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Impact of pharmacist-led interventions on guideline-directed medical therapy optimization in heart failure with reduced ejection fraction patients

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ABSTRACT

This study aims to evaluate the impact of pharmacist intervention on guideline-directed medical therapy (GDMT) utilization and dose optimization in heart failure with reduced ejection fraction (HFrEF) patients. A prospective pre–post intervention study was conducted at the Heart Failure Medication Therapy Adherence Clinic (HF-MTAC), Hospital Pulau Pinang, Malaysia, enrolling 70 HFrEF patients through convenience sampling. Each patient was followed up for 9 months, receiving pharmacist-led interventions, medication reviews, and collaborative therapeutic recommendations with physicians. GDMT utilization and dose optimization were evaluated at baseline and post-intervention using the McNemar test and Wilcoxon signed-rank test. Among 70 enrolled patients (median age: 59.5 years), 63 completed the study. Pharmacist intervention significantly increased the use of angiotensin receptor-neprilysin inhibitor (ARNI) (42.9% to 58.7%, $p < 0.001$), mineralocorticoid receptor antagonist (MRA) (73.0% to 90.5%, $p = 0.007$), and sodium–glucose cotransporter 2 (SGLT2) inhibitors (25.4% to 49.2%, $p < 0.001$). Quadruple GDMT use rose from 12.7% to 42.9% ($p < 0.001$). The proportion of patients achieving ≥50% target doses of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker/ARNI improved (31.7% to 63.9%, $p < 0.001$), while beta-blocker dose optimization increased (22.2% to 33.3%, $p = 0.039$). In conclusion, pharmacist intervention in HF-MTAC significantly improved GDMT utilization and dose optimization, particularly for ARNI, MRA, and SGLT2 inhibitors.

INTRODUCTION

Heart failure (HF) is a complex clinical syndrome characterized by a wide range of symptoms and physical signs. Common symptoms include breathlessness, fatigue, and ankle swelling. Physical signs may include elevated jugular venous pressure, pulmonary crackles, and peripheral edema [1]. HF typically results from structural or functional abnormalities of the heart, leading to reduced cardiac output and/or elevated intracardiac pressures at rest or during exertion [1]. A major subtype is HF with reduced ejection fraction (HFrEF), defined as an ejection fraction (EF) of less than 40%, indicating impaired systolic function. HFrEF poses significant clinical challenges due to its symptomatic burden and the associated global impact on patients, healthcare systems, and economies [2].

The prevalence of HF globally ranges from 3 to 20 cases per 1,000 individuals, increasing to 100 per 1,000 among those aged 65 and older [2]. Worldwide, over 20 million people are affected by HF, with Southeast Asia reporting a significantly higher prevalence (4.5%–6.7%) compared to other regions (0.5%–2.0%) [3,4]. In Spain, the prevalence of HFrEF was substantially high when assessed using the Dapagliflozin and prevention of adverse outcomes in heart failure study criteria, highlighting the substantial burden of this condition [5]. Likewise, the CARLA Study,

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which focused on the elderly population in Germany, reported an age-standardized prevalence of HFrEF at 3.8% in women and 4.6% in men among individuals aged 45 to 83. These findings underscore the considerable impact of HFrEF in older populations [6].

Hospitalizations due to HF are frequent, accounting for 6%–10% of all acute medical admissions, with 25%–50% of patients readmitted within 6 months [2,7]. Among patients with HFrEF, such hospitalizations are particularly concerning, as they are associated with a higher risk of adverse outcomes. Studies indicate that a substantial proportion of older patients hospitalized with HFrEF do not receive guideline-directed medical therapy (GDMT), thereby increasing their risk of poor outcomes following discharge [8]. Despite advancements in treatment, mortality rate remains high, with approximately 6% of patients dying during hospitalization and 25% within 1 year of the initial admission [7].

HF, particularly HFrEF, places a significant economic burden on healthcare systems. In the United State., annual HF costs reach USD 108 billion, largely driven by hospital admissions and readmissions [9]. HFrEF contributes disproportionately to this burden due to frequent and prolonged hospitalizations, which escalate healthcare expenditures. Managing HFrEF carries a lifelong financial impact, with patients facing high treatment costs despite longer survival [10]. Recently, smartphone-based remote monitoring has shown promise in reducing secondary care costs associated with HFrEF, though implementation remains challenging in low-resource settings [11]. In low- and middle-income countries, particularly in Southeast Asia, limited healthcare resources and high disease prevalence further amplify financial challenges in HF management [3]. These economic pressures underscore the need for better management strategies to mitigate the clinical and financial impacts of HFrEF.

