2022 to August 2023.

Methods

Study design: Prospective study.

Selection criteria:

• Patients diagnosed heart failure with reduced ventricular ejection fraction (biplane EF≤ 40%) on 2D echocardiography.

• Diagnosis of chronic coronary syndrome based on exploratory test: MSCT, excercise test, invasive coronary angiography (Significant CAD was defined by invasive coronary angiography as ≥ 50% stenosis of the left main stem, ≥ 70% stenosis in another coronary vessel).

• Successful percutaneous coronary intervention: final TIMI flow grade 3 and residual stenosis ≤20%.[10]often treated conservatively due to revascularization risks. Revascularization outcomes are largely unknown in SCAD presenting with ST-segment elevation myocardial infarction (STEMI

• Completeness of revascularization was defined as revascularization of all lesions with significant stenosis in a major epicardial coronary artery or in their major branch.[11]

• 2D echocardiography assessed left ventricular systolic function, left ventricular longitudinal strain (GLS index) before intervention and 90 days after intervention. Left ventricular ejection fraction (EF) improved significantly if the improvement in biplane EF after 90 days compared to the initial time was ≥ 5%. [12]

Statistical analysis

• The collected data were stored in Excel and analyzed by Stata 17.

• Results are presented as mean ± standard deviation for normally distributed variables, median and interquartile range for non-normally distributed variables. Compare the mean value of normally distributed variables using T-test while non-normally distributed variables use Wilcoxon–Mann–Whitne. Compare two qualitative variables using the Chi-square test. A p value <0.05 is considered statistically significant.

RESULTS

Patients characteristics

Among 40 patients in the study, 85% of patients were male, the average age was 68.3 ± 10.2, the lowest age was 41, the highest age was 85. Proportion of risk factors cardiovascular diseases such as hypertension, diabetes, dyslipidemia, smoking, overweight and obesity are 72.5%, 37.5%, 10%, 52.5%, 17.5% respectively. Baseline characteristics of study patients are presented in detail in table 01.

***Table 01**. Patient's characteristics*

Age (years)	68.3 ± 10.2
Sex	
Male	34 (85%)
Female	6 (15%)
Risk factor	
Hypertension	29 (72.5%)
Diabetes	15 (37.5%)
Dyslipidemia	4 (10%)
Smoking	21 (52.5%)
Outweighed, Obesity (BMI≥23)	7 (17.5%)
Clinical characteristic	
NYHA III/IV	17 (42,5%)
CCS III/IV	23 (57.5%)
Systolic (mmHg)	133.8 ± 21.1
Diastolic (mmHg)	80.1 ± 12.3
Heart rate (bpm)	82.2 ± 14.7
Biochemical parameters	
NT-proBNP (pg/mL)	1534 (450-3622)
Creatinine (umol/L)	95.5 (87-127)
Troponin Ths (ng/L)	15.79 (9.7-23.5)
Characteristics of coronary artery disease	
1 coronary branch	9 (22.5%)
2 coronary branches	15 (37.5%)
3 branches or LM	16 (40%)
Complete revascularization	17 (42.5%)
Number of stents per patient	1 (1-2)

Alteration of clinical symptoms after PCI

***Table 02**. Alteration of clinical symptoms after PCI*

	Before intervention	After intervention	p
NYHA	2.6 ± 0.7	2.2 ± 0.5	0.002
I, II, III, IV	23 (57,5%)	38 (95%)	
	17 (42.5%)	2 (5%)	
CCS	2.6 ± 0.7	1.7 ± 0.5	<0.001
I, II, III, IV	17 (42.5%)	39 (97.5%)	
	23 (57.5%)	1 (2.5%)	

Of 40 patients, 42.5% of them had NYHA level III or IV (30% NYHA III, 12.5% NYHA IV). At 90 days after intervention, only 5% of patients had NYHA level III and 0% of patients had NYsHA level IV (P=0.002). In the study patient group, the level of chest pain decreased from 57.5% of patients with CCS level III or IV to 2.5% of CCS level III and 0% of CCS level IV (P<0.01).

Alteration in the function of the left ventricle after PCI

***Table 03**. Alteration in the function of the left ventricle before and after 90 days of intervention*

	Before intervention	After 90 days of intervention	p
Dd (mm)	56.4 ± 6.9	54 ± 6.9	<0.001

	Before intervention	After 90 days of intervention	p
Ds (mm)	45.3 ± 8.8	42.1 ± 8.6	<0.001
Vd (ml)	160.4 ± 44.2	146.4 ± 43.1	<0.001
Vs (ml)	100.3 ± 43	91.3 ± 44.6	0.003
FS (%)	19.6 ± 7.9	22.3 ± 7.2	0.021
IVSd (mm)	9.6 ± 1.9	9.5 ± 1.8	0.898
IVSs (mm)	12.3 ± 2.3	12.1 ± 2.2	0.629
LVPWd (mm)	9.1 ± 1.7	9.1 ± 1.5	0.921
LVPWs (mm)	12.9 ± 2.5	13.0 ± 2.0	0.645
LVMi (g/m3)	126.3 ± 40.6	121.4 ± 36.6	0.405
EF biplane	32.8 ± 7.2	38.7 ± 7.3	<0.001
GLSA4C	-10.4 ± 3.97	-13.6 ± 4.3	<0.001
GLSA2C	-10.6 ± 3.8	-13.1 ± 4.2	<0.001
GLSA3C	-9.8 ± 3.7	-12.3 ± 4.6	<0.001
GLSAvg	-10.3 ± 3.6	-13 ± 4.1	<0.001
GLS basal	-11.2 ± 3.8	-14 ± 4.5	<0.001
GLS mid	-9.3 ± 4.4	-11.8 ± 3.9	<0.001
GLS apical	-11.5 ± 5.1	-14.3 ± 5.9	0.005

Left ventricular ejection fraction before and after 90 days of intervention were 32.8 ± 7.2% and 38.7 ± 7.3% respectively, the difference was statistically significant (p<0.001). The average values of total left ventricular longitudinal strain before intervention and 90 days after intervention were -10.3 ± 3.6% and -13 ± 4.1%, respectively, the difference was statistically significant (<0.01). Like other strain indices such as 2-chamber, 3-chamber, 4-chamber longitudinal strain, strain in the base, middle and apical regions of the left ventricle after intervention all improved compared to before intervention group and the difference was significant.

Correlation between complete revascularization and improved ejection fraction

***Table 04**. Correlation between complete revascularization and improved ejection fraction*

Improved LVEF ≥ 5%	Complete revascularization		Total
	Yes	No	
Yes	14	4	18
No	3	19	22
Total	17	23	40

The rates of significant and insignificant LVEF improvement were 4.67 (14/3) and 0.21 (4/19), with OR=22.17 (p < 0.001), for the complete-revascularization and non-complete-revascularization groups, respectively. Thus, patients with complete coronary revascularization have a significantly higher ability to improve LVEF than the group of patients without complete coronary revascularization (OR=22.17; p<0.001).

DISCUSSION

This study was designed to assess alterations in the systolic function of the left ventricle among patients who underwent successful percutaneous coronary intervention and had chronic coronary syndrome accompanied by a reduced ejection fraction of the left ventricle. In conclusion, a considerable improvement in left ventricular systolic function is observed in both LVEF and GLS following to the intervention. There are number of studies have yielded consistent findings. In a research conducted by Yusuke Adachi, a cohort of 47 patients with heart failure with reduced ejection fraction (HFrEF) who had revascularization procedures such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) were examined. The study revealed a significant improvement in left ventricular ejection fraction (LVEF), with an increase from an average of 35.7 ± 8.6% to 44.3 ± 12.6% (p < 0.01).[13] Furthermore, the mean LVEF improved from 24.8 ± 9.9% to 31.4 ± 13.3% after higher-risk percutaneous coronary intervention in patients with ischemic cardiomyopathy, according to a study of 689 patients by Juan J. Russo. This represents a net increase of 6.5 ± 10.8% (p < 0.001). The findings of this study align with those of Kirschbaum (2010) in patients with multivessel disease and impaired left ventricular function. Complete revascularization resulted in a significant improvement in ejection fraction (EF), from 46 ± 12% to 51 ± 13% (p < 0.0001). However, incomplete revascularization did not lead to any change in EF, as indicated by values remaining at 49 ± 11% to 49 ± 10% (p < 0.88). Similarly, unsuccessful revascularization did not result in any significant change in EF, with values decreasing from 49 ± 13% to 47 ± 13% (p <

0.11).[14] Therefore, the use of percutaneous coronary intervention in individuals diagnosed with chronic coronary syndrome accompanied by a reduced left ventricular ejection fraction leads to improved left ventricular systolic function throughout a 90-day monitoring period. Additionally, total revascularization demonstrates notable efficacy in this scenario.

CONCLUSION

Percutaneous coronary intervention in chronic coronary syndrome and reduced left ventricular ejection fraction patients had improved left ventricular systolic function, especially in the complete-revascularization group.

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Prognostic value of the severity of tricuspid regurgitation on Doppler echocardiography in patient with heart failure with reduced ejection fraction

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▶ Received: 18 October 2023
Accepted: 20 November 2023
Published online: 30 November 2023

To cite: Ha QD, Khong NH, Pham MT. *J Vietnam Cardiol 2023*;**107E**:47-53

ABSTRACT

Background: Tricuspid regurgitation severity has recently gained attention as a prognostic predictor of outcome events in patients who have left-sided heart failure. This study sought to define the relationship between tricuspid regurgitation and outcome in patients with heart failure with reduced ejection fraction.

Objective: To investigate the characteristics of tricuspid regurgitation by Doppler echocardiography in patients with heart failure and reduced ejection fraction. To explore the association between the severity of tricuspid regurgitation and short-term mortality and hospital readmission in the study patients.

Methods: 116 heart failure-reduced ejection fraction patients were enrolled in this study, followed up, and evaluated after 3 - 6 months.

Results: 48.3% of patients have mild tricuspid regurgitation, 33.6% of patients have moderate tricuspid regurgitation, and 18.1% of patients have severe tricuspid regurgitation. 47 events (40.5%) occurred: 11 deaths (9.5%) and 38 readmissions (32.8%). A Kaplan - Meier curve showed that the survival rate of the severe tricuspid regurgitation group was significantly lower than the group with mild to moderate tricuspid regurgitation. A multivariate Cox regression model identified that tricuspid regurgitation severity was an independent predictor of 3-to-6-month mortality or readmission (HR 1.94; CI 95% 1.30 - 2.91).

Conclusion: Tricuspid regurgitation severity was an independent predictor of reduced ejection fraction in patients with heart failure.

Keywords: tricuspid regurgitation, mortality.

INTRODUCTION

Heart failure is a clinical syndrome caused by structural and/or functional changes in the heart due to various pathological causes. The disease has a high incidence, mortality rate, and treatment costs[1]. According to updated 2021 statistics from the American Heart Association, it is estimated that the prevalence of heart failure is around 6 million people, accounting for 1.8% of the total US population[2] and over 23 million people worldwide. It is estimated that by 2030, there will be over 8 million people (1 in 33 people will have heart failure). Therefore, heart failure remains a top concern in public health care.

In recent years, much data has

shown that significant (moderate-severe) tricuspid regurgitation can lead to impaired function and reduced survival, especially in patients with heart failure. There have been increasing studies on the characteristics and prognostic value of tricuspid regurgitation, from which appropriate and timely treatment options are proposed, reducing the burden of disease caused by tricuspid regurgitation.

Echocardiography is currently the most widely used method to assess the degree of tricuspid regurgitation. In Vietnam, there have been very few studies examining in detail the prognostic value of tricuspid regurgitation in patients with heart failure and EF < 40%. Therefore, we conduct the research topic **"Prognostic value of tricuspid regurgitation severity on echocardiography in patients with heart failure and reduced ejection fraction"** with two objectives:

Clinical and subclinical characteristics in hospitalized patients with heart failure and reduced ejection fraction.

The value of tricuspid regurgitation severity on echocardiography in predicting mortality and heart failure rehospitalization in the above group of patients.

OBJECTS AND METHODS

* Patient selection criteria

All study patients have been diagnosed with heart failure with reduced EF according to 2021 ESC guidelines. Patients agreed to participate in the study.

* Exclusion criteria

Patients with organic tricuspid valve disease, severe left-sided valve disease, other valve diseases due to rheumatic heart disease, prosthetic valves, congenital heart disease, and pacemaker implantation. Patients with COPD, asthma, other chronic or acute lung diseases, end-stage renal disease on dialysis, patients with poor echocardiographic images, patients with acute internal or surgical conditions, and patients who refused to participate in the study.

* Study setting

Study patients were recruited at the Vietnam National Heart Institute.

* Research methods

Study design

Retrospective study: patients were hospitalized from August 2020 to July 2021, all patients were followed up until August 2022.

Prospective study: patients hospitalized from September 2022 to June 2023, all patients will be followed up until September 2023.

Sampling method and sample size

Convenience sampling: Hospitalized patients.

Data collection

- All admitted patients underwent medical history, physical examination for signs and symptoms of heart failure, and necessary investigations (ECG, chest X-ray, NT-proBNP, echocardiography) to meet the diagnostic criteria for heart failure with reduced EF and did not have exclusion criteria.

- Perform echocardiography according to the research protocol to collect tricuspid regurgitation parameters as required.

- Follow up with patients during hospitalization and after discharge to assess outcomes: all-cause mortality, heart failure rehospitalization based on the interview questionnaire.

- Echocardiographic parameters were measured according to the American Society of Echocardiography guidelines. The severity of tricuspid regurgitation was classified based on 3 parameters: Vena Contracta width (VC), regurgitant jet area, and the ratio of tricuspid regurgitant area to right atrial area. VC was used as the diagnostic criterion for grading tricuspid regurgitation, and the other two parameters were additionally evaluated for comparison. Vena Contracta is the narrowest part of the regurgitant jet as it passes through the tricuspid valve, measured on the four-chamber view from the color Doppler aliasing, defining tricuspid regurgitation severity based on Vena Contracta: mild <0.3cm, moderate: 0.3-0.69cm, and severe ≥0.7cm.

Data analysis

All collected data will be analyzed using standard statistical methods on a computer with SPSS software version 20.0.

RESULTS

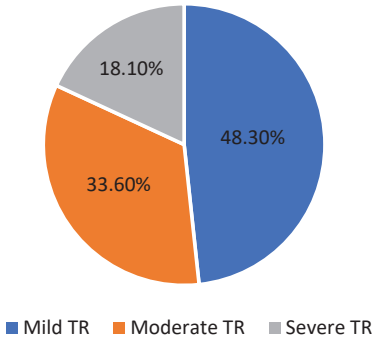

***Figure 1**. Distribution of tricuspid regurgitation severity in the study population*

Among 116 study patients, mild tricuspid regurgitation was the most common at 48.3%. This was followed by moderate (33.6%) and severe tricuspid regurgitation (18.1%).

General characteristics of study subjects

***Table 1**. Clinical and subclinical characteristics in the study patients*

Characteristics	Overall (n =116)	Mild TR (n=56)	Moderate TR (n=39)	Severe TR (n= 21)	p
Age	63.0±14.2	61.7±14.1	65.6±14.5	61.4±13.7	0.363
Male	86 (74.1)	39 (69.6)	30 (76.9)	17 (81.0)	0.534
Heart rate	94.3±22.4	87.5±20.7	100.2±20.5	101.7±25.7	**0.005**
Troponin T	40 (24 – 84.8)	31 (20.3 - 241)	30.4 (24.4 -75.3)	56.5 (33- 94.5)	0.317
NYHA I	11 (9.5)	6 (10.7)	4 (10.3)	1 (4.7)	0.587
NYHA II	43 (37.1)	23 (41.1)	13 (33.3)	7 (33.3)	0.587
NYHA III	55 (47.4)	26 (46.4)	18 (46.2)	11 (52.4)	0.587
NYHA IV	7 (6.0)	1 (1.8)	4 (10.3)	2 (9.5)	0.587
NT-proBNP	1575 (444 - 4657)	807 (300 - 2841)	1503 (444 - 4687)	4829.5 (2467 - 7134)	**0.007**
Creatinine	117.7±79.5	104.4±91.3	124.7±64.3	139.8±66.6	**0.0014**
SBP	121.4±21.1	123.0±20.2	120.7±21.3	118.7±23.7	0.713

Our study was conducted on a total of 116 patients hospitalized with heart failure and EF <40%, of which 74.1% were male, with a mean age of 63.0±14.2. Among the 116 study patients, 3 patients died in the hospital, the total deaths during follow-up were 11 patients (9.5%), and 38 patients (32.8%) were rehospitalized for heart failure. Total events were 47 patients, accounting for 40.5%. Heart rate, NT-proBNP level, creatinine in the severe tricuspid regurgitation group were statistically significantly higher than the mild and moderate groups (p<0.01).

