Adherence to gdmt treatment for heart failure out-patients – single center registry

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ABSTRACT

Background: GDMT treament has demonstrated to heart failure can improve heart failure survival and reduce hospital admission.

Objective: This study evaluated the use of guideline-directed medical therapy (GDMT) for heart failure with reduced and mild reduced ejection fraction (HFrEF) in outpatient department in Hanoi Heart Hospitaland its impact on patients' midterm outcome.

Method: Medical records of 1131 patients with HFrEF and HFmrEF followed at Hanoi Heart Hosspital, facility 1 From September 2019 to March 2021 were reviewed. The prescription rates of recommended pharmacological agents and their dosages were evaluated.

Results: The population includes 711 male (62.9%) and 420 female (37.1%), with an average age of 64,96 ± 14,49 years. The mean and median time of follow up were 10,59 ± 2,77 month (the shortest follow-up time was 3 months, the longest was 15 months). The prescription rate of β-blockers, ACEI/ARB/ARNI, MRA were 74.36%, 80.9% and 69.5% respectively. After follow-up, these rates were 86.75%, 86.52% and 68.9%, correspondingly. After follow-up, the highest rate of prescription over 50% dosages of these drugs in the range given were Spiranolactone, it was achieved 56.15%, followed by Losartan, Bisoprolol, Nebivolol, all above 30%. The initial LVEF was 37.93 ± 8.58%, and at the end of the follow – up period, the LVEF achieved 40.26 ± 9.44%, significantly improved. 168 patients (14.85%) were admitted to the hospital at least once during the follow-up period; mong them, 133 patients (79.2%) were hospitalized once, 30 patients (17.8%) were hospitalized twice, and five patients (3.0%) were hospitalized at least three times. Mortality was 1.9% (18 patients) during the follow-up period.

Conclusion: The rate of heart failure GDMT drugs using for outpatients in our center is rather high but there are gaps that need to be filled to enhance the outcome of HFrEF and HFmrEF patients.

Keyword: *Heart failure, guideline, GDMT*

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I. INTRODUCTION

Heart failure is characterized by frequent episodes of recurrence, with a predicted re-hospitalization rate of over 50% and a one-year mortality rate of over 30%. [1;2] Despite many advances in diagnosis and treatment, the mortality rate for heart failure is 50% within five years after diagnosis, making it the most frequent discharge diagnosis. It causes a significant economic burden on the national healthcare system (total cost, $39,2 billion in 2009). [3]

In this situation, improving the management of outpatient with heart failure has been proposed as the foundation for preventing frequent hospital admissions and thus cost.[13] Treatment for outpatients with heart failure is multifaceted and includes several steps listed in the American College of Cardiology/American Heart Association (ACC/AHA). [4]

Vietnam currently has no studies evaluating the situation of applying guideline treatment. Therefore, this study was conducted with the following objectives:

- To assess the adherence to heart failure GDMT for outpatients in Hanoi Heart Hospital

- To assess the outcome of patients followed in heart failure clinic, Hanoi Heart Hospital.

II. PATIENT AND METHOD

Patient Selection criteria: patients over 18 years of age, diagnosed with heart failure and LVEF ≤ 50%. All of these patients were managed in the outpatient heart failure program at Hanoi Heart Hospital.

Study period: from September 2019 to March 2021 at the Outpatient Department of Hanoi Heart Hospital.

Study design: Cross-sectional analysis, retrospective study.

Study variables: Collecting data according to a standardized form for patients in the outpatient heart failure program diagnosed with heart failure, and retrieve data from the outpatient medical records of patients. The patients included in the study were those enrolled in the Heart Failure Program from September 2019 to March 2021. Although the patients were not enrolled at the same time, the time of enrollment was considered as the initial follow-up point, and subsequent data collection occurred at 1, 3, 6, and 12 months after treatment. The data was monitored throughout the study period. Therefore, patient data entry may be stopped when patients died, at the end of the study, or when data was lost because these patients did not continue treatment in the heart failure program and received treatment at another unit, and could not be contacted to collect data.