There is substantial evidence supporting that treatment with GDMT, titrated to the maximally tolerated or target dose, improves survival, reduces the risk of HF hospitalizations, and enhances functional capacity [1,2,12]. GDMT consists of four key pillars: angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs)/angiotensin receptor-neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium–glucose cotransporter 2 (SGLT2) inhibitors, unless contraindicated [13]. Despite strong evidence supporting the benefit of GDMT, achieving target doses remains challenging due to factors such as hemodynamic instability [13]. Studies indicate that fewer than 25% of HF patients receive optimal GDMT dosing [12,14]. Pharmacists have been shown to play a key role in addressing this gap in care. Pharmacist-led interventions have been shown to significantly improve the attainment of target doses for renin-angiotensin system (RAS) inhibitors – including ACEI/ARB/ARNI, beta-blockers, and MRAs [15,16]. In addition, pharmacist involvement has been associated with faster GDMT optimization and increased prescription rates of ARNIs and SGLT2 [13]. These findings underscore the importance of pharmacist-led care in optimizing HF management.

HF remains a significant global health challenge, requiring multidisciplinary care approaches to improve patient outcomes. Pharmacists contribute to the management of HFrEF through medication optimization; however, their specific role within multidisciplinary teams in Malaysia is not well defined. Most evidence on GDMT in HFrEF is derived from Western populations, leading to limited understanding of prescribing patterns and treatment optimization within the Malaysian healthcare context. Therefore, this study aimed to evaluate the impact of pharmacist-led interventions on GDMT utilization and dose optimization in patients with HFrEF in Malaysia. The findings are expected to provide insights that support and enhance the role of pharmacists in the management of HFrEF.

MATERIALS AND METHODS

Study design

This prospective pre–post intervention study was conducted from January 2022 to June 2023 at the Cardiology Department of Hospital Pulau Pinang, Malaysia. Patient recruitment started in January 2022 and continued until September 2022, when the target sample size of 70 patients was reached. Each participant was followed up for 9 months to evaluate outcomes. Patients enrolled in January 2022 completed their follow-up in October 2022, while those recruited in the final batch (September 2022) completed follow-up in June 2023. Eligible participants were enrolled using a convenience sampling method.

Inclusion and exclusion criteria

Adult patients aged 18 years and older, diagnosed with HFrEF (EF < 40%), and attending the HF Clinic of Hospital Pulau Pinang for the first time on or after January 1, 2022, were eligible for inclusion. In addition, patients were required to meet at least two criteria outlined in the HF Medication Therapy Adherence Clinic (HF-MTAC) Protocol established by the Ministry of Health Malaysia [17]. These criteria included recent hospitalization due to acute decompensation (within 90 days post-discharge), a new diagnosis of HF, the need for intensive management to optimize evidence-based pharmacotherapy, or poor adherence to medications or fluid restrictions. Patients were excluded if they were pregnant or lactating, had psychiatric conditions, or had a life expectancy of less than 6 months due to terminal illness.

Sample size determination

The sample size for this study was determined using the formula for paired sample *t*-tests [18], appropriate for evaluating changes in GDMT use in the same group of HFrEF patients before and after pharmacist intervention. The calculation was guided by previous research on pharmacist-led interventions for GDMT optimization. A previous study reported approximately a 20% improvement in GDMT adherence following pharmacist intervention [13]. Based on this finding, a clinically meaningful adherence increase of 0.20 was assumed. Using a significance level of 0.05% and 80% power, the initial sample size was calculated as 49 patients. To account for a potential 30% dropout rate, the final target was increased to 70

patients, ensuring sufficient statistical power to detect clinically meaningful improvements in GDMT optimization.

Pharmacist intervention and services received by patients

The patients who fulfilled the inclusion criteria were enrolled in the pharmacist-led HF-MTAC. In Malaysian government hospitals, the HF-MTAC was established to improve the management of HF patients [17]. This pharmacist-led outpatient service collaborates with physicians and other healthcare professionals to promote medication adherence and reduce unplanned emergency visits or hospital admissions due to acute HF exacerbations. Currently, nine government hospitals in Malaysia offer this pharmacist-led HF service. The first such clinic was introduced at Hospital Pulau Pinang in 2010. It operates once a week, involving a multidisciplinary team including two physicians, two pharmacists, two nurses, and physiotherapists, who collectively manage around 30 patients per session.

At the HF-MTAC, pharmacists assessed patients prior to physicians' consultation, playing a vital role in delivering comprehensive, patient-centered care. Their approach followed a structured framework based on the HF-MTAC Protocol by the Ministry of Health Malaysia [17]. The pharmacists initiated patient interactions by reviewing current medications and assessing adherence. They provided in-depth counselling on various aspects of HF management, including lifestyle modifications, proper medication use, symptom recognition, and disease management.

Beyond counselling, pharmacists actively engaged in treatment planning by discussing therapeutic strategies with patients, reviewing laboratory results, and monitoring those on warfarin therapy. They also provided physicians with therapeutic recommendations, which included medication titration, dosage adjustments, GDMT optimization, or the need for additional laboratory tests. Each pharmacist-led intervention session typically lasted 20–30 minutes. In addition, pharmacists ensured that patients received their prescribed medications and offered further counselling when necessary.

