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Heart Failure Outcomes with Predischarge Guideline Directed Medical Therapy Prescribing Patterns among Hospitalized Patients with Heart Failure with Reduced Ejection Fraction

Wasawat Srikaseatsrakul MD[1], Katiman Sonthikaew MD[1],

[1] *Division of Cardiology, Department of Medicine, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok 10300, Thailand*

Corresponding author
Katiman Sonthikaew
katiman@nmu.ac.th
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ABSTRACT

Objective: To assess the rates of heart failure (HF) readmission or all-cause mortality at 6 months among hospitalized patients with heart failure with reduced ejection fraction (HFrEF) based on the comprehensiveness of guideline-directed medical therapy (GDMT) prescribed at discharge.

Materials and Methods: This therapeutic study with a retrospective cohort design included patients with a first time hospitalized diagnosis of HFrEF at Vajira Hospital, Faculty of Medicine, Navamindradhiraj University, between January 1, 2018, and May 30, 2022. Patients were categorized into three groups according to the number of GDMT prescribed: GDMT1 (none or one agent), GDMT2 (two agents), and GDMT3 (three agents). The primary outcome is 6-month HF readmission or all-cause mortality were retrospectively collected.

Results: A total of 382 patients (65.2% male, mean age 64.4 ± 14.6 years) were included. Most patients had ischemic cardiomyopathy (43.7%), and the distribution of patients into the three groups was 31.4%, 39.3%, and 29.3% in GDMT1, 2, and 3, respectively. HF readmission or all-cause mortality were significantly lower in patients receiving more comprehensive GDMT: hazard ratio (HR) 0.32 (95% confidenc interval (CI): 0.16-0.65, p = 0.001) for GDMT3 versus GDMT1 and HR 0.42 (95% CI: 0.24-0.72, p = 0.002) for GDMT2 versus GDMT1. However, there was no statistically significant difference in the rate of 6-month all-cause mortality among the three groups.

Conclusion: Achieving three GDMT agents before discharge in patients hospitalized with HFrEF is associated with a significant reduction in 6-month HF readmission or all-cause mortality.

Keywords: guideline-directed medical therapy, heart failure readmission, heart failure with reduced ejection fraction, hospitalization, predischarge medication

INTRODUCTION

Guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF) has been strongly supported by randomized controlled trials and is endorsed in international guidelines.[1,2] The four key pharmacologic pillars of GDMT include renin-angiotensin-aldosterone system (RAAS) blockage or angiotensin receptor–neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter 2 (SGLT2) inhibitors. In addition, these medications have been shown to reduce heart failure (HF)–related hospital readmissions and mortality while significantly improving the quality of life of patients.[3] The benefit of GDMT also extend into the hospitalized and predischarge period, although patients in this phase may not receive the full recommended medication regimen.[4] As a result, in 2021, the European Society of Cardiology HF guidelines[5] recommend that GDMT medications should be initiated as early as possible—preferably during hospitalization—and, when feasible, introduced simultaneously.

However, the recent guideline[5] did not specify the optimal number of medications for predischarge initiation. Furthermore, several trials have highlighted only the benefits of various combinations of contemporary HF therapies, and the real-world evidence remains limited in the predischarge stage of care.[6] In this study, we aim to investigate the HF outcomes in patients discharged with differing degrees of GDMT implementation. Specifically, we compared the outcome between patients received four recommended medications with those received some medications.

MATERIALS AND METHODS

In this retrospective cohort study, we included patients hospitalized at Vajira Hospital, Faculty of Medicine, Navamindradhiraj University, between January 1, 2018, and May 30, 2022. The inclusion criteria were patients aged ≥ 18 years who were either newly diagnosed with HFrEF (left ventricular ejection fraction (LVEF) ≤ 40%) or who had a previous diagnosis and loss to follow up for 6 months. We excluded patients who had septic shock or no medical history, HF caused by severe valvular heart disease, or life-threatening comorbidity with a life expectancy of less than 1 year, including those with dependent for renal replacement therapy. The primary outcome was the composite of HF readmission or all-cause mortality rates at 6 months. The secondary outcomes were the 30-day HF readmission rate, 6-month cardiovascular death rate, 6-month acute myocardial infarction rate, and 6-month acute ischemic stroke rate.