The study variables included clinical symptoms of heart failure according to NYHA classification, blood pressure parameters, heart rate at each follow-up visit.

Exploration of co-morbidities or medical history (such as ischemic heart disease, hypertension, atrial fibrillation, history of stroke, diabetes, valvular heart disease, chronic lung disease, dilated cardiomyopathy, hypertrophic cardiomyopathy, congenital heart disease, pacemaker implantation, heart surgery, medications being treated (Digixin, diuretics, ACEIs, ARBs, beta-blockers, etc.), medication adherenced (consistent, inconsistent, discontinued), and changed the medication during monitoring.

Recording the results of echocardiography to evaluate left ventricular size (Dd, Ds), ejection fraction (EF), and estimated pulmonary artery systolic pressure. Electrocardiogram and blood test results were also recorded during the treatment follow-up period.

Collecting data on medication use: Name of medication, dosage, and the combination of medications treatment heart failure each patient during 12 months at each follow-up visits: initial follow-up, after 1 month, after 3 months, after 6 months, and after 12 months of treatment in the heart failure program.

Collecting data on the cause of hospitalization and initiating factors of each heart failure exacerbation in patients (if applicable).

For patients who have lost follow-up data after a certain period of treatment in the program, contact them via phone to inquire about the reason for discontinuation of follow-up and current treatment status.

Statistical analysis: The data were described as percentages for categorical variables and mean ± SD for continuous variables. Data analysis is performed using SPSS 24.0 statistical software. The medical statistical algorithm was used to process the collected data with the STATA 12.0 software. The Mann–Whitney U test and Kruskal-Wallis variance analysis (ANOVA) were used as non-parametric tests, and a p-value <0,05 was considered statistically significant.

Ethical considerations: Patients' information was kept confidential. The study was conducted for scientific research purposes.

III. RESULTS

From September 2019 to March 2021, 1131 patients were enrolled in the outpatient heart failure clinic; among them, 529 patients (46,8%) having LVEF < 40% and 602 patients (53,2%) with LVEF from 41 to 49% and. There were 711 male patients (62,9%) and 420 female patients (37,1%), with a mean age of 64,96 ± 14,49 years. The mean follow-up time was 10.59 ± 2.77 months (max: 15 months, min: 3 months).

Clinical, Subclinical Characteristics.

Table 1: Change NYHA over time

		Baseline	**3-6 months**	**9-12 months**	**p**
NYHA n(%)	I	620(54,75%)	645(58,1%)	677(67,3%)	0,005
	II	455(40,3%)	432(38,9%)	326(32,4%)	0,005
	III	56(4,95%)	18(1,6%)	0	0,015
	IV	0	15(1,4%)	3(0,3%)	0,015
SBP(X ±SD)		115,0±14,15	113,9±16,63	115,8±14,69	115,0±14,15	0,656
DBP(X ±SD)		65,08±10,58	65,4±16,74	64,5±11,17	65,08±10,58	0,665
HR(X ±SD)		77,72±12,83	76,3±11,87	76,46±14,03	77,72±12,83	0,776

Echocardiography	EF (X ±SD)	37,93± 8,58	39,77± 9,22	40,26 ±9,44	p< 0,0001
	Dd (X ±SD)	55,72 ±7,24	54,57± 6,83	53,42 ±6,83	p< 0,0001
	Ds (X ±SD)	48,65± 7,66	47,1 ± 7,93	44,1± 7,7	p< 0,0001
	EF (X ±SD)	37,93± 8,58	39,77± 9,22	40,26 ±9,44	p<0,0001
	EF > 50%		86(7,74%	75(8,94%)	

Commentary: The NYHA classification shows significant changes throughout each the follow-up visit, with mainly class I and II observed after 9 to 12 months of treatment. Three patients with NYHA class IV ultimately died. The heart rate and blood pressure of the patients remained unchanged during the follow-up period. The EF, Dd, and Ds improved throughout treatment, and these changes were statistically significant.