Patients' medication use was evaluated by the pharmacist and recorded at baseline and during each follow-up visit. The present study focused on optimizing GDMT, particularly beta-blockers, RAS inhibitors, and SGLT2 inhibitors. Optimal GDMT was defined as receiving ≥50% of the target dose of beta-blockers or RAS inhibitors or any dose of MRA and SGLT2 inhibitors by the 9-month follow-up visit [14]. The proportion of patients receiving triple or quadruple GDMT was also analysed. Triple therapy was defined as the use of RAS inhibitors, a beta-blocker, and an MRA, while quadruple therapy included SGLT2 inhibitors in addition to triple therapy, as recommended by the 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure [19].

Data collection

All patients were monitored for 9 months from their enrolment date. Clinic visits were scheduled according to appointment dates determined by the physician. Follow-up frequency was tailored to disease stability, with most patients seen every 3–6 months. To maintain participation, the principal investigator conducted periodic phone follow-ups. Throughout the study, all relevant data were systematically reviewed, extracted, and recorded using a data collection form designed by the principal investigator.

Data analysis

Data analysis focused on assessing changes in GDMT utilization and dosage optimization before and after the pharmacist intervention. Normally distributed data were presented as mean ± SD, while non-normally distributed data were expressed as median with interquartile range (IQR). IBM SPSS Statistics version 27 was used for data entry and analysis. GDMT usage, including the proportion of patients on triple or quadruple therapy, was evaluated at baseline and 9-month follow-up using the McNemar test for categorical variables. For numerical variables, such as GDMT dosage adjustments, the Wilcoxon test was applied to the non-normally distributed data to assess changes over time.

Data analysis was conducted to identify factors associated with the prescribing of key components of GDMT, including ARNI, MRA, SGLT2i, and the use of quadruple GDMT. In addition, the analysis aimed to determine predictors for achieving optimal doses of beta-blockers and RAS inhibitors. The patient's demographic and clinical characteristics were used as independent variables in the regression models. Univariable logistic regression was first employed to explore the individual association between each patient characteristic and the outcomes of interest. Variables that demonstrated a p-value of less than 0.10 in the univariable analysis were considered for inclusion in the subsequent multivariable logistic regression models. Multivariable logistic regression was then performed to identify independent predictors of GDMT prescribing and dose optimization. A backward stepwise elimination method was applied to refine the models, retaining variables with statistical significance at $p < 0.05$. Adjusted odds ratios and 95% confidence intervals (CIs) were reported to quantify the strength and direction of associations.

RESULTS

Patient's demographic and clinical characteristics

At baseline, a total of 70 patients were recruited (Table 1). The median age of patients was 59.5 years (IQR: 49.25–66.25). Most patients were aged 46–60 years (35.7%). The majority of the patients were male (77.1%) and of Malay ethnicity (44.3%). The predominant aetiology of HF was ischaemic (84.3%). Most of the patients were unemployed or retired (68.6%) and were married (88.6%). Only 11.4% of the patients were active smokers, while 44.3% were ex-smokers. The median EF at enrolment was 26.0% (IQR: 19.68–30.00). Most patients had five or more comorbidities (55.7%). Hypertension (72.9%) and diabetes mellitus (60.0%) were the most common types of comorbidities. During the 9-month study period, the median number of patient visits to the HF-MTAC clinic was 2.0 (IQR: 2.0–3.0).

Of the 70 patients enrolled in the study, 63 completed the 9-month follow-up period, while seven patients were lost to follow-up due to mortality. Table 1 presents a subgroup analysis

Table 1. Demographic and clinical characteristics of patients at baseline, withdrawal, and study completion.

Characteristics	Patients enrolled at baseline	Patient withdrawal*	Patients completed
	N (%)	*N* (%)	*N* (%)
Age group			
<30 years	13 (18.6)	0 (0.0)	13 (20.6)
30–45 years	24 (34.3)	1 (14.3)	23 (36.5)
46–60 years	25 (35.7)	2 (28.6)	23 (36.5)
61–75 years	6 (8.6)	3 (42.9)	3 (4.8)
76–90 years	2 (2.9)	1 (14.3)	1 (1.6)
Gender			
Male	54 (77.1)	7 (100)	47 (74.0)
Female	16 (22.9)	0 (0.0)	16 (25.4)
Ethnicity			
Malay	31 (44.3)	2 (28.6)	29 (46.0)
Chinese	24 (34.3)	3 (42.9)	21 (33.3)
Indian	15 (21.4)	2 (28.6)	13(20.6)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Aetiology of heart failure			
Ischemic	59 (84.3)	7 (100)	52 (82.5)
Non-ischemic	6 (8.6)	0 (0.0)	6 (9.5)
Unknown	5 (7.1)	0 (0.0)	5 (7.9)
Working status			
Employed	22 (31.4)	1 (14.3)	21 (33.3)
Unemployed or retired	48 (68.6)	6 (85.7)	42 (66.7)
Marital status			
Single	5 (7.1)	0 (0.0%)	5 (7.9%)
Married	62 (88.6)	6 (85.7%)	56 (88.9%)
Divorced	3 (4.3)	1 (14.3%)	2 (3.2%)
NYHA classification			
NYHA I-II	63 (90.0%)	5 (71.4%)	58 (92.1%)
NYHA III-IV	7 (10.0%)	2 (28.6%)	5 (7.9%)
Smoking history			
Yes	8 (11.4)	1 (14.3)	7 (11.1)
No	31 (44.3)	2 (28.6)	29 (46.0)
Ex-smoker	31 (44.3)	4 (57.1)	27 (42.9)
Education level			
Primary	10 (14.3)	1 (14.3)	9 (14.3)
Secondary	41 (58.6)	4 (57.1)	37 (58.7)
Tertiary	19 (27.1)	2 (28.6)	17 (27.0)
Number of comorbidities			
1–2	5 (7.1)	2 (28.6)	3 (4.8)
3–4	26 (37.1)	5 (71.4)	21 (33.3)
≥5	39 (55.7)	0 (0.0)	39 (61.9)
Types of comorbidities			
Hypertension	51 (72.9)	5 (71.4)	46 (73.0)
Diabetes mellitus	42 (60.0)	6 (85.7)	36 (57.1)
Hyperlipidemia	40 (40.5)	2 (28.6)	38 (60.3)
Chronic kidney disease	25 (35.7)	3 (42.9)	22 (34.9)
Atrial fibrillation/ atrial flutter	4 (5.7)	0 (0.0)	4 (6.3)
Number of visits			
1	13 (18.6)	3 (42.9%)	5 (7.4%)
2	29 (41.4)	4 (57.1%)	28 (44.4%)
3	19 (27.1)	0 (0.0%)	24 (38.1%)
4	6 (8.6)	0 (0.0%)	5 (7.0%)
5	1 (1.4)	0 (0.0%)	1 (1.6%)
6	1 (1.4)	0 (0.0%)	0 (0.0%)
7	1 (1.4)	0 (0.0%)	0 (0.0%)