***Table 2**. Echocardiographic characteristics in the study of patients*

Parameters	Overall (n =116)	Mild TR (n=56)	Moderate TR (n=39)	Severe TR (n= 21)	p
LA size	42.1±7.2	40.2±5.1	42.1±7.8	47.2±8.5	**0.0005**

Parameters	Overall (n =116)	Mild TR (n=56)	Moderate TR (n=39)	Severe TR (n= 21)	p
LVEDD	60.3±8.8	60.3±8.1	59.0±8.2	62.8±8.8	0.241
LVESD	50.8±9.1	50.5±9.3	49.5±8.8	53.9±9.0	0.200
EF biplane	29.9±6.3	30.9±6.8	29.4±5.8	28.4±5.7	0.186
RVID1	37.3±9.2	34.8±4.6	37.9±6.9	42.9±9.2	**< 0.0001**
RVID2	29.5±6.2	27.6±4.5	29.9±5.7	34.0±8.8	**0.0002**
RVID3	*71.4±9.3*	*70.7±8.3*	*70.7±9.7*	*74.7±11.1*	0.211
TAPSE	17.5±3.6	18.6±3.4	16.8±3.9	16.0±3.1	**0.005**
FAC	35.4±8.6	37.9±7.6	34.8±8.4	29.5±9.0	**0.0004**
RVSP	41.1±15.0	32.8±8.6	44.4±14.3	57.1±14.8	**0.0001**
TR jet area	5.0±4.6	1.8±1.8	5.7±3.0	12.1±3.7	**0.0001**
Vena Contracta	3.8±3.5	1.3±0.7	4.4±1.2	9.8±3.2	**0.0001**
RA area	18.6±7.1	14.6±3.5	19.6±5.5	27.6±8.1	**0.0001**
TR jet/RA ratio	0.23±0.17	0.11±0.08	0.28±0.13	0.45±0.11	**0.0001**
TR jet direction					
Eccentric	27 (23.3)	0 (0.0)	7 (18.0)	20 (95.2)	**< 0.001**
Central	89 (76.7)	56 (100)	32 (82.1)	1 (4.8)	
Mitral regurgitation					
Mild	33 (29.2)	25 (45.5)	7 (18.9)	1 (4.8)	**< 0.001**
Moderate	35 (31.0)	19 (34.5)	12 (32.4)	4 (19.1)	
Severe	45 (39.8)	11 (20.0)	18 (48.7)	17 (76.2)	
Aortic regurgitation					
Mild	60 (83.3)	29 (93.6)	20 (80.0)	11 (68.8)	0.042
Moderate	9 (12.5)	1 (3.2)	3 (12.0)	5 (31.5)	
Severe	3 (4.2)	1 (3.2)	2 (8.0)	0 (0.0)	

The mean LVEF (biplane) was 29.9 ± 6.3%, with no difference between the study groups. The mean left atrial diameter was 47.2 ± 8.5mm. The left atrial size in the severe TR group was larger than the mild and moderate TR groups; this difference was statistically significant (p<0.01). The right ventricle in the severe TR group was more dilated compared to the mild-moderate TR groups with larger transverse and longitudinal diameters (p<0.01). The RVSP and right ventricular systolic function parameters like TAPSE and FAC were also higher in the severe TR group compared to the other two groups (p<0.01). Regarding echocardiographic parameters of tricuspid regurgitation, TR jet area, vena Contracta width, and the ratio of TR jet area to the right atrial area were larger in the severe TR group compared to the other two groups (p<0.01). Most severe TR jets were eccentric, while central jets were commonly seen in mild-moderate TR. There was a correlation between mitral regurgitation and tricuspid regurgitation severity, with severe mitral regurgitation having a higher rate of severe tricuspid regurgitation compared to the other two groups (p<0.01). There was no correlation between tricuspid regurgitation severity and aortic regurgitation severity.

Prognostic value of tricuspid regurgitation severity on echocardiography in predicting short-term mortality and rehospitalization in the study patients.

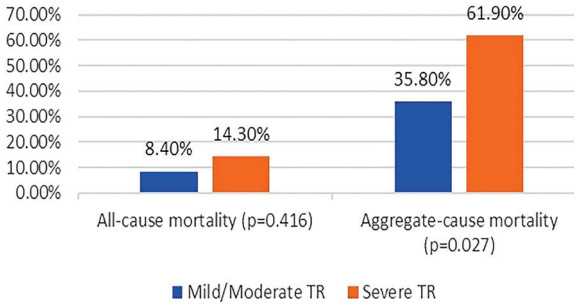

***Figure 2**. Rates of combined events and mortality according to tricuspid regurgitation severity*

- At the end of the study, the rate of combined events in the severe tricuspid regurgitation group was statistically significantly higher compared to the mild and moderate tricuspid regurgitation groups (61.9% vs 35.8% p = 0.027).

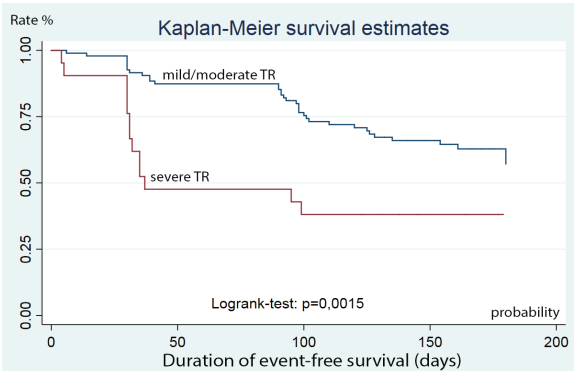

***Figure 3**. Kaplan-Meier curves showing event-free survival probability according to tricuspid regurgitation severity*

Comparison of event-free survival rates according to tricuspid regurgitation severity at 3-6 months of follow-up showed statistically significant differences p=0.0015.

***Table 3**. Univariate and multivariate regression models of tricuspid regurgitation severity and other prognostic factors with combined events*

	Univariate		Multivariate	
	HR(95%CI)	P	HR(95%CI)	P
Age	1.01 (0.98 - 1.02)	0.592		
Male	0.88 (0.47 - 1.63)	0.676		
Smoking	0.68 (0.34 - 1.37)	0.281		
Hypertension	0.74 (0.42 - 1.32)	0.315		
Atrial fibrillation	1.20 (0.61 - 2.36)	0.603		
Heart failure history	0.54 (0.07 - 3.90)	0.539		
Admission SBP	0.99 (0.98 - 1.01)	0.496		
Heart rate	1.01 (0.99 - 1.02)	0.612		
NYHA	1.23 (0.83 - 1.82)	0.302		
Hemoglobin	0.99 (0.97 - 1.002)	0.098	0.98 (0.96 - 0.99)	**0.002**
Serum creatinine	0.94 (0.86 - 1.03)	0.201		
Troponin T (per 100 unit increase)	0.999 (0.977 - 1.02)	0.933		
NT - proBNP (per 100 unit increase)	1.003 (0.999 - 1.008)	0.093	1.002 (0.998 - 1.006)	0.305
Creatinine (per 50 unit increase)	1.07 (0.94 - 1.23)	0.299		

	Univariate		Multivariate	
	HR(95%CI)	P	HR(95%CI)	P
LVEF	0.99 (0.95 - 1.03)	0.605		
Right ventricular dilation	1.03 (0.25 - 4.27)	0.963		
TAPSE < 17	1.39 (0.77 - 2.50)	0.270		
FAC < 35	1.35 (0.75 - 2.44)	0.321		
RVSP	1.01 (0.99 - 1.03)	0.149	0.98 (0.95 - 1.01)	0.129
Tricuspid regurgitation severity				
Mild/Moderate	1	c	1	
Severe	1.64 (1.19 - 2.27)	**0.003**	1.94 (1.30 - 2.91)	**0.001**

The univariate regression model showed that the prognostic factor for combined events in the study patients was tricuspid regurgitation severity, with HR 1.64 (95% CI 1.19 to 2.27; p = 0.003).

The Kaplan-Meier curve in Figure 3 compared the rates of combined events (all-cause mortality and heart failure rehospitalization) in heart failure patients with reduced ejection fraction according to tricuspid regurgitation severity over 3-6 months of follow-up, showing statistically significant differences (p=0.0015). Multivariate Cox regression analysis demonstrated that tricuspid regurgitation severity was an independent prognostic factor for combined events within 3-6 months of follow-up (HR 1.94, 95% CI 1.30 - 2.91; p = 0.001).

DISCUSSION

Normally, there is a flow of blood from the superior vena cava into the right atrium throughout the systole. This flow ceases at the end of systole. The flow into the right atrium restarts at the beginning of diastole and continues until atrial contraction causes flow reversal. In people with tricuspid regurgitation, the flow into the right atrium during systole is reduced and in cases of severe regurgitation, the flow reverses from the right ventricle into the right atrium and superior vena cava. In severe tricuspid regurgitation, there are changes in right atrial compliance, reversed flow from the right ventricle into the superior vena cava continues throughout systole, and flow from the superior vena cava into the right atrium only occurs early in diastole. Sometimes, the regurgitant flow is nearly equal to the forward flow filling the right ventricle. As a result, cardiac output decreases.

Increased pressure in the right atrium leads to increased pressure in the systemic venous system and increased pressure in all organs. Chronic venous hypertension causes dysfunction of the liver, kidneys, gastrointestinal tract, brain, and many other organs.

The consequence is salt and water retention, which causes edema, pleural effusion, and ascites and can lead to multiorgan failure commonly seen in severe tricuspid regurgitation.

In our study, the rates of mild, moderate and severe tricuspid regurgitation in patients with reduced ejection fraction heart failure were 48.3%, 33.6%, and 18.1%, respectively. The Kaplan-Meier curve showed that all-cause mortality and rehospitalization at 3-6 months of follow-up were significantly higher in the severe tricuspid regurgitation group compared to the mild-moderate group (logrank p=0.0015). This is similar to the study by Koelling et al. (2002)3 of 1421 patients with reduced ejection fraction heart failure, with 1-year follow-up showing severe tricuspid regurgitation increased the risk of adverse events (p=0.001). In the study by Benfari et al. (2019), 4 of 13,026 patients with reduced ejection fraction heart failure from 2003 to 2011, more severe tricuspid regurgitation was associated with increased mortality

or hospitalization (p<0.001). According to Bartko et al. (2019), 5 in 382 patients with reduced ejection fraction heart failure, tricuspid regurgitation severity also predicted mortality and adverse events (p<0.001).

With univariate regression analysis, our study found tricuspid regurgitation severity to be a prognostic factor for combined events in patients with reduced ejection fraction heart failure. Similar results were found by Agricola et al. (2006)6 with univariate Cox regression analysis (p=0.01). After adjusting for other prognostic factors, we identified two independent risk factors for mortality and rehospitalization in patients with reduced ejection fraction heart failure: hemoglobin level and tricuspid regurgitation severity. According to the study by Bartko et al., in 382 patients with reduced ejection fraction heart failure, tricuspid regurgitation severity (HR 2.14, 95% CI 1.53-2.00; p<0.001) also had prognostic value for mortality or rehospitalization in heart failure patients.

CONCLUSION

In hospitalized patients diagnosed with heart failure with reduced ejection fraction, the severity of tricuspid regurgitation is associated with an increased risk of mortality or rehospitalization over 3-6 months of follow-up. Tricuspid regurgitation severity is an independent prognostic factor for mortality or rehospitalization in patients with heart failure with reduced ejection fraction, with a hazard ratio of 1.94 (95% confidence interval 1.30-2.91).

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Physician's perception on the diagnosis and treatment of heart failure in Vietnam

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▶ Received: 21 October 2023
Accepted: 25 November 2023
Published online: 30 November 2023

To cite: Nguyen DTT, Pham MH, Phan TD, *et al. J Vietnam Cardiol 2023*;**107E**:54-61

ABSTRACT

Objective: Assess the perception of cardiologists, internists, and other specialties on the diagnosis and treatment of heart failure in Vietnam.

Subjects and methods: Cross-sectional study, on cardiologists, internists and other specialties at some hospitals in the country.

Results: The study was conducted on 806 physicians nationwide with a mean working time of 7.4 ± 7.1 years. Correct perception of the physician of heart failure is relatively high. However, the perception of cardiologists is better than the non-cardiologists (including internists and other specialties) on the diagnose and treatment heart failure, heart failure with preserved ejection fraction and reduced ejection fraction.

Conclusion: Cardiologists' perception of heart failure is better than the non-cardiologists. We need to improve education and training for physicians about heart failure.

Key words: heart failure, physician's perception, Vietnam.

INTRODUCTION

Heart failure (HF) is a major global health issue with high morbidity and mortality rates.[1] Currently, there are over 23 million people worldwide living with heart failure,[1] In the United States alone, approximately 6.2 million people have the condition[1] and 500,000 new cases are diagnosed each year.[2] From 2012 to 2030, direct medical costs to treat heart failure are projected to increase from $21 billion to $53 billion.[3]

In Vietnam, the number of heart failure patients is also quite high. In 2007, there were 1,962 heart failure inpatients at Vietnam National Heart Institute, accounting for 19.8% of total hospital admissions.[4] According to the 2017 Health Statistics Yearbook, the mortality rate due to heart failure accounted for 0.4% of all-cause mortality, ranking 10th among the leading causes of death in Vietnam.[5] Despite advances in treatment, the overall prognosis remains very poor with a 5-year mortality rate of up to 50%.[6,7]

Over four decades, we have witnessed tremendous advances in heart failure treatment. 1987 marked an important milestone in heart failure history when enalapril was shown to reduce mortality in patients with congestive heart failure.[8] Since then, other drugs emerged to alleviate symptoms and prolong life in heart failure patients. Currently, many heart failure therapies exist including medical therapy, device therapy, phenotype-directed therapy, etc.[9] This requires physicians to

continuously update their knowledge. Insights into etiology, diagnosis and treatment influence how a physician approaches heart failure management. Thus, physicians play a major role in shaping the disease course for individual patients. To enhance effectiveness of heart failure care and management, many countries worldwide have implemented new approaches to improve physicians' knowledge on heart failure treatment.

Internationally, there have been some studies evaluating physicians' practices in diagnosing and treating heart failure. In Vietnam, no research has been done on this issue. Therefore, we conduct a study entitled "The Current Status of Vietnamese Internists' Knowledge on Diagnosing and Treating Heart Failure" with the goal assessing physican's perception on diagnosing and treating heart failure in Vietnam in order to have educational measures to raise doctoers's knowledge.

SUBJECTS AND METHODS

Study subjects

Inclusion criteria:

Cardiologists or general internists, some other specialties: critical care, surgery, traditional medicine, etc. nationwide

Exclusion criteria:

Physicians who did not consent to participate in the study.

Method

Study design: Cross-sectional descriptive study.

Sample size: Estimated using proportion estimation method

$$n = Z^2_{1-\alpha/2}\frac{p(1-p)}{d^2}$$

Where:

- $Z^2_{1-\alpha/2}$ is the reliability coefficient corresponding to statistical significance level α = 0.05

- d is the margin of error, 5%

- p: the proportion of physicians with adequate clinical practice in treating heart failure with preserved ejection fraction, 0.45

Thus, the estimated sample size is 380. In reality, we recruited 806 physicians.

Study duration: 01st April, 2022 – 01st May, 2023

Implementing unit: Vietnam Heart Association

Data collection: Survey via email questionnaires

Data analysis

Data was entered into Excel. Strict data validation was enabled to avoid errors. Afterwards, data was transferred to SPSS 26.0 for management and analysis. Data was analyzed and presented as frequencies and percentages. Chi-square test p-values were used to denote differences between independent variables and the dependent variable.

Results are presented in tables or charts using appropriate statistical graphs: normally distributed continuous variables as mean ± standard deviation, and categorical variables as absolute (percentage) values: n (%). P-value < 0.05 was considered statistically significant.

Research ethics

The study complied with ethical regulations in biomedical research.

RESULTS

Table 1*. General characteristics of study subjects*

Characteristics		Number n = 806
Gender	Male	490 (60.8)
	Female	316 (39.2)
Specialty	Cardiology	408 (50.6)
	Internal Medicine	288 (35.7)
	Others	110 (13.6)
Level	Central	196 (24.3)
	Provincial	359 (44.5)
	District	251 (31.1)
Region	Northern	345 (42.8)
	Central	171 (21.2)
	Southern	290 (36.0)
Years in practice (years)	$\bar{X} \pm SD$ (min – max)	7.4 ± 7.1 (0 - 40)

Comments: Among 806 subjects. 60.8% were

male and 39.2% were female. 50.6% were cardiologists. 35.7% were internists. and 13.6% had other specialties (surgery. critical care. traditional medicine. etc.). 24.3% worked at central hospitals. 44.5% at provincial hospitals. and 31.1% at district hospitals. 42.8% were from the North. 21.2% from the Central. and 36% from the South.

***Table 2**. Common ancillary tests in diagnosing heart failure*

	Cardiology	Internal Medicine	Others	p (cardiology vs non-cardiology)
Echocardiogram	400 (98)	285 (99)	106 (96.4)	0.425
NT-proBNP	397 (97.3)	279 (96.9)	105 (95.5)	0.501
Troponin T	24 (5.9)	36 (12.5)	15 (13.6)	**0.001**
CK-MB	7 (1.7)	29 (10.1)	12 (10.9)	**< 0.001**
Ferritin	5 (1.2)	6 (2.1)	3 (2.7)	0.260
Blood lactate	3 (0.7)	6 (2.1)	1 (0.9)	0.218

Comments: The appropriate understanding of troponin, CK-MB in diagnosing heart failure was statistically significantly different between cardiologists and non-cardiologists with p<0.05.

***Table 3**. The most important goal in treating heart failure*

	Cardiology (n=408)	Internal Medicine (n=288)	Others (n=110)	p (cardiology vs non-cardiology)
Reduce mortality	298 (73)	177 (61.5)	75 (68.2)	0.010
Prevent rehospitalization due to heart failure progression	200 (49)	140 (48.6)	48 (43.6)	0.217
Improve clinical status. function and quality of life	231 (56.6)	182 (63.2)	64 (58.2)	0.170

Comments: More cardiologists (73%) identified reducing mortality as the most important goal compared to non-cardiology groups (61.5% and 68.2%), which was statistically significant with p<0.05.