The researchers collected electronic data from patients with acute decompensated HF who were admitted at Vajira Hospital within the previous 5 years. Then, we enrolled patients based on the inclusion and exclusion criteria. We collected basic patient information such as underlying disease, HFrEF etiology, renal function, hematocrit (HCT), LVEF, and medicines prescribed at the time of hospital discharge. We defined GDMT as therapy including angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blockers (ARBs) or ARNIs, beta-blockers (bisoprolol, carvedilol, nebivolol, metoprolol succinate), MRAs, and SGLT2 inhibitors. We stratified the patients into the following three groups: GDMT1, none or one GDMT; GDMT2, two GDMTs; and GDMT3, three or more GDMTs. We collected prognostic information within 6 months after discharge, including 30-day HF readmission, 6-month HF readmission, 6-month all-cause mortality, 6-month cardiovascular mortality, acute myocardial infarction, and acute ischemic stroke. The data were collected and entered into the case record forms. The Ethics Committee of the Faculty of Medicine, Vajira Hospital, Navamindradhiraj University, approved the study (COA 080/2565) and the investigators were certified in Good Clinical Practice.

We determined the sample size used in this research based on the study by Yamaguchi et al.,[7] in which the HF readmission rate was 25.3% when given an error of 20%. We estimated the required sample size in this study to be ≥ 377. The continuous variables are presented as the mean ± standard deviation or median with interquartile range, depending on the distribution. Categorical variables are presented as counts and percentages. The treatment group comparisons were performed using analysis of variance or Kruskal–Wallis test depending on the distribution of the continuous data. We used Chi-square tests to compare the categorical variables between the three groups. The Kaplan–Meier estimates and log-rank tests were used to describe the cumulative incidence of outcomes. We used Cox proportional hazards models, adjusted for key covariates (age, sex, body mass index, anemia, chronic kidney disease (CKD) stage IV–V, type 2 diabetes, hypertension (HT), coronary heart disease, and atrial fibrillation), to calculate the

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hazard ratios with 95% confidence interval (CI). Subgroup analyses (ischemic vs. nonischemic cardiomyopathy) were conducted. A p-value of < 0.05 was considered significant. We performed all analyses using IBM SPSS Statistics version 28.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Of the 1,537 patients admitted to Vajira Hospital with acute decompensated HF over the past 5 years, 382 met the inclusion criteria. The distribution of patients across the groups was 31.4%, 39.3%, and 29.3% in the GDMT1, 2, and 3 groups, respectively. Table 1 summarizes the baseline characteristics. The mean patient age was 64.4 ± 14.6 years, and 62.5% were male. The average LVEF was 30.2% ± 7.3%. The mean systolic blood pressure was 143.6 ± 28.0 mm Hg, the mean heart rate was 99.8 ± 23.7 bpm, and the mean HCT was 37.3% ± 7.2%.

In the investigation for the etiology of HFrEF, 65.2% of patients underwent coronary angiography and 3.7% underwent cardiac magnetic resonance imaging. The findings identified ischemic cardiomyopathy in 43.7% of cases, nonischemic cardiomyopathy in 28.8%, and an undetermined etiology in 27.5%. Toxin exposure—primarily to amphetamines—was reported in 4.2% of nonischemic patients. Common comorbidities included dyslipidemia (88.7%), HT (87.7%), and coronary artery disease (63.1%). However, we found significant differences among the groups in terms of age, creatinine value, CKD stage, HCT value, LVEF, and etiology of cardiomyopathy.