*The patient was withdrawn from the study due to death

comparing the baseline characteristics of the patients who died with those who completed the study. The majority of deceased patients (85.8%) were aged 46 years and above, whereas only 42.9% of surviving patients fell within the same age group. In terms of functional status, as assessed by the NYHA classification, 28.6% of the mortality group were classified as NYHA class III–IV, compared to just 7.9% among those who completed the study (Table 1).

Proportion of patients prescribed with GDMT according to drug group

Significant improvements in the utilization of various components of GDMT were observed following the pharmacist intervention, except for beta-blockers (Table 2). Following the pharmacist-led intervention, the proportion of patients prescribed ARNI increased significantly from 42.9% at baseline to 58.7% post-intervention ($p < 0.001$) (Table 2). Multivariable logistic regression analysis identified age as an independent negative predictor of ARNI prescription, with each additional year associated with a decrease in the odds of being prescribed ARNI (adjusted OR = 0.92; 95% CI: 0.87–0.97; $p = 0.003$). In addition, patients with tertiary education were significantly more likely to receive ARNI, even after adjusting for other covariates (adjusted OR = 11.74; 95% CI: 1.22–113.43; $p = 0.033$) (Table 3).

The prescription rate of MRA increased significantly from 73.0% at baseline to 90.5% at the 9-month follow-up ($p = 0.007$) (Table 2). Multivariable logistic regression analysis revealed that a higher number of clinic appointments was independently associated with MRA initiation (adjusted OR = 4.94; 95% CI: 1.16–21.04; $p = 0.031$). Conversely, patients who were already prescribed MRA at baseline were significantly less likely to initiate new MRA therapy during the study period (adjusted OR = 0.11; 95% CI: 0.01–0.80; $p = 0.029$) (Table 3).

Table 2. Proportion of patients prescribed with various component of GDMT.

Types of GDMT	Baseline[a] (*n* = 63); *N* (%)	95% CIs	9th month[a] (*n* = 63); *N* (%)	95% CIs	McNemar test result
Beta-blockers					
Bisoprolol	57 (90.5%)		60 (95.2%)		
Carvedilol	1 (1.6%)		0 (0.0%)		
Total	58 (92.1%)	83.6%–97.0%	60 (95.2%)	88.3%–98.7%	$p = 0.625$
None[b]	5 (7.9%)		3 (4.8%)		
ACEI/ARB/ARNI					
Perindopril/Coversyl plus[c]	25 (39.7%)		21 (33.3%)		$p = 0.388$
Losartan	2 (3.2%)		2 (3.2%)		
Candesartan	0 (0.0%)		0 (0.0%)		
Telmisartan	0 (0.0%)		0 (0.0%)		
Valsartan	0 (0.0%)		0 (0.0%)		
ARNI	27 (42.9%)	30.9%–55.6%	37 (58.7%)	46.5%–70.1%	$p < 0.001$
Total	54 (85.7%)	74.6%–93.3%	60 (95.2%)	88.3%–98.7%	$p = 0.031$
None[b]	9 (14.3%)		3 (4.8%)		
MRA	46 (73.0%)	60.3%–83.4%	57 (90.5%)	80.9%–96.1%	$p = 0.007$
SGLT2i	16 (25.4%)	15.4%–38.4%	31 (49.2%)	36.7%–61.7%	$p < 0.001$

[a]The analysis included only patients who completed the study.

[b]Patients who were not prescribed the drug.