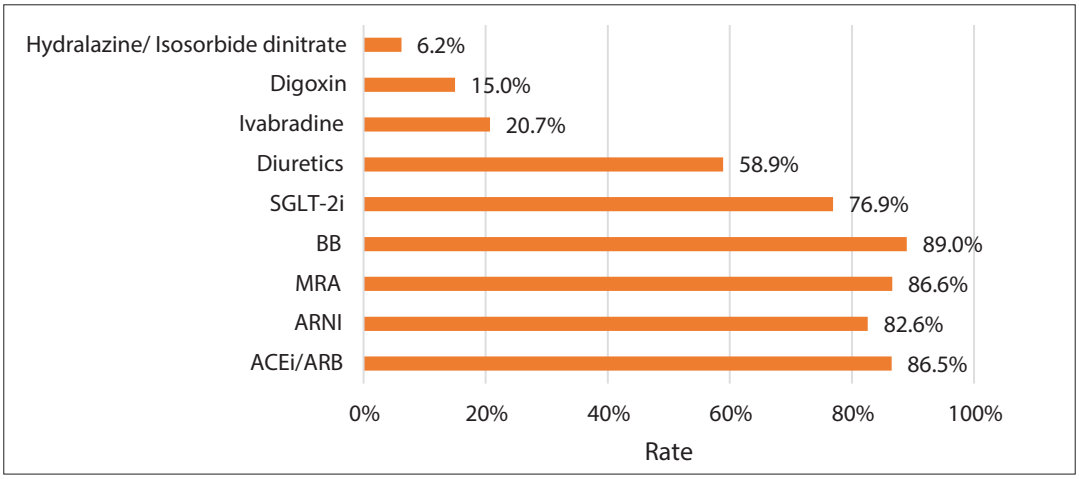

***Chart 1**. Essential and commonly used medications for treating heart failure*

Comments: The majority of physicians correctly identified beta-blockers (89%), MRAs (86.6%), ACEi/ARBs (86.5%), ARNIs (82.6%), SGLT2is (76.9%), and diuretics (58.9%) as commonly used in treating heart failure.

Table 4*. Essential and commonly used heart failure medications by cardiologists vs non-cardiologists*

	Cardiology (n=408)	Internal Medicine (n=288)	Others (n=110)	p 2 groups (cardiology vs non-cardiology)
ACEi/ARB	351 (86)	248 (86.1)	98 (89.1)	0.707
ARNI	359 (88)	225 (78.1)	82 (74.5)	**< 0.001**
MRA	365 (89.5)	249 (86.5)	84 (76.4)	**0.016**
Beta-blocker	377 (92.4)	249 (86.5)	91 (82.7)	**0.002**
SGLT2i	351 (86)	202 (70.1)	67 (60.9)	**< 0.001**
Diuretics	248 (60.8)	158 (54.9)	69 (62.7)	0.279
Ivabradine	92 (22.5)	59 (20.5)	16 (14.5)	0.194
Digoxin	43 (10.5)	58 (20.1)	20 (18.2)	**< 0.001**
Hydralazine/ Isosorbide dinitrate	14 (3.4)	26 (9)	10 (9.1)	**0.001**

Comments: The appropriate understanding of ARNIs, MRAs, beta-blockers, SGLT2is, digoxin, hydralazine for treating heart failure was statistically significantly different between cardiologists and non-cardiologists with p<0.05.

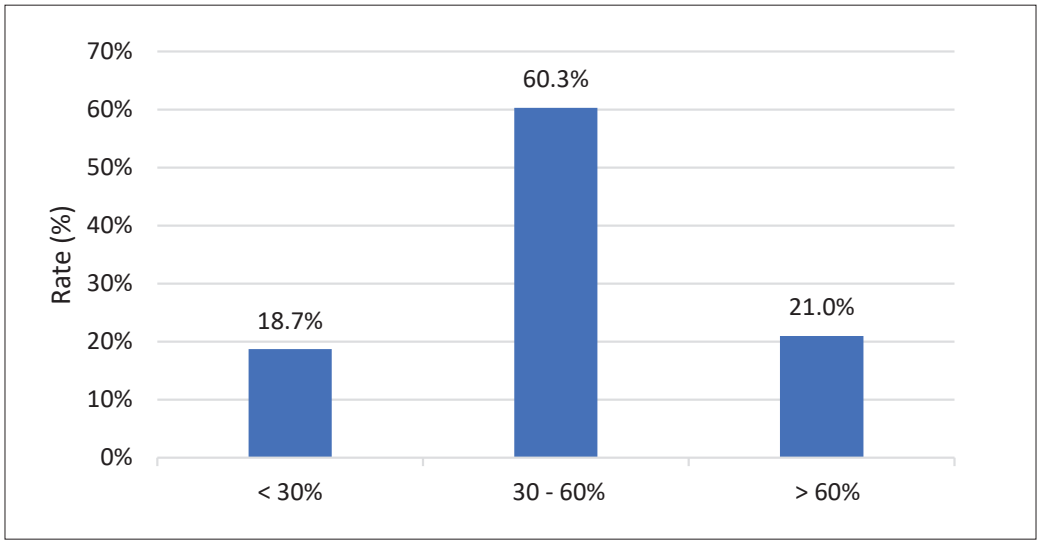

Chart 2*. Proportion of HFpEF among total heart failure patients*

Comments: The majority of physicians correctly identified the proportion of heart failure with preserved ejection fraction to be 30-60%, accounting for 60.3%.

***Table 5**. Diagnosing heart failure with preserved ejection fraction*

Characteristics	Cardiology	Internal Medicine	Others	p (cardiology vs non-cardiology)
Diagnostic scores:				
H_2FPEF	303 (74.3)	189 (65.6)	86 (78.2)	0.103
HAS-BLED	18 (4.4)	37 (12.8)	19 (17.3)	**< 0.001**
HFA–PEFF	188 (46.1)	127 (44.1)	51 (46.4)	0.699
PEP-CHF	57 (14)	66 (22.9)	16 (14.5)	**0.013**

Comments: The inappropriate understanding of HAS-BLED, PEP-CHF in diagnosing HFpEF was statistically significantly different between cardiologists and non-cardiologists with p<0.05.

***Table 6**. Medications proven to improve outcomes in HFpEF patients - cardiologists vs non-cardiologists*

	Cardiology	Internal Medicine	Others	p (cardiology vs non-cardiology)
ACEi/ARB	183 (44.9)	159 (55.2)	65 (59.1)	**0.001**
ARNI	201 (49.3)	177 (61.5)	64 (58.2)	**0.001**
MRA	165 (40.4)	154 (53.5)	54 (49.1)	**0.001**
Beta-blocker	145 (35.5)	130 (45.1)	55 (50)	**0.002**
SGLT2i	335 (82.1)	194 (67.4)	73 (66.4)	**< 0.001**
Diuretics	55 (13.5)	49 (17)	22 (20)	0.088
Digoxin	4 (1)	15 (5.2)	1 (0.9)	**0.006**

Comments: The appropriate understanding of ACEi/ARB, ARNI, MRA, beta-blocker, SGLT2i, digoxin in improving HFpEF outcomes was statistically significantly different between the cardiology and non-cardiology groups with p<0.05.

***Table 7**. Diagnosing heart failure with reduced ejection fraction by physicians*

	Cardiology	Internal Medicine	Others	p 2 groups
Risk factors	205 (50.2)	183 (63.5)	78 (70.9)	**< 0.001**
Clinical symptoms	357 (87.5)	258 (89.6)	98 (89.1)	0.387
Left ventricular ejection fraction	368 (90.2)	269 (93.4)	103 (93.6)	0.090
Structural/functional evidence	274 (67.2)	192 (66.7)	74 (67.3)	0.922
Elevated natriuretic peptides	322 (78.9)	191 (66.3)	67 (60.9)	**< 0.001**
Pulmonary congestion on X-ray	178 (43.6)	115 (39.9)	39 (35.5)	0.155
Elevated troponin	32 (7.8)	28 (9.7)	14 (12.7)	0.183

Comments: The appropriate use of risk factors and natriuretic peptides to diagnose HFrEF was statistically significantly different between cardiologists and non-cardiologists with p<0.05.

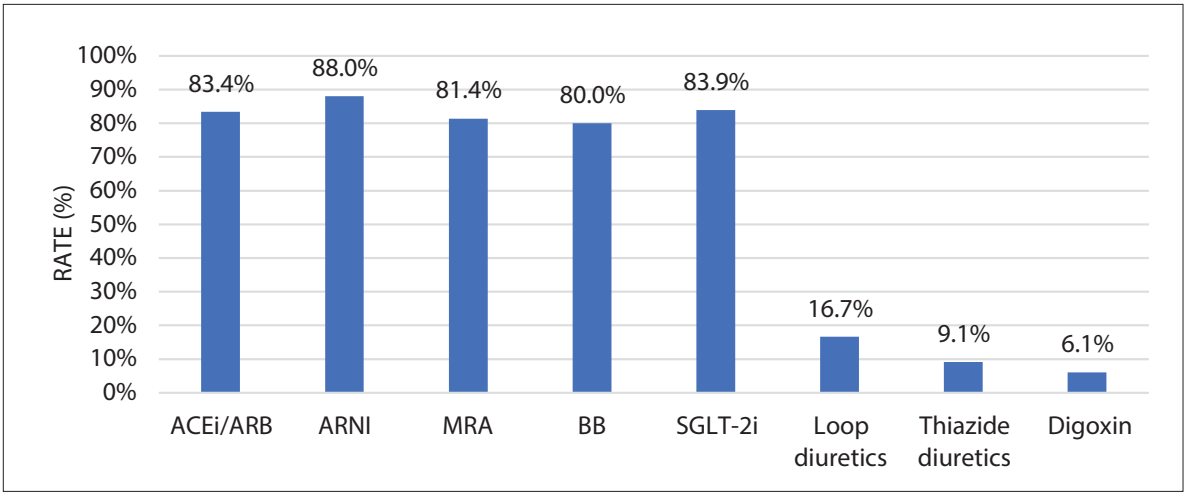

***Chart 4**. Medications proven to improve prognosis in HFrEF patients*

Comments: Most doctors correctly identified ACEi/ARB (83.4%), ARNI (88%), MRA (81.4%), beta-blocker (80%), SGLT2i (83.9%) as having evidence to improve prognosis in HFrEF patients.

***Table 8**. Medications with evidence to improve HFrEF prognosis - cardiologists vs non-cardiologists*

	Cardiology	Internal Medicine	Others	p (cardiology vs non-cardiology)
ACEi/ARB	354 (86.8)	230 (79.9)	88 (80)	0.009
ARNI	376 (92.2)	245 (85.1)	88 (80)	< 0.001
MRA	358 (87.7)	216 (75)	82 (74.5)	< 0.001
Beta-blocker	356 (87.3)	210 (72.9)	79 (71.8)	< 0.001
SGLT2i	362 (88.7)	238 (82.6)	76 (69.1)	< 0.001
Loop diuretics	53 (13)	53 (18.4)	29 (26.4)	0.004
Thiazide diuretics	24 (5.9)	30 (10.4)	19 (17.3)	0.001
Digoxin	18 (4.4)	27 (9.4)	4 (3.6)	0.045

Comments: Cardiologists had better understanding than non-cardiologists regarding medications proven to improve HFrEF prognosis. The proportion of doctors correctly identifying ACEi/ARB, ARNI, MRA, beta-blocker, SGLT2i as improving HFrEF prognosis was significantly higher in the cardiology group compared to the non-cardiology group with p<0.05.

The proportion of doctors incorrectly identifying loop diuretics, thiazides, digoxin as improving HFrEF prognosis was significantly higher in the non-cardiology group compared to cardiology with p<0.05.

DISCUSSION

General knowledge on diagnosing and treating heart failure among our study subjects was quite good. 98.1% of subjects correctly understood echocardiography to assess ejection fraction, with no difference between cardiology and non-cardiology

groups (p>0.05). 96.9% of doctors were aware of NT-proBNP biomarkers for diagnosing heart failure, again with no difference between groups (p>0.05). The proportion of doctors with incorrect understanding of ancillary heart failure diagnostic tests was very low: troponin 9.3%; CK-MB 6%, ferritin 1.7%, etc. This shows there was no difference in awareness of basic diagnostic tests for heart failure between doctor groups. In Milan Gupta's survey[10], there were differences in the use of natriuretic peptides due to cost and availability of tests, with cardiology and internal medicine groups utilizing them more than family medicine. In our study, most doctors identified reducing mortality as the most important goal in treating heart failure (68.2%), with a higher rate in cardiology (73%) than non-cardiology groups (61.5% and 68.2%) (p<0.05). The proportion of doctors correctly identifying commonly used essential medications for treating heart failure was very high: beta-blockers highest at 89%, MRAs 86.6%, ACEi/ARBs 86.5%, ARNIs 82.6%, SGLT2is 76.9%, diuretics 58.9%. However, some still had misconceptions: ivabradine 20.7%; digoxin 15%; hydralazine 6.2%. Appropriate understanding of ARNIs, MRAs, beta-blockers, SGLT2is, digoxin, hydralazine for treating heart failure was significantly higher in cardiology than non-cardiology (p<0.05). Although many had correct understanding, some still had misconceptions, likely because they lacked heart failure training - cardiologists had better awareness than non-cardiologists.

60.3% of doctors stated HFpEF prevalence was 30-60%. This is similar to Milan Gupta's study at 42%[10], and S.Angela's study with 56% HFrEF, 21% HFmrEF, 23% HFpEF among 42,061 heart failure patients.[11] Only 45.4% correctly understood the HFA-PEFF score since it is unpopular and not used clinically - we need more HFpEF diagnostic education. Meanwhile, significantly more non-cardiologists than cardiologists had misconceptions about using HAS-BLED and PEP-CHF scores to diagnose HFpEF (p< 0.001 and 0.013). 74.7% correctly understood that SGLT2is improve HFpEF prognosis. This rate was lower for drugs not improving HFpEF outcomes: ARNIs 54.8%, ACEi/ARBs 50.5%, MRAs 46.3%, beta-blockers 40.9%. This demonstrates updated knowledge on HFpEF treatment. Cardiologists had better understanding than non-cardiologists. Significantly more non-cardiologists incorrectly thought ACEi/ARBs, ARNIs, MRAs, beta-blockers, digoxin improve HFpEF outcomes (p<0.05). Significantly more cardiologists correctly understood SGLT2is improve HFpEF outcomes (p<0.05). Similarly, Milan Gupta[10] found family physicians were more likely than internists and cardiologists to think ACEi/ARBs, beta-blockers, loop diuretics and MRAs improve HFpEF prognosis (p<0.001). Their study preceded the EMPEROR-Preserved trial[12] demonstrating SGLT2is improve HFpEF prognosis, thus we examined awareness of updated evidence.

Cardiologists had significantly better understanding of using natriuretic peptides to diagnose HFrEF than non-cardiologists (p< 0.001<0.05). Meanwhile, more non-cardiologists used risk factors to diagnose HFrEF (p<0.05), thus cardiologists were better at HFrEF diagnosis. Most doctors correctly identified ACEi/ARBs (83.4%), ARNIs (88%), MRAs (81.4%), beta-blockers (80%), SGLT2is (83.9%) as proven to improve HFrEF prognosis. Cardiologists had superior awareness compared to non-cardiologists of medications improving HFrEF prognosis. Significantly more cardiologists correctly identified ACEi/ARBs, ARNIs, MRAs, beta-blockers and SGLT2is as improving HFrEF prognosis (p<0.05); while significantly more non-cardiologists incorrectly identified loop diuretics, thiazides and digoxin (p<0.05). This difference is understandable since cardiologists receive more heart failure training and clinical experience than non-cardiologists.

CONCLUSION

Physicians' knowledge of heart failure was relatively good, however there were still differences in appropriate understanding between cardiologists and non-cardiologists. Cardiologists had superior awareness than non-cardiologists regarding all aspects of heart failure - diagnosis and management of general heart failure, heart failure with preserved ejection

fraction, and heart failure with reduced ejection fraction. Heart failure patients should be managed and treated by cardiologists. More education is needed to improve non-cardiology physicians' knowledge.

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Evaluation of the relationship between nutritional status and 1-year mortality rate in patients with acute heart failure admitted at Vietnam National Heart Institute

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▶ Received: 27 October 2023
Accepted: 28 November 2023
Published online: 30 November 2023

To cite: Nguyen TH, Pham MT, Pham TT, *et al. J Vietnam Cardiol 2023*;**107E**:62-72

ABSTRACT

Background: Heart failure continues to be a leading cause of hospitalization worldwide, and acute heart failure (AHF) poses a significant risk of morbidity and mortality in the short term[1]. Acute heart failure (AHF) is a clinical syndrome with different triggering factors and manifests either as new onset or as an acute decompensation of chronic HF[5,6].

In Vietnam, heart failure also accounts for a considerable proportion. Hospitalized heart failure patients at the Vietnam National Heart Institute in 2007 were 1,962 patients, accounting for 19.8% of total admissions.[10] According to the 2010 statistics of the Ministry of Health, the incidence was 43.7%, of which the mortality rate was 1.2%. According to the 2015 statistical yearbook of the Department of medical service administration - Ministry of Health, the mortality rate from heart failure in 2013 accounted for 0.51% of total deaths from all causes, ranking 10th among the causes of death in Vietnam

Despite being actively treated and symptom improvement, patients hospitalized with AHF still have a considerable risk of mortality ranging from 10-20% within the next 6 months[2,7-9].

Subjects & methods: A total of 103 patients were successfully followed up in the first year. The mean follow-up time was 1 year.

Results: The main result of the study was the all-cause mortality rate within 1 year was 68%.