Table 2 shows the patterns of predischarge GDMT. In total, 31.4% of patients received one or fewer GDMT agents (GDMT1), 39.3% received two agents (GDMT2), and 29.3% received three or more agents (GDMT3). Beta-blockers were the most frequently prescribed (91.1%), primarily bisoprolol (49%; mean dose 2.9 ± 2.7 mg/day; 21.5% achieved the target dose). This was followed by ACEIs, ARBs, or ARNIs (67.5%), with losartan being the most commonly prescribed (33.5%; mean dose 44.1 ± 27.1 mg/day; 14.8% achieved the target dose), and MRAs, mainly spironolactone (36.1%; mean dose 14.8 ± 6.9 mg/day; 19.6% achieved the target dose). Other commonly used medications included furosemide (78.3%) and SGLT2 inhibitors (4.2%). In the GDMT2 group, RAAS blockage plus beta-blocker was the most common combination (84%). A beta-blocker plus MRAs and RAAS blockage plus MRAs were administered to 10.7% and 4.7% of patients, respectively.

Six months after hospital discharge, 83 patients (21.4%) were readmitted for acute HF, and 21 patients (5.5%) died. The composite event rates across GDMT1, 2, and 3 were 39.2%, 19.3%, and 12.5%, respectively. In addition, the Kaplan–Meier analysis demonstrated a statistically significant difference in cumulative incidence of 6-month heart HF readmission or all-cause mortality among the groups (log-rank test, p = 0.001) (Figure 1). In the multivariate analyses (Table 3), the composite outcome of 6-month HF readmission or all-cause mortality differed significantly among the three groups (p < 0.001). GDMT3 had a 64% decrease in composite outcomes when compared with GDMT1 (hazard ratio (HR) = 0.36, 95% CI: 0.18-0.70, p = 0.003), and GDMT2 had a 31% decrease in composite outcomes compared with GDMT1 (HR = 0.49, 95% CI: 0.29-0.81, p = 0.006).

When analyzed separately (Table 4), the 6-month HF readmission rates were 37.5% in GDMT1, 16.7% in GDMT2, and 11.6% in GDMT3. In the multivariate analyses, the rates of HF readmission at 6 months also showed significant differences among the groups: GDMT3 had a 68% lower rate of HF readmission than GDMT1 did (HR = 0.32,95% CI: 0.16-0.65, p = 0.001), while GDMT2 had a 48% lower rate of HF readmission than GDMT1 did (HR = 0.42, 95% CI: 0.24-0.72, p = 0.002). However, there was no statistically significant difference in the multivariate analyses of 6-month all-cause mortality among the three groups (p = 0.164).

In patients with nonischemic cardiomyopathy, the 6-month HF readmission or all-cause mortality rates were significantly lower (77% of composite outcome) in GDMT3 than in GDMT1 (HR = 0.23 95% CI: 0.07-0.77). Among patients with ischemic cardiomyopathy, there was no statistically significant difference in 6-month all-cause mortality among the three groups (Table 4). Other outcomes including cardiovascular death, stroke, and myocardial infarction, also showed no significant differences.

DISCUSSION

Our results demonstrated that patients with HF who initiated a greater number of appropriate GDMT agents before discharge had a significantly reduced rate of the composite of 6-month HF readmission or all-cause mortality (HR = 0.36 95% CI: 0.18-0.70, p = 0.003).