[c]Coversyl plus consists of the combination of perindopril and indapamide.

The use of SGLT2 inhibitors increased significantly from 25.4% at baseline to 49.2% following the pharmacist-led intervention ($p < 0.001$) (Table 2). In the multivariable logistic regression analysis, tertiary education was independently associated with a higher likelihood of SGLT2 inhibitor prescription (adjusted OR = 13.65; 95% CI: 1.19–156.60; $p = 0.036$). In addition, lower EF was significantly associated with increased SGLT2 inhibitor use, with each percentage point decrease in EF corresponding to a higher odds of prescription (adjusted OR = 0.86; 95% CI: 0.78–0.95; $p = 0.004$) (Table 3).

Proportion of patients prescribed with quadruple GDMT and receiving optimal GDMT doses

Multivariable logistic regression analysis identified EF and the number of baseline GDMT components as significant predictors of quadruple therapy utilization. Specifically, lower EF was associated with increased likelihood of receiving quadruple GDMT (adjusted OR = 0.88; 95% CI: 0.80–0.97; $p = 0.012$), while a higher number of baseline GDMT components also significantly predicted quadruple therapy initiation (adjusted OR = 2.73; 95% CI: 1.03–7.03; $p = 0.037$) (Table 3). Following the 9-month pharmacist-led intervention, the proportion of patients receiving quadruple GDMT increased markedly from 12.7% to 42.9% ($p < 0.001$) (Table 4).

When examining dose optimization, the proportion of patients achieving the optimal dose of all four GDMT components rose significantly from 3.2% at baseline to 15.9% post-intervention ($p = 0.008$) (Table 4). In univariable logistic regression analysis, only the number of baseline GDMT components was significantly associated with achieving optimal quadruple therapy (OR = 3.24; 95% CI: 1.06–9.98; $p = 0.040$). Due to the limited number of outcome events, a multivariable model for this outcome was not constructed.

Median daily doses of GDMT before and after pharmacist intervention

Overall, there was a significant increase in the prescribed median daily dose of GDMT compared to the baseline for bisoprolol, perindopril, and ARNI. Particularly, the median daily dose of ARNI showed a drastic increment from 100.00 to 200.00 mg ($p < 0.001$) (Table 5).

Proportion of patients on optimal doses of beta-blockers and RAS inhibitors before and after pharmacist intervention

A significant improvement was observed in the proportion of patients receiving optimal doses of both beta-blockers and RAS inhibitors following the pharmacist-led intervention (Table 6). Specifically, the proportion of patients receiving ≥50% of the target beta-blocker dose increased from 22.2% at baseline to 33.3% at 9 months ($p = 0.039$). Notably, none of the patients were receiving 100% of the target beta-blocker dose at baseline, whereas 3.2% ($n = 2$) achieved full dose optimization by the end of the study period (Table 6). Multivariable logistic regression analysis identified baseline optimization status as the strongest predictor of achieving optimal beta-blocker dosing at follow-up (adjusted OR = 51.86; 95% CI: 5.79–466.26; $p < 0.001$) (Table 7).

Table 3. Univariable and multivariable logistic regression models identifying factors associated with prescribing ARNI, MRI, SGLT2i, and Quadruple GDMT.

Variables	Univariable logistic regression			Multivariable logistic regression		
	Regression coefficient (b)	Crude odds ratio (95% CI)	*p*-value	Regression coefficient (b)	Adjusted odds ratio (95% CI)	*p*-value
Determinants of ARNI prescribing proportion in patients						
Age	−0.08	0.92 (0.88–0.97)	0.002	−0.09	0.92 (0.87–0.97)	0.003
Education level						
Primary	0	1				
Secondary	0.75	2.11 (0.76–9.74)	0.338	2.22	1.25 (0.20–7.78)	0.811
Tertiary	2.71	15.00 (1.98–113.56)	0.009	2.46	11.74 (1.22–113.43)	0.033
Determinants of MRI prescribing proportion in patients						
Number of appointments given	1.44	4.23 (1.07–16.73)	0.040	1.60	4.94 (1.16–21.04)	0.031
Proportion of patients prescribed MRA at baseline	−1.91	0.15 (0.02–0.90)	0.038	−2.24	0.11 (0.01–0.80)	0.029
Determinants of SGLT2i prescribing proportion in patients						
Education level						
Primary	0	1		0	1	
Secondary	2.03	7.58 (0.86–66.81)	0.068	1.38	3.96 (0.41–38.75)	0.237
Tertiary	2.96	19.20 (1.88–196.54)	0.013	2.61	13.65 (1.19–156.60)	0.036
EF	−1.15	0.86 (0.78–0.94)	0.001	−0.15	0.86 (0.78–0.95)	0.004
Determinants of quadruple GDMT prescribing proportion in patients						
Education level						
Primary	0	1		0	1	
Secondary	1.38	4.87 (0.55–43.13)	0.155	0.60	1.82 (0.17–19.15)	0.619
Tertiary	2.96	19.20 (1.88–196.54)	0.013	2.46	11.75 (0.98–141.06)	0.052
EF	−0.11	0.89 (0.82–0.97)	0.008	−0.13	0.88 (0.80–0.97)	0.012
Number of patients prescribed GDMT at baseline	0.92	2.51 (1.13–5.65)	0.023	1.00	2.73 (1.03–7.03)	0.037

Table 4. Proportion of patients prescribed with triple and quadruple GDMT and receiving optimal GDMT doses.

