WOLKITE UNIVERSITY COLLEGE OF MEDICAL SCIENCES
DEPARTEMENT OF INTERNAL MEDICINE

MAGNITUDE AND FACTORS INFLUENCING OPTIMAL ESCALATION OF GUIDELINE-DIRECTED MEDICAL THERAPY AMONG CHRONIC HEART FAILURE PATIENTS WITH REDUCED EJECTION FRACTION IN COMPREHENSIVE HOSPITALS OF CENTRAL ETHIOPIAN REGION, ETHIOPIA. A CROSS SECTIONAL STUDY.

A THESIS TO BE SUBMITTED TO WOLKITE UNIVERSITY, COLLEGE OF HEALTH SCIENCES; INTERNAL MEDICINE DEPARTMENT IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE SPECIALTY CERTIFICATE PROGRAM IN INTERNAL MEDICINE.

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Magnitude and Factors Influencing Optimal Escalation of Guideline-Directed Medical Therapy Among Chronic Heart Failure Patients with Reduced Ejection Fraction in Comprehensive Hospitals of Central Ethiopian Region, Ethiopia. *A Cross Sectional Study*.

A Thesis To Be Submitted To Wolkite University, College Of Health Sciences; Internal Medicine Department In Partial Fulfillment Of The Requirement For The Specialty Certificate Program In Internal Medicine.

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APPROVAL SHEET

We hereby certify that we have read and evaluated this Thesis titled "**Magnitude and Factors Influencing Optimal Escalation of Guideline-Directed Medical Therapy Among Chronic Heart Failure Patients with Reduced Ejection Fraction in Comprehensive Hospitals of Central Ethiopian Region, Ethiopia. A Cross Sectional Study**." prepared under our guidance prepared by **Dr. Abdulfetah Abdulhakim** We recommend that the Thesis shall be submitted as fulfilling the requirements for the award of Certificate of Specialty in Internal Medicine.

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As members of the Board of Examiners of the Certificate of Specialty in Internal Medicine Thesis open defence examination, we have read and evaluated this thesis prepared by **Dr. Abdulfetah Abdulhakim,** and examined the candidate. We hereby certify that, the thesis is accepted for fulfilling the requirements for the award of the **Certificate of Specialty in Internal Medicine.**

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DEDICATION

Dedicated to my mother, for her endless love and support.

DECLARATION

I Dr. Abdulfetah Abdulhakim Beshir hereby declare that this thesis titled “Magnitude and factors influencing optimal escalation of guideline-directed medical therapy among chronic heart failure patients with reduced ejection fraction in comprehensive hospitals of central Ethiopian region, Ethiopia, a cross sectional study” is my original work and has been carried out and written by me, except where acknowledged and referenced. This thesis has not been submitted, in whole or in part, for any other degree or qualification at any other institution. All sources of information, data, and ideas used in this work have been properly cited.

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ABREVIATIONS AND ACRONYMS

ACEIs/ARBs: Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

ARNIs: Angiotensin receptor-neprilysin inhibitors

BBs: Beta-blockers

CBHI: community-based health insurance

CKD: chronic kidney disease

DCMP: dilated cardiomyopathy

DM: diabetes mellitus

GDMT: Guideline-directed medical therapy

GP: general practitioner

HF: Heart failure

HFrEF: Heart failure with reduced ejection fraction

HHD: hypertensive heart disease

IHD: ischemic heart disease

LVEF: Left ventricular ejection fraction

MRA: Mineralocorticoid receptor antagonist

MRC: Medical Referral Clinic

NEMMCSH: Nigist Eleni Mohammed memorial comprehensive and specialized hospital

SGLT2Is: Sodium-glucose cotransporter 2 inhibitors

WCSH: Worabe comprehensive specialized hospital

WUSH: Welkite University Specialized Hospital

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ABSTRACT

Background: Guideline-directed medical therapy (GDMT) substantially reduces morbidity and mortality in patients with heart failure with reduced ejection fraction (HFrEF). However, real-world implementation and dose optimization of GDMT remain sub-optimal in many low-resource settings. This study assessed the magnitude and factors influencing optimal escalation of GDMT among HFrEF patients in comprehensive hospitals of Central Ethiopia.

Methods: A mixed-methods, institution-based cross-sectional study was conducted among adult HFrEF patients attending medical referral clinics in selected comprehensive hospitals in Central Ethiopia. Quantitative data were collected from 93 patients using structured tools and analyzed with SPSS version 23. multivariable logistic regression was used to identify factors associated with GDMT optimization. In parallel, key informant interviews were conducted with clinicians and pharmacists, and facility observations were performed to explore system-level barriers. Thematic analysis was used for qualitative data.

Results: Although most patients received at least one component of GDMT, none achieved optimal beta-blocker dosing, and 63% were taking less than 25% of the recommended target dose. Use of sodium-glucose co-transporter 2 inhibitors (SGLT2is) was very limited. On multivariable analysis, higher systolic blood pressure (AOR = 1.047, 95% CI: 1.003–1.093), the absence of community-based health insurance (CBHI) (AOR = 0.288, 95% CI: 0.091–0.915), and longer duration of heart failure (AOR = 1.572, 95% CI: 1.055–2.344) were independently associated with mineralocorticoid receptor antagonists (MRAs) use. No significant predictors were identified for angiotensin converting enzyme inhibitor (ACEI), and SGLT2I escalation. Qualitative findings revealed limited availability of GDMT medications, lack of training on heart failure management, absence of local guidelines and protocols, high patient load, and supply chain and insurance-related constraints as major barriers to optimization.

Conclusion: Optimal escalation of GDMT among HFrEF patients in Central Ethiopia is markedly sub-optimal, particularly for beta-blockers and newer therapies. System-level and provider-level barriers, rather than patient factors, predominantly limit implementation. Strengthening drug supply systems, clinical guidelines, provider training, and alongside improving the effectiveness of CBHI, is essential to translate evidence-based recommendations into improved patient outcomes.

Keywords: HFrEF, guideline-directed medical therapy, GDMT, dose optimization, Ethiopia, heart failure.

1. INTRODUCTION

1.1 Background of the study

Heart failure (HF) is a common clinical syndrome in which symptoms result from a structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood specially HFrEF. (1) It is a global epidemic which affects more than 64 million people worldwide and associated with significant disability, mortality and health care costs. There are presently about 14 million patients with HF, and about 2.5 million HF-related hospitalizations per year in Europe. (2,3) Over the past decades, prognosis of HF has slightly improved, but mortality and hospitalization rates remain high, and many patients progress to advanced HF with few treatment options. (3) HFrEF is a distinct form of cardiac failure characterized by left ventricular ejection fraction (LVEF) $\leq$ 40% on echocardiography. Global data suggest that approximately 50% of heart-failure patients have reduced ejection fraction. (4) There is a lack of robust Ethiopian data quantifying the proportion of HFrEF among heart-failure populations in hospital or community settings.

