JIMMA UNIVERSITY

INSTITUTE OF HEALTH, FACULTY OF MEDICAL SCIENCES, DEPARTMENT OF INTERNAL MEDICINE

Optimization of Guideline directed Medical Therapy and associated factors, among adult heart failure patients on follow up at Jimma University Medical Center follow up clinic, Jimma, Southwest Ethiopia; a Cross-sectional Study.

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A Research paper to be Submitted to Department of Internal Medicine, Institute of Health, Jimma University for Partial Fulfilment of the Requirements for Specialty Program in Internal Medicine.

April, 2024
Jimma Ethiopia

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April, 2024

Jimma Ethiopia

DECLARATION

I agree to accept responsibility for the scientific, ethical and technical conduct of the research thesis and for provision of required progress reports as per terms and conditions of the faculty of Medical Sciences in effect at the time the grant is forwarded as the result of this application.

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ABSTRACT

Background:

Heart failure (HF) poses a significant global health concern, with substantial morbidity, mortality, and economic burden. Among heart failure patients, those with reduced ejection fraction (HFrEF) constitute around 60%. Recent society guidelines recommend use of Guideline medical therapy (GDMT) which include four group of pillar drugs at their optimal dose in order to reduce not only hospitalization but also heart failure symptom and mortality. Despite this recommendation the drugs are underutilized because of different factors.

Objective: To assess the magnitude of utilization of GDMT and associated factors among patients with HFrEF at JUMC cardiac follow up clinic of Jimma University Medical Center**.**

Methods: A cross-sectional study was conducted on selected patients with HFrEF on follow up between June 2023 and Sept 2023at ambulatory care clinic of Jimma University Medical Center, Ethiopia. Data was collected through patient interview and review of medical records. Collected data was first cleaned, edited and entered into a computer and analyzed using software program SPSS Version 24. Adjusted Odds Ratio with 95% CI was used to measure strength of association. A P-value of <0.05 is considered statistically significant for associated factors.

Result: The study's findings indicate that only **12 patients (4.7%)** received guideline-directed medical therapy, and this achievement was substantially correlated with the diagnosis of hypertension (**AOR: 10.62, 95% CI: 1.14-98.37**) and diabetes mellitus (**AOR: 7.73, 95% CI: 3.85-19.86**). Despite high prescription rates for ACEIs/ARBs **244(96.1%**), beta-blockers (**226 patients, 85.97%**), and MRAs **218(85.82%**), the prescription of SGLT2 inhibitors was notably infrequent **22(8.7%**). Moreover, a relatively small percentage of patients achieved target dosages, with just **76(29.9%)** for ACEIs/ARBs, **32(12.6%)** for MRAs, and **9(3.5%)** for beta-blockers.

The primary barrier to this was physician inertia, with a significant number of patients not receiving dosage escalations without documented reasons: **129(76%)** for ACEIs/ARBS, **109 (49.8%)** for beta-blockers, and **147(79%)** for MRAs. SGLT2 inhibitors were not offered to **161 patients (63.4%)**. Medication-related side effects or intolerance also hindered the achievement of target dosages for **31(18%)** of ACEIs/ARBs, **61(21.5%)** for beta-blockers, and **25(13.4%)** for

MRAs. Furthermore, cost was cited as a barrier for **10 (5.7%)** of ACEIs/ARBs, **61(21.5%)** of beta-blockers, and **14 (7.5%)** of MRAs users.

Conclusion and recommendation: The study sheds light on a notable gap in the application of guideline-directed medical therapy, with only a minority of patients reaching the advised target doses. Given the underuse of SGLT2 inhibitors and the low rate of achieving target doses for essential medications, it might be beneficial for healthcare systems to consider strategies that can help to overcome physician inertia, which hinder the delivery of optimal patient care. Furthermore, enhancing the availability and affordability of SGLT2 inhibitors may be advantageous in the context of their prescription patterns.

Keywords: Heart failure, reduced ejection fraction, guideline directed medical therapy, optimization, Jimma university, Jimma, Ethiopia.

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Table of Contents

List of Tables

Table of figures

ACRONYMS AND ABBREVIATIONS

ACEI	Angiotensin Converting Enzymes Inhibitors
ARB	Angiotensin II receptor blocker
ARNI	Angiotensin receptor neprilysin inhibitor
RAAS	Renin–Angiotensin–Aldosterone system
SGL2	Sodium glucose cotransporter 2
MRAs	Mineralocorticoid receptor antagonist
BMI	Body Mass Index
BB	Beta-Blockers
BP	Blood Pressure
HR	Heart rate
CHF	Congestive Heart Failure
HFmrEF	Heart Failure with mid-Range ejection fraction
HFrEF	Heart Failure with reduced Ejection Fraction
HFpEF	Heart Failure with preserved Ejection Fraction
GDMT	Guideline directed medical therapy
JUMC	Jimma University Medical Center
RFT	Renal Function Test
SPSS	Statistical Package for Social Science

CHAPTER ONE

1. INTRODUCTION

1.1. Background

Heart failure (HF) is a multifaceted clinical illness caused by any anatomical or functional abnormality in ventricular filling or ejection of blood. (1) and It has been classified as a global pandemic, impacting around 63.4 million individuals globally.(2)

Depending on the ejection fraction heart failure can be classified as HF with reduced EF (HFrEF), HF with mildly reduced EF (HFmrEF), HF with preserved EF (HFpEF) and HF with improved EF (HFimpEF), among which patient with HFrEF accounts for the substantial portion.(2)