INTRODUCTION

Heart failure (HF) has become a global public health burden due to its high incidence and associated costs.[1] In the United States, there are over 1 million hospitalizations annually for acute heart failure (AHF). Combined in the US and Europe, there are about 1 million hospitalizations annually with a primary diagnosis of heart failure.[2] Although hospitalization rates in the US and Europe have declined, early post-discharge mortality and readmission rates have hardly changed over a long period. Recent data show that heart failure rates in Southeast Asian countries are similar to global figures, with heart failure accounting for up to 20% of hospital admissions and 30-day mortality of heart failure patients (HF pts)

reaching 17% (around 10% in the Philippines, 17% in Indonesia).[3]

Malnutrition is a very common condition in HF patients and may be due to various mechanisms, such as low nutrition due to intestinal edema and anorexia,[4] hepatic dysfunction,[5] increased cytokine-induced catabolism,[6] insulin resistance, and other mechanisms.[7] Some studies suggest that malnutrition status, assessed by different clinical scoring systems, may also affect clinical outcomes in middle-aged and elderly patients hospitalized for acute HF.[8] According to Basta et al., nearly 55% of the study population with ST-segment elevation myocardial infarction (STEMI) were malnourished. Those individuals had a higher risk of death from any cause compared to those with normal nutritional status. It is important to accurately assess patients' nutritional status.[9]

Anker et al., Zapatero et al. have demonstrated that nutritional status is an independent prognostic factor in patients with acute or chronic heart failure.[10,11] Some nutritional screening tools such as the Mini Nutritional Assessment-Short Form (MNA-SF) and Nutritional Risk Screening (NRS-2002) have been developed to assess malnutrition risk in patients with HF.[12,13] Due to the complexity of calculating these indices and the subjectivity of questionnaires, the value and generalization of nutritional indices and questionnaires may vary according to examiners' experience and patients' recall. In contrast, some biochemical nutritional indices, including body mass index, total cholesterol, serum albumin and total lymphocyte count have been proposed to predict survival in HF patients.[14-16] There are many tools to assess nutritional status, however the NUTRIC score is recommended for use in the ICU.[17] Currently, there have been no studies at the Heart Institute investigating mortality of patients with acute heart failure and nutrition, therefore this study aims to assess the impact of nutritional status on in-hospital and 1-year mortality rates in patients with acute heart failure.

Objectives:

1. Determine nutritional status on admission and 1-year mortality rate of patients with acute heart failure.

2. The relationship between nutritional status and mortality in the first year of patients with acute heart failure.

SUBJECTS AND METHODS

Study design

A cross-sectional descriptive study was conducted on 103 patients diagnosed with acute heart failure or acute decompensated chronic heart failure from January 01st, 2019 to December, 2020 who had complete information on readmission or mortality within 1 year after discharge. Survey data was collected from medical records and telephone interviews.

Selection criteria

- Patients admitted and diagnosed with acute heart failure according to 2016 ESC criteria with standards as outlined in the overview

- Patients 18 years and older

- Patients consented to participate in the study and provided sufficient information

The Nutrition Risk in Critically ill (NUTRIC) score

Age, comorbidities, number of days hospitalized before ICU admission, total APACHE II score assessing disease severity, and SOFA score assessing organ failure within 24 hours of admission.[18,19] A NUTRIC score ≥5 indicates higher malnutrition risk, while a score <5 indicates lower risk. APACHE II score: Assesses disease severity collected within 24 hours of admission. These signs are collected from medical records. APACHE II score is calculated according to Knaus.[18]

***Table 1**. NUTRIC score sheet (Heyland 2011)*

NUTRIC Score = Nutritional risk score in critically ill patients.

NUTRIC score without IL-6

Variables		Points
Age	<50	0
	50-74	1
	≥74	2
APACHE score	<15	0
	15-19	1
	20-27	2
	≥28	3

Variables		Points
SOFA score Organ failure assessment	<6	0
	6-9	1
	≥10	2
Number of comorbidities	0-1	0
	≥2	1
Days hospitalized before ICU admission	0-<1	0
	≥1	1
Total mNUTRIC score		

Sum points. If ≥ 5 points: High malnutrition risk. If <5 points: Low malnutrition risk.

Data analysis

- All data was processed using SPSS 20.0 and Excel software.

- 24-hour food survey: Recording food tracking sheets by asking patients, caregiver nurses, other trackers. Using the photo book for food surveys from the Institute of Nutrition in 2014. Nutritional values were calculated based on the Vietnamese Food Composition Table from the Institute of Nutrition in 2007. Dietary assessment was performed in Excel.

RESULTS

Nutritional status on admission

Table 3.1. *Nutritional assessment indices on admission*

Index	Overall	Male	Female	P
Weight (kg)	53.02 ± 10.75 Min: 33; Max: 94	56.2 ± 10.3	47.5 ± 9.2	p<0.05 (T-test)
Height (cm)	158.27 ± 7.84 Min: 140; Max: 177	162.5 ± 5.1	150.7 ± 5.9	p<0.05 (T-test)
Mid-arm circumference (cm)	25 Min: 17; Max: 36	25.0 ± 3.3	24.0 ± 2.8	p>0.05 Man-Whitney
Overall BMI (kg/m^2)	21.08 ± 3.45 Min: 15.1; Max: 34.5	21.2 ± 3.5	20.9 ± 3.4	p>0.05 Chi-square
BMI (kg/m^2) no edema group	21.07 Min: 15.6; Max: 30	21 Min: 15.6; Max: 30	20.9 Min: 15.6; Max: 28	p>0.05 Chi-square
mNUTRIC Score	4.0 Min: 1; Max: 8	3.8 ± 1.6	4.3 ± 1.4	p>0.05 Man-Whiney
Malnutrition by BMI (21 pts - 20.4%)		14 (21.2%)	7 (18.9%)	p>0.05 Fisher's Exact test

Comments: BMI: The malnutrition risk by Nutric score was lower in those with BMI <18.5 than those with BMI≥ 18.5, this difference was not statistically significant with p>0.05.

Age: There was a statistically significant difference in malnutrition risk by Nutric score between age groups with p<0.05.

Gender: Malnutrition risk was lower in males than females, this difference was not statistically significant with p>0.05.

Mechanical ventilation: Malnutrition risk was 5.1 times higher in the ventilation group than the non-ventilation group, this difference was statistically significant with p<0.05.

Number of comorbidities: The more diseases a patient had, the higher the malnutrition risk. Those with more than 2 diseases had a 12.1 times higher malnutrition risk than those with 2 or fewer diseases, this difference was statistically significant with p<0.05.

Infection: Malnutrition risk was 1.4 times higher in the infection group than the non-infection group, this difference was not statistically significant with p>0.05.

Vasopressors: Malnutrition risk was 2 times higher in the vasopressor group than the non-vasopressor group, this difference was not statistically significant p>0.05.

***Table 3.2**. Nutritional status on admission according to criteria*

Criteria		On admission	Total
By BMI	Malnutrition	21 (20.4%)	103 (100%)
	No malnutrition	82 (79.6%)	
By GLIM ASPEN 2015	Malnutrition	35 (34%)	103 (100%)
	No malnutrition	68 (66%)	
By mNUTRIC score	High risk mNUTRIC ≥5	37 (35.9%)	103 (100%)
	Low risk mNUTRIC <5	66 (64.1%)	

Comments: On the first day of admission, BMI assessment showed 20.4% were malnourished. Assessment by GLIM criteria of ASPEN 2015 showed 34% were malnourished. Assessment by mNUTRIC score showed 35% were at high malnutrition risk, 65% were at low risk.

***Table 3.3**. Relationship between nutritional status by mNUTRIC score and related factors*

Criteria		High risk NUTRIC ≥5	Low risk NUTRIC <5	OR (95% CL)	P
BMI	BMI<18.5	6	15	0.7(0.2-1.9)	p>0.05*
	BMI≥18.5	31	51	1	
Age	<60 years	1	20		**p<0.05****
	60-74 years	9	30		
	≥ 75 years	27	16		
Giới	Male	20	46	0.5(0.2-1.2)	p>0.05**
	Female	17	20	1	
Ventilation	Yes	28	25	5.1 (2.1-12.6)	**p<0.05****
	No	9	41	1	
Number of comorbidities	>2 diseases	35	39	12.1 (2.7-54.7)	**p<0.05****
	≤ 2 diseases	2	27	1	
Infection	Yes	25	40	1.4(0.6-3.2)	p>0.05**
	No	12	26	1	
Vasopressors	Yes	19	23	2 (0.9-4.5)	p>0.05**
	No	18	43	1	

** Chi square test, * Fisher's Exact test

Comments: Age: There was a statistically significant difference in malnutrition risk by Nutric score between age groups, p<0.05. Mechanical ventilation: Malnutrition risk was 5.1 times higher in the ventilation group than the non-ventilation group, this difference was statistically significant, p<0.05. Vasopressors: Malnutrition risk was 2 times higher in the vasopressor group than the non-vasopressor group, this difference was not statistically significant, p>0.05.

Relationship between nutritional status and mortality in the first year

***Table 3.4**. Mortality rate in the first year*

	Died		Survived		Total	
	N	%	n	%	N	%
After 1 year	70	68	33	32	103	100%

Comments: In the first year there were 70 patient deaths, accounting for 68%.

***Table 3.5**. Comparison of nutritional status between surviving and deceased patients*

Index	Total		Survived		Died		P
	N	%	n	%	N	%	
BMI <18.5	21	100%	8	38.1	13	61.9	P=0.5 Chi-square
BMI ≥ 18.5	82	100%	25	30.5	57	69.5	
mNutric: 0-4 (Low malnutrition risk)	67	100	29	43.3%	38	56.7%	P=0.01 Chi-square
mNutric ≥ 5 (High malnutrition risk)	36	100%	4	11.1%	32	88.9%	

Comments: The malnutrition group had a 61.9% mortality rate while the non-malnutrition group had a 69.5% mortality rate, the difference was not statistically significant with p>0.05.

In the high malnutrition risk group the mortality rate was 88.9%, higher than the 56.7% mortality rate in the low risk group, the difference was statistically significant with p<0.05.

***Table 3.6**. Relationship between mNutric score and mortality*

Factor	OR	95% CI	P
mNutric score	1.655	1.196 - 2.291	0.002

Comments: For every 1 point increase in mNutric score, the risk of mortality increases by 1.65 times.

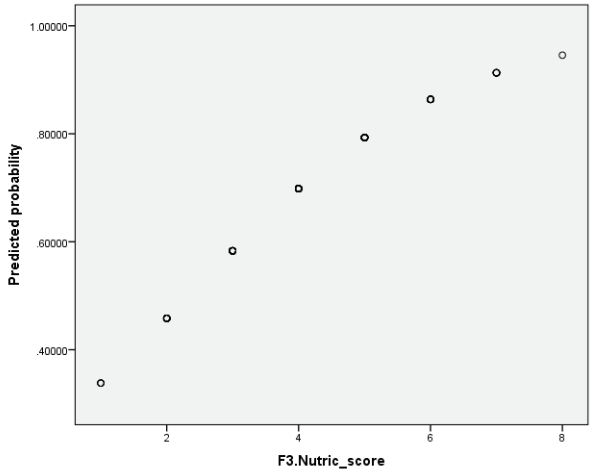

***Figure 1**. Relationship between malnutrition risk mNutric score and predicted probability of mortality*

Comments: So there is a linear relationship between malnutrition risk score and predicted probability of mortality according to the chart.

***Table 3.7**. Relationship between factors and mortality in the first year*

Factor	Odd ratino	95% confidence interval	Statistical significance
Age	1.07	1.03-1.11	0.01
BMI	1.11	0.97-1.3	0.14
Malnutrition risk	0.3	0.04-1.8	0.2
mNutric score	1	0.6-1.7	0.9

Comments: In this study, only age was an independent factor leading to mortality with OR=1.07, 95% CI: 1.03-1.11, p=0.01<0.05.

DISCUSSION

Nutritional status on admission

Assessment by BMI showed the malnutrition rate was 20.4%, obesity rate 11.6%. The malnutrition rate was higher than in the study by Miró Ò (2017) on AHF patients with a malnutrition rate of 1.3%, while the obesity rate was lower than Miró Ò (72.6%).[21] This difference is because the author studied a large sample size in Spain over 1 year. The malnutrition rate was also higher than in the study by Cox ZL (2020) in admitted AHF patients with a malnutrition rate of 3%, and the obesity rate in our study was lower than Cox ZL's study with an obesity rate of 69%. [22] Our malnutrition rate was fairly similar to the study by Seko Y (2020) in ADHF patients with a malnutrition rate of 24.8%, the obesity rate was also lower than Seko Y (16.4%).

Assessment of malnutrition by GLIM criteria of ESPEN 2015 showed 35% of ICU patients had malnutrition by BMI at admission. Assessment by mNUTRIC score also showed 35.9% of ICU patients had high malnutrition risk (NUTRIC score ≥5) at admission.

This result was lower than the study by Lee Z-Y et al. on ICU patients with 56% having high malnutrition risk by NUTRIC score, Rosa M et al. on ICU patients with 50% having high risk by NUTRIC score. [23,24] The difference may be because the study population of Lee Z-Y comprised only mechanically ventilated patients on admission, while ours included both ventilated and non-ventilated patients. This result was higher than the study by Coltman et al. in the US (26%), Nguyen Huu Hoan et al. in the ICU of Bach Mai hospital (2016) which was 27%. [25,26] The explanation for this could be that the subjects in this study had acute heart failure, mostly on pre-existing chronic heart failure, along with other conditions like kidney failure, diabetes, hypertension, arrhythmias - an elderly population with accompanying age-related digestive and absorptive impairments. The difference with Nguyen Huu Hoan's results is that most ICU patients in that study were first-time admissions, with previously normal nutritional status.

In this study, when applying the ESPEN diagnostic criteria for malnutrition, i.e. combining additional criteria of unintentional weight loss and decreased fat-free mass with raising the BMI limit between normal and malnutrition to <20 kg/m^2 for subjects <70 years old and <22 kg/m^2 for subjects ≥70 years old, the malnutrition rate of hospitalized patients increased. This is appropriate when considering the physiological changes of the elderly. Height decreases with age, thus increasing the normal BMI limit in the elderly, and raising the limit between normal and malnourished to 20 kg/m^2 for those <70 years old and 22 kg/m^2 for those ≥70 years old.[27] The presence of fluid-electrolyte resuscitation, enteral and parenteral

nutrition, localized or generalized edema, dialysis, gastric tube placement, abdominal paracentesis, or conditions like kidney failure, liver failure, etc. in ICU patients causes pseudo weight gain, affecting BMI results. Therefore, if only the BMI index is used to assess the nutritional status of these subjects, it would lead to missed cases.

It has been recommended that all patients should be nutritionally screened within 48 hours of hospital admission.[28] Patients at risk of malnutrition should then undergo a full nutritional assessment. An international consensus on changing the definition of malnutrition has emphasized the role of inflammation.[27] The American Society for Parenteral and Enteral Nutrition (ASPEN) has recognized the importance of the inflammatory factor in the characteristics of malnutrition and recommended criteria-based classifications of patients. The presence of two or more criteria determines the presence of malnutrition, [29,30] including insufficient energy intake compared to estimated energy requirements, weight loss including unintentional weight loss occurring at any body mass index, loss of muscle mass, loss of subcutaneous fat, localized or generalized fluid accumulation, reduced functional activity with acute illness or injury, chronic illness and starvation-induced malnutrition.

For ICU patients, collecting information encounters many obstacles such as mechanical ventilation, impaired consciousness, long hospital stays, and frequent caregiver changes, so the pre-admission diet history and gastrointestinal symptoms are difficult to gather. Weight can be affected by fluid balance status, as HF patients use diuretics, or poor heart function causes fluid retention and edema, or fluid infusion is required to maintain hemodynamics, and the above-mentioned factors influencing fluid status. Physical examination - muscle mass can be used as a more objective tool since it does not require asking the patient, but assessing decreased muscle mass and fat mass may be obscured by symptoms of edema or ascites. Of all the tools, only NRS 2002 and NUTRIC score include both nutritional status and disease severity. Therefore, the American Society of Parenteral and Enteral Nutrition and American Society of Critical Care Medicine guidelines have clearly stated that the recommended nutritional screening tools for ICU patients are NRS 2002 and NUTRIC score.[18,19] The NRS 2002 score requires determining weight loss and dietary changes for nutritional assessment, which poses some difficulties in severely ill patients where this information is hard to gather. The NUTRIC score does not depend on these criteria as it collects clinical and test parameters of the patient, hence it is recommended for use in ICUs.[28] According to our study, the mean mNutric score was 4.0 (Min 1, Max 8), mean APACHE II score was 16.52±2.85 (Min 8, Max 27). This result was lower than the study by Heyland et al. (2011), which had a mean APACHE II score of 23±4.5[31].

The rate of patients at high malnutrition risk at admission was 35.9%, higher than Nguyen Huu Hoan's study (2016) in the ICU which was 27%,[26] lower than Kalaiselvan et al.'s study (2017) on mechanically ventilated patients where 42.5% were at high risk,[32] according to Mendes et al. (2017) in an ICU in Portugal 48.6% were at high malnutrition risk by NUTRIC score.[33] The difference could be because our study subjects had acute heart failure, while Nguyen Huu Hoan's study was on ICU patients with other diseases who may have had normal nutritional status before admission. Compared to Kalaiselvan, their study population was mechanically ventilated ICU patients for over 48h, while ours included both ventilated and non-invasively ventilated or oxygen supported patients. As for Mendes et al., that was a national, multicenter, observational study conducted in 15 multidisciplinary intensive care units (ICUs) across Portugal over 6 months with diverse and multi-departmental patients, while we only conducted the study in a single cardiovascular ICU.

Mortality in the first year

The 1-year mortality rate of 68% was higher than Krista Siirilä-Waris et al. [34] in their study on characteristics, outcomes and 1-year mortality prognosis in 620 acute heart failure patients

hospitalized at 14 hospitals in Finland. The cumulative mortality at 3 and 6 months was 15.0 and 20.0%. After 1 year, there were 171 (27.4%) deaths. This difference could be because our study sample size was smaller at around 103 patients, focused on a severely ill group with the majority being in intensive care on mechanical ventilation, and our unit is the final stage of cardiovascular care. In a study on acute heart failure by Ovidiu Chioncel et al.[35] collecting data from the ESC Long-Term HF Registry with follow-up from admission to 1 year on 6,629 AHF patients, the all-cause 1-year mortality rate was 26.7% and 1-year hospitalization for HF was 25.9%. Cardiovascular deaths accounted for 57.2% of all deaths in the overall study sample. Similar to in-hospital mortality rates, the highest 1-year mortality rates were observed in patients with cardiovascular disease (54.0%), low admission systolic blood pressure (34.8%), and in congested patients with impaired perfusion (29.8%).