The management of HFrEF has seen significant scientific breakthrough in recent decades, and the ability to alter the natural history of the disease has never been better. Large-scale, multicenter randomized controlled trials (RCTs) have conclusively shown that novel GDMTs, involving ARNIs, Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), β-blockers (BB), MRAs, and SGLT2is, significantly improve the prognosis of patients suffering from HFrEF.(5–8)

However, the importance of rapid and structured up-titration of GDMT became clearer with findings from the STRONG-HF study, which demonstrated that an expedited GDMT up-titration protocol in patients with acute heart failure significantly reduced rates of re-hospitalization and all-cause mortality. (9)

Accordingly, contemporary heart failure guidelines emphasize early and simultaneous initiation of multiple evidence-based therapies. The 2021 European Society of Cardiology (ESC) guidelines recommend a comprehensive GDMT approach including ARNIs (or ACE inhibitors if ARNI is not feasible), β-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter-2 inhibitors (SGLT2is) for HFrEF. (10) Similarly, the 2022 American College of Cardiology/American Heart Association/Heart Failure Society of

America (ACC/AHA/HFSA) guidelines endorse early initiation of these four cornerstone therapies to improve survival, reduce hospitalization, and enhance quality of life in patients with HFrEF.

Unfortunately, clinical guidelines are not always fully followed in practice, and many patients receive doses below the minimum effective level or do not receive all the drugs that could improve their prognosis. (11) Underutilization of such life-prolonging treatments at trial-proven doses, with subsequent unacceptably poor outcomes have been reported.(12)

There are many challenges to implementing GDMT, the most important being patient-related factors (comorbidities, advanced age, frailty, cognitive impairment, poor adherence, low socioeconomic status), treatment-related factors (intolerance, side-effects) and healthcare-related factors that influence availability and accessibility of HF care.(2)

2. STATEMENT OF THE PROBLEM

Heart failure with reduced ejection fraction (HFrEF) is major cause of morbidity and mortality worldwide. (3) Despite evidence that optimal GDMT can save lives and prevent hospitalizations many patients receive doses below the minimum effective level or do not receive all the drugs.(1,11)

Globally, real-world data reveal that the use and dose optimization of GDMT for HFrEF remain sub-optimal. A recent systematic review and meta-analysis involving over 1.5 million patients found large treatment gaps, with marked under-use and under-dosing of renin–angiotensin system inhibitors, β-blockers, and mineralocorticoid receptor antagonists particularly in low- and middle-income countries.(13) In sub-Saharan Africa, regional reviews consistently report poor uptake and low achievement of target doses for core GDMT agents, reflecting a major implementation gap.(14) In Ethiopia, available evidence indicates that only about 12% of patients with HFrEF receive optimized GDMT, despite the high burden of heart failure admissions in tertiary hospitals. (15) This gap may be attributed to patient-related, provider-related, and system-related factors such as medication intolerance, comorbidities, lack of follow-up, limited resources, and inadequate awareness or adherence to treatment protocols.(2,15) Yet there is scarcity of study about the factors that influence the optimal and aggressive up-titration of GDMTs across developing countries like Ethiopia.

Understanding these factors is crucial for improving the management and outcomes of patients with HFrEF. Therefore, this study assesses the factors influencing optimal escalation of guideline-directed medical therapy among heart failure patients with reduced ejection fraction in comprehensive hospitals of the Central Ethiopian Region. The results of this study generate evidence that can guide strategies to enhance heart failure management and reduce preventable morbidity and mortality.

3. SIGNIFICANCE OF THE STUDY

This study is significant because it generates locally relevant evidence on the barriers and facilitators influencing optimal escalation of GDMT among HFrEF patients in the Central Ethiopian Region. Identifying these factors is essential for designing targeted interventions that can enhance the uptake and proper titration of evidence-based therapies.

The study's results highlight patient, system, and provider-related barriers to achieving optimal dosing of essential heart failure medications such as ACE inhibitors/ARBs/ARNIs, beta-blockers, MRAs, and SGLT2 inhibitors. Furthermore, these findings offer critical evidence to inform policymakers and hospital administrators in designing strategies to enhance heart failure care, optimize resource allocation, ensure medication availability, and strengthen provider training initiatives. Therefore, by addressing these barriers, the study has the potential to contribute to improved treatment adherence, reduced hospitalizations, enhanced survival, and better quality of life for patients with HFrEF in central Ethiopia. It will also serve as a baseline for further research and policy formulation aimed at strengthening heart failure care across the country.

4. LITERATURE REVIEW

Heart failure (HF) remains a major cause of morbidity, mortality and health-care utilization worldwide. Randomized trials over the last decade have established several pharmacologic classes that reduce mortality and HF hospitalizations in patients with heart failure with reduced ejection fraction (HFrEF).(1,5–8)

In STRONG-HF trial the safety, tolerability, and efficacy of rapid optimization helped by NT-pro BNP testing in hospitalized patients for acute heart failure with reduced ejection fraction was assessed. In this study patients in the rapid up-titration arm the ACEI/ARB/ARNI, beta-blocker, MRA doses were aggressively up-titrated in a structured manner targeting >/= 50% in the first week and 100% in the next week. If the target were not achieved the dose was maintained or adjusted accordingly. The study clearly showed that structured and aggressive up titration of GDMT is safe, well tolerated, and significantly improved clinical outcomes.(9)

However, real-world data indicate that many patients with HFrEF do not receive optimized GDMT. The CHAMP-HF registry data revealed that a significant proportion of outpatients were treated with doses that are lower than those with proven efficacy in clinical trials. Likewise, a significant proportion of patients still do not receive all drug classes that could improve their prognosis. (2) A similar results were noted in a cross sectional study on patterns of GDMT utilization in Addis Ababa selected hospitals, retrospective study conducted from September 1, 2018, to July 31, 2023 in university of Gondar comprehensive specialized hospital and in a cross sectional study conducted from August 2022 to October 2022 on utilization and optimization of beta blockers on HFrEF patients at cardiology clinic of Tikur Anbessa hospital in Ethiopia.(15–17)

This regional context characterized by resource limitations, variable access to diagnostics (echo, natriuretic peptides), and inconsistent outpatient follow-up shapes HF outcomes and the feasibility of medication up-titration.

Similarly, the ESC HF long-term registry showed that less than one-third of patients received medications at recommended doses despite high prescription rates of GDMT.

There are many challenges to implementing GDMT, the most important being patient-related factors (comorbidities, advanced age, frailty, cognitive impairment, poor adherence, low socioeconomic status), treatment-related factors (intolerance, side-effects) and healthcare-related factors that influence availability and accessibility of HF care. Furthermore, advanced age, hypotension, poor cardiac function, renal insufficiency, and recent hospitalization for HF were frequently associated with lower dosages.(9,18,19)

While institutional reports and recent reviews document sub-optimal GDMT use and poor HF outcomes in Ethiopia, there remains a lack of region-level, multicenter data specifically on factors that influence escalation of GDMT to target doses. limited evidence comparing institutional/systemic versus individual provider/patient drivers of sub-optimal escalation; and scarce information on how adoption of newer, evidence-based therapies is evolving in routine practice in Ethiopian hospitals.