The rate of taking medication and the rate of achieving the target dose

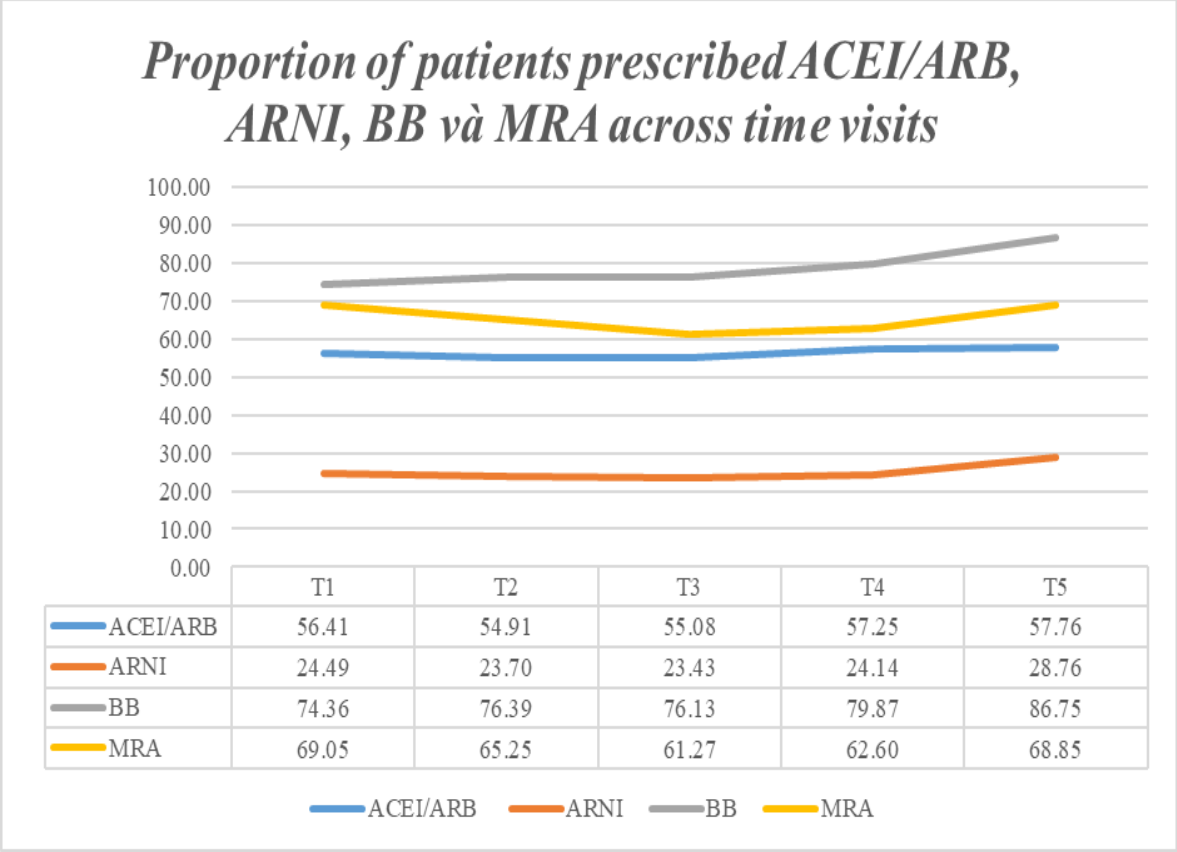

Fig 1: Proportion of patients prescribed heart failure medications across time visits

Commentary: The rate of taking RAS medications (AECI/ARB/ARNI) and beta blockers at the baseline were 80,9% and 74,36% respectively. At the end of the monitoring period, these rates increased to 86,52% and 86,75%.