Table 1 Characteristics of Patients at Baseline

Baseline Characteristics	Total (n = 382)	GDMT1 (n = 120)	GDMT2 (n = 150)	GDMT3 (n = 112)	P-value*
Male	249 (65.2)	77 (64.2)	97 (64.7)	75 (67.0)	0.892
Age (years)	64.4 ± 14.6	68.6 ± 15.3	63.1 ± 14.0	61.7 ± 13.8	0.001
BMI (kg/m²)	24.4 ± 4.9	24.3 ± 5.3	24.2 ± 4.6	24.8 ± 4.9	0.573
SBP (mmHg)	143.6 ± 28.0	142.0 ± 26.9	145.4 ± 29.5	142.8 ± 27.3	0.610
Heart rate (bpm)	99.8 ± 23.7	96.2 ± 22.9	102.2 ± 24.2	100.4 ± 23.5	0.135
HCT (%)	37.3 ± 7.2	35.3 ± 7.6	37.3 ± 7.3	39.4 ± 6.1	< 0.001
Anemia (HCT < 30 %)	64 (16.8)	28 (23.3)	27 (18.0)	9 (8.0)	0.007
Cr (mg/dl)	1.2 (0.9, 1.6)	1.7 (1.2, 2.6)	1.1 (0.9, 1.5)	1.0 (0.8, 1.2)	< 0.001
CKD IV	43 (11.3)	34 (28.3)	7 (4.7)	2 (1.8)	< 0.001
CKD V	33 (8.6)	18 (15.0)	15 (10.1)	-	< 0.001
LVEF (%)	30.2 ± 7.3	30.3 ± 6.5	31.7 ± 7.2	27.9 ± 7.9	< 0.001
T2DM	162 (42.4)	58 (51.7)	90 (60.0)	67 (60.4)	0.297
HT	335 (87.7)	112 (93.3)	131 (87.3)	92 (82.1)	0.034
DLP	339 (88.7)	109 (90.8)	136 (90.7)	94 (83.9)	0.159
Old CVA	52 (13.6)	16 (13.3)	25 (16.7)	11 (9.8)	0.277
CAD	241 (63.1)	83 (69.2)	94 (62.7)	64 (57.1)	0.164
AF	241 (21.7)	29 (24.2)	31 (20.7)	23 (20.5)	0.736
Hyperthyroid	83 (2.4)	1 (0.8)	4 (2.7)	4 (3.6)	0.369
Hypothyroid	9 (4.5)	9 (7.5)	5 (3.3)	3 (2.7)	0.143
Toxin	17 (4.2)	3 (2.5)	8 (5.3)	5 (4.5)	0.506
CAG/MRI					0.002
No	119 (31.2)	49 (40.8)	39 (26.0)	31 (27.7)	
CAG	249 (65.2)	68 (56.7)	109 (72.7)	72 (64.3)	
MRI	14 (3.7)	3 (2.5)	2 (1.3)	9 (8.0)	
Etiology					0.003
Non ischemic cardiomyopathy	110 (28.8)	24 (20.0)	41 (27.3)	45 (40.2)	
Ischemic cardiomyopathy	167 (43.7)	52 (43.3)	74 (49.3)	41 (36.6)	
Undetermined	105 (27.5)	44 (36.7)	35 (23.3)	26 (23.2)	

Abbreviations: AF, atrial fribrillation; BMI, body mass indexed; bpm, beats per minute; CAD, coronary artery disease; CAG, coronary angiogram; CKD, chronic kidney; Cr, creatinine; CVA, cerebrovascular disease; DLP, dyslipidemia; GDMT, guideline directed medical therapy; GDMT1, none or one GDMT; GDMT2, two GDMT; GDMT3, three more than three GDMT; HCT, hematocrit; HT, hypertension; kg/m², kilogram square metre; LVEF, left ventricle ejection fraction; mg/dl, milligrams per deciliter; mmHg, millimeter of mercury; MRI, magnetic resonance imaging; n, number; SBP, systolic blood pressure; T2DM, type2diabetes melitus

Data are presented as frequency (percentage) or mean ± standard deviation or median (interquartile range).

*P-value by Chi-square, Fisher exact test, independent sample t-test, or Mann-Whitney U test. Significant level at P < 0.05.

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Table 2 Medication before Discharge