Because achieving target doses (not just prescription) of core therapies is critical to realize mortality and re-hospitalization benefits observed in trials, there is an urgent need for studies that systematically identify barriers and facilitators of GDMT escalation in the Ethiopian context. The planned study focuses on comprehensive hospitals in the Central Ethiopian Region directly addresses this gap and can inform practical strategies (training, drug procurement, clinic pathways, monitoring protocols) to improve outcomes.

The literature supports that HFrEF is an important and potentially preventable contributor to morbidity and death in Ethiopia, that GDMT reduces adverse outcomes when optimally implemented, and that Ethiopia like many Sub-Saharan countries faces multilevel barriers to medication optimization. A targeted study to identify the specific factors that influence GDMT escalation in comprehensive hospitals produces actionable evidence for clinicians, hospital managers and policymakers to close the implementation gap and improve patient outcomes.

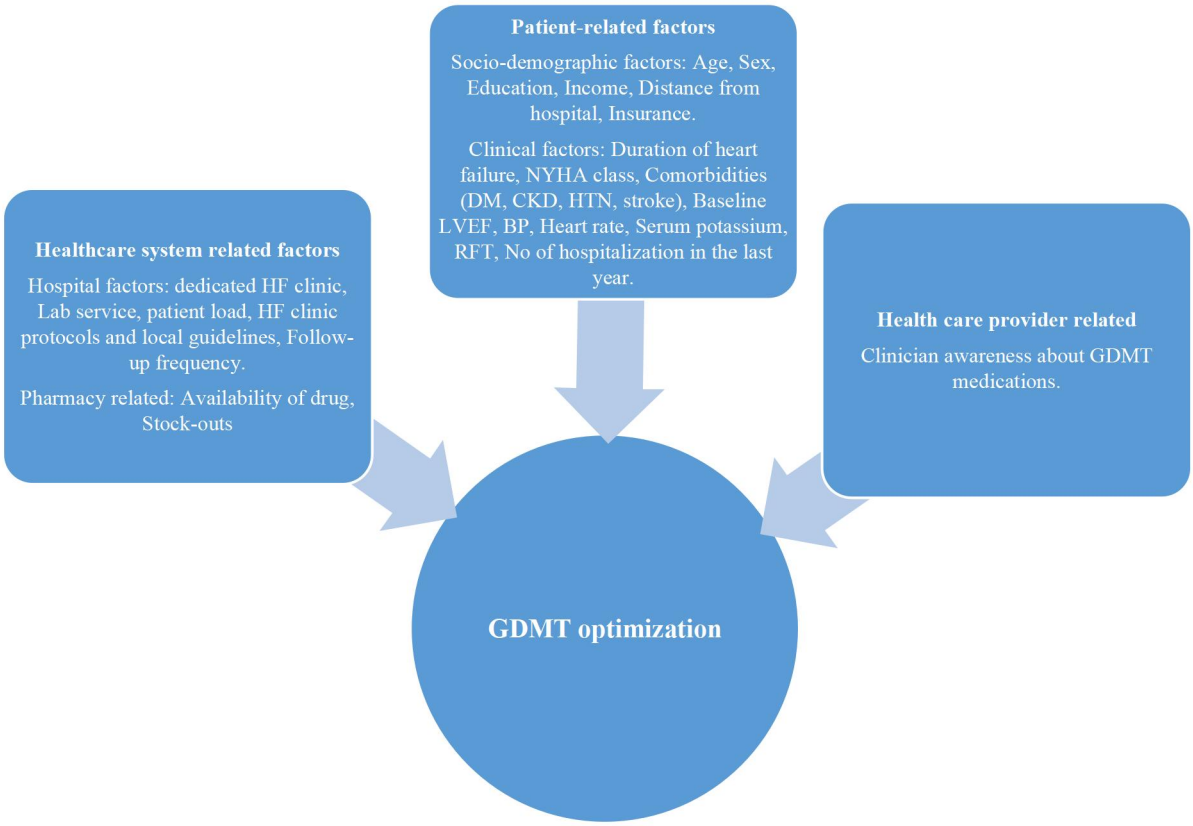

Figure 1: Conceptual framework illustrating relationships between independent variables and optimal escalation of GDMT in HFrEF.

5. OBJECTIVES OF THE STUDY

5.1. General objective

To assess the magnitude and factors influencing optimal escalation of guideline-directed medical therapy (GDMT) among patients with heart failure with reduced ejection fraction (HFrEF) in comprehensive hospitals of Central Ethiopia.

5.2. Specific objectives

To determine the magnitude of optimal escalation of GDMT among HFrEF patients visiting cardiac clinics in comprehensive hospitals of the central Ethiopian region during the study period.

To identify patient, treatment and healthcare system related factors associated with optimization of GDMT among HFrEF patients visiting cardiac clinics in comprehensive hospitals of the central Ethiopian region during the study period.

6. METHODS AND MATERIALS

6.1. Study Area and period

The study was conducted in comprehensive hospitals located in the Central Ethiopian region which includes Welkite university comprehensive specialized hospital, Worabe comprehensive specialized hospital and Nigist Eleni Mohammed memorial comprehensive hospital. The region is situated in the central part of Ethiopia and surrounds the capital city, Addis Ababa. It is one of the newly established regional states, characterized by rural and semi-urban populations. The main economic activities in the area include agriculture, trade, and small-scale industries.

The health care system in the region follows the national three-tier structure consisting of primary health care units, general hospitals, and specialized referral hospitals. The Central Ethiopian Region have 3 comprehensive specialized hospitals, 4 general hospitals, and 24 primary hospitals and 2 private general hospitals providing services to the population. These hospitals have provided health care services for over 10,561,000 people in their total catchment area. The comprehensive specialized hospitals provide both inpatient and outpatient services, including internal medicine, and serve as referral centers for chronic heart failure patients coming from various districts within the region. The average monthly adult medical referral clinic visiting heart failure patients in each hospital obtained through phone call with the HMIS (Health Management Information System) department of each respective hospital are 40, 73, and 58 for Welkite university comprehensive specialized hospital, Worabe comprehensive specialized hospital and Nigist Eleni Mohammed memorial comprehensive hospital respectively.

The study was conducted from Nov, 2025 to Dec, 2025 G.C.

6.2. Study design

This study employed a cross-sectional mixed-methods design to assess the magnitude and factors influencing optimal escalation of GDMT among HFrEF patients in comprehensive hospitals of the Central Ethiopian region.

6.3. Source and Study population

6.3.1. Quantitative Component

All adult patients with HFrEF visiting the comprehensive hospitals medical referral clinics during the study period.

6.3.2. Inclusion criteria

Age ≥ 18 years.

Diagnosed heart failure patients with reduced ejection fraction (LVEF≤40).

Follow-up for at least three months since diagnosis or discharge.

Provide informed consent.

6.3.3. Exclusion criteria

Patients with incomplete records regarding GDMT.