In general, low- and middle-income countries have a higher burden of HFrEF than high-income countries, and they also face more challenges in accessing and adhering to guideline-directed medical therapy (GDMT).(3)

The recent society guidelines has proved that disease amelioration and cardiovascular mortality reduction are currently obtained by following guidelines-directed medical therapy (GDMT) that includes beta blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), mineralocorticoid receptor antagonists (MRAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2Is) if they are initiated early and tittered to maximum tolerated dose.(4)

How ever large global observational studies showed that usage of ARBS/ACEIS , MRA , B blockers was suboptimal. (5) Similarly large placebo-controlled trials shows ACE-Is, β-blockers, and aldosterone antagonists were under-utilized.(6)

It can be difficult to properly up-titrate several types of HF drugs since patients with HF usually have several comorbidities and need polypharmacy .(7) Moreover, a variety of explanations for the underutilization of therapies suggested by guidelines have been put forth. Among multiple factors, Patient-related factors like age, frailty, and comorbidities that cause intolerance or

contraindications and Non-medical variables include affordability, such as the price of prescription drugs, and, more broadly, access to health-care systems are the major ones.(8)

1.2. Statement of the problem

Treatment of HFrEF has been suggested by recent society guidelines to regularly utilize Renin-Angiotensin System Inhibition with (ACEIs or ARB or ARNIs), beta-blockers ,MRAs and SGLIs2.(4)

In spite of these guidelines, they are frequently underused or administered at dosages below that advised in the majority of patients with heart failure.(9,10)

A number of reasons for the underutilization of guideline recommended therapies have been proposed. Patient factors like old age, Low BMI and comorbidities, could directly lead to drug intolerance or contraindications to prescribed medications. Renal dysfunction was associated with underutilization of RAS blockades and MRAs, whereas COPD and/or asthma were associated with underutilization of beta-blockers.(11)

However, little is known about the optimal use ACEI and BB, MRAs and SGLT2 inhibitors among heart failure patients in our setting. Therefore, this study aimed to investigate the magnitude and associated factors for optimization of GDMT in chronic heart failure patients with reduced ejection fraction.

That will be crucial in the development of potential intervention methods to close the gap between recommended clinical practice in guidelines and actual clinical practice in our system and pinpoint areas for improvement in the treatment of heart failure patients.

1.3. Significance of the study

There is a lack of information on prevalence and factors related to the use and optimization of GDMT in Ethiopia, where the burden of HFrEF is high and the health system faces many challenges. The purpose of this study is to assess the current Use of GDMT In patients at Jimma University medical center at cardiac follow up clinic, one of the largest and oldest Teaching hospital in Ethiopia serving a large population.

This study also assesses factors affecting initiation and optimization of the four pillar drugs., such as patient Clinical characteristics, comorbidities, drug availability and affordability, level of discussion between care provider and patients about optimal drug use, and health system factors.

The research will ultimately contribute to improving the management and outcomes of HFrEF in Ethiopia and other resource-limited settings, as well as advancing the scientific knowledge and evidence base to optimize GDMT.

CHAPTER TWO

2. Literature review

HF is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.(12)

Most deaths in HF patients (both inpatient and outpatient), particularly sudden death and deteriorating HF, are related to cardiovascular causes. in general, HFrEF has a higher all-cause death rate than HFpEF.(13,14)

2.1 Overview of Guideline directed medical therapy

2.11 ACE Inhibitors

One of the most amazing developments in the management of cardiovascular illnesses has been the introduction of angiotensin-converting enzyme inhibitors (ACE inhibitors). No matter how severe the congestive heart failure (CHF), the hemodynamic advantages are linked to improved CHF signs and symptoms as well as a reduction in mortality. The advantages of ACE inhibitors include a complex mechanism that involves preventing LV remodeling that occurs over time, preventing sudden death and arrhythmogenicity, and maintaining the structural integrity of the atherosclerotic process and it is conceivable that ACE inhibitors have a class impact in the treatment of LV dysfunction.(15)

The suggested daily target dosages of ACEIs are 20–40 mg enalapril, 10 mg Ramipril, 150 mg captopril, 20–40 mg Lisinopril, 40 mg fosinopril, 4 mg trandolapril, 40 mg quinapril, or 8–16 mg perindopril, per the evidence-based recommendation.(16,17)

2.12 B Blockers

When beta-blockers are used at optimal dose, they have been shown to relieve symptoms, lower hospitalization rates, improve left ventricular function, and increase survival in chronic HF

patients with low ejection fraction.(16,17) Although beta-blockers have been shown to be beneficial in treating HFrEF, they are frequently underutilized in actual clinical practice.(18,19)

Only carvedilol, sustained-release metoprolol succinate, and bisoprolol have been shown in several randomized clinical studies to reduce morbidity and mortality, according to evidence-based recommendations .(12,20). The recommended daily target doses of evidence-based beta-blockers are 200 mg metoprolol, 10 mg bisoprolol, and 50 mg carvedilol.(21)

2.13. SGL2 INHIBITORS

SGLT2 inhibitors were initially created as oral glucose lowering medications for the treatment of diabetes mellitus and enhance the excretion of glucose in the urine. They have, however, recently shown promising results for the treatment of HFrEF in both diabetic and nondiabetic patients.(22) Although the exact mechanism is unknown, it is hypothesized that the observed effect is partly due to promotion of osmotic diuresis and natriuresis, and Other additional theories have also been put out, such as those that modify the metabolism of uric acid, affect the metabolism and hematopoiesis of the myocardium, change the pathways involved in programmed cell death, (23) decrease the production of cytokines, and lessen myocardial fibrosis.(24)