Types of GDMT	Baseline *N* (%)	95% CIs	9th month *N* (%)	95% CIs	McNemar test result
Triple GDMT	29 (46.0%)	33.9%–58.5%	27 (42.9%)	30.9%–55.6%	$p = 0.815$
Triple GDMT with optimize dose	1 (1.6 %)	0.0%–8.5%	7 (11.1%)	4.6%–21.6%	$p = 0.070$
Quadruple GDMT	8 (12.7%)	5.6%–23.5%	27 (42.9%)	30.9%–55.6%	$p < 0.001$
Quadruple GDMT with optimize dose	2 (3.2%)	0.4%–10.9%	10 (15.9%)	8.0%–27.7%	$p = 0.008$

The proportion of patients receiving ≥50% of the target dose of RAS inhibitors doubled over the course of the study, increasing from 31.7% at baseline to 63.9% at 9 months ($p < 0.001$) (Table 6). Among these patients, 6.3% ($n = 4$) were receiving 100% of the optimal dose at baseline, which increased to 20.6% ($n = 13$) by the end of the intervention period. Multivariable logistic regression analysis identified several significant predictors of achieving optimal RAS inhibitor dosing. Younger age was associated with higher likelihood of dose optimization (adjusted OR = 0.96; 95% CI: 0.91–1.00; $p = 0.048$). In addition, patients who were already on an optimized dose at baseline were substantially more likely to maintain or achieve optimal dosing (adjusted OR = 29.09; 95% CI: 3.32–254.99; $p = 0.002$). The number of baseline GDMT components also remained a significant predictor (adjusted OR = 2.73; 95% CI: 1.03–7.03; $p = 0.037$) (Table 7).

Table 5. Median daily doses of GDMT before and after pharmacist intervention.

GDMT[a]	Median, mg (IQR)		Wilcoxon Signed-Rank test result
	Baseline	9th months	
Bisoprolol[a]	2.50 (2.50–4.69); *n* = 57	2.50 (2.50–5.00); *n* = 60	*p* = 0.002
Perindopril[b]	4.00 (2.00–4.00); *n* = 25	4.00 (3.00–5.00); *n* = 21	*p* = 0.034
ARNI[c]	100.00 (100.00–100.00); *n* = 27	200.00 (100.00–400.00); *n* = 37	*p* < 0.001

[a]The analysis only included patients who were on bisoprolol throughout the study period. Three patients initiated bisoprolol by the end of the study, while one patient discontinued it due to bradycardia. Another patient switched from carvedilol to bisoprolol.

[b]The analysis included only patients who were on perindopril throughout the study period. Eight patients switched from perindopril to ARNI, while four patients initiated perindopril by the end of the study.

[c]The analysis included only patients who were on ARNI throughout the study period. Eight patients switched from perindopril to ARNI, while two patients initiated ARNI by the end of the study.

Table 6. Proportion of patients on optimal doses of beta-blockers and ACEI/ARB/ARNI before and after pharmacist intervention.

	Baseline *N* (%)	9th month *N* (%)	McNemar test result
B-blockers (≥50% of target dose); *n* = 63	14 (22.2%)[a]	21 (33.3%)[b]	*p* = 0.039
ACEI/ARB/ARNI (≥50% of target dose); *n* = 63	20 (31.7%)[c]	40 (63.9%)[d]	*p* < 0.001

[a]None of the patient was on 100% of optimal dose at baseline.

[b]2 (3.2%) patients were on 100% of optimal dose at 9th month.

[c]4 (6.3%) patients were on 100% of optimal dose at baseline.

[d]13 (20.6%) patients were on 100% of optimal dose at 9th month.

Table 7. Univariable and multivariable logistic regression models identifying factors associated with prescribing optimal dose of beta-blockers & RAS inhibitors.

Variables	Simple logistic regression			Multiple logistic regression		
	Regression coefficient (b)	Crude odd ratio (95% CI)	*p*-value	Regression coefficient (b)	Adjusted odd ratio (95% CI)	*p*-value
Determinants of optimal dose of beta-blockers prescribing proportion in patients						
Gender						
Woman	0	1				
Man	−1.70	0.18 (0.05–0.62)	0.006	−0.96	0.38 (0.08–1.95)	0.248
Proportion of patients on optimize dose of beta-blockers at baseline	4.20	66.63 (7.60–583.78)	<0.001	3.95	51.86 (5.79–466.26)	<0.001
Determinants of optimal dose of RAS inhibitors prescribing proportion in patients						
Age	−0.02	0.98 (0.94–1.02)	0.230	−0.05	0.96 (0.91–1.00)	0.048
Proportion of patients on optimize dose of RAS inhibitors at baseline	2.99	19.91 (2.44–162.20)	0.005	3.57	29.09 (3.32–254.99)	0.002
Number of GDMT at baseline	0.92	2.51 (1.13–5.65)	0.023	1.00	2.73 (1.03–7.03)	0.037

Optimal dose: ≥50% of target dose.