6.3.4. Qualitative Component

Key informants were Six clinicians (three general practitioners, two residents and two internists) with >1 year of experience and Five pharmacists, including a hospital pharmacy head, an inpatient pharmacy head, two clinical pharmacists, and one dispenser. Purposive sampling was used, continuing until information saturation was reached.

6.3.5. Observation

Medical referral clinics, hospital pharmacies, and patient–clinician interactions were observed.

6.4. Sample size

Sample size for this study was calculated using a single population proportion formula. Taking the proportion of patients receiving GDMT (four GDMT drugs) to be 12% from the earlier study reported in Ethiopia (15). The sample size was calculated as: n= Z@/2p(1-p)/d2, where n= the required sample size; p= proportion of patients receiving all of the four GDMT drugs= 0.12; Z@/2= the critical value at 95% confidence level= 1.96, and d= margin of error= 5%. Accordingly, the required sample size became 163, finite population correction was applied, formula; $n_{adj} = n_0/1+(n_0-1/N)$; Where N is total eligible patients during the study period, which became 172 (average eligible patients for all of the hospitals visiting in 1 months is 86 from HMIS reports), n_0= uncorrected sample, which is 163. The final result becomes 84, with 10% non-response added to get a final sample size of 93 patients.

6.5.Sampling method

The study was conducted in three comprehensive hospitals in the Central Ethiopian Region. All patients with heart failure with reduced ejection fraction (HFrEF) who meet the inclusion criteria during the data collection period constituted the source population. To ensure representativeness, the sample size was allocated to each hospital proportionally based on the average monthly case flow of HFrEF patients. Systematic random sampling was planned to select individual patients using a sampling interval (k) calculated as k = N/n, where N is the total number of eligible patients in each hospital and n is the allocated sample size for that hospital. A random starting point was chosen, and every kth patient was selected.

In practice, due to the number of eligible patients relative to the sample size, the sampling interval (k) was 1 for two hospitals and 2 for the third hospital. This ensured that all hospitals contributed the allocated number of patients to the study sample (N = 93).

6.6. Study variables

6.6.1. Dependent variable

Optimization of GDMT medications

6.6.2. Independent variables

Socio-demographic factors: - Age, Sex, Education, Income, distance from hospital, Insurance.

Clinical factors: - Duration of heart failure, NYHA class, Comorbidities (DM, CKD, HTN, stroke), Baseline LVEF, BP, Heart rate, Serum potassium, RFT, No of hospitalization in the last year.

Health system factors: - Availability of drug, Stock-outs, Follow-up frequency, Clinician awareness about GDMT medications, and Hospital factors (dedicated HF clinic, Lab service, patient load, HF clinic protocols and local guidelines).

6.7. Data collection method and tools

Data were collected using a structured questionnaire and qualitative data collection guides, which consisted of four major components. The first part captured patients' Socio-demographic and clinical characteristics. The second, third, and fourth parts were designed for key informant interviews with clinicians, interviews with pharmacists, and observation of

clinical and pharmacy practices, respectively. The patient Socio-demographic and clinical data were collected through chart review and patient interviews by trained general practitioners assigned at each hospital. One GP from each hospital was trained on the study objectives, data collection procedures, and ethical considerations prior to data collection. The qualitative data, including clinician interviews, pharmacist interviews, and observation of clinics and pharmacies, were conducted. A structured interview guide was used to ensure consistency across participants. During each interview, responses were documented in detail by trained data collector at the time of data collection. Although interviews were not audio-recorded, careful efforts were made to capture participants' responses as accurately and comprehensively as possible. The structured format of the tool helped maintain uniformity across interviews and minimize interviewer variability. Observations were carried out using a structured observation checklist. All data collectors received orientation on confidentiality, informed consent, and standard procedures to ensure data quality and consistency across sites.

6.8. Operational definitions

HFrEF: HF with left ventricular ejection fraction (LVEF) of 40% or less and is accompanied by progressive left ventricular dilatation and adverse cardiac remodeling.

Optimal GDMT dose: when a patient is taking four of ACC/AHA/HFSA and ESC latest guidelines recommended groups of GDMT therapies with their target doses. These groups of medications include: ACEIs /ARNIs /ARBs, Beta-blockers, MRAs and SGLT2Is.

Target doses of GDMT medications: ARNIs (sacubitril/valsartan 97/103 mg BID) or ACEIs (eg. Enalapril 10-20mg BID, Lisinopril 20-40mg daily) or ARBs (eg. Losartan 150mg po daily) and three of Beta-blockers (eg: Bisoprolol 10mg daily, Metoprolol succinate 200mg daily), MRAs (eg. Spironolactone 25-50mg po daily) and SGLT2Is (eg. Dapagliflozin 10mg po daily).

Less than twenty five percent of the daily dose of beta-blocker: less than 50mg of beta-blocker.

6.9. Data quality assurance

Data collectors received one-day training on the collection tool and deployed to collect data after the principal investigator convinced of their competency. The primary investigator of the study followed the data collection process to minimize incompleteness, missing information

and inconsistencies. Pretest study was conducted at Butajira general hospital medical referral clinic on 2 patients, 2 pharmacists, 1 internist and 1 GP to ensure the clarity, simplicity and effectiveness of the data collection instrument. Necessary modifications were made before the actual data collection began. The primary investigator checked the collected data completeness and it was transferred from Google form to excel.

6.10. Data analysis

Data that was in excel form was transferred to SPSS V23 for analysis. Continuous variables presented as mean with standard deviation. Categorical variables presented as frequencies and percentages. Bivariate analysis was performed to assess the crude association between each independent variable and optimal escalation of GDMT. Variables with p-value ≤ 0.25 were selected for multivariable logistic regression analysis. Prior to multivariable modelling, assumptions were checked for linearity of continuous variables with the logit using the Box–Tidwell test, multicollinearity using variance inflation factors (VIF < 5), and model fitness using Hosmer-Lemeshow goodness-of-fit test. Statistical significance was taken at $p < 0.05$.

6.11. Ethical considerations

Ethical clearance was obtained from the Institutional Review Board of Welkite University, College of Medicine and Health Sciences. An ethical approval letter was written to the Regional Health Bureau to get a support letter for the hospitals. Permission was secured from each hospital administration before data collection.

The purpose, benefits, and possible risks of the study was clearly explained to each participant in Amharic. Oral informed consent was obtained from all participants before inclusion in the study. Confidentiality was maintained by avoiding personal identifiers and using codes instead of names. The collected data was used only for the purpose of this research, and participants had the right to withdraw at any stage of the study without any penalty or loss of benefits.

6.12. Dissemination of findings

The findings of this study will be disseminated to key stakeholders to inform improvements in heart failure care and GDMT optimization. The final thesis will be submitted to Welkite

university specialized hospital department of internal medicine in partial fulfillment of the requirements for the degree in Internal Medicine.

The results will be presented to participating comprehensive hospitals and shared with clinicians, pharmacists, and hospital administrators written summaries. In addition, a report will be provided to the regional health authorities to support evidence-based planning for medication supply, training, and guideline implementation.