SGLT2 inhibitors decreased the composite of cardiovascular death or HF hospitalization by roughly 25% in the DAPA-HF and EMPEROR-Reduced trials when compared to placebo .(22,25,26). Dapagliflozin significantly reduced the risk of cardiovascular death (18%) and all-cause mortality (17%).Due of the aforementioned impact, SGLT2 inhibitors are recommended in patients with HFrEF. (27)

2.14. Mineralocorticoid receptor antagonists

Most available data confirms that blocking aldosterone receptors with spironolactone in addition to standard treatment significantly lowers the risk of morbidity and mortality in patient with severe heart failure with reduced ejection fraction**.**(28,29) In patients with HFrEF and moderate symptoms, eplerenone also decreased both the risk of mortality and the chance of hospitalization**.**(30) According to recent 2022 AHA/ACC/HFSA Guideline for the Management

of Heart Failure recommendation. (31) The initial dose of spironolactone plus eplerenone is 25 mg orally daily, which is gradually raised to 50 mg daily orally after a month; for eGFR 31 to 49 mL/min/1.73 m2, the amount should be cut in half. They also recommend Frequent assessments of blood potassium levels and renal function should be undertaken according to clinical state, generally 1 week, then 4 weeks, then every 6 months after commencing or escalating MRA, with more frequent testing for clinical instability.(27)

2.2 Utilization of Guideline directed medical therapy

According to the results of a QUALIFY worldwide prospective observational longitudinal study of 7092 CHF outpatients from 36 countries, adherence to guideline-recommended drugs is rather good, but the dose of prescribed CHF medications is inadequate.(The proportion of patients on target dose and 50% of target dose was low (27.9% and 63.3% for ACEIs, 14.8% and 51.8% for beta-blockers, respectively)**.** (32)

The percentage of patients taking target dose (100%) for ACEI was 7.6%, for beta-blockers it was 0.8%, and for MRA it was 1% in a retrospective cross-sectional study conducted on 364 patients with HFrEF at TASH. Utilization of over 50% of target dosage was 36.7% for ACEI, 6.6% for beta-blockers, and 49% for MRA. In comparison to individuals without diabetes, patients who had diabetes were administered larger dosages of ACEI ($p = 0.001$).(33)

In one study done in tertiary hospital among eligible patients, ACE-i/ARB were prescribed in 81.4% (293 of 360) and beta blockers in 94.4% (442 of 468). Of these patients, 10.6% were prescribed target doses of ACE-i/ARB and 12.4% were prescribed target doses of beta blockers. Utilization of other categories of GDMT was lower, with 54% of eligible patients prescribed MRAs and 27% prescribed an ARNi. In most cases, the reasons for nonprescription or under-dosing of GDMT were not apparent on review of the health record or discussion with the patient.(34)

A study done in tertiary hospital of southern Nigeria on 166 HFrEF patients regarding optimization of GDMT shows that the prevalent causes of heart failure were hypertensive heart disease (70.5%), followed by dilated cardiomyopathy (15.7%) and valvular heart disease (6.6%). The use of diuretics was prevalent among study cohorts at 87.4%, followed by Mineralocorticoid

antagonist (MRAs) (78.3%), ARB/ACEI/ARNI (68.1%), beta blockers (40.4%), and less than a third of patients were on SGLT2 inhibitors (28.9%) and Only about 2.4% of the study cohorts had dose optimization over the study period.(35)

2.3 Factors Associated with Underutilization

According to European study on Determinants and clinical outcome of up titration of ACE-inhibitors and beta-blockers in patients with heart failure: Independent predictors for achieving lower percentages of recommended ACE-inhibitor/ARB dose were female sex, country of inclusion, lower BMI and eGFR, and higher alkaline phosphatase values whereas Predictors for usage of lower beta-blocker doses were higher age, country of inclusion, lower heart rate and diastolic blood pressure (DBP), and signs of congestion.(36) Marked differences in dose-up titration were found across Europe. Lower ACE-inhibitor/ARB and beta-blocker doses were achieved in South and Central European countries, while Scandinavian countries achieved higher ACE-inhibitor/ARB and beta-blocker doses.(36)

According to the European Society of Cardiology Heart Failure Long-term Registry, the majority of patients who were not on treatment had a documented contraindication or previous medication intolerance. (37) Despite this, just 29% of patients were on target ACEI doses and 18% were on target beta-blocker doses, with about one-third having no documented explanation for failure to up-titrate.26 In contrast, in RCTs, at least 50-60% of patients reached goal dosages.(38–42)

Whereas a study done in Israel showed that achieving upper range doses of ACEI/ARB and BB in HFrEF out patients in treatment up titration program was associated with greater BMI and DM, respectively**.**(43)

According to a study done in Ethiopia, on treatment optimization of beta-blockers in chronic heart failure therapy, Prior hospitalization [Adjusted Odds ratio (AOR) 0.38, 95% confidence interval (CI) 0.19–0.76], dose of furosemide > 40 mg (AOR 0.39, 95% CI 0.20–0.76), ischemic heart disease (AOR 3.27, 95% CI 1.66–6.45), atrial fibrillation (AOR 4.41, 95% CI 1.38–14.13) were significantly associated with the utilization of beta-blockers .(44)