Nutritional status and mortality in the first year

Recent data from the ESC-HF pilot study shows that all-cause mortality and hospitalization rates within 1 year for hospitalized HF patients are very high (17% and 44% respectively).[36] Increased risk of malnutrition is quite common in cardiovascular patients. At the same time, malnutrition is associated with longer hospital stays, more frequent hospitalizations and readmissions, increased risk of treatment-related complications, and even increased risk of death. Therefore, this is a public health issue because it increases treatment costs for patients.[37-39] In our study, the high malnutrition risk group accounted for 31.1% of total patient deaths.

The mortality rate was 88.9% in the high malnutrition risk group, higher than the 56.7% mortality rate in the low risk group, with statistically significant difference at $p<0.05$.

In the study by Antonio Zapatero[11] et al. on the impact of obesity and malnutrition in patients with acute heart failure in Spain from 2006-2008, a total of 370,983 heart failure admissions were analyzed, with 41,127 (11.1%) diagnosed with obesity and 4,105 (1.1%) malnourished. The overall in-hospital mortality rate was 12.9% and the risk of readmission was 16.4%. Obese patients had lower risk of in-hospital mortality (odds ratio [OR]: 0.65, 95% confidence interval [95% CI]: 0.62-0.68) and early readmission (OR: 0.81, 95% CI: 0.78-0.83) than non-obese patients. Malnourished patients had a much higher risk of in-hospital mortality (OR: 1.83 95%CI: 1.69-1.97) or readmission within 30 days after discharge (OR: 1.39, 95%CI: 1.29-1.51), even after adjusting for possible confounding factors.

The prevalence of malnutrition increased with age and number of comorbidities.[40] For HF disease, a recent meta-analysis showed the prevalence of malnutrition risk ranged from 16% to 90%, particularly high in patients with acute HF (AHF) (75–90%).[41] Thus in our study, the 1-year mortality rate of 68% was also similar to this study. Moreover, malnutrition was significantly associated with higher morbidity and mortality rates in heart failure patients,[41] and described as a short-term[42] and long-term[43-45] prognostic factor in patients hospitalized for acute heart failure. Additionally, a recent trial demonstrated that nutritional intervention in malnourished patients hospitalized for heart failure reduced long-term all-cause mortality and heart failure rehospitalization.[46]

Currently, malnutrition screening is recommended on hospital admission in elderly patients[40] and is often overlooked in emergency care. In addition, little is known about the prevalence and impact of malnutrition risk on short-term mortality rates in elderly patients presenting to emergency departments with AHF. Therefore, malnutrition risk needs to be explored as a modifiable prognostic factor to establish routine screening of malnutrition status in emergency situations in elderly AHF patients.

The PICNIC study (Nutritional Condition Intervention Program in Malnourished Patients With Heart Failure) results showed that nutritional intervention in malnourished patients with acute heart failure reduced all-cause mortality and risk of heart failure rehospitalization.[47] Guidelines from the European Society of Cardiology for treatment of acute heart failure recommend monitoring body

weight and preventing malnutrition in heart failure patients.[48] However, there are no specific nutritional recommendations for elderly patients at risk of AHF.

Regarding AHF, a randomized, multicenter, controlled clinical trial conducted on 120 malnourished patients hospitalized for heart failure demonstrated that 6 months of personalized nutritional intervention helped reduce the risk of mortality from any cause and the risk of heart failure rehospitalization after 1 year.[47] The efficacy of this nutritional intervention did not differ between patients with or without decreased blood albumin,[49] and was maintained at 2 years.[50]

CONCLUSION

Nutritional status correlated with increased risk of in-hospital mortality. The malnutrition risk assessment score mNutric was correlated with predicted mortality probability. For every 1 point increase in mNutric score, the mortality rate increased by 1.65 times (95% CI: 1.03-1.11) p=0.01. Patients with high malnutrition risk had higher 1-year mortality rates than patients with low malnutrition risk according to the mNutric score.

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Differences in clinical characteristics and mortality of de novo acute heart failure and acutely decompensated chronic heart failure: A prospective cohort study

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▶ Received: 29 October 2023
Accepted: 28 November 2023
Published online: 30 November 2023

To cite: Truong MC, Tran KH, Chau NH. J *Vietnam Cardiol 2023*;**107E**:73-79

ABSTRACT

Background: Acute heart failure carries a high risk of mortality. Understanding the characteristics and outcomes of acute heart failure subgroups may have important implications for clinical risk stratification.

Objective: We examined the clinical characteristics and rates of the 12-month all-cause mortality in a cohort of patients hospitalized with acute heart failure according to heart failure duration new-onset or de novo acute heart failure and acutely decompensated chronic heart failure (ADCHF).

Methods and Materials: The cohort study, with a 12-month follow-up, was conducted at Nhan Dan Gia Dinh Hospital in Vietnam from February 2022 to October 2023.

Results: Among 316 patients with acute heart failure, 159 patients (50%) were admitted presenting de novo AHF, while the remaining 157 patients (50%) exhibited ADCHF. Patients with ADCHF were characterized by a higher proportion of elders, comorbidities including chronic kidney disease and atrial fibrillation, and a larger left atrial diameter than those with de novo acute heart failure. The rates of mortality in patients with ADCHF were 1.69 times more than in patients with de novo acute heart failure (the hazard ratio (HR): 1.69 (The 95% confidence interval (CI 95%): 1.10 - 2.60, p = 0.016). However, patients with ADCHF had not an independent predictor of 12-month mortality after adjusting factors in multivariable Cox regression models, including age, chronic pulmonary disease, diabetes mellitus, coronary heart disease, atrial fibrillation, sodium, hemoglobin, N-terminal prohormone BNP (NT-proBNP).

Conclusions: Among patients hospitalized with acute heart failure, acutely decompensated chronic heart failure was associated with poorer outcomes.

Keywords: Acute heart failure, de novo heart failure, acutely decompensated chronic heart failure, all-cause mortality.

INTRODUCTION

Acute heart failure (AHF) is the rapid onset of worsening of signs and symptoms of heart failure and usually requires emergency care[1]. AHF is a

leading cause of hospitalization in patients aged > 65 years and is associated with high mortality. In-hospital mortality ranges from 4% to 10% [2,3], post-discharged 1-year mortality can be 25% - 30%[4-6].

Based on the temporal progression of AHF, the European Society of Cardiology (ESC) 2021 classifies AHF into two categories: de novo AHF, which presents in patients with initial AHF decompensation, and acutely decompensated chronic heart failure, which corresponds to an exacerbation of heart failure in patients with at least one previous decompensation[1]. However, there has been little investigation of how these groups compare to their characteristics and mortality. De novo acute heart failure may have a higher in-hospital mortality[2] but have lower post-discharge mortality[7,8]. Understanding the characteristics and outcomes of these two distinct subpopulations may have important implications for clinical risk stratification. We examined the clinical characteristics and rates of all-cause mortality in a cohort of patients hospitalized with heart failure, stratifying as to whether the patients presented with de novo or worsening of chronic heart failure.

METHODS

Study population

The study was designed as a cohort investigation. The patients with AHF were hospitalized in Nhan Dan Gia Dinh Hospital from February 2022 to October 2023. Diagnosis of acute heart failure followed 2021 ESC Guidelines1. Diagnosis of AHF was defined as the rapid onset or worsening of symptoms and/or signs of heart failure, such as pulmonary crackles, peripheral edema, and cardiomegaly. Inclusion of criteria in this study was: (1) Patients admitted with a diagnosis of AHF; (2) Patients over 18 years of age; (3) Patients in response to a diuretic drug, inotropic drug or vasodilators; (4) NT-proBNP > 2000 pg/ml. Exclusion ones were: end-stage renal or liver disease, pregnancy, and malignancy.

Data on the demographic characteristics and laboratory tests were collected from the medical record. Venous blood sampling for bio-markers was obtained 48 hours after admission. Patients followed up for 12 months after discharge. The primary endpoint was all-cause mortality. Survival or death status was confirmed by reviewing the death certificates, telephone interviews, and data from the eHospital software of Nhan Dan Gia Dinh Hospital. The study protocol adhered to the Declaration of Helsinki and received approval from the Ethics Committee of Biomedical Research at the University of Medicine and Pharmacy at Ho Chi Minh City (21598-DHYD) before initial patient recruitment. All patients gave informed consent.

Statistical analysis

Sample size: Based on the previous study, the mortality rates of patients with acute decompensated chronic heart failure had been 32.9%[9] in 1 year. With a statistical power of 0.9 for detecting a significant difference ($p = 0.05$, two-sided), 152 patients were required to test the hypothesis of the difference in mortality rate between both groups.

Continuous variables and categorical data are expressed as means ± standard deviation (SD) and percentages, respectively. The clinical characteristics of the patients at baseline by the different categories of AHF were compared with the use of the t-test for continuous variables and the chi-square test for categorical variables. Kaplan-Meier survival analysis was used to graphically present survival estimates according to the different categories of AHF and the subsequent 1-year survival probability. The difference in cumulative mortality rates of the two AHF groups was compared using the log-rank test. Multivariate Cox proportional hazard regression modeling was used to assess the independent effect of AHF type on the primary end point of all-cause mortality. The covariates were independent predictors in the mortality of AHF patients which identified in literature, including age, chronic pulmonary disease, chronic coronary disease, atrial fibrillation, sodium, hemoglobin, and NT-proBNP10. Statistical significance was accepted for a 2-sided $p < 0.05$. The statistical analysis was performed with R Statistical Software (R 4.3.1: R Foundation for Statistical Computing, Vietnam).

RESULTS

From February 2022 to October 2023, 316 patients were hospitalized with a diagnosis of either ADCHF or de novo AHF. Based on our classification of the different AHF groups, 157 (50%) patients were classified as ADCHF and 159 (50%) patients as de novo AHF. The median age of the study population was 67.4 ± 14.8 years, and 52% were women. Baseline characteristics of the 2 AHF groups are presented in Table 1.

The comparison between both groups showed that patients admitted for de novo AHF were younger 4 years (65.4 ± 6 years vs 69.4 ± 6 years, p = 0.018), hypertensive heart disease increased 1.6 times (11.3% vs 7.0%, p = 0.04), had a 6 beats/minute higher heart rate (99.4 ± 23.2 beats/minute vs 93.8 ± 23.1 beats/minute, p = 0.031), had a higher 11 mmHg systolic blood pressure (137.2 ± 27.5 mmHg vs 126 ± 26.1 mmHg, p < 0.001), had a higher 5 mmHg diastolic blood pressure (80.9 ± 14.1 mmHg vs 75.1 ± 14.6 mmHg, p < 0.001). There were significant differences in the etiology of heart failure; patients with ADCHF had increased 1.3 times chronic coronary disease (22.6% vs 29.3%, p = 0.04), increased 1.5 times valvular heart disease (12.6% vs 19.1%, p = 0.04), increased 1.3 times cardiomyopathy disease (15.1% vs 19.1%, p = 0.04). In addition, patients with ADCHF had increased 1.4 times atrial fibrillation (28.3% vs 39.5%, p = 0.036), increased 1.9 times chronic kidney disease (21.4% vs 41.4%, p = 0.04) and increased 2 mm left atrial diameter (38.8 ± 8.2 mm vs 41.9 ± 8.9 mm, p = 0.001)

Mortality

During 12 months, there were 87 died patients (27.5%) in follow-up 316 patients. The mortality rate was significantly lower in patients with de novo AHF than ADCHF (20.8% vs 34.4%; p = 0.007). Kaplan-Meier plot showed a higher mortality rate in ADCHF with a significant difference (p = 0.015) compared to that in de novo AHF (Figure 1).

Cox model analysis showed that patients with ADCHF had an increased mortality rate of 1.69 times de novo AHF (HR: 1.69 (CI 95%: 1.10 - 2.60, p = 0.016)). However, the mortality hazard ratio was insignificantly different after adjustment for age, chronic pulmonary disease, diabetes mellitus, coronary heart disease, atrial fibrillation, sodium, hemoglobin, and NT-proBNP (Table 2).

***Table 1**. Multivariate Cox Regression analysis to identify factors associated with 1 year all-cause mortality in acute heart failure patients*

	Hazard ratio	95% confidence interval	p Value
ADCHF	1.35	0.85 - 2.13	0.19
Age	1.02	1.00 - 1.04	0.002
Chronic pulmonary disease	1.84	1.03 - 3.26	0.03
Diabetes mellitus	0.89	0.56 - 1.40	0.61
Coronary artery disease	1.11	0.55 - 1.45	0.65
Atrial fibrillation	1.44	0.88 - 2.36	0.15
Sodium	0.96	0.94 - 0.99	0.01
Hemoglobin	0.98	0.98 - 0.99	0.02
NT-proBNP	1.00	1.00 - 1.00	0.08

ADCHF, acutely decompensated chronic heart failure; NT-proBNP, N-terminal prohormone BNP.

***Table 2**. Baseline characteristics of 316 patients with de novo acute heart failure versus acutely decompensated chronic heart failure*

Variable	De novo AHF n=159	ADCHF n=157	p Value
Demographics			
Age (years)	**65.4 ± 6**	**69.4 ± 6**	**0.018**
Women, n (%)	75 (47.2)	89 (56.7)	0.090
Aetiology of heart failure			**0.04**
Chronic coronary disease, n (%) Hypertensive heart disease, n (%) Valvular heart disease, n (%) Cardiomyopathy, n (%) Others, n (%)	36 (22.6) 18 (11.3) 20 (12.6) 24 (15.1) 61 (38.4)	46 (29.3) 11 (7.0) 30 (19.1) 30 (19.1) 40 (25.5)	
Past medical history			
Smoking, n (%)	55 (34.6)	51 (32.5)	0.692
Hypertension, n (%)	112 (70.4)	118 (75.2)	0.346
Diabetes mellitus, n(%)	56 (35.2)	69 (43.9)	0.113
Coronary artery disease, n (%)	57 (35.8)	70 (44.6)	0.113
Valvular heart disease, n (%)	22 (13.8)	28 (17.8)	0.330
Atrial fibrillation, n (%)	45 (28.3)	62 (39.5)	**0.036**
Cerebrovascular accident/transient ischemic attack, n (%)	14 (8.8)	17 (10.8)	0.546
Chronic pulmonary disease, n (%)	21 (13.2)	17 (10.8)	0.516
Chronic kidney disease, n (%)	34 (21.4)	65 (41.4)	**0.003**
Clinical presentation			
Systolic blood pressure, mmHg	137.2 ± 27.6	126.9 ± 26.1	**< 0.001**
Diastolic blood pressure, mmHg	80.9 ±14.2	75.1 ± 14.6	**< 0.001**
Heart rate (beats/min)	99.4 ± 23.2	93.8 ± 23.1	**0.031**
Laboratory findings			
Hemoglobin, g/dl	120.5 ± 23.9	118 ± 23.5	0.396
Serum creatinine, µg/l	132.2 ± 108.3	135.4 ± 56.1	0.745
Sodium, mmol/l	135.7 ± 6.8	135.2 ± 5.8	0.481
NT-proBNP, pg/ml	9637 ± 8528	10417 ± 9234	0.436
Echocardiography			
Left ventricle end-diastolic diameter, mm	51.7 ± 9.9	53.4 ± 11.3	0.152
Left atrial diameter, mm	38.8 ± 8.2	41.9 ± 8.9	**0.001**
Left ventricular ejection fraction, %	43.2 ± 16.2	41.8 ± 16.6	0.428
All-cause mortality, %	33 (20.8)	54 (34.4)	**0.007**

Bold-faced values indicated statistical significance at P <0.05; AHF, acute heart failure; ADCHF, acutely decompensated chronic heart failure; NT-proBNP, N-terminal prohormone BNP.

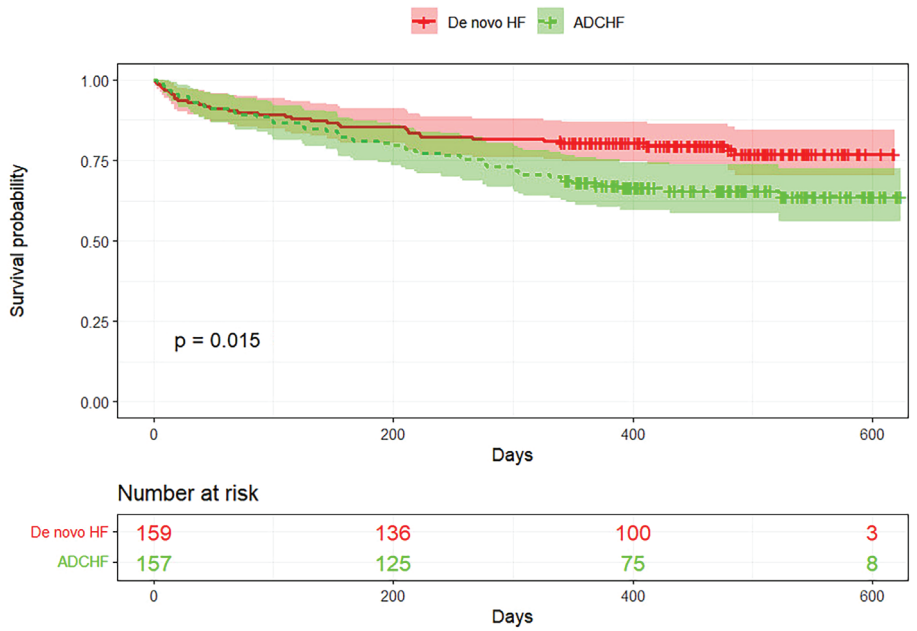

***Figure 1**. Kaplan-Meier curves in patients with acutely decompensated chronic heart failure (green line) versus de novo acute heart failure (red line) for death within 1 year. Acutely decompensated chronic heart failure (ADCHF), heart failure (HF)*

DISCUSSIONS

In this cohort study of all acute heart failure patients admitted to Nhan Dan Gia Dinh Hospital. We found that approximately 50% of those presented de novo AHF. We compared clinical characteristics and outcomes of de novo AHF and ADCHF patients. Our study yielded four major findings. First, ACDHF patients were older and had comorbidities, which were similar to de novo AHF patients, except for chronic kidney disease and atrial fibrillation. Second, de novo AHF had a higher heart rate and blood pressure level upon arrival at an emergency department. Third, there was a larger left atrial remodeling in patients with ADCHF. Finally, there was a graded relationship between increasing heart failure duration of heart failure and the rate of all-cause mortality, with a longer duration of heart failure associated with higher mortality rates.