Efforts will be made to publish the study finding results in a peer-reviewed journal to contribute to the wider body of knowledge on heart failure management in low-resource settings.

7. RESULT

7.1.Quantitative findings

A total of 93 patients with chronic heart failure with reduced ejection fraction were included in the final analysis. This corresponds to 100% of the calculated sample size, indicating that the planned sample size was fully achieved.The mean age was 53 ± 11 years, and 57% were male. Half of the patients were covered by community-based health insurance (CBHI). The median duration of heart failure was 2 years. Most patients were in NYHA class II or below (73%), while 27% were in class III–IV. The majority had an LVEF between 30–40% (83%), with 17% having LVEF <30%. The mean systolic and diastolic blood pressures were 115 ± 11 mmHg and 68 ± 12 mmHg, respectively, with a mean heart rate of 82 ± 14 bpm. Mean serum creatinine was 0.90 ± 0.25 mg/dL. Serum potassium was within the normal range (3.5–5.5 mmol/L) in 71% of patients, while 2% had hypokalemia (<3.5 mmol/L). Potassium was not measured in 27% of patients. The majority had an LVEF between 30–40% (83%), with 17% having LVEF <30%. The mean systolic and diastolic blood pressures were 115 ± 11 mmHg and 68 ± 12 mmHg, respectively, with a mean heart rate of 82 ± 14 bpm. Mean serum creatinine was 0.90 ± 0.25 mg/dL and mean potassium was 4.0 ± 0.2 mmol/L. Hypertension was the most common comorbidities (19%), followed by atrial fibrillation (10%) and diabetes mellitus (8%). Dilated cardiomyopathy was the leading underlying cause of heart failure (65%), followed by ischemic heart disease (30%). (Table 1)

Table 1: Baseline characteristics of patients, ccontinuous variables (N=93).

Variable	Mean ± SD
Age (years)	53 ± 11
Duration of HF (years)	2 (IQR=2)
SBP (mmHg)	115 ± 11
DBP (mmHg)	68 ± 12
Heart rate (bpm)	82 ± 14
Serum creatinine (mg/dL)	0.90 ± 0.25

Table 2: Baseline characteristics of patients, Categorical variables (N=93).

Variables	Categories	Proportion
Sex	Male	57%
	Female	43%
CBHI status	Yes	50%
	No	50%
NYHA class	II and below	73%
	III–IV	27%
LVEF category	30–40%	83%
	<30%	17%
Serum potassium (mmol/L)	3.5-5.5mmol/L	71%
	<3.5mmol/L	2%
	Not done	27%
Comorbidities	Hypertension	19%
	Diabetes mellitus	8%
	CKD	2%
	Atrial fibrillation	10%
	Stroke	1%
Underlying cause of HF	Dilated cardiomyopathy	65%
	Ischemic heart disease	30%
	Chronic rheumatic valvular HD	2%
	Hypertensive HD	2%
	Peripartum cardiomyopathy	1%

7.1.1. GDMT Utilization

In this study the proportion of patients that are on Beta-blocker, ACEIs, MRA, and SGLT2Is are 100%, 89%, 71% and 13% respectively. (Figure 2) There was no single patient that achieved four of the GDMT medications. No patient achieved optimal dose of beta-blocker and 63% of patients were taking <25% of the target daily dose, indicating substantial under dosing. For MRA, SGLT2Is and ACEIs the proportion of patients that achieved target doses were 69%, 14% and 10% respectively as shown in figure 3. Enalapril was the only ACEI available in all of the hospitals. Metoprolol succinate was the standard beta-blocker but metoprolol tartrate was used when succinate was unavailable. Spironolactone and Dapagliflozin were the only MRA and SGLT2I prescribed respectively.

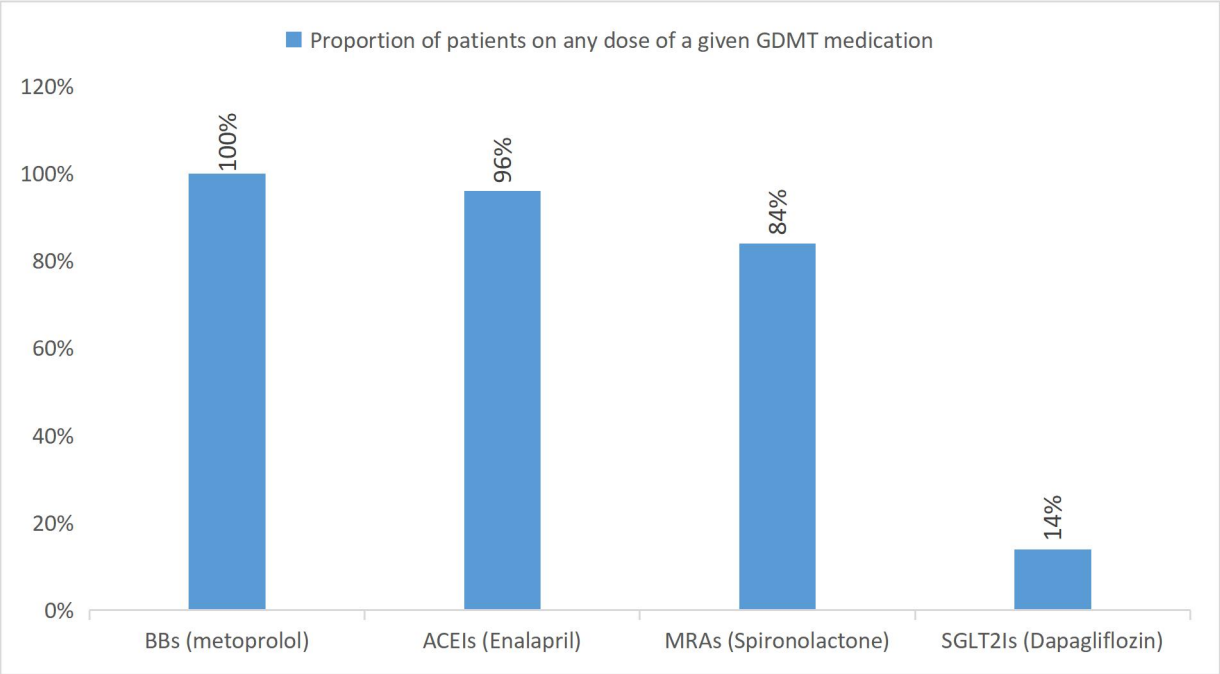

Figure 2: Proportion of patients on any dose of GDMT medications.