2.5. **Conceptual Framework**

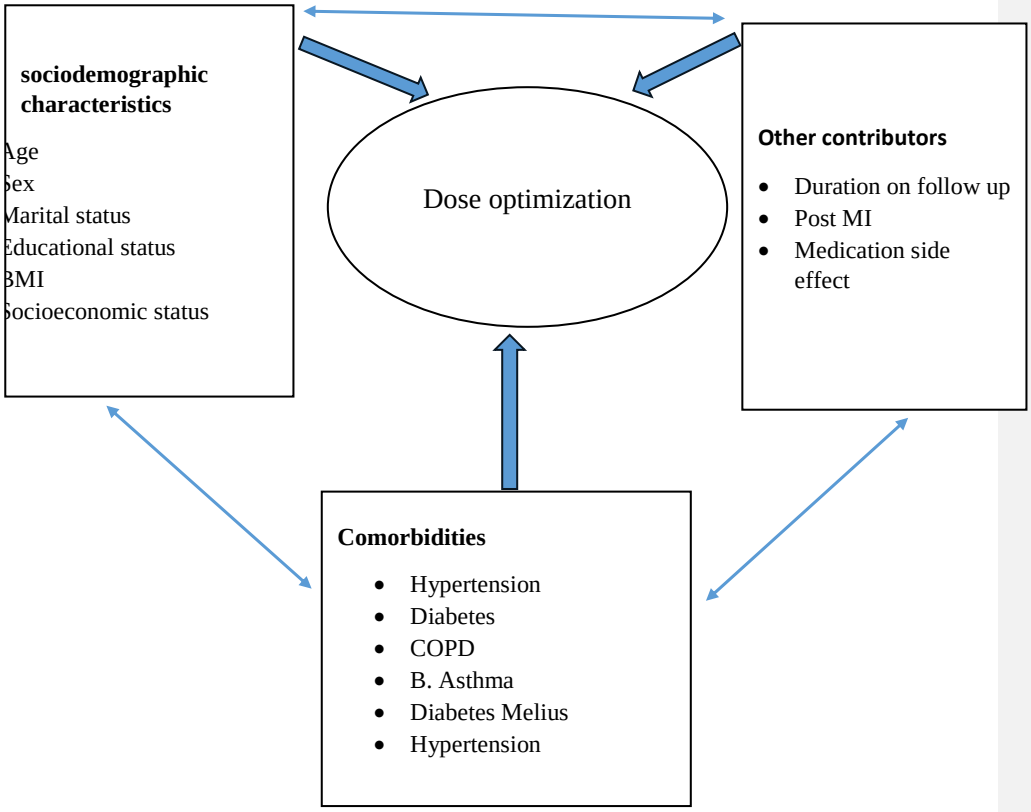

Figure 1: Conceptual framework showing factors affecting optimization of GDMT in patients with HFrEF at JUMC cardiac follow up clinic of Jimma University Medical Center.

CHAPTER THREE: OBJECTIVES

3.1. General objective

- ✓ To investigate the magnitude of utilization of GDMT and associated factors among patients with HFrEF at JUMC cardiac follow up clinic of Jimma University Medical Center.

3.2. Specific objectives

- ✓ To assess the magnitude of titration of GDMT among patients with HFrEF
- ✓ To determine the possible contributing factors for optimization GDMT among patients with HFrEF

CHAPTER FOUR:MATERIALS AND METHODS

4.1. Study area

The study will be conducted at JUMC, which is located in Jimma town in Southwest of Ethiopia, in Oromia region, 350 km southwest of capital, Addis Ababa. Jimma zone comprises Jimma town and its nearby woredas with estimated population of 2,486,155. JUMC is the only referral teaching hospital in this largest region of the country. The hospital gives health services at inpatient and outpatient level as a referral hospital with catchment area of 15 million populations in the South West of the country. The department of Internal Medicine has a total of 78 beds with about 2650 annual admissions. There is one cardiac clinic and the total number of cardiac patients on follow up are 1870. Checkup is twice per week (every Wednesday and Friday). The service is provided by cardiologists, cardiology fellows', internists, medical residents and general practitioners

4.2. Study design and study period

A hospital-based retrospective, cross-sectional study design was used. The study was conducted from **November 2023– march 2024 GC.**

4.3. Source population

All patients who are on follow up at JUMC cardiac clinic within the study period.

4.4. Study population

Adult Heart Failure patients with reduced ejection fraction on follow up at JUMC cardiac clinic during the study period.

4.5. Inclusion and Exclusion Criteria

4.5.1. Inclusion criteria

- Patients > 18 years old,
- Patient who had a regular follow-up for at least 6 months at the outpatient cardiac clinic.
- Patients with impaired LVEF of < 40 % in recent echo done at least within the last 2 years

4.5.2 Exclusion criteria

- Patients, whose basic medical records are lost or incomplete for important variables, and

- Patients who refused to participate in the study.

4.6 Sample size

The sample was calculated using the single population formula with margin of error 5%, and 95% confidence interval. Accordingly, calculated sample size was 384 considering prevalence of 50%. The sample size was calculated by using the following formula:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Where n = sample size,

Z = Z statistic for a level of confidence (1.96),

P = expected prevalence or proportion (50%, P = 0.5), and

d = precision (5%, d = 0.05).

n = 384.

Since the total population is <10,000 the finite population correction formula will be used to determine the final sample size.

Nf= n/(1+(n/N))

n = sample size, Nf = actual sample size

N = total number of adult patients with HFrEF on chronic follow up is about 700 to 800 in 2023 (data taken from **HMIS** of the hospital). N=750

Therefore, the sample size will be: Nf = 384/(1+(384/750) = 254

By adding 10% contingency a total of 116 patients will be sampled. =**279**

4.7 Sampling procedure

Consecutive sampling of clients (convenient sampling) coming to the clinic on their appointment dates was conducted.