Patients with ADCHF often experience comorbidities[11], and our investigation identified that chronic kidney disease and atrial fibrillation dominated the others. The former is one of the most common comorbidities in AHF patients, with a prevalence ranging from 30% to 67%[12,13]. It stands as an independent prognosis factor in the mortality of AHF patients. Our study disclosed a significant difference in the ratio of chronic kidney disease in ADCHF patients, resulting from impaired kidney function possibly arising from renal vein congestion during the AHF period, heart failure medications, and frequent fluid overload during the treatment of chronic heart failure. The impaired kidney function in ADCHF patients could be unrecoverable and culminate in the progression of chronic kidney disease. The latter is both a cause and consequence of heart failure and also plays a significant role in exacerbating the condition. Atrial fibrillation induces heart failure through the mechanism of diminished left atrial contractile function due to increased left ventricular filling pressure and reduced cardiac output, particularly in patients with diastolic heart

failure. The presence of atrial fibrillation is associated with adverse outcomes in heart failure patients[14,15]. It can be said that the occurrence of atrial fibrillation and chronic kidney disease are poor prognostic factors in ADCHF patients.

An intriguing finding in our study was the graded relationship between heart failure duration and all-cause mortality rates. Nevertheless, this is intuitive due to the older and larger left atrial diameter of patients with longstanding heart failure and the association between increasing heart failure duration and subsequent risk of outcomes. The results may be due to prolonged exposure to neurohormonal activation and greater maladaptive cardiac remodeling and may reflect the natural course of the disease. However, our findings contrast with those of the acute study of clinical effectiveness of nesiritide and decompensated heart failure (ASCEND-HF)[16], where this graded relationship was not found. The reasons for this are unclear but may be attributed to essential differences in patient characteristics, including age, ethnicity, and prevalence of comorbidity. In addition, patients with de novo AHF had higher blood pressure and heart rate, possibly because they had not undergone drug therapy[17]. Previous studies showed that preserved or high blood pressure during an AHF episode is associated with a better prognosis[10], which is consistent with the results observed in our study.

The limitations of our study were: (1) Because the study was conducted in one setting, the findings might not help to reflect the health care conditions of other health settings in Vietnam; (2) We did not control data on drug doses during hospitalization or at the time of discharge and follow-up, which might affect mortality; (3) The study did not investigate precipitating factor of the AHF. Despite these limitations, the present prospective cohort study provided new insights into differences in admission between variables de novo AHF and ADCHF as well as predictive of mortality.

CONCLUSIONS

In our cohort study, including the patients hospitalized with HF, acutely decompensated chronic heart failure had a tendency for poorer outcomes compared with de novo AHF. These findings may have important implications for risk stratification in acute heart failure.

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Heart failure in patients with hypertrophic obstructive cardiomyopathy

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▶ Received: 29 October 2023
Accepted: 25 November 2023
Published online: 30 November 2023

To cite: Pham NM, Nguyen TN, Nguyen NQ, *et al. J Vietnam Cardiol 2023*;**107E**:80-85

ABSTRACT

Hypertrophic cardiomyopathy is a hereditary cardiac disease, diverse in clinical manifestations, cardiac structure and natural progression. Patients with disease are associate with a broad range of clinical presentations, from patients who are asymptomatic, accidentally discovered during routine examination, to patients with chest pain, dyspnea, syncope, and even sudden death. We are presenting the clinical case of a young male patient with hypertrophic cardiomyopathy with rather large left ventricular wall thickness about 37mm who was hospitalized with severe dyspnea accompanied by tachycardia episodes and hypotension. The patient underwent electrical cardioversion, Doppler echocardiography, stress Doppler echocardiography with treadmill, cardiac MRI, basic blood tests, coronary CT angiography and ventriculography. The results showed the patient had a very high NT-proBNP level of 16,271 pg/mL; echocardiography showed asymmetric left ventricular hypertrophy, a maximum resting LVOT gradient of 28 mmHg, increasing to 64 mmHg at peak stress, preserved left ventricular systolic function and grade III left ventricular diastolic dysfunction; greatly increased left ventricular mass of 199.6 g/m^2, and delayed contrast enhancement involving the subendocardium of both ventricles and transecting the left ventricular free wall on cardiac MRI. We also discuss various treatment option for this young man.

Keywords: Hypertrophic cardiomyopathy (HCM), HOCM, heart failure.

INTRODUCTION

Hypertrophic cardiomyopathy is the most common hereditary cardiovascular disease, with an estimated prevalence of 0.2 - 0.5% of the general population, and is one of the leading causes of sudden cardiac death, especially (primarily) in patients under 35 years of age. HCM is characterized by disorganized arrangement of cardiac muscle cells, interstitial fibrosis and asymmetric or concentric left ventricular hypertrophy that cannot be explained solely by volume or pressure overload [1-4]. Hypertrophic cardiomyopathy encompasses a wide range of clinical manifestations from asymptomatic, with the disease discovered accidentally during routine examination, ECG abnormalities, or from family screening after a diagnosis

in a first-degree relative; to symptoms such as dyspnea, chest pain and syncope, and even sudden death may be the first presentation. Fatigue and dyspnea occur due to diastolic dysfunction and decreased cardiac output. Maron's 1997 study showed that most patients with HCM have some degree of heart failure according to the NYHA classification, with class I in about 34% to 43% of the cases, class II in 25%, class III in 40%, and 3% with class IV.[5] Palpitations, chest tightness, syncope can occur due to atrial arrhythmias, ventricular arrhythmias or mechanical obstruction in patients with increased left ventricular outflow tract gradient [5].

We report the case of a patient with hypertrophic cardiomyopathy hospitalized with severe dyspnea, palpitations, chest tightness, accompanied by fainting, diagnosed with: Atrial Fibrillation – Heart Failure – Hypertrophic Obstructive Cardiomyopathy.

CLINICAL CASE

A 19-year-old male patient was diagnosed with hypertrophic cardiomyopathy 12 years ago. He had regular follow-up and was on regular medication with Bisoprolol 2.5mg/day. His father also had obstructive hypertrophic cardiomyopathy and had undergone alcohol septal ablation. The patient was hospitalized for dyspnea, significant fatigue, and palpitations for the past 2 days; no cough or fever. On admission, he had NYHA class III dyspnea, few moist rales (crackles) bilaterally, rapid small pulse of 155 beats/minute, hypotension with BP 80/50 mmHg, cold clammy skin, profuse sweating, 2 cm hepatomegaly, and mild bilateral leg edema.

Admission ECG: atrial flutter with 2:1 AV block, ventricular rate 157 beats/minute, complete right bundle branch block.

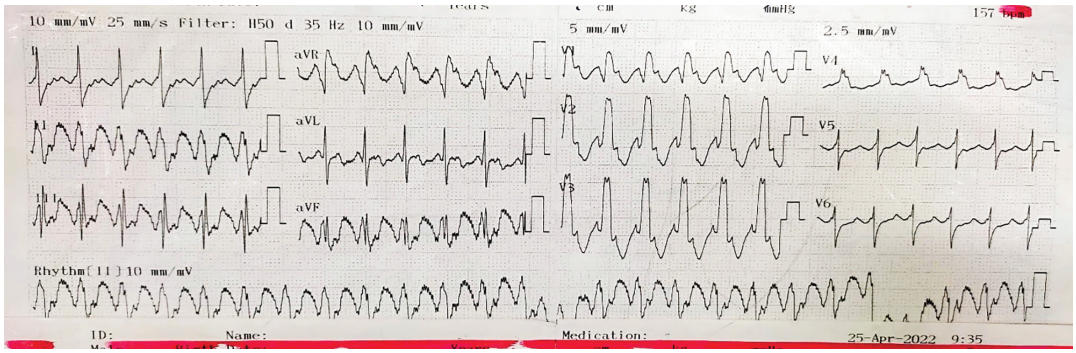


***Figure 1**. The patient's admission electrocardiogram*

The patient underwent emergency electrical cardioversion. After cardioversion, the ECG showed sinus rhythm, rate of 54 beats/minute, persistent complete right bundle branch block, bifascicular block with second degree AV block.

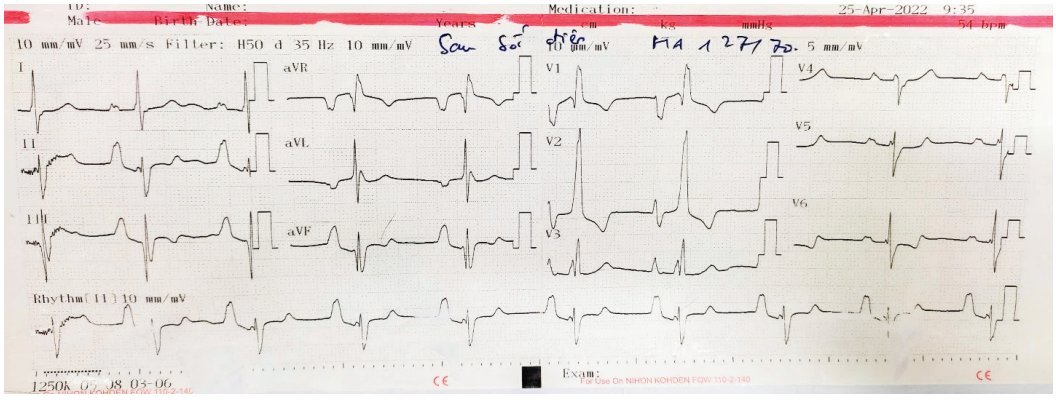


***Figure 2**. The patient's electrocardiogram after electrical cardioversion*

The patient's blood test results showed a very high NT-proBNP level (16,271 pg/mL).

***Table 1**. Paraclinical test indices*

Test Index	Result	Reference Range
Red blood cell count (T/L)	5.55	4.5 – 5.9
Hemoglobin (g/L)	169	135 – 175
White blood cell count (G/L)	8.41	4 – 10
NT-proBNP (pg/mL)	**16271**	< 125
Troponin T-hs (ng/L)	**86.59**	=< 14
AST (GOT) (U/L)	**166**	5 – 34
ALT (GPT) (U/L)	**320**	0 – 55
Urea (mmol/L)	7.2	3.2 – 7.4
Creatinine (umol/L)	107	63.6 – 110.5
FT4 (pmol/L)	16.12	12 – 22
TSH (uU/mL)	3.370	0.27 – 4.2

Echocardiography showed thickening of left ventricular wall with interventricular septum thickness of 30mm during end-diastolic, end-diastolic left ventricular posterior wall of 20mm; right ventricular free wall thickness was 10.7mm. Moderate mitral and mild tricuspid regurgitation. SAM sign presented. Maximum left ventricular outflow tract gradient was 28 mmHg at rest, 64 mmHg on peak stress. Left ventricular systolic function was preserved (Biplane EF 68%), diastolic function, however, was impaired (Grade III diastolic dysfunction). Minimal pericardial effusion.

Abdominal ultrasound showed hepatomegaly with heterogeneous liver parenchyma, no focal lesions. Right pleural effusion thickness of 9 mm, ascites up to 18 mm in the deepest area.

Cardiac MRI confirmed asymmetric left ventricular hypertrophy,with greatly increased left ventricular mass (199.6 g/m^2). Subendocardial perfusion defect involving the apex, mid and base of left ventricle. Delayed gadolinium enhancement showing fibrosis involving the subendocardium of both ventricles and transecting the anterior-septal left ventricular free wall. Left ventricular chamber not dilated, left ventricular systolic function preserved with EF 70%. Massively dilated left atrium. Moderate mitral regurgitation. Increased T2 mapping (50.5 ms) and ECV (48%) values.

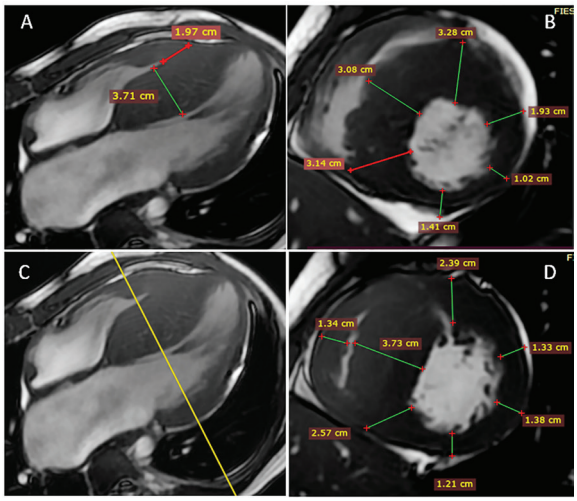


***Figure 3**. A, B, C, D: Images of cardiomyopathy hypertrophy in multiple sections. C, D, E: Late gadolinium enhancement images of the heart in different slices*

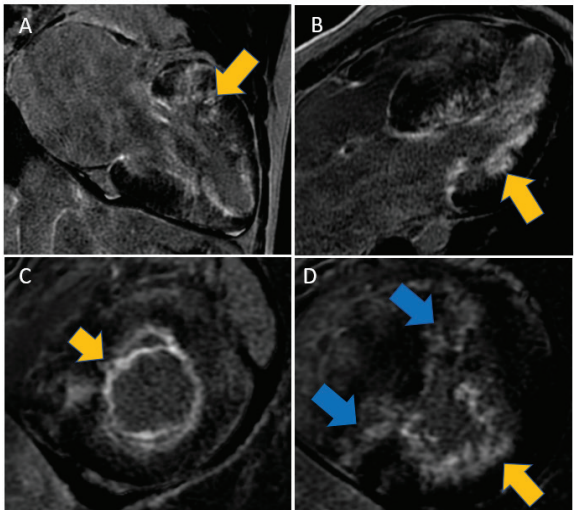


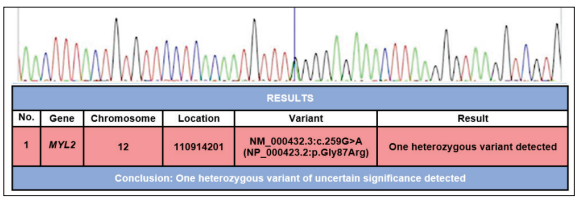
***Figure 4**. A, B, C, D: Late gadolinium enhancement images of the heart in different slices (yellow arrows: subendocardial enhancement, blue arrows: transmural enhancement)*

The patient underwent coronary DSA, which showed normal coronary arteries with a small septal branch. Ventriculography showed hypertrophic

cardiomyopathy. Cardiac chamber pressure measurements: Left ventricular pressure 135/34/72 mmHg at rest, 147/32/73 mmHg on stimulation; LVOT pressure 105/35/63 mmHg; Ao pressure 98/70/87 mmHg.

24-hour Holter monitoring did not show significant ventricular arrhythmias, no AV block of any degree during the entire recording time, rare ventricular ectopy.

We performed genetic testing for the patient and his parents. Results detected a MYL2 gene mutation in both the patient and his father.

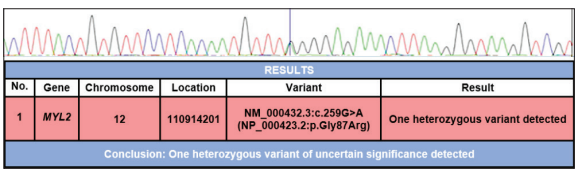


RESULTS

No.	Gene	Chromosome	Location	Variant	Result
1	*MYL2*	12	110914201	NM_000432.3:c.259G>A (NP_000423.2:p.Gly87Arg)	One heterozygous variant detected

Conclusion: One heterozygous variant of uncertain significance detected

***Figure 5**. The patient's genetic test results*



RESULTS

No.	Gene	Chromosome	Location	Variant	Result
1	*MYL2*	12	110914201	NM_000432.3:c.259G>A (NP_000423.2:p.Gly87Arg)	One heterozygous variant detected

Conclusion: One heterozygous variant of uncertain significance detected

***Figure 6**. The patient's father's genetic test results*

With the patient's test results, some salient points can be seen: 1) Despite the patient's young age (19 years old), he has very severe left ventricular hypertrophy (maximal wall thickness up to 37 mm) and greatly increased left ventricular mass (199.6 g/m^2). 2) Clear heart failure manifestations (NYHA class III dyspnea, congestion with hepatomegaly, pericardial effusion, pleural effusion, ascites, elevated NT-proBNP level), although left ventricular systolic function is preserved, there is grade 3 diastolic dysfunction. 3) The patient had dangerous arrhythmias causing syncope, admission ECG showing rapid atrial flutter with ventricular rate of 157 beats/minute. 4) Cardiac MRI showed subendocardial perfusion defects involving the apex, mid and base of the left ventricle, however coronary DSA was normal, consistent with the pathophysiology of HCM where excessive left ventricular hypertrophy leads to myocardial supply-demand mismatch, additionally the high left ventricular end-diastolic pressure affects subendocardial blood flow 5) Genetic testing results detected a heterozygous variant in the MYL2 gene in both the patient and his father, which is a relatively rare variant in the HCM population (<2%).

The patient was treated with diuretics for congestion. After the condition has improved, he was treated with beta blockers. After 5 days of treatment, the patient's clinical condition improved significantly with resolution of dyspnea and palpitations. 24-hour Holter after 5 days of treatment showed no dangerous ventricular or atrial arrhythmias.