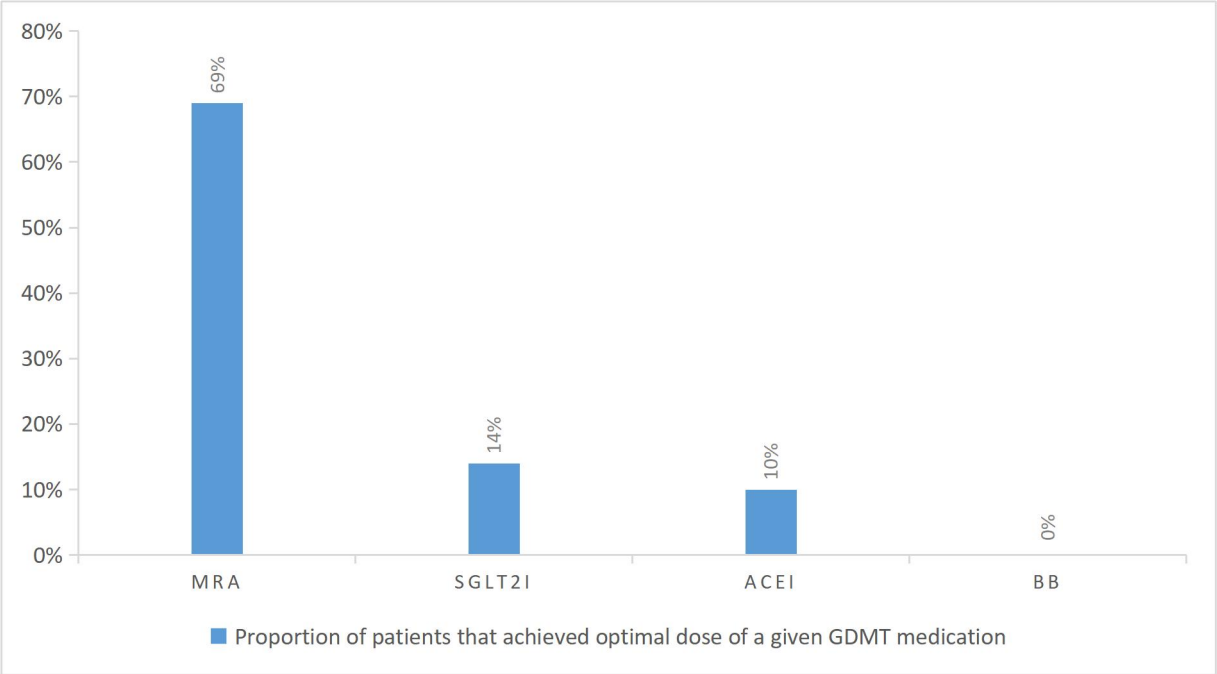

Figure 3: Proportion of patients that achieved optimal dose of each GDMT medications.

The wide spread of combinations underscores the heterogeneity of GDMT use and the lack of standardized escalation across the study hospitals. (Figure 4)

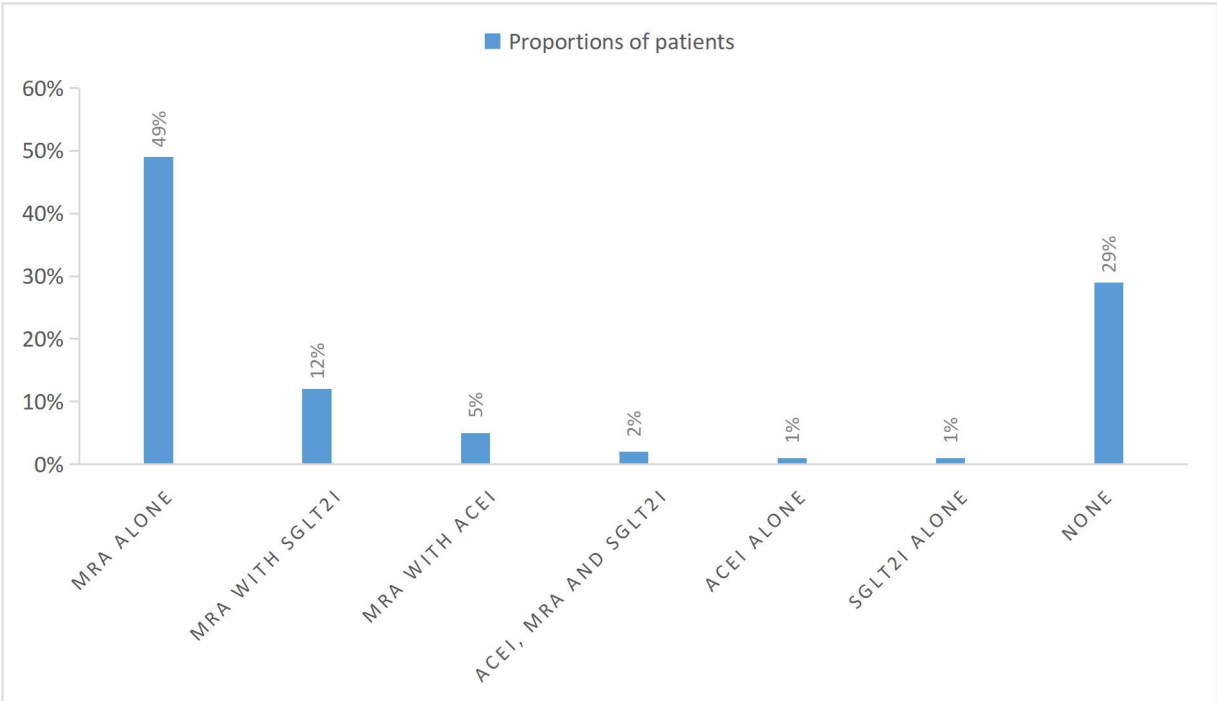

Figure 4: Patterns of optimal Guideline-Directed Medical Therapy Combinations Among HFrEF Patients (N= 93).

7.2. Qualitative findings

7.2.1. Clinician Interviews

All general practitioners reported that they had never received formal training on heart failure management, and there was no regular update or continuing medical education on GDMT they said “We were never given any formal training on heart failure management. What I know is mostly from medical school and personal reading. Since then, there has been no structured update specifically on GDMT.”. They also reported the absence of local guidelines, protocols, or checklists for managing HFrEF patients in their hospitals. Instead, they relied on external online resources such as Medscape and UpToDate when they needed information saying “In our hospital, there is no local guideline or protocol for managing HFrEF patients. We don’t have a checklist or standardized approach.”. The GPs and residents also said that “there is a high daily patient load, typically 40-50 patients visit per day, which limited time for detailed assessment and medication titration as all the patients (cardiac and non-cardiac) patients are seen together in one clinic”. All GPs and residents indicated that echocardiography is not always available. They initiate GDMT once an echocardiographic is obtained, but subsequent follow-up and titration depend on the patient’s clinical status, rather than structured dose-escalation schedules. None of the GPs were familiar with the guideline-recommended target doses of GDMT medications saying “We usually start low, but honestly, we don’t always know how far to go with the dose”. They also reported limited familiarity with newer heart failure therapies, particularly SGLT2 inhibitors. All of the interviewed Internists residents and GPs perceived that about 20-50% of their HFrEF patients are on optimal GDMT, one internist replied “In our hospital about 50% of patients are I think on optimal dose of GDMT”. Clinicians emphasized that drug availability and cost are the most important barriers to GDMT optimization. They also noted that even patients enrolled in CBHI often cannot access these drugs due to stock-outs.