4.8 Data extraction tools and methods

Data collectors used a structured checklist prepared by reviewing literature. The demographic data, imaging results, data regarding GDMT dosing and associated factors for under titration, will be extracted using the checklist. The data collection team was comprised of three residents and one two general practitioner and one supervisor.

4.9 Variables

4.9.1 Dependent variable

- ✓ **Dose optimization**

4.9.2 Independent variables

- ✓ Age, sex, residence, duration on follow up, LVEF, Marital Status, Educational Status, Occupation Number of Hospital Admissions, hypertension, diabetes, COPD, Bronchial Asthma, Renal dysfunctions, duration of heart failure, time since the last hospitalization medication side effect, adherence to physicians and cost of medication

4.10. Operational definition

- ✓ **Target dose**: The maximum recommended drug dose in HFrEF is suggested based on previous landmark trials.
- ✓ **ACEIs Target dose**: -lisinopril, enalapril, and fosinopril 20 mg/day, captopril1 50-100 mg/ day and ramipril 10 mg/day
- ✓ **ARBs Target dose**: - Valsartan 320 mg/day, losartan100 mg/day and Candesartan 32 mg/ day.
- ✓ **Beta-blockers Target dose**- Metoprolol 200 mg/day, carvedilol 50 mg/day, carvedilol phosphate extended-release 80 mg/day, bisoprolol 10 mg/day, Atenolol 100 mg
- ✓ **MRA Target dose**- Spironolactone 50 mg/day

- **Optimal Dose-** Up titrated to the Target dose or less if patient develops **side effect or in tolerance to the drug**
- **GDMT Optimized-** GDMT is said to be optimized if the patient is taking all of the four pillar drugs at optimal dose.

4.11. Data quality control

Investigators of the study was controlling the overall activity. Training was given for the data collection team on the data collection process. Data quality was ascertained by designing the proper data collection materials and through continuous supervision. The medical chart number of the patient checked whether clinically matched or not. Completeness, accuracy and consistency of data collection checked on each day of the data collection period. All completed data collection form then examined for completeness and consistency during data entry and analysis.

4.12. Data processing, analysis and management

The collected data was checked, coded, and entered in to Epi-Data version 3.2 and analyzed using software program SPSS 24.0. Descriptive analysis like frequency, percent, mean, table, and graph used to describe and present the data. Adjusted Odds Ratio with 95% Confidence interval was used to measure strength of association. Variables with $p \leq 0.05$ was considered as statistically significant.

4.13. Ethical consideration

Ethical clearance was obtained from the Jimma University, College of Health and Medical Science, Health Research Ethics Review Committee prior to data collection. Official permissions will be asked from JUMC administration and inpatient director. Information gained from medical records held anonymous and confidential.

4.14. Dissemination plan

The finding of the study will be submitted to the department of Internal Medicine, School of Medicine and College of Health and Medical Sciences Jimma University in partial fulfillment of the requirements for specialty in Internal medicine. A copy of the research will be given to the hospital administration. The finding also be presented for different workshops and seminars and will be published in a peer-reviewed journal

CHAPTER FIVE: RESULT

A total of 254 patients were included in this study. The mean [± standard deviation (SD)] age of the patients was 57.58±10.86 years, and 61% were males. The most common cause of heart failure was ischemic heart disease 132(52%) and followed by cardiomyopathy 74(29.1%). The duration of heart failure was more than two years in 178(70.1%) of the patients. The majority of patients 141(55.5%), had were in New York Heart Association (NYHA) class II symptoms. Around two third of patients have at least one known comorbidity, the most frequently identified comorbidities 105(41.3%) were hypertension, followed by diabetes mellitus 54(21.3%), the mean [± standard deviation (SD)] Ejection fraction at diagnosis was 31.35±5.56. (**Table 1and 2)**

Table 1. Sociodemographic characteristics of HF patients with reduced ejection fraction having follow up at Jimma University Medical Center chronic follow up clinic

variables	Category	Frequency	Percent
Age	<65	163	64.2
	≥65	91	35.8
Sex	Male	155	61
	Female	99	39
Residence	Rural	152	59.8
	Urban	102	40.2
Educational level	No formal education	81	31.9
	Primary school	94	37.0
	Secondary school	48	18.8
	Diploma/degree	31	12.2
Marital status	Married	159	62.6
	Widowed	49	19.2
	Single	22	8.7
	Divorced	24	9.4
Occupational status	Farmer	103	40.6
	Employed	40	15.7
	Retired	35	13.8
	Unemployed	35	13.8
	Merchant	25	9.8
	Daily labor	16	6.3
Monthly income	Low income	190	74.8
	low-middle income	40	15.7
	high-middle income	24	9.4

Table 2. Clinical characteristics of HF patients with reduced ejection fraction having follow up at Jimma University Medical Center chronic follow up clinic

Variables	Category	Frequency	Percent
Cause of HF	Ischemic heart disease	132	52.0
	Cardiomyopathy	74	29.1
	Hypertensive heart disease	35	13.8
	Valvular heart disease	13	5.1
Duration of heart failure	≥2	178	70.1
	<2	76	29.9
NYHA class at presentation	I	71	28.0
	II	141	55.5
	III	42	16.5
Having comorbidity	Yes	169	66.5
	No	85	33.5
Frequently identified comorbidities	Hypertension	105	41.3
	Diabetics mellites	54	21.3
	Atrial fibrillation	34	13.4
	Renal dysfunction	22	8.7
	Asthma	24	9.4
	Chronic obstructive pulmonary disorder	18	7.1
	Stroke	12	4.7
	RVI	6	2.4
	Thyrotoxicosis	2	0.8
Ejection fraction at Diagnosis	Mean ±SD	31.35±5.56	
	More than 2 admissions	50	19.7
	2 admissions	118	46.5
	1 admission	82	32.3
	No admission	4	1.6
Blood pressure	SBP (Median (IQR)	121(110-132.5)	
	DBP (Median (IQR)	74(68-81)	
Hert Rate	Median (IQR)	81.5(74-95)	
Respiratory Rate	Median (IQR)	21(19-23)	