Medication	Total (n = 382)	GDMT1 (n = 120)	GDMT2 (n = 150)	GDMT3 (n = 112)
ACEI/ ARB / ARNI	258 (67.5)	12 (10.0)	134 (89.3)	112 (100.0)
Enalapril (ACEI)	103 (27.0)	4 (3.3)	52 (34.7)	47 (42.0)
Dose (mg/day)	6.8 ± 5.7	6.3 ± 2.5	7.1 ± 6.7	6.5 ± 4.7
Losartan (ARB)	128 (33.5)	8 (6.7)	67 (44.7)	54 (47.3)
Dose (mg/day)	44.1 ± 27.1	46.9 ± 24.8	44.4 ± 27.3	43.3 ± 27.7
Sacubitril/Valasartan (ARNI)	37 (9.7)	-	9 (6.0)	7 (6.3)
Dose (mg/day)	29.1 ± 44.3	-	29.4 ± 34.5	57.5 ± 62.4
Other ACEI/ ARBs	11 (2.9)	-	6 (4.0)	5 (4.5)
Beta-blocker	348 (91.1)	93 (77.5)	143 (95.3)	112 (100.0)
Bisoprolol	187 (49.0)	50 (41.7)	69 (46.0)	68 (60.7)
Dose (mg/day)	2.9 ± 2.7	2.6 ± 2.1	3.2 ± 3.6	2.9 ± 2.7
Carvedilol	154 (40.3)	42 (35.0)	71 (47.3)	41 (36.6)
Dose (mg/day)	11.2 ± 10.1	13.9 ± 13.1	10.7 ± 9.9	9.1 ± 5.1
Nebivolol	8 (2.1)	2 (1.7)	3 (2.0)	3 (2.7)
Dose (mg/day)	4.2 ± 4.7	6.3 ± 5.3	2.9 ± 1.9	4.2 ± 1.4
Spironolactone/ MRAs	138 (36.1)	4 (3.3)	23 (15.3)	111 (100.0)
Dose (mg/day)	14.8 ± 6.9	12.5 ± 0.0	16.8 ± 9.5	14.4 ± 6.3
Furosemide	299 (78.3)	88 (73.3)	113 (74.3)	98 (87.5)
dose(mg/day)	40 (20, 80)	40 (20, 80)	40 (20, 80)	40 (20, 80)
SGLT2inhibitor	16 (4.2)	3 (2.5)	9 (6.0)	4 (3.6)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNIs, angiotensin receptor-neprilysin inhibitors; GDMT, guideline directed medical therapy; GDMT1, none or one GDMT; GDMT2, two GDMT; GDMT3, three more than three GDMT; mg, milligrams; MRAs, mineralocorticoid receptor antagonists; SGLT2, sodium-glucose cotransporter

Data are presented as frequency (percentage) or mean ± standard deviation.

Notably, even partial implementation of GDMT was associated with better outcomes compared with no therapy or just one agent. The finding is similar to that of an Asian real-world cohort study,[8] which found that even small doses of GDMT were associated with improved outcomes compared with no dose or nonusage. These results support the current guideline recommendations that encourage the early and comprehensive implementation of GDMT in patients with HFrEF.[1,2]

Furthermore, the findings of this study align with the broader evidence highlighting the benefits of GDMT in the HFrEF predischarge phase.[9,10] For example, a multicenter observational Japanese registry[4] (PRE-UPFRONT-HF) found that the implementation of GDMT in hospitalized patients with HF was significantly associated with a lower incidence of composite outcomes, including death and hospitalization for HF. The only key difference between that study and the current one is that patients in our study had a lower rate of SGLT2 medication use (only 4%), which reflects suboptimal adherence to the recommended GDMT regimen. This may be attributed to our study period (2018-2022), during which the adoption of