DISCUSSION

Hypertrophic cardiomyopathy is a condition that we encounter more and more frequently in clinical practice. Diagnosis and treatment have had many advances thanks to developments in echocardiography and imaging modalities like cardiac CT and MRI. Additionally, the genetic factor is an important issue that has been studied extensively in recent years, since hypertrophic cardiomyopathy exhibits **autosomal dominant inheritance** of alleles or non-alleles, with mutations in at least 12 genes encoding sarcomeric proteins. The majority of mutations (>70%) are located in the genes encoding β-myosin heavy chain, troponin T and myosin-binding protein C. We have a very typical clinical case with all the classic symptoms of hypertrophic cardiomyopathy, which here is also characterized by heart failure manifestations in a young patient. Arrhythmic presentations like atrial fibrillation and AV block were also seen in this patient. Echocardiography and cardiac MRI also show typical findings with septal hypertrophy and significant left ventricular outflow tract gradient. Additionally, in this patient genetic testing was done which detected a heterozygous variant in the MYL2 gene in both the patient and his father, a relatively rare variant in the HCM population (<2%).

In fact, in current conditions in Vietnam and globally, diagnosis is no longer a difficult issue, apart

from some challenges with the high costs of certain tests like cardiac MRI, or genetic testing in patients and related family members [6-8]. However, treatment is not a simple issue. Although there has been progress in treatment of heart failure, specific therapy for HCM has not been truly proven yet, apart from some recent studies on Mavacamten, a gene-targeted drug that can reduce LVOT gradient. The 2020 EXPLORER-HCM trial, a phase 3 clinical trial enrolled 429 patients across 68 cardiovascular centers in 13 countries, showed that Mavacamten (starting at 5mg dose) compared to placebo can improve pVO2 and NYHA functional class, LVOT gradient as well as heart failure assessment scores like KCCQ-CCS and Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness of Breath score (HCMSQ-SoB), while drug tolerability was similar to placebo [9]. A pooled analysis of 539 patients from 4 major clinical trials with average patient age of 57.9 years and average 29.3 weeks of follow-up showed the Mavacamten group had improved clinically (LogOR=0.65; p=0.01) and more patients had reduced NYHA dyspnea score (LogOR=0.64; p=0.001). Improvements in KCCQ and PVO2 scores were not clearly significant (p=0.08 and 0.42), meanwhile the Mavacamten group showed a trend of LV EF reduction on echo. Thus, Mavacamten is a new drug with potential for clinical use, however its efficacy still requires more studies to demonstrate [10]. Additionally, the drug is not yet available in the Vietnamese market, so more time is needed to truly have clinical experience in Vietnamese patients.

Heart failure in hypertrophic cardiomyopathy patients, especially those with symptoms or reduced EF, still mainly follows general guidelines for acute and chronic heart failure [11]. This includes medical therapies, ICD/CRT-D implantation and ventricular assist devices as well as heart transplantation... Medical treatment for HFrEF is based on large randomized controlled trials, including ACE inhibitors/ARBs, beta blockers, ARNI, MRAs, SGLT2 inhibitors [11]..., especially in the late stages of HCM when left ventricular function deteriorates. In early stages of disease, when left ventricular systolic function is still compensated or only mildly or moderately reduced (HFpEF or HFmEF), we can currently still treat according to the 2023 updated European Society of Cardiology guidelines on diagnosis and treatment of chronic heart failure [12]. (Treatment of HCM in early stages when left ventricular systolic function is preserved or only mildly or moderately reduced currently based on recommendations of 2023 updated ESC guidelines on diagnosis and treatment of chronic heart failure). For obstructive HCM patients like the young patient above, in addition to heart failure treatments per guidelines, non-vasodilating beta blockers can be used as first-line to treat and improve heart failure, if beta blockers have little to no effect or poor tolerability, verapamil and diltiazem are alternatives. However, verapamil and diltiazem are contraindicated in hypotension, dyspnea at rest or in children <6 years old, and when the gradient is >100mmHg. For cases with severe symptoms poorly responsive to medical therapy, disopyramide and septal reduction procedures are recommended. Currently, surgical myectomy is preferred over alcohol septal ablation with recommendations from both ESC and ACC [6,7], especially in young patients who are still surgical candidates. Alcohol septal ablation can also be done based on the Heart Team's decision in experienced centers, or depending on patient and family preferences. In patients with atrial fibrillation/flutter, anticoagulation or DOACs/warfarin should be used regardless of CHADS2VAS2 score [6]. Additionally, ICD implantation should be considered if patients have uncontrolled dangerous ventricular arrhythmias despite medical therapy. If all above treatments fail, heart transplantation should be considered for patients (although still rarely performed in Vietnam). [6]

In this patient, despite the LVOT gradient not being very high at 64mmHg on echo and 49mmHg on cath, with 30mm septal thickness, and concomitant valvular disease, the severe heart failure symptoms despite medical therapy may warrant consideration of more aggressive approach. According to current ESC and ACC guidelines, the appropriate treatment would likely be surgical myectomy followed by

mitral valve repair. After operation, depending on the clinical condition, additional treatments like ICD implantation or AF ablation may be indicated if ventricular arrhythmias persist. Additionally, thorough counseling of the family and patient regarding the hereditary nature of the disease and potential consequences on future generations is important. New drugs like Mavacamten may also be an option in this case, however the drug is not yet available in Vietnam and there is no experience with use in Vietnamese patients yet.

CONCLUSION

Hypertrophic cardiomyopathy nowadays is a not uncommon hereditary disease, and can be diagnosed more easily than before with advanced diagnostic tools like echocardiography and cardiac MRI, especially at specialized centers like the Vietnam National Heart Institute. However, treatments are still challenging, with patients presenting increasingly complex genotype-phenotype manifestations like the clinical case above. Although currently in Vietnam there are no specialized treatment guidelines for cardiomyopathies in general or hypertrophic cardiomyopathy specifically, current ESC and ACC guidelines show that a comprehensive approach with a well-trained Heart-team is compulsory to manage complex cardiovascular patients like those with HCM.

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Heart failure management model at University Medical Center Ho Chi Minh City

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▶ Received: 10 November 2023
Accepted: 28 November 2023
Published online: 30 November 2023

To cite: Vu HV, Nguyen CT, Pham DDQ, *et al. J Vietnam Cardiol 2023*;**107E**:86-92

ABSTRACT

The program has three key components - human resources, management tools, and research training. It takes a multidisciplinary approach involving various specialists. Nurses play a central role in educating and connecting with patients.

Management tools include a patient handbook for self-monitoring, a specialized heart failure clinic for post-discharge follow-up, and use of standardized data variables and the REDCap platform for streamlined data collection and analysis.

The program follows the EuroHeart data standards and has expanded to involve other hospitals in collaborative data collection and sharing of program experiences.

Additional activities include training courses for medical staff, conferences to discuss program challenges/solutions, and a patient club to strengthen doctor-patient relationships.

Standardized, multicenter management programs can optimize patient care, provide valuable real-world data to advance heart failure research in Vietnam, and continuously improve outcomes.

In summary, the UMC-HCMC program exemplifies a systematic, patient-centered approach to heart failure care aiming to reduce mortality and hospitalizations. Key next steps are expanding to more sites and patient groups, and conducting further research.

HEART FAILURE MANAGEMENT MODEL AT UNIVERSITY MEDICAL CENTER HO CHI MINH CITY

With the spirit of adhering to the recommendations of Associations and the effort to improve outcomes in heart failure patients, while creating a suitable environment to collect real-world data reflecting the heart failure epidemiology in Vietnam, University Medical Center Ho Chi Minh City has implemented and applied a heart failure management model with 3 components: human resources, management tools, and research training (Figure 1).

a. Human resource

Heart failure management at University Medical Center Ho Chi Minh City is also based on a multidisciplinary coordination, including cardiologists, rehabilitation physicians, nutritionists, palliative care specialists, other specialties, and the nursing force. All share the same focus of caring for heart failure patients to improve their

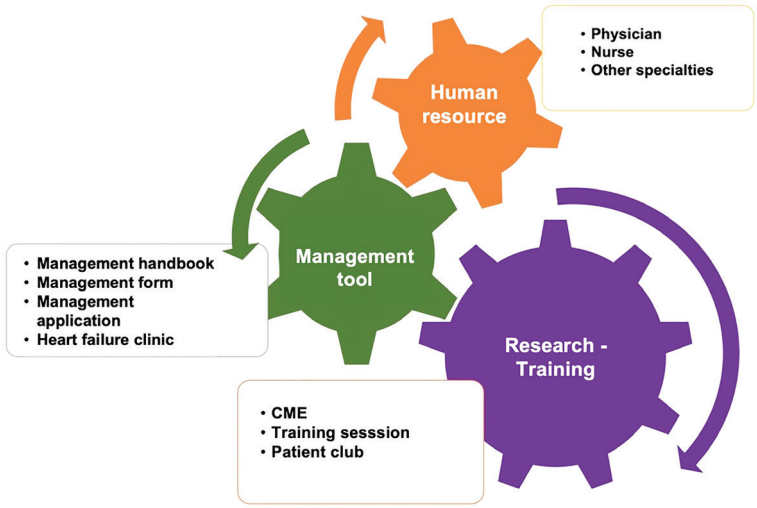

***Figure 1**. Key components of the heart failure management program at University Medical Center Ho Chi Minh City*

prognosis and quality of life. Among them, nurses are the core force, playing the role of directly connecting patients and doctors, being the main communication channel for patients, listening to their feelings as well as sharing and advising necessary information about daily living and treatment. Understanding the important role of nurses, University Medical Center Ho Chi Minh City has organized basic to advanced training courses for nurses. In basic training, nurses are provided with overview knowledge about heart failure, nutrition, home exercise regimen for heart failure patients, as well as signs to monitor at home, lifestyle modification methods, and palliative care for this population (Figure 2).

***Figure 2**. A basic nurse training session in the heart failure management program at University Medical Center Ho Chi Minh City*

In advanced nurse training, nurses are trained on medication precautions for heart failure patients; instructed on how to care for patients with acute heart failure, as well as provided health education skills - situational management, while exchanging information and supporting decision making when patients have questions related to their condition (Figure 3).

***Figure 3**. An advanced nurse training session in the heart failure management program at University Medical Center Ho Chi Minh City*

b. Management tools

Heart failure patient handbook

The heart failure patient handbook was created with the goal of improving patients' knowledge about their own condition, while also having a more proactive attitude by directly recording blood pressure, heart rate values, as well as any daily complaints (if any). This handbook will be given and instructions on its use as well as basic knowledge to note at home explained by the nurse directly caring for the patient in the hospital before the discharge date (Figure 4). This will help make the follow-up process continuous from inpatient to outpatient.

***Figure 4**. Overview of the heart failure patient handbook at University Medical Center Ho Chi Minh City*

Heart failure clinic

In August 2022, the heart failure clinic at University Medical Center Ho Chi Minh City was established (Figure 5). This is a solid step to follow up patients in the early period after discharge, adjust medications and monitor side effects if any, while also being a place for heart failure patients to feel more assured, helping maintain adherence and pay more attention to their own condition.

+ The nursing system will be assigned to remind patients about follow-up appointments by directly calling or through smartphone apps. They are also the ones who directly communicate with and inquire about patients, assist patients with daily questions; as well as monitor patient medication adherence. During this period, nurses will also enter patient information into the REDCap software, including current status, events if any, symptoms and complaints, outpatient lab tests, and current medications.

+ Doctors examining at the Heart Failure Clinic will record symptoms, any side effects, and directly assess the patient's condition to optimize guideline-directed medical therapy accordingly.

+ At home, patients will self-monitor blood pressure, heart rate, their own symptoms, and any questions if any. From there, patients can contact the nursing system via smartphone apps, directly call the cardiology department switchboard, or come to the heart failure clinic for consultations on their questions as well as treatment adjustments if necessary.

***Figure 5**. Inauguration day of the Heart Failure Clinic at University Medical Center Ho Chi Minh City*

Heart failure management variables: EUROHeart and REDCap

The heart failure management program at University Medical Center Ho Chi Minh City also follows global trends by promptly updating the necessary variables in patient management as well as appropriate variables for the hospital's actual situation to synchronize and smoothly operate heart failure management. The variables based on the EUROHeart data standards will also be a valuable data source on the real-world epidemiology and management status of heart failure in Vietnam. From there, we will have meaningful research projects and high value scientific papers that connect with organizations worldwide. The EUROHeart model in heart failure management is divided into 9 components (Figure

6), with variables classified into 3 levels according to increasing depth; with level 1 having 84 mandatory variables; level 2 having 79 additional variables; and level 3 being country or center-specific variables. At University Medical Center Ho Chi Minh City, the heart failure management program collects data based on 84/84 level 1 variables, 42/79 level 2 variables, and 47 level 3 variables. These variables are included in 4 forms: HF0 for inpatient data collection, HF1 for data collection at 1 month after discharge, similarly HF2 and HF3 correspond to 3 months and 12 months after discharge. Currently, with this management approach, inpatient data at University Medical Center Ho Chi Minh City has enrolled over 230 patients after 7 months of implementation.

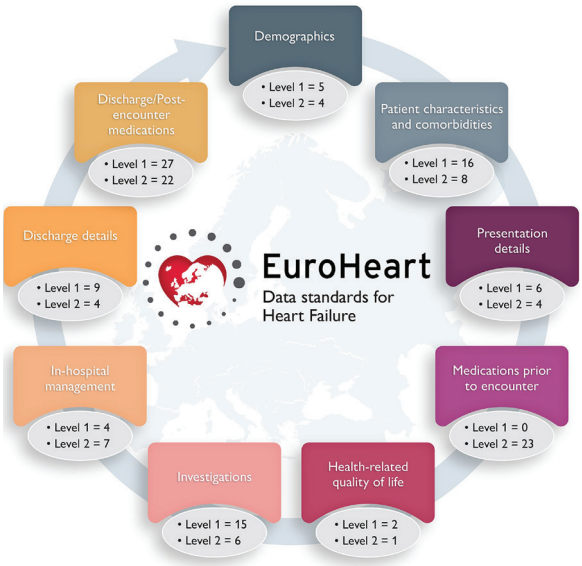

***Figure 6**. Overview of EUROHeart in heart failure management assessment and basis for randomized trials*

The collected data will be directly entered into the REDCap platform. REDCap is a secure web application for building and managing online surveys and databases. REDCap was specifically designed to support data capture and management for research studies and scientific programs; thus, REDCap is now used in over 150 countries, and is the main tool for the heart failure management program at University Medical Center Ho Chi Minh City. With REDCap, entered data will be directly statistically analyzed on this platform in real time. This enables more seamless and meticulous management. From REDCap, data can be easily retrieved into suitable formats for analysis and reporting. At the same time, through REDCap, different cardiovascular centers can together collect and store data from their own centers within the same management program. Currently, the REDCap-based heart failure management program at University Medical Center Ho Chi Minh City has the participation of Thong Nhat Hospital and An Giang Cardiovascular Hospital (Figure 7). The centers will perform data entry and jointly attend a monthly online meeting to share achievements as well as difficulties each center encountered in the past month; thereby helping improve data quality and the management program itself. This is the premise for this program to spread, enrolling a large number of patients, reflecting the overall picture of heart failure and heart failure management in Vietnam.

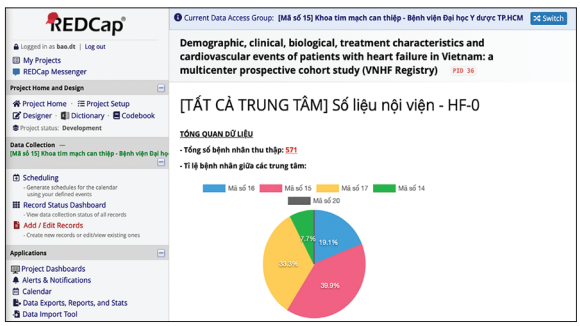

***Figure 7**. Real-time monitoring of heart failure management data on the REDCap application*

c. Research training

The successful establishment of a heart failure management program along with a large, reliable data source forms the foundation for organizing training courses, continuous medical education activities, as well as forming patient clubs. Exchanging and sharing difficulties, challenges as well as experiences and solutions to overcome these obstacles have been maximized at conferences, enabling centers to learn from each other and bring the greatest benefits to heart failure patients

(Figures 8 and 9). In addition, the heart failure patient club established at University Medical Center Ho Chi Minh City is also a bridge to make the bond between healthcare staff and patients stronger (Figure 10). Patients' questions and concerns are answered; their thoughts and aspirations listened to and acknowledged; at the same time, each activity is an opportunity to share knowledge and skills to help heart failure patients improve their quality of life after discharge and work with healthcare professionals on the path of reducing mortality from this common disease.

***Figure 8**. Representatives from participating hospitals at the Heart Failure Management Workshop, held during the New Trends in Cardiovascular Therapeutics Conference (NTCC 2023)*

***Figure 9**. Sharing experiences in heart failure management between University Medical Center Ho Chi Minh City and An Giang Cardiovascular Hospital*

***Figure 10**. Heart failure patient club at University Medical Center Ho Chi Minh*

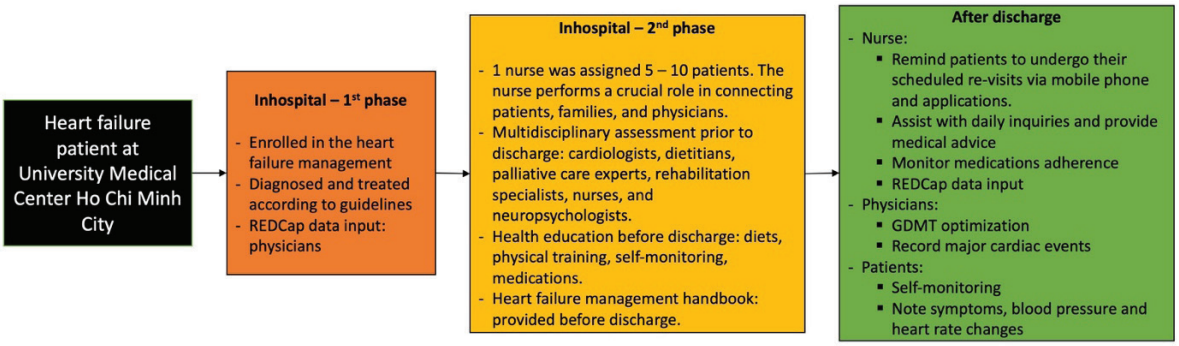

***Figure 11**. Summary of the basic structure and functions of the heart failure management model at University Medical Center Ho Chi Minh City*

CONCLUSION

Heart failure patients have poor long-term prognosis. There are many effective medications and treatments for heart failure, but optimizing medications and heart failure support devices remains a major issue in heart failure management. Close connection between heart failure patients and healthcare professionals is a classic problem in current heart failure management worldwide.