DISCUSSION

Despite robust evidence supporting GDMT in reducing hospitalization and mortality among HF patients [20], its real-world implementation remains suboptimal [21]. The efficacy of GDMT in HF is well established across all age groups [22]. Current clinical guidelines recommend pharmacological treatment based primarily on left ventricular EF, categorized as HF with preserved EF, mildly reduced EF (HFmrEF), or HFrEF, rather than on patient age [1,2,19]. Nevertheless, GDMT remains under-prescribed in older adults [23], often

due to increased frailty, a higher prevalence of comorbid conditions, and the complexities associated with polypharmacy. These factors necessitate a more nuanced and individualized therapeutic approach in older populations, carefully weighing the potential benefits of GDMT against the risks of adverse effects and drug interactions [22]. Optimizing GDMT across age groups is therefore essential, not only to ensure equitable care but also to maximize clinical outcomes in both younger and older patients.

In the present study, the overall adoption rate of GDMT exceeded 80% by the end of the study period, with the exception of SGLT2 inhibitors, which remained below 50%. These findings contrast with real-world data from the CHAMP-HF registry in the United States [24], where only 73.4% of patients received RAS inhibitors, 67.0% were prescribed beta-blockers, and 33.4% were treated with MRAs. The results of the present study are consistent with those reported by Patil *et al*. [13] in a study that involved a pharmacist-led HF clinic, demonstrating that the utilization rates of the three foundational components of GDMT (beta-blockers, RAS inhibitors, and MRAs) were consistently higher than those of SGLT2 inhibitors.

SGLT2 inhibitors have only recently been established as a cornerstone therapy for HF, with dapagliflozin becoming the first agent in this class to receive approval from the United States Food and Drug Administration in May 2020 [25]. As a result, their uptake in Malaysia remains relatively limited compared to other components of GDMT, which have been available for a longer duration. In addition, the high cost of SGLT2 inhibitors has led to the implementation of a quota system in Malaysian government hospitals, restricting the annual supply for patients with HF. Access is further constrained by their classification under the A* prescribing category, which limits prescribing authority to consultant cardiologists at government tertiary care centres during the study period. To address this issue, pharmacists can play a key role in implementing targeted screening protocols to identify high-risk HF patients who would derive the greatest benefit from SGLT2 inhibitors, thereby ensuring the optimal use of limited quota allocations.

This study demonstrated a significant increase in the proportion of patients receiving ARNI, MRA, and SGLT2 inhibitors following the pharmacist intervention. However, the increase in beta-blocker utilization was not statistically significant, likely due to an already high baseline prescription rate (92.1%) of beta-blockers prior to the intervention. Notably, the beta-blocker utilization rate in the present study was significantly higher than the 66.3% reported in a recent investigation by Patil *et al*. [13], which examined patients with HFrEF at the Salem Veterans Affairs Medical Center in the United States. The lower utilization rate observed in that study may be partially explained by the older age profile of the patient population, with a reported median age of 71 years (IQR: 63–74). Existing evidence indicates that older individuals with stable congestive HF are approximately twice as likely to experience intolerance to bisoprolol compared to younger populations enrolled in larger clinical trials [26], potentially contributing to reduced prescribing rates in this demographic. Meanwhile, in recent years, the use of ARNIs has increased, reflecting updated clinical guidelines that recommend ARNIs as a preferred alternative to ACEIs for patients with HFrEF, due to their superior efficacy in reducing hospitalization and mortality risks [19]. As a result, pharmacists have frequently initiated therapeutic switches from perindopril to ARNIs, which likely accounts for the observed rise in ARNI utilization and the corresponding decline in perindopril prescriptions in the present study.

The present study analysed changes in the dosages of GDMT, with particular emphasis on beta-blockers, perindopril, and ARNI. In clinical practice, up-titrating GDMT doses remains a significant challenge due to various patient-specific factors and tolerability issues. Dosage adjustments must be individualized, considering each patient's therapeutic response, adverse effects, and hemodynamic stability [22]. Several barriers to achieving guideline-recommended target doses have been identified, including impaired renal function, hyperkalemia, and socioeconomic constraints [23]. In this study, the median doses of GDMT were significantly higher at the 9-month follow-up compared to baseline. In addition, the proportion of patients prescribed quadruple GDMT increased significantly by the end of the study period. This outcome aligns with the primary objective of the pharmacist-led HF-MTAC, as outlined in the Malaysian MTAC protocol for HF management [17], which emphasizes the optimization and maintenance of GDMT dosing. Similar findings have been reported in international studies, where pharmacist-led HF clinics have demonstrated superior outcomes in GDMT utilization and dose optimization [12,13].