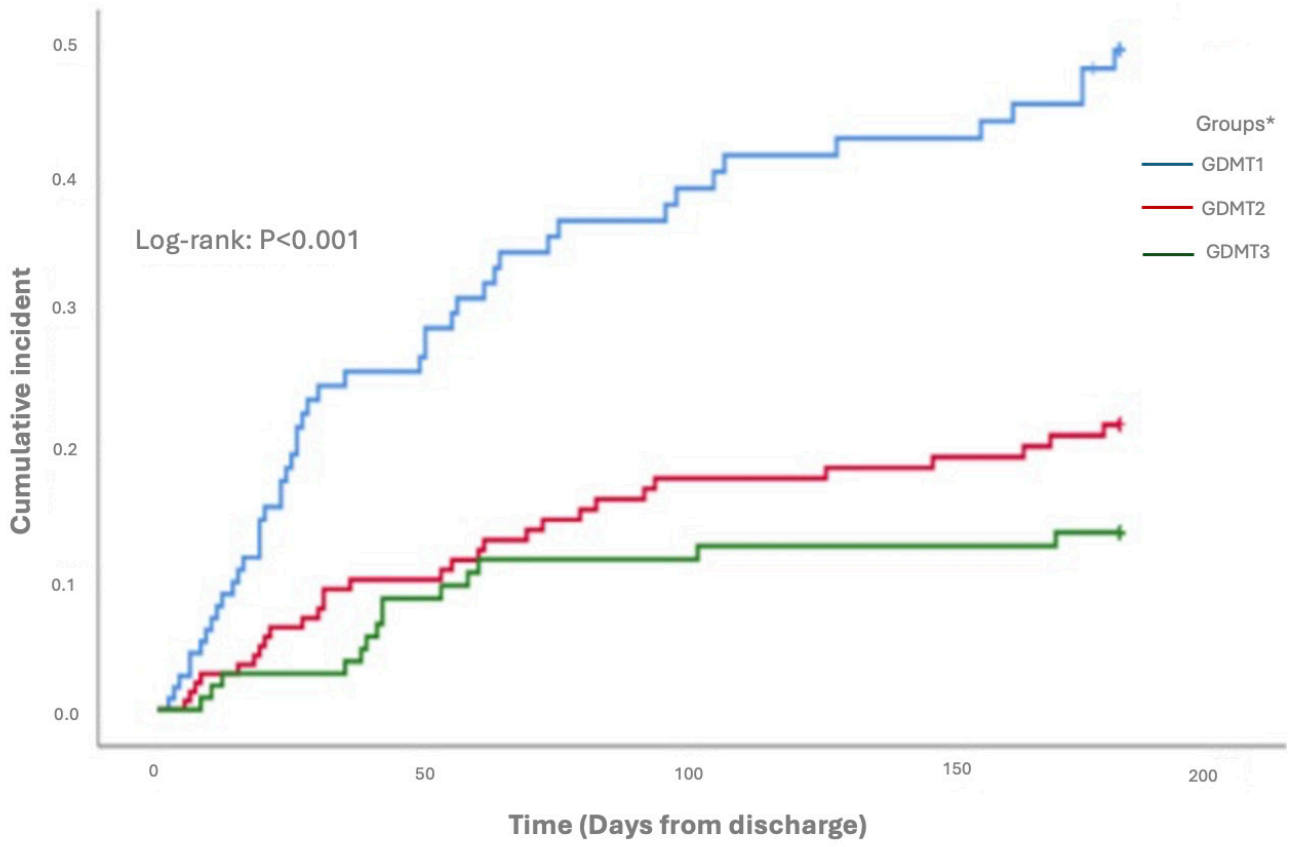

Figure 1 Cumulative Incidence of 6-Month HF Readmission or All-Cause Mortality
Abbreviations: GDMT, guideline-directed medical therapy; GDMT1, none or one GDMT; GDMT2, two GDMT; GDMT3, three more than three GDMT

SGLT2 inhibitors for HFrEF was still evolving or to issues related to drug cost and low socioeconomic status in Thailand. Nevertheless, our findings support the general principle that more comprehensive GDMT initiated before discharge leads to better outcomes, even when the complete four pillar foundation drugs are not used.

Interestingly, although HF readmission rates were signifi antly affected, there was no statistically significant difference in 6-month all-cause mortality among the three groups (p = 0.164). This fin ing contrasts with earlier studies that used intensified GDMT strategies, including earlier initiation of SGLT2 inhibitors and ARNI or more aggressive postdischarge management during the transitional phase.[11] For instance, the STRONG-HF randomized controlled trial[12] achieving at least half target doses within 2 weeks titrated postdischarge, whereas our observational study involved low doses (e.g., enalapril 6.8 mg/day) and optimization of only the three traditional GDMT pillars. This suggests that the advantages of early GDMT may become more obvious over a longer follow-up period. Alternatively, the lack of SGLT2 and the limited statistical power of this outcome could have contributed to the absence of a significant difference in mortality.