Among the enrolled patients, **244(96.1%)** are using ACEIs or ARBs, while **226 (88.97%)** and **218(85.82%)** of patients are on beta-blockers and MRAs (spironolactone), respectively. Only **22 (8.7%)** of the patients started on SGLT2 inhibitors. Of these, only **97 (38.2%)** of ACEIs/ARBs, **52(18.9%)** of MRA, and **51(17.3%)** of beta-blockers were used at the optimal dose. GDMT was optimized in **12 (4.7%)** of the patients **(refer to Table 3, Figures 2, 3, and 4).**

Table 3. commonly used medications in HF patients with reduced ejection fraction having follow up at Jimma University Medical Center chronic follow up clinic

Variables	Frequency	Precent
Commonly used medication		
Beta-blockers	226	88.97
ACEIs	218	85.82
MRAs(spironolactone)	218	85.82
Antiplatelets	130	51.18
Statins	128	50.39
Loop diuretics	84	33.07
ARBs	26	10.23
Cardiac glycosides(digoxin)	8	3.14
Anticoagulants	22	8.66
Sodium glucose transporter inhibitors	22	8.66

ACEIs: Angiotensin converting enzymes inhibitors, ARBs: Angiotensin receptor blockers

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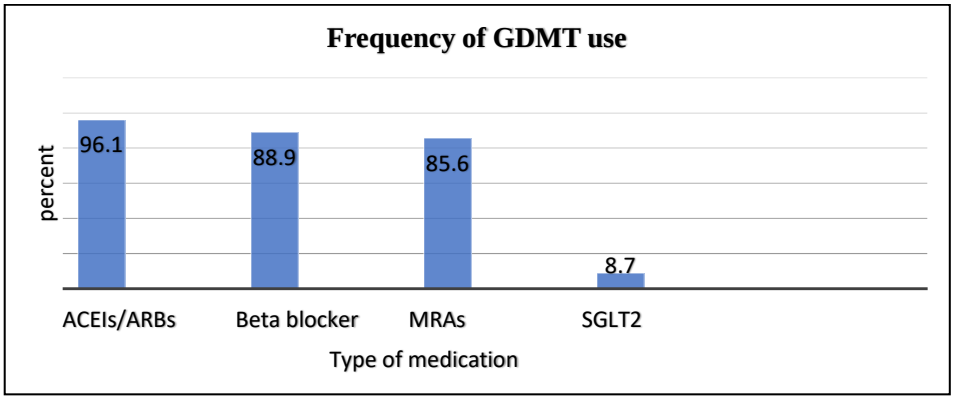
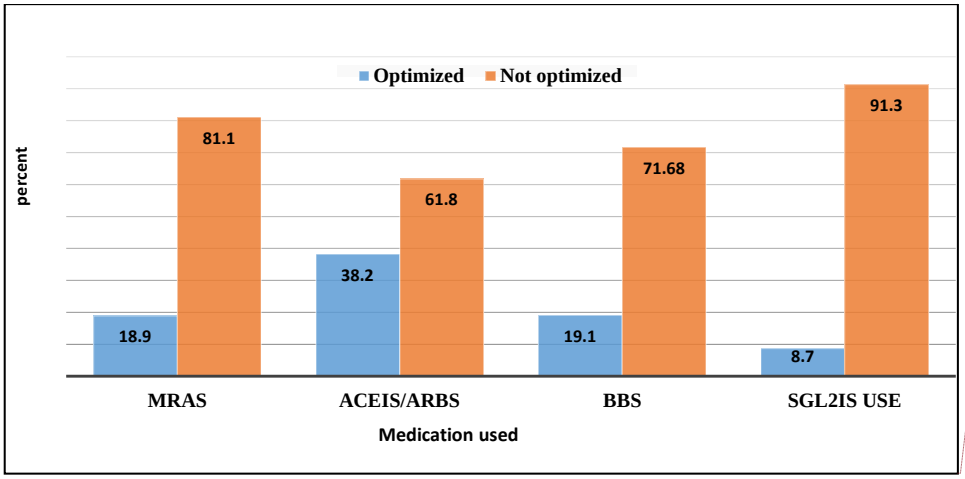


MRAs: Mineralocorticoid antagonist, SGLT2: Sodium glucose transporter 2 (SGLT2) inhibitors, ACEIs: Angiotensin converting enzymes inhibitors, ARBs: Angiotensin receptor blocker

Figure 2. Use of each four class of drugs in HF patients with reduced ejection fraction having follow up at Jimma University Medical Center chronic follow up clinic