Table 2: Medication combination Rate

	Baseline (n=1131)	**The end of the study (n=1006)**
Beta Blocker + ACEI	12,64%	5,9%
Beta Blocker + ARB	32,07%	34,7%
Beta Blocker + ARNI	22,37%	23,6%
MRA + ACEI	9,73%	4,4%
MRA +ARB	26,17%	22,9%
MRA + ARNI	23,69%	21,9%
MRA + ACEI + Beta Blocker	9,7%	4,4%
MRA +ARB+ Beta Blocker	26,1%	22,9%
MRA + ARNI+ Beta Blocker	22,4%	21,9%
Total		

Commentary*: The rate of taking MRA, combined beta blockers and ARNI//ACEI/ARB group, or combined all three medication groups is quite high.*

Table 3: Achieving the target dose rate

Medication		**Baseline**		**The end of the study**	
		Proportion of patients taking medication	Proportion of patients achieving ≥ 50% target dosage	Proportion of patients taking medication	Proportion of patients achieving ≥ 50% target dosage
ACEI	**Lisinopril**	6,01%	4,41%	5,78%	11,11%
	Valsartan	24,87%	0,37%	31,3%	2,19%
	Losartan	13,02%	30,37%	12,3%	32,69%
	ARNI	24,49%	3,64%	24,14%	4,98%
Beta Blocker	**Metoprolol**	40,5%	2,0%	50,4%	3,52%
	Bisoprolol	23,9%	22,97%	30,4%	33,9%
	Nebivolol	9,96%	34,88%	5,3%	31,25%
	Carvedilol			0,66%	0%
MRA	**Spiranolacton**	69,05%	60,98%	62,60%	56,15%

Commentary**:** The highest proportion achieving ≥ 50% target dosage is Losartan, Nebivolol and Spiranolacton.

The hospitalization and adherance rate of patients with heart failure.

All hospitalizations included in the study were those that occurred at the Hanoi Heart Hospital. For patients who were followed up, hospitalizations at other hospitals were not collected.

Table 4: Hospital Readmision

	Total	**Hospitalization once**	**Hospitalization twice**	**Hospitalization ≥ 3 times**
The number of patients hospitalized ≥ 1 time	168/1131	133(79,2%)	30(17,8%)	5(3,0%)
BN tử vong	18	8(44,4%)	7(38,9%)	3(16,7%)

Commentary*: The proportion of patients who were hospitalized at least once during the follow-up period was 14,85%.*

Table 4: Re-hospitalization trigger factors

	Total		**EF 40- 50 %**		**EF <40%**	
	n	%	n	%	N	%
Acute coronary syndrome	27	2,39	7	1,16	20	3,78
Infection	12	1,06	6	1,00	6	1,13
Myocarditis	5	0,44	1	0,17	4	0,76
Acute kidney failure	12	1,06	5	0,83	7	1,32
Rapid drop in blood pressure or cardiac arrest	5	0,44	0	0	5	0,95
Acute stroke	11	0,97	7	1,16	4	0,76
Acute exacerbation of heart failure	5	0,44	2	0,33	3	0,57
Hospitalization for CABG/valve replacement	44	3,89	32	5,32	12	2,27
Pericardial effusion drainage procedure	10	0,88	6		4	

Commentary: Among the monitored patients, 18 cases accounted for 1.59% mortality rate. The causes of death were infection, ventricular tachycardia/fibrillation, coronary heart disease, stroke with hemorrhagic transformation, and end-stage heart failure.

Table 6: Number of patients monitored during treatment stages

	Baseline	**3 – 6 months**	**9 – 12 months**
Total	1131	1110	1006
The number of patients drop out the program		21(1,8%)	104(9,2%)
The number of patients death/ Total number of patients drop out the program	0	15(71,4%)	3 (2,8%)

Commentary: 21 patients (1,8%) dropped out after 3-6 months of treatment, and 104 patients (9,2%) dropped out after 9-12 months

IV. DISCUSSION

4.1. Clinical and paraclinical characteristics

The NYHA classification changed significantly throughout the follow-up period, with predominantly class I and II at 9-12 months of treatment; 3 patients had class IV NYHA and subsequently died. At the baseline, the percentage of NYHA class I and II was 54,75% and 40,3%, respectively. After 9-12 months of treatment, these percentages increased to 67,3% and 32,4%, respectively. The percentage of NYHA class III was 4,95% at baseline, which decreased to 0% after the treatment period. However, there was no change in blood pressure and heart rate during the entire treatment process, which can be explained by the suboptimal take of medications.