7.2.2. Pharmacist Interviews

Most pharmacists reported that they were not familiar with angiotensin receptor neprilysin inhibitors (ARNIs) and were only partially familiar with SGLT2 inhibitors for heart failure management they replied “we are familiar with the drugs like ACEIs, ARBs, BBs and even SGLT2Is because even though the drug is not available in or pharmacy patients come with these medications from private pharmacies. But we are not familiar with ARNIs”. Availability of heart failure medications varied markedly across hospitals. In one hospital enalapril and

metoprolol only, In another metoprolol succinate, Spironolactone, and enalapril and in another enalapril only are available. This indicates severe limitations in GDMT availability, especially for Metoprolol succinate, SGLT2 inhibitors, and ARNIs. Pharmacists reported that heart failure medications were not given sufficient attention in procurement and planning processes Most of the pharmacists interviewed said “One factor that may affect the consistent availability of these medications is hospitals have their own planing and for example in our hospital drugs are grouped as very essential, essential non-essential all of these medications are in a group non-essential except for Enalapril”. Although drugs are classified as very essential, essential, and non-essential, only enalapril was consistently classified as essential, and classification varied by hospital. Pharmacists identified multiple reasons for inconsistent drug availability: Hospital affordability constraints, Unavailability at EPSS, and even in private markets, with import delays, Inappropriate use of CBHI funds, High turnover rate when drugs are available, and Poor quarterly forecasting and under planning. To manage shortages, pharmacists reported that they often dispense medications for short durations only, rather than full-month supplies.

7.2.3. Observation Findings

Observations were conducted in medical referral clinics, hospital pharmacies, and patient-clinician interactions across all study hospitals. There were no isolated cardiac clinics in any hospital. Chronic patients, including those with HFrEF, were seen at general medical referral clinics. Two hospitals had specific days dedicated to heart failure patients, but otherwise patients were seen alongside general chronic cases. Most clinicians were residents, with a maximum of second-year residents in two hospitals. The other one hospital’s predominant clinicians are GPs. Internists are consulted based on the complexity of the case in all of the hospitals. In one of the hospitals there is an occasional programmed biweekly visit by cardiologists mainly for echocardiography otherwise in all of the hospitals there is no cardiologists. The average consultation time per patient was approximately 10 minutes. No written or electronic heart failure guidelines were observed in any hospital. There were no protocols, algorithms, or wall charts to support GDMT initiation or titration. Routine vital signs like blood pressure were available in all of the hospitals. Laboratory monitoring (creatinine and potassium) was performed for most patients. Subsequent treatment plans were not systematically documented in patient charts. Appointments for clinically stable patients were scheduled every 2-3 months rather than for optimization of heart failure medications.

There was no formal system to address insurance denials or high out of pocket costs. Availability of heart failure medications are limited and inconsistent Two hospitals had enalapril, spironolactone, and metoprolol tartrate and One hospital had enalapril only. No hospital had multiple dose formulations of the same drug, limiting flexibility for dose titration.

7.3. Variables that are independently associated with optimal escalation of GDMT on multivariable analysis

On multivariable logistic regression, higher systolic blood pressure (AOR = 1.047, 95% CI: 1.003–1.093), the absence of CBHI (community-based health insurance) (AOR = 0.288, 95% CI: 0.091–0.915), and longer duration of heart failure (AOR = 1.572, 95% CI: 1.055–2.344) were independently associated with optimal MRA dosing. (Table 3) Patient's Socio-demographic or clinical variables were not significantly associated with ACEI, or SGLT2i escalation on multivariable analysis. Dapagliflozin was rarely available and used. Since all patients were under-dosed with beta-blockers, the dependent variable was constant, and no statistical association with independent variables could be assessed.

Table 3: Variables that are independently associated with optimal escalation of MRA (Spironolactone) and those that have no association.

Independent variables	AOR	p-value	95% CI	
			Lower	Upper
Male sex	.820	.800	.178-	3.792
Any of chat, alcohol or cigarette use	.610	.505	.143-	2.606
Higher SBP	1.047	.036	1.003-	1.093
Higher DBP	.999	.969	.934-	1.068
Higher number of comorbidities	.496	.076	.229-	1.077
CBHI enrollment	0.288	0.035	0.091-	0.915
LVEF at the time of diagnosis	.893	.893	.174-	4.597
Longer duration of HF	1.572	0.026	1.055-	2.344

8. DISCUSSION

This study assessed the magnitude and factors influencing optimal escalation of GDMT among patients with HFrEF in comprehensive hospitals of Central Ethiopia using a mixed-methods approach. Both the quantitative and qualitative components consistently demonstrated that optimal GDMT use and dose escalation remain suboptimal in the study settings.

This study reveals substantial underutilization of most components of GDMT in patients with chronic heart failure with reduced ejection fraction. Although this pattern is consistent with both global and local reports, the magnitude of underutilization observed in this study appears more pronounced than in many previously published studies. In addition, there was marked under prescription of newer GDMT agents, SGLT2is, which is also in line with findings from other local studies.(11,13,20–22)

The higher systolic blood pressure increasing the likelihood of being on a higher MRA dose, is likely reflecting clinicians' reluctance to up-titrate therapy in patients with borderline blood pressure. This is consistent with clinical practice, where hypotension is a common barrier to GDMT optimization and similar association was noted in a study conducted recently in Addis Ababa, Ethiopia.(23) The finding that CBHI status was negatively associated with optimal use of MRA therapy may reflect the structural constraints faced by insured patients who primarily receive care in public hospitals. These facilities often experience limited diagnostic capacity, medication stock-outs, and financial constraints that delay investigations and hinder the timely initiation of GDMT. As a result, although CBHI provides nominal financial protection, it may not translate into effective access to essential heart failure therapies such as spironolactone in routine practice. Longer duration of heart failure was associated with better MRA escalation, possibly because clinicians have more time to optimize therapy over repeated follow-ups. This finding aligns with some local studies. (21) However, the observation that even long-standing patients were rarely on optimal beta-blocker doses suggests missed opportunities for structured titration.

The findings in qualitative and quantitative study indicates that under-titration is not driven mainly by patient characteristics, but rather by system-level barriers such as limited drug availability, high workload, lack of guidelines, and insufficient provider training all strongly supported by the qualitative findings. This finding is also consistent with a study published in Addis Ababa, Ethiopia in 2026. (23) While the Addis Ababa study focused on overall GDMT adherence, our study identified specific clinical and system-level predictors of MRA use,

including systolic blood pressure, community-based health insurance (CBHI) status, and duration of heart failure. Importantly, the qualitative components of both studies converge on similar barriers to optimal GDMT implementation. The Addis Ababa study reported gaps in adherence and clinical practice, while our qualitative findings further elucidate the underlying causes, including lack of formal training in HF management, absence of local guidelines and protocols, high patient load, limited medication availability, and supply-chain and insurance-related constraints. These shared themes underscore that underutilization of GDMT in Ethiopia is driven mainly by health-system and provider-level limitations.