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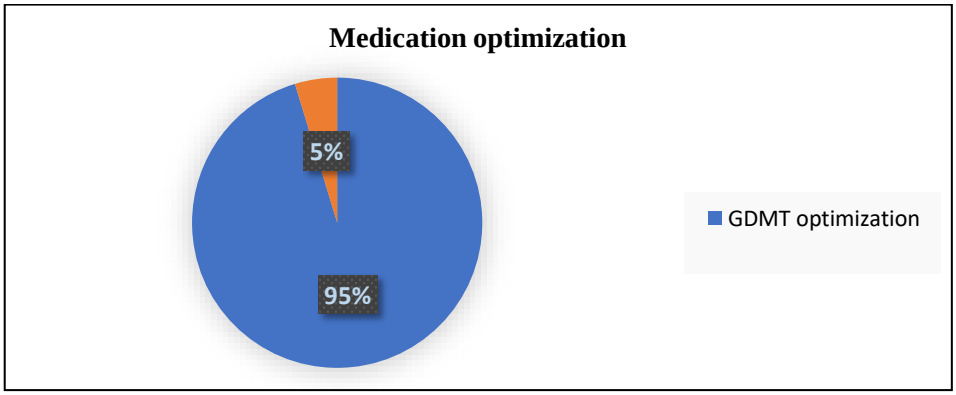
MRAs: Mineralocorticoid antagonist, SGLT2: Sodium glucose transporter 2 (SGLT2) inhibitors, ACEIs: Angiotensin converting enzymes inhibitors, ARBs: Angiotensin receptor blockers

Figure 3. Optimization of each four class of drugs in HF patients with reduced ejection fraction having follow up at Jimma University Medical Center chronic follow up clinic



GDMT: Guideline direct medical therapy

Figure 4. GDMT optimization among HF patients with reduced ejection fraction having follow up at Jimma University Medical Center chronic follow up clinic.

Among patients whom medication is not at target dose, on majority of the patients (129(76%) of ACEIs, 109(49.8%) of BBs and 147(79%) of MRAs) has no known reason for not escalating the drug and SGL2 Inhibitor was not offered for 161(63.4 %) of patients. conversely (31(18%),61(21.5%) and 25(13.4%) of patients ACEIs/ARBS, BBs and MRAs respectively) did not reach target dose due to development of Medication related side effect or intolerance. And only 46(18.1%) of patients had ever discussed with their physician regarding the importance of optimal use of GDMT **(Table 4, Figure 5 and 6)**

Table 4. Medication related side effect and the reason for not achieving target dose among HF patients with reduced ejection fraction having follow up at Jimma University Medical Center chronic follow up clinic.

Variables	Categorical	Frequence	Precent
Medication related effect			
ACEIs N (235)	Not known side effect	185	72.8%
	Cough	25	9.8%
	Renal dysfunction	24	9.4%
	Hyperkalemia	**16**	6.3%
	Hypotension	11	4.3%
BBs N (209)	no known side effect	155	74.16%
	Dizziness or light headedness	23	9.1%
	worsening of asthma or COPD symptoms	14	8.13%
	Near syncope or syncope	**9**	3.5%
	Hypotension	**14**	
Reason for not achieving target dose			
Why **ACEIs/ARBS** reached target dose N (156)	NO known reason	129	76%
	developed side effect	31	18%
	The drug was expensive	10	5.7%
Reason for not achieving target dose of **B blocker**	No known reason	109	49.8%
	The drug was expensive	47	27.9%
	developed side effect	61	21.5%
	Other	2	0.9%
Reason for not achieving target dose of **Spironolactone**	No known reason	147	79%
	developed side effect or contra indication	25	13.4%
	drug is expensive	14	7.5%
Reason for not **initiating SGL2 inhibitor**	The drug was not offered	**161**	**63.4%**
	The drug is expensive	57	22.4%
	I couldn't find the drug	12	4.7%
	Other	4	1.2%

GDMT: Guideline direct medical therapy, ACEIs: Angiotensin converting enzymes inhibitors, ARBs: Angiotensin receptor blockers, BBs: Beta blockers.

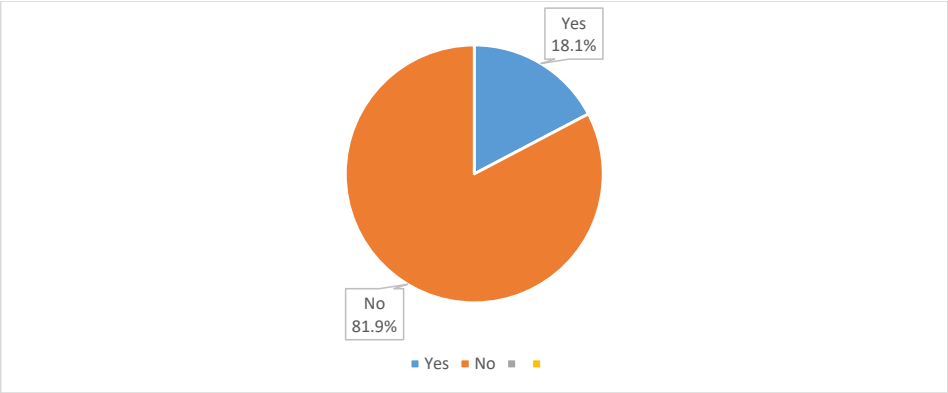


Figure 5. percent of patients who ever had discussed with physician or pharmacist about the importance of escalating the drugs among patients with reduced ejection fraction having follow up at Jimma University Medical Center chronic follow up clinic