The average SBP of the study group was 115,0±14,15, which was lower than that in the EFICA study (126 ± 39 mmHg). Higher or lower than normal blood pressure is also a factor to be considered in the treatment of heart failure patients and may affect the prognosis of the disease. The SBP after 3-6 and 9-12 months of treatment was 113,9±16,63 and 115,8±14,69, respectively, with no change in this index after the treatment process.

At the baseline, the average EF was 37,93±8,58, with Dd and Ds indices of 55,7±7,24 and 48,65±7,66, respectively When comparing Dd and Ds indices between the EF 40-50% and EF < 40% groups, the Dd and Ds indices in the EF < 40% group were higher and statistically significant.

After 3-6 and 9-12 months of treatment, the average EF was 39,77±9,22 and 40,26±9,44, respectively, with improved EF over the treatment period This change was statistically significant with p<0,0001 In addition, the Dd and Ds indices also improved significantly over the treatment period.

After 3-6 months of treatment, 86 patients had an EF improvement of >50%, and after 9-12 months of treatment, an additional 75 patients had an EF improvement of >50% The group of patients with EF improvement of >50% were those with NYHA class I or II and high adherence to treatment.

In us study, the mean follow-up time was 10.59 ± 2.77 months (max: 15 months, min: 3 months). In fact, guideline adherence was defined as good or poor according to the prescription of angiotensin-converting enzyme inhibitors,

angiotensin receptor blockers, β-blockers, and mineralocorticoid receptor antagonists.[15] And there were a small number of patients in our study who dropped out of treatment.

4.2. Rate of taking mediication and achieving target dose

The initial rate of taking beta-blocker among patients was 74,36%, and after 12 months of treatment, this rate increased significantly to 86,75% This rate was higher than that found in the THAI ADHERE study (26,1%; 24%), but lower than that reported in the US ADHERE (56%; 64%) and EHFSII (43,2%; 61,4%) studies.[6;7]

The initial rate of taking mineralocorticoid receptor antagonist (MRA) was 69,05%, and after 12 months of treatment, this rate decreased slightly to 68,85% Although the change was not significant, it was higher than that found in the THAI ADHERE study (17,1%; 12,5%) [7] The initial rate of taking ACEI/ARB/ARNI was 80,9%, and after 12 months of treatment, this rate increased significantly to 86,52% This rate was higher than that found in the THAI ADHERE study (ACEI/ARB: 257%/ 28,1%) [6], and similar to previous studies (80-86%) [8;9] The high rate of taking these medications can explain the statistically significant improvement in our patients' EF index and the significant proportion of patients with an improvement in EF of > 50%

To achieve the treatment goals of heart failure, it is important to optimize the dose of therapy[14]. When compared to other global studies, such as the QUALIFY study, a multicenter study conducted on 6669 patients in 36 countries within 15 months of discharge, aimed to assess adherence to heart failure treatment guidelines The results showed that up to 22% of patients were not prescribed ACEI/ARB, beta-blockers, or MRA without any contraindications The proportion of patients using ACEI/ARB and beta-blockers with doses ≥ 50% was 55,0% Only 23% of patients with reduced ejection fraction achieved the target dose of ACEI/ARB and beta-blockers in the study.[10] The TSOC - HFrEF study in Taiwan followed up 1509 patients with reduced ejection fraction for one year after hospitalization The study showed that about 60% of patients with reduced ejection fraction at discharge were prescribed ACEI/ARB and beta-blockers The proportion of patients achieving target doses for ACEI/ARB and beta-blockers after one year of follow-up was 250% and 40%, respectively.[11] The study by Reyes et al in 2016 showed that about 90% of heart failure patients were prescribed ACEI/ARB, but the proportion of patients prescribed beta-blockers was only 40%.[12]

Although the rate of taking medication to improve the prognosis of heart failure was relatively high, the rate of achieving the target dose was low for both ACEI/ARB/ARNI and beta-blockers, and there was no change in the rate of achieving target dose after treatment. The rate of achieving target dose for MRA was above 50%. This explains why the blood pressure and heart rate indices in our study did not change after treatment, and why we suggest optimizing medication group to achieve optimal outcomes for outpatient heart failure patients