Generally, the findings indicate that suboptimal GDMT escalation in Central Ethiopian hospitals is driven primarily by system-level and provider-level barriers rather than patient-level factors. These include medication unavailability, lack of training, absence of protocols, insurance limitations, and high clinical workload.

9. STRENGTHS AND LIMITATIONS

A key strength of this study is the use of a mixed-methods design, allowing triangulation of quantitative data with real-world insights from clinicians, pharmacists, and direct observation. However, the cross-sectional design limits causal inference, and some laboratory data were missing. The study was also limited to comprehensive hospitals in one region, which may affect generalizability.

10. CONCLUSION

In conclusion, optimal escalation of GDMT among HFrEF patients in Central Ethiopia is extremely low, particularly for beta-blockers and SGLT2 inhibitors. None of the patients in this study achieved target beta-blocker dosing, and the use of SGLT2 inhibitors was minimal. Both quantitative and qualitative findings indicate that underutilization is driven mainly by provider-related, and system-level barriers rather than patient factors alone.

11. RECOMMENDATIONS

Clinicians should have regular, structured training programs on HFrEF management and GDMT titration should be implemented, with emphasis on safe up-titration of beta-blockers and MRAs. Clinicians should adopt standardized dose-escalation algorithms to ensure patients are systematically moved toward target doses when clinically stable.

Hospitals should develop and implement local HF treatment protocols aligned with international guidelines. Dedicated HF follow-up clinics or clinic days should be established to allow time for GDMT optimization.

Essential GDMT drugs, including SGLT2Is and ARNIs, should be included consistently in national and hospital procurement lists. CBHI coverage should be expanded to include newer HF medications to reduce financial barriers.

Strengthen drug forecasting and supply systems to avoid stock-outs of beta-blockers, MRAs, ACEIs/ARBs/ARNI, and SGLT2 inhibitors.

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13. ANNEXES

Annex I: Verbal informed consent script

Participants were told the purpose of the study, the procedures (interview and chart review), that no additional tests or treatments would be given, that there were no expected risks, and no direct benefits, that all information would be kept confidential and used only for research, and that participation was voluntary with the right to refuse or withdraw at any time without affecting their care. After this explanation, verbal informed consent was obtained before data collection.

Annex II: Questionnaires

Socio-demographic data and clinical and laboratory related characteristics

1. Participant ID; _____
2. Age(years); _____
3. sex; a) male b) female
4. Educational level
    a) No formal education
    b) Primary school
    c) High school
    d) Diploma
    e) Degree and above
5. Occupation;
    a) Student
    b) Government employee
    c) Merchant
    d) Housewife
    e) Farmer
    f) Other:
6. Monthly income (ETB)_____
7. Estimated distance from hospital (KM); _____
8. Usage of healthcare insurance; a) yes b) no
9. Blood Pressure(mmhg); _____
10. Baseline Heart rate(bpm)_____
11. Underlying cause of heart failure: _____
12. Duration since HF diagnosis (in years/months); _____
13. How long since the patient was started on GDMT (in years/months); _____
14. Previous hospitalization due to heart failure: a) yes b) no
15. If your answer is yes, how many times in the past 1 year?
16. NYHA functional class at the time of interviewing;
17. LVEF; a) 30-40% b) <30%
18. Comorbidities; _____
19. Serum Creatinine (mg/dl); _____

20. Serum potassium(mEq/L); _____

21. GDMT drugs the patient is on; _____

22. Additional medications other than GDMT medications; _____

23. Medication-related side effects; _____

24. Reason for not up-titrated GDMT drugs to a target dose; _____

Clinician- related factors interview tool

1. Clinician at MRC; a) Internist b) GP
2. Year of clinical experience;
3. Knowledge of GDMT;
    a) familiarity with the current guidelines of ESC, ACC/AHA/HFSA recommended GDMT medications;
    b) Drugs that the clinician knows:
    c) What is the goal of titration?
    d) How often dose escalated?
4. Attitude towards GDMT;
    a. Belief of the physician on optimal escalation of GDMT medications and its benefits.
    b. Familiarity in adjusting GDMT medications
    c. How frequent the patients on GDMT should be appointed for GDMT dose escalation?
    d. How the physician handles side effects of GDMT medications.
5. Health practice related:
    a) Do you usually start all eligible HFrEF patients on GDMT?
    b) Do you attempt to reach target doses in most patients?
    c) Which medication class is most commonly up-titrated in your practice? ___

Pharmacy- supply related interview tool

1. Pharmacist position
2. Participant ID
3. How familiar are you with GDMT drug classes (ACEi/ARB/ARNI, beta-blockers, MRAs, SGLT2 inhibitors)?
4. Are you involved in drug procurement and forecasting?
5. Are you involved in dispensing cardiovascular medications?
6. Are you involved in clinical pharmacy service (ward rounds, medication review and counselling)?
7. Which groups of GDMT medications are available in your pharmacy
8. Which of the groups of GDMT medications are frequently unavailability or stocked?
9. What are the most common reasons for stock outs?
10. Have you ever asked about the availability of GDMT (HF) medications by the clinicians?
11. What is your involvement in ensuring these drugs are consistently available to clinicians and patients?
12. What challenges do you face in sourcing and distributing GDMT medications?
13. How do you manage stock levels to avoid shortages?
14. How do you coordinate with pharmacies, hospitals, and distributors to ensure timely delivery?
15. What are the most common causes of GDMT drug shortages (import delays, manufacturing issues, regulatory hurdles)?
16. Are there partnerships with local or international suppliers that improve reliability?
17. How do you communicate with physicians and pharmacists about stock levels and availability?
18. Are there feedback loops where clinicians inform you about prescribing trends or anticipated demand?
19. What improvements in logistics infrastructure would help optimize GDMT availability?
20. 20- In the last 3 months ACEIs/ARBs/ARNIs consistently available?
21. If the above question answered no, why?
22. In the last 3 months beta-blockers consistently available?
23. If the above question answered no, why?
24. In the last 3 months MRAs consistently available?
25. If the above question answered no, why?

26. In the last 3 months SLT2Is consistently available?

27. If the above question answered no, why?

Clinical area and pharmacy observation tool

1. Setting ID;
2. Availability of written or electronic heart failure guidelines in clinical areas;
3. Presence of GDMT protocols, algorithms or wall charts;
4. Availability of basic monitoring tools;
5. Presence of multidisciplinary care structure (cardiologist, Internist, pharmacist, nurses)
6. Physical availability of GDMT drugs on the day of observation
7. Availability of starter doses and target doses;
8. Evidence of recent stock- outs;
9. Documentation of contraindication to GDMTs;
10. Evidence of dose titration plans documented on charts;
11. Follow up appointment for dose titration;
12. Time spent per patient consultation;
13. Does the clinician discuss GDMT titration in the visit (e.g., "let's increase your dose")? Why?
14. Observed patient counselling during visit
15. Is there a clear process for addressing insurance denials or high out-of-pocket costs for patients?
16. Other pertinent observation (on clinical setting or pharmacy that may affect GDMT optimization;