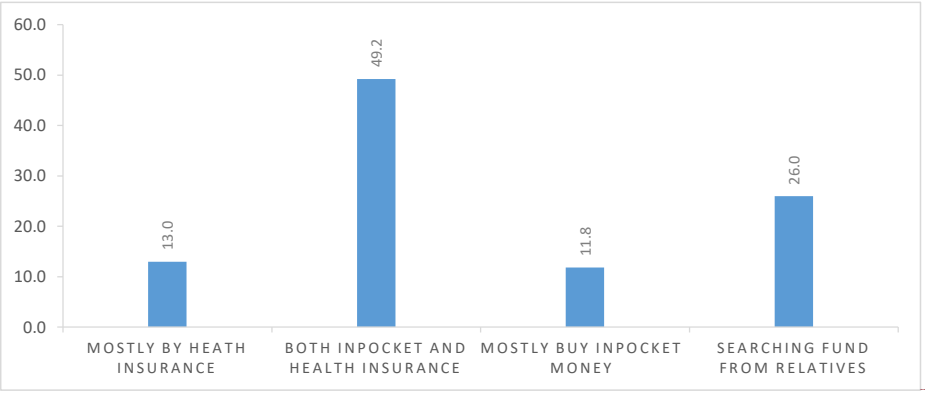


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Figure 6. Cost of medication coverage during treatment among HF patient with reduced ejection fraction of HF patients with reduced ejection fraction having follow up at Jimma University Medical Center chronic follow up clinic

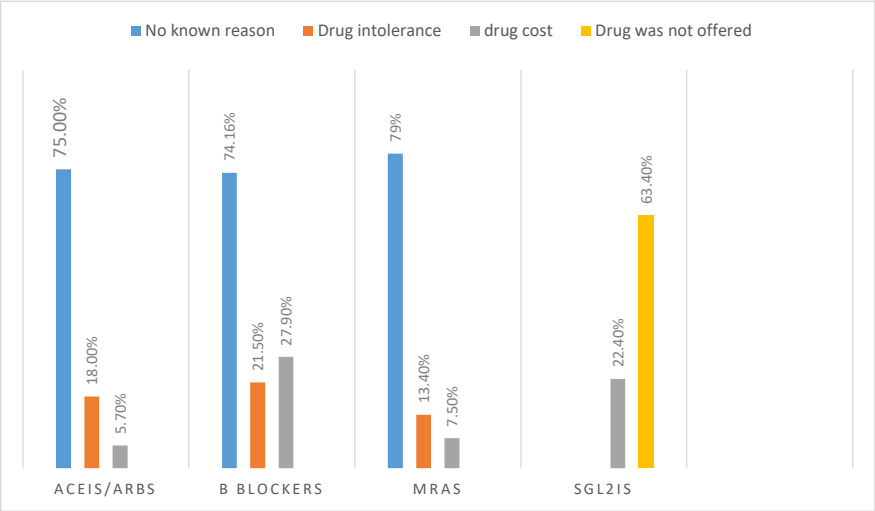

Figure 7. Reasons for not achieving target doses of ACEIs/ARBS. BB, MRAS and reason for not initiating SGLU2 inhibitors

Factors associated with optimization of GDMT was identified using univariable and multivariable regression model. Living in rural area (AOR: 3.9, 95%CI:1.98-15.50), having comorbidities like hypertension (AOR: 10.62, 95%CI: 1.14-8.37), and diabetes mellites (AOR:7.73, 95%CI:3.85-19.86) were significantly associated with optimization of GDMT. **(Table 5)**

Table 5. Factors associated with optimization of GDMT among HF patients with reduced ejection fraction having follow up at Jimma University Medical Center chronic follow up clinic.

Variables	**Dose optimization**					
Sex	**optimized**	**Not optimized**	**COR (95% CI)**	**p-value**	**AOR (95%CI)**	**p-value**
Female	2(2.0%	97(98.0%)	1		1	
Male	10(6.5%)	145(93.5%)	0.12(0.299-1.394)	0.064	0.23(0.04-1.27)	0.093
Residence						
Urban	8(7.8%)	94(92.2%)	1		1	
Rural	4(2.6%)	148(97.4%)	3.15(0.922-10.749)	0.067	3.90(1.98-15.50)	**0.050**
Duration of heart failure						
<2	3(3.9%)	73(96.1%)	1		1	
≥2	9(5.1%)	169(94.9%)	0.77(0.203-2.933)	0.047	0.84(0.18-3.84)	0.822
Having comorbidity						
No	3(3.5%)	82(96.5%)	1		1	
Yes	9(5.3%)	160(94.7%)	24.59(1.26-480.65)	0.035	10.44(1.60-57.84)	**0.023**
Hypertension						
No	4(2.7%)	145(97.3%)	1		1	
Yes	8(7.6%)	97(92.4%)	2.99(0.876-10.202)	0.080	10.62(1.14-8.37)	**0.038**
Diabetes mellites						
No	4(2.0%)	195(98.0%)	1		1	
Yes	8(14.8%)	46(85.2%)	8.47(2.447-29.370)	0.001	7.73(3.85-19.86)	**0.001**
Atrial fibrillation						
No	10(4.5%0	210(95.5%)	1		1	
Yes	2(5.9%)	32(94.1%)	1.31(0.275-6.265)	0.033	1.008(0.150-6.79)	0.994
Uses of diuretics						
No	6(3.5%)	164(96.5%)	1		1	
Yes	6(7.1%)	78(92.9%)	2.10(0.657-6.729	0.211	2.07(0.53-7.98)	0.293

COR: Crude odd ratio, CL: Confidence intervals, AOR: Adjusted odd ratio

CHAPTER SIX: DISCUSSION

Optimization of medical therapy is recommended in guidelines for better patients' outcomes, however in clinical practices, there are significant gaps, with suboptimal use and dosing of evidence-based therapies**.** And only a small percentage of patients are placed on Guideline recommended doses of HF therapy.

This study was aimed at assessing the frequency of use of Guideline- directed Medical Therapy (GDMT) and the proportion of HF