The present study does not quantify the projected reductions in hospitalizations or mortality associated with the observed improvements in GDMT utilization. Nevertheless, potential clinical outcomes can be inferred from established evidence. For instance, ARNI therapy, as demonstrated in the PARADIGM-HF trial, significantly reduced all-cause mortality by 16% and the risk of first HF hospitalization by 21% [27]. Similarly, beta-blockers have consistently shown a 34%–35% reduction in all-cause mortality across major landmark trials [28,29]. The optimization of GDMT is a Class I recommendation in the European Society of Cardiology guidelines [1]. In the present study, pharmacist-led interventions not only improved the overall utilization of GDMT but also significantly increased the proportion of patients achieving optimal GDMT doses. These findings are consistent with those reported by Patil *et al*. [13], who documented a significant increase in the proportion of patients reaching target doses of both beta-blockers and RAS inhibitors following 90 days of pharmacist-driven optimization. However, the overall attainment of target doses remained suboptimal in the present study, with fewer than 20% of patients receiving triple or quadruple therapy at recommended targets.

The optimal timeframe and frequency of patient visits required for GDMT up-titration in HFrEF remain uncertain. Previous research has demonstrated successful titration over an average duration of 13 weeks, involving approximately five clinical visits to a pharmacist-managed outpatient clinic [30]. In contrast, the present study observed that 60% of patients attended only one to two HF-MTAC visits over a 9-month period, which may have contributed to the lower proportion achieving optimal dosing. Similarly, Fiuzat *et al*. [14] reported that only 15.5%

of patients attained optimal GDMT doses within 6 months. Higher visit frequency was associated with better GDMT optimization, particularly in the guided therapy arm [14]. These findings underscore the importance of extended follow-up and more frequent pharmacist-led interventions to support GDMT optimization. In alignment with the 2022 AHA/ACC/HFSA guideline, an optimized titration schedule may involve an initial follow-up within 2 weeks of diagnosis, followed by biweekly visits for dose adjustments and monitoring [19]. Once optimal doses are achieved, patients can transition to monthly or bi-monthly visits for ongoing assessment and adherence support [19]. This structured approach facilitates timely GDMT optimization within the recommended 3 to 6 months and may improve clinical outcomes [19].

The role of age, ethnicity, and visit frequency as factors influencing therapy optimization warrants further investigation, particularly in diverse and resource-limited healthcare settings. The findings of this study demonstrated a substantial increase in the prescription of quadruple GDMT following the pharmacist-led intervention, indicating successful intensification of HF therapy. Patients with lower EF were more likely to receive quadruple therapy, aligning with guideline recommendations [19] that prioritize comprehensive treatment for those with more severe systolic dysfunction. In addition, patients who were already prescribed a greater number of GDMT components at baseline were significantly more likely to progress to quadruple therapy, suggesting that early initiation facilitates full regimen optimization over time. These results underscore the positive impact of pharmacist-led interventions in enhancing adherence to HF treatment guidelines [1,19] and supporting the comprehensive implementation of GDMT.

Strengths and limitations of the study

This study possesses several methodological strengths that enhance its internal validity and clinical relevance. The prospective pre–post intervention design enabled real-time data collection, minimizing recall bias and allowing for direct comparison of GDMT optimization before and after the pharmacist-led intervention. Conducted at a tertiary care hospital with an established pharmacist-led HF-MTAC clinic, the study was supported by a structured framework that ensured consistent and standardized delivery of the intervention.

The absence of a control group in this study may limit its internal validity, interpretability, and generalizability. The relatively short follow-up period (9 months) and the limited number of pharmacist-led visits (median of two to three per patient) may have constrained the extent of GDMT optimization. Conducting the study at a single center also restricts the generalizability of findings, particularly given the predominance of male participants (77.1%), patients with ischemic HF (84.3%), and unemployed/retired (68.6%) Malaysians. Furthermore, external factors such as comorbidities, medication tolerability, and socioeconomic barriers were not extensively evaluated, which may have influenced the achievement of target doses. Future research should incorporate longer follow-up periods, broader patient populations, and diverse socioeconomic groups to better assess the long-term impact of pharmacist-led interventions on GDMT adherence and clinical outcomes.

CONCLUSION

This study demonstrated that pharmacist intervention in a HF-MTAC significantly improved the utilization and dose optimization of GDMT, particularly for ARNI, MRA, and SGLT2 inhibitors. However, beta-blocker utilization remained unchanged due to a high baseline prescription rate. Despite these improvements, the proportion of patients achieving optimal GDMT doses remained suboptimal, likely due to the limited follow-up duration and visit frequency. These findings highlight the crucial role of pharmacists in optimizing HF pharmacotherapy and underscore the need for extended follow-up and more frequent pharmacist-led interventions to enhance GDMT adherence and dose titration.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVAL

This study adhered to the ethical principles outlined in the Declaration of Helsinki and the Malaysian Good Clinical Practice Guidelines. It was registered with the National Medical Research Register (NMRR) and received ethical approval from the Medical Review & Ethics Committee (MREC), Ministry of Health Malaysia (approval number: NMRR ID-21-02460-PL0 (IIR)). In addition, approval was obtained from the Human Research Ethics Committee of Universiti Sains Malaysia (JEPeM) (JEPeM Code: USM/JEPeM/22080532).

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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