Standardized heart failure management models will help many patients benefit from advances in heart failure treatment, strengthen the bond between healthcare staff and heart failure patients. Thereby, contributing to reducing mortality, reducing hospitalizations for heart failure, and improving quality of life for heart failure patients. Standardized, multi-center heart failure management models will provide valuable real-world statistics in each region, from which clinical trials can be conducted to adjust and impact heart failure management models to continuously improve them, bringing practical benefits to patients and the healthcare system.

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

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▶ Received: 25 October 2023
Accepted: 25 November 2023
Published online: 30 November 2023

To cite: Pham TMD, Nguyen HH. *J Vietnam Cardiol 2023*; **107E**:93-99

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 care [1]. 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 HFrEF [2]. 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 guidelines-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 activity [6]. 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 importance [13].

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 intolerance[14]. 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 tolerate [15].

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 failure [2]. 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 ≤ 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 m^2, 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 arm [17].

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 stable [14]. 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 ≤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.
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 ≥ 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 diabetes [18]. 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 dapagliglozin and empagliflozin in reducing all-cause mortality, cardiovascular death, and improving renal function in hospitalized HFrEF patients [19].

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 estasblish 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 goals [11].

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 specilized 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.

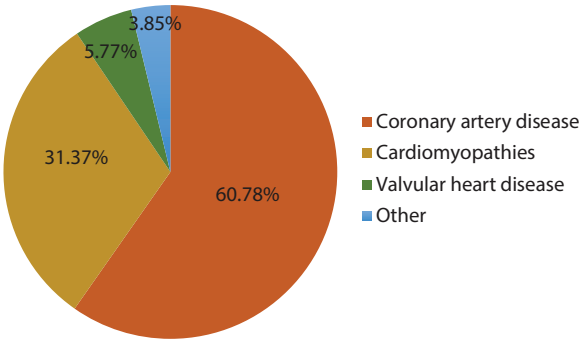
- Gender: female predominates, with 59.7%.

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.

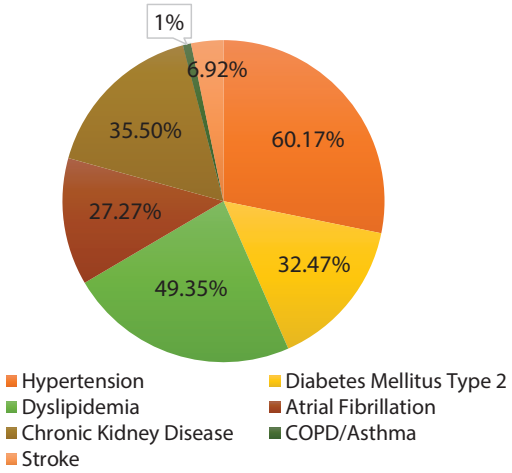
Comorbidities

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.

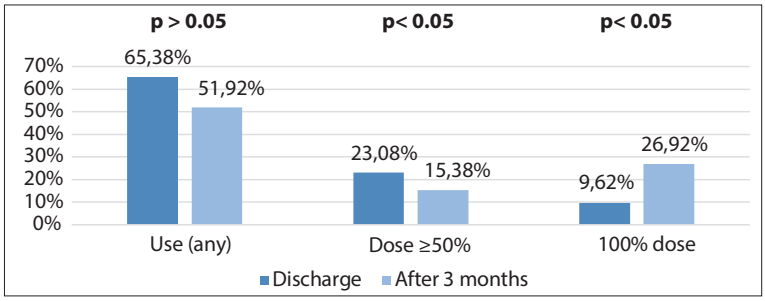


***Picture 2**. Comorbidities in HF patients at Nhan dan Gia Dinh Hospital*

Rates of foundational medication use in HFrEF patients

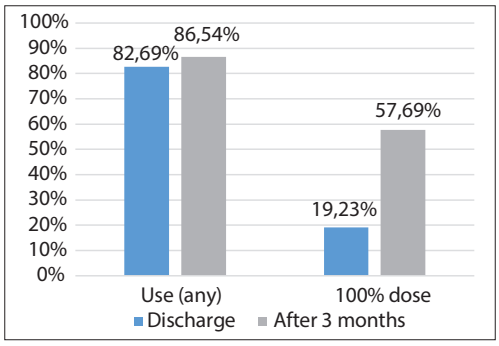
At time of discharge and after 3 months, we documented the rates at which foundational therapies are prescribed.

RAS Inhibition



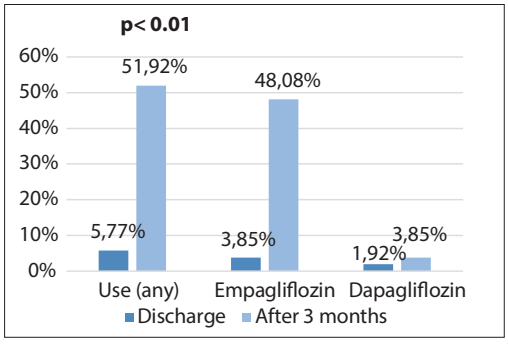
***Picture 3**. The prescription of RAS inhibitors at discharge and 3-month post-discharge*

Aldosterone Antagonists



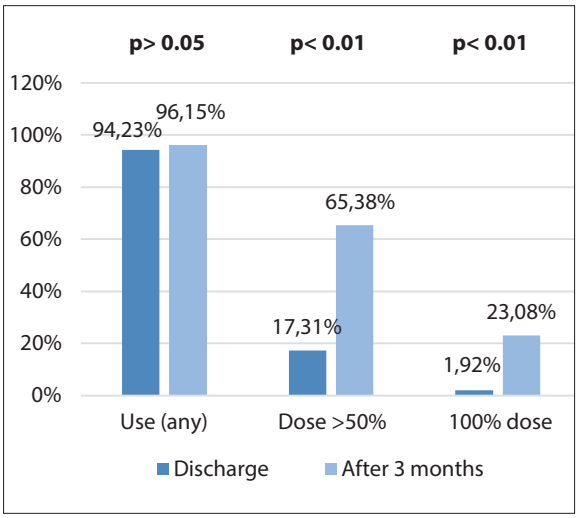
***Picture 4**. The prescription of Aldosterone antagonists at discharge and after 3 months*

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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Timing for combined diuretic therapy in acute heart failure: should we continue waiting for the poor response?

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▶ Received: 26 October 2023
Accepted: 20 November 2023
Published online: 30 November 2023

To cite: Van DH, Piter MB, Bui VH, *et al. J Vietnam Cardiol 2023*;**107E**:100-104

ABSTRACT

Decongestion is an important primary goal in acute heart failure treatment. Loop diuretics remain a fundamental role in congestion management and symptom improvement in patients with acute heart failure. Diuretic combination contributes to achieving better diuretic efficacy. However, the optimal timing for diuretic combination in clinical practice has not been distinctly recommended in current guidelines.

Keywords: acute heart failure, congestion, diuretic combination.

INTRODUCTION

Acute heart failure (AHF) is a clinically complex condition characterized by severe signs and/or symptoms of heart failure that require unplanned or emergency medical support.[1] In-hospital mortality, short-term, and long-term mortality rates are high in patients with AHF patients especially in the elderly.[2,3] Congestion accounts for nearly 90% of patients with AHF and may predominantly occur in the vascular system (intravascular congestion) or in the interstitium (tissue congestion), or often involves a combination of both mechanisms.[2,4] Congestion which resulting from increased left ventricle filling pressures, plays a significant role in the pathophysiology of organ damage in patients with AHF.[5] Improving congestion is one of the primary goals in the immediate phase of AHF management.[1] Loop diuretic is mentioned as cornerstone therapy in alleviating congestion in AHF patients. Additionally, combining other diuretics such as thiazides, acetazolamide, or tolvaptan with loop diuretics has been shown to improve congestion and symptoms.[1,4,6–8] However, the optimal timing for combining diuretics has not been uniformly established in recommendations.[1,6,8] This review will summarize the evidence regarding the timing of diuretic combination. Should we initiate diuretic combination therapy early or wait for clinical poor response before adding a second diuretic agent in patients with AHF?

METHODOLOGY

A review of the literature related to the therapeutic management of acute heart failure was carried out. The searches were carried out in Vietnamese and English language, in specialized databases of medical

publications such as PubMed/Medline, Scopus, Epistemonikos, SciELO and Trip medical database.

The search terms acute heart failure, decongestion and combined diuretic therapy were used as keywords. The inclusion criteria were established: the period of publication of the articles, between 1994 and 2023; the design of the study: randomized clinical trials, systematic reviews with meta-analysis, systematic reviews without meta-analysis, exploratory reviews, clinical practice guidelines. Approximately 86 original and review articles were consulted and 28 were selected. Articles written in languages other than those mentioned above were excluded.

IMPROVING CONGESTION WITH DIURETIC COMBINATION IN ACUTE HEART FAILURE

Congestion is defined as the accumulation of fluid in the intravascular compartment and the interstitial space, resulting from increased cardiac filling pressures caused by renal sodium and water retention.[9] Fluid accumulation originating in the intravascular compartment leads to decompensated heart failure, progressively elevating venous pressure, resulting in tissue congestion. Most AHF patients exhibit a combination of intravascular and tissue congestion, although dominance of either mechanism may occur. In cases of predominant intravascular congestion, patients often present with high blood pressure along with signs and symptoms such as increased jugular venous pressure, dyspnea, third heart sound (S3), and orthopnea. Vasodilators play a crucial role in managing these cases. Conversely, in cases of typical tissue congestion, patients frequently exhibit pitting edema, rales, and ascites, where intravenous diuretics are a preferred option.[4]

Several congestion scores such as EVEREST, EMPAROSPONSE-AHF, OPTIMIZE-HF, ASCEND-HF, and PROTECT have been established based on peripheral edema, orthopnea, dyspnea, jugular vein distension, rales, fatigue, and NT-proBNP levels. [4,10–15] In clinical practice, assessing congestion levels can be based on orthopnea, jugular venous pulsation, hepatomegaly, edema, 6-minute walk test, NT-proBNP levels, chest X-ray, inferior vena cava diameter, and lung ultrasound.[7]

Loop diuretics which inhibit the Na-K-2Cl symporter at the ascending loop of Henle, promoting sodium and chloride excretion.[16] For congestion management, loop diuretics help improve respiratory status and reduce left ventricular filling pressure.[17] AHF patients exhibit a decreased response to loop diuretics compared to healthy individuals. Additionally, there might be diuretic resistance due to increased catecholamines in those manifesting clinical congestion.[18] Hence, using intravenous loop diuretics with suitable doses is recommended. Moreover, diuretic response should be evaluated every 2 or 6 hours of diuretic therapy to adjust loop diuretic dosage.[1,8] Higher dose of loop diuretics are associated with adverse effects such as diuretic resistance, neurohormonal activation, electrolyte imbalances, and worsening renal function. Combining other diuretics such as thiazides, mineralocorticoid receptor antagonists, acetazolamide, and vasopressin antagonists may enhance the diuretic effect to mitigate these adverse effects and augment efficacy.[19] Although blood filtration may be considered in refractory congested patients despite high-dose diuretics or diuretic combinations, its superiority over conventional pharmacological treatment in AHF patients with renal impairment remains unproven.[1,8,20] Recent trial designed to demonstrate the effectiveness of SGLT2 inhibitors on congestion relief in AHF patients.[21]

TIMING FOR DIURETIC COMBINATION IN ACUTE HEART FAILURE

Some observational or randomized controlled trials with small sample sizes have demonstrated the increased diuretic effect of a second diuretic agent in combination with furosemide in AHF patients (Table 1). However, the timing of combining these medications is not explicitly addressed and lacks consistency across studies.[21–25] Notably, two recent large-scale studies, CLOROTIC and ADVOR trials, observed clinical efficacy but also lacked uniformity regarding the timing of combining diuretics. The CLOROTIC trial, encompassing

230 AHF patients with an average age of 83 years old, of whom 48% were female, indicated that combining hydrochlorothiazide (HCTZ) with loop diuretics improved diuretic response in AHF heart failure patients by enhancing weight loss at 72 and 96 hours. However, there was no difference observed in improving dyspnea between the two groups. Additionally, the HCTZ diuretic group exhibited a significantly higher incidence of renal impairment compared to the placebo group (46.5% in the HCTZ group vs. 17.2% in the placebo group). In CLOROTIC trial, HCTZ or placebo was administered orally and initiated within 24 hours of hospital admission.[27] The ADVOR trial, involving 519 AHF patients with an average age of 78 years old, of whom 62.6% were male, showed the benefit of intravenous acetazolamide in combination with loop diuretics in effectively improving congestion based on criteria such as successful decongestion within 3 days of randomization, congestion score, or successful decongestion at discharge compared to placebo. Moreover, there were no significant differences observed in the incidence of new-onset renal injury, hypokalemia, hypotension, or adverse effects between the two study groups. The timing of combining a second diuretic with loop diuretics was defined as the first-time use of the second diuretic daily.[28]

Both the European Society of Cardiology (ESC) and the Vietnam National Heart Association (VNHA) emphasize considering combining a second diuretic with loop diuretics in patients with persistent or refractory edema unresponsive to escalating loop diuretic doses (Class IIa, level B).[1,8] Similar recommendations are also provided by the American College of Cardiology (ACC) for patients not showing improvement in signs and symptoms of congestion.[6] The optimal timing for combining diuretics remains inconsistent across guidelines. While the ESC and VNHA outline a diuretic use protocol in AHF patients and emphasizes considering combining diuretics after two assessments of clinical response and urinary sodium (4–12 hours after the initial dose of loop diuretics), the American College of Cardiology does not provide a specific time frame for combining diuretics. The improvement of congestion in acute or critically ill AHF patients is a crucial goal that needs to be promptly addressed.[1,6,8] Combining a second diuretic on a loop diuretic background enhances diuretic efficacy and improves congestion symptoms.[1,6,8] The lack of data concerning the timing of combining diuretics and the benefit in improving congestion may be the reason for the lack of consensus regarding the timing of combining diuretics. Future trials are needed to address the question of the optimal timing for combining a second diuretic to rapidly improve congestion and alleviate symptoms in AHF patients.

CONCLUSION

Acute heart failure represents a multifaceted pathological state characterized by substantial fluid retention. Loop diuretics play a crucial role in congestion relief in AHF patients. Diuretics combination can enhance fluid excretion and alleviate symptoms of congestion. However, the optimal timing for combining diuretics lacks consensus across clinical trials and is not explicitly addressed in current treatment guidelines. Future studies will guide strategies to optimize diuretic combinations aiming for early improvement in congestion and symptoms for patients with AHF.

Table 1. *Timing of diuretic combination in several trials*

Author, Year, Patients number, Design	2nd diuretic and administration timing	Results
Channer et al, 1993, 33 patients, randomised clinical trial[22]	Bendrofluazide and metolazone. Unresponsive to intravenous loop diuretics for 48 hours.	5 – 5.6 kg weight loss after the addition of bendrofluazide and metolazone.
Mouallem, 1995, 32 patients, observational study[23]	Thiazide. During acute period.	4.8 kg weight loss.

Author, Year, Patients number, Design	2nd diuretic and administration timing	Results
Dormans, 1996, 20 patients, observational study[24]	Thiazide. During acute period.	6.7 kg weight loss. increasing daily urine volume. increasing fractional sodium excretion.
Piardi, 2021, 51patients, randomized, single-center, parallel, double-blind, placebo-controlled clinical trial[25]	Thiazide Within 1st day of admission	1,78 kg weight loss/day.
Tien M.H. Ng, 2013, 242 patients, retrospective study[26]	Metolazone At least 6 hours after the first bolus doses of furosemide	increasing hourly urine output.
CLOROTIC trial, 230 patients, prospective, double-blind, placebo-controlled trial[27]double-blind, placebo-controlled trial, including patients with AHF randomized to receive HCTZ or placebo in addition to an intravenous furosemide regimen. The coprimary endpoints were changes in body weight and patient-reported dyspnoea 72 h after randomization. Secondary outcomes included metrics of diuretic response and mortality/rehospitalizations at 30 and 90 days. Safety outcomes (changes in renal function and/or electrolytes	Hydrochlothizide. Within 24 hours after admission.	HCTZ group were more lose weight at 72 hours than placebo group. No significant differencses in patient-reported dyspnea. More impaired renal function in HCTZ group.
ADVOR trial, 519 patients, multicenter, parallel-group, double-blind, randomized, placebo-controlled Trial[28]	Acetazolamide Acetazolamide was administered with the first dose of loop diuretics.	Acetazolamide group were more successful decongestion, higher urine output and natriuresis than placebo group.

ACKNOWLEDGMENT

None.

CONFLICTS OF INTEREST

The authors declare no competing interests.

LIST OF ABBREVIATIONS

ACC = American College of Cardiology;
AHF = Acute heart failure;
ESC = European Society of Cardiology;
HCTZ = Hydrochlorothiazide;
VNHA = Vietnam National Heart Association.

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