4.3. Rate of hospitalization and adherence of patients with heart failure

In the patient population being monitored, the patient with the highest number of hospital re-hospitalization was recorded five times and died in the 15th month of follow-up Each re-

hospitalization was due to arrhythmia, despite optimal treatment with ARNI, beta blockers, Verospiron, and Forxiga The patient underwent electrophysiological two times, but not all extra-atrial ventricular foci were eliminated The patient was also implanted with an ICD, but the battery was quickly depleted, and one month after replacement, the patient died due to ventricular fibrillation and could not be resuscitated Furthermore, the number of patients with emergency hospitalization and hospitalization rates divided by EF showed that the number of patients with emergency hospitalization and the number of patients with emergency hospitalization of two or more times in the EF < 40% group was higher than that in the EF 40-50% group However, this difference was not statistically significant

In the hospitalized patient group, there were 71 patients (42,3%) who were hospitalized once and diagnosed with heart failure, 62 patients (36,9%) who were hospitalized once but had previously been treated for heart failure, 30 patients (17,8%) who were re-hospitalized twice, and 5 patients (3%) who were re-hospitalized three or more times. The reasons for these re-hospitalized were due to factors such as acute coronary syndrome, infection, myocarditis, acute renal failure, arrhythmia, acute stroke, or surgical hospitalization. Throughout the follow-up period, no patient was recorded to have discontinued treatment leading to hospitalization for acute heart failure. Among the contributing factors, a large number of patients were admitted due to indications for surgery and acute coronary syndrome, followed by infection, acute renal failure, and acute stroke.

The most common factors leading to hospitalization in patients with heart failure in our study were acute coronary syndrome or hospitalization with indications for coronary artery bypass grafting or valve replacement, followed by infection and acute kidney injury. The overall infection rate in the EFICA study, which was conducted in Europe, was lower (3%), which could be explained by the fact that our country is located in the tropical region, where the risk of contracting infectious diseases is higher, and our epidemiological hygiene and vaccination rates for influenza and pneumococcus are not high enough.[5]

18 patients, accounting for 1,59% of deaths during follow-up, died due to infection, ventricular tachycardia/ventricular fibrillation, myocardial infarction, stroke with hemorrhagic transformation, and end-stage heart failure. This rate was recorded during re-hospitalization or follow-up among patients who had dropped out during the study. Among these causes of death, end-stage heart failure accounted for 67%, followed by infections and arrhythmias accounting for 11% of all death causes. 5% of patients died from myocardial infarction and 6% from stroke. These stroke patients underwent reperfusion therapy, but later suffered from hemorrhagic transformation and died, with or without decompressive craniectomy.

After 3 to 6 months of treatment, 21 patients (1,8%) were dropped out the program, of which 15 patients (71,4%) died, and the remaining 6 patients (28,6%) either discontinued treatment or treatment at another facility without providing data. After 9 to 12 months, 104 patients (9,2%) were dropped out the program, of which 3 patients (2,8%) died and the remaining 86 patients (82.6%) discontinued treatment or treatment at lower-level facilities due to not referred health insurance.

The patients followed only up for 3 months belonged to the following groups: after PCI or CABG/valve replacement surgery, patients only followed the program for an additional 2 months, then sought treatment at another healthcare facility, or patients who were diagnosed with heart failure in the final stage of the year, after 3 months of treatment in the new year, were not able to obtain a referable certificate and continued treatment at another healthcare facility. A few patients died or discontinued treatment after 3 months of treatment.

Limitations of the study:

+ Noncomplete follow-up in inpatient and outpatient treatment. There is a need for closer communIication to provide patients with better advice and follow-up. There should be communication with hospitals to establish a heart failure network, manage and monitor patient information more closely and comprehensively.

+ Training and guidance for young doctors and nurses need to be continuous and consistent to ensure adherence with current treatment guidelines.

V. CONCLUSION

The rate of heart failure GDMT drugs using for outpatients in our center is rather high but there are gaps in prescription and uptitration of GDMT drugs that need to be filled to enhance the outcome of HFrEF and HFmrEF patients.

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