The study also explored whether the benefits of predischarge GDMT varied according to the underlying etiology of HFrEF, specifically in patients with ischemic cardiomyopathy (43.7% of the cohort) and nonischemic cardiomyopathy (28.8%). In the nonischemic group, we observed favorable outcomes in GDMT 3, whereas we observed no significant benefit in the ischemic group. These etiology-specific findings are noteworthy. Prior research, such as the study by Silverdal et al.,[13] suggested that patients with nonischemic HFrEF may exhibit a more favorable response to GDMT, whereas those with ischemic HFrEF may be limited by myocardial scar. However, this interpretation should be made

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Table 3 Effectiveness of Groups on 6-Month Readmission or All-Cause Mortality

Groups	6-Month Readmission or All-Cause Mortality		6-Month Readmission		6-Month All-Cause Mortality	
	Multivariable Analysis*		Multivariable Analysis*		Multivariable Analysis*	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
GDMT1	Reference		Reference		Reference	
GDMT2	0.49 (0.29-0.81)	0.006	0.42 (0.24-0.72)	0.002	1.24 (0.40-3.82)	0.708
GDMT3	0.36 (0.18-0.70)	0.003	0.32 (0.16-0.65)	0.001	0.73 (0.15-3.45)	0.688

Abbreviations: CI, confidence interval; GDMT, guideline directed medical therapy; GDMT1, none or one GDMT; GDMT2, two GDMT; GDMT3, three more than three GDMT; HR, hazard ratio

*Multivariable analysis adjusted for sex, age, body mass index, anemia, chronic kidney disease stage IV, chronic kidney disease stage V, Type 2 diabetes mellitus, hypertension, coronary artery disease and atrial fibrillation.

Table 4 Subgroup Analysis of Effectiveness in 6-Month HF Readmission or All-Cause Mortality

Groups	Ischemic		Non-Ischemic	
	Univariable Analysis		Univariable Analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
GDMT1	Reference		Reference	
GDMT2	0.49 (0.22-1.07)	0.074	0.40 (0.14-1.14)	0.086
GDMT3	0.47 (0.18-1.22)	0.122	0.23 (0.07-0.77)	0.017

Abbreviations: CI, confidence interval; GDMT1, none or one GDMT; GDMT2, two GDMT; GDMT3, three more than three GDMT; HR, hazard ratio

cautiously due to limitations in the subgroup analysis, including small sample sizes and the fact that nearly one-third of patients had an undetermined etiology of cardiomyopathy, which might have influenced the results.

Although the data from the network meta-analysis conducted by Tromp et al.[6] offer a benchmark for what is considered "optimal" GDMT and our study provides valuable real-world evidence on predischarge GDMT patterns, we identified a potential gap, with 31.4% of patients discharged on none or monotherapy instead of combined therapy and widespread underdosing. For example, only 15% of those given losartan, 21% of those given bisoprolol, and 20% of those given spironolactone achieved 50% of target recommended doses, and this pattern is consistent with the findings from other observational studies worldwide.[14] Therefore, the current study highlights a significant opportunity for quality improvement in clinical practice. Contributing factors include therapeutic inertia, drug tolerability concerns in the immediate postdecompensation phase, and systemic barriers to GDMT implementation before discharge.[15]

Several crucial limitations must be acknowledged. First, this study is susceptible to inherent limitations, such as selection bias, information bias, and being conducted at a single center. Second, we did not assess dose up-titration: the study categorized patients according to the number of GDMT agents, not by target doses. Postdischarge up-titration data were also unavailable, although this is a critical component of optimal GDMT. Finally, this study is limited by a small sample size, a low number of events, and a relatively short duration, which may not be long enough to observe other important outcomes, such as all-cause mortality and cardiovascular death.

CONCLUSION

Achieving three GDMTs before discharge in patients hospitalized with HFrEF is associated with a significant reduction in 6-month HF readmission or all-cause mortality.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Author Contributions

Conceptualization: K.S.
Data curation: W.S.
Formal analysis: K.S.
Funding acquisition: K.S.
Investigation: W.S.
Methodology: W.S.
Project administration: W.S.
Resources: W.S.
Software: W.S.
Supervision: K.S.
Validation: K.S.
Visualization: K.S.
Writing – original draft preparation: K.S.
Writing – review & editing: K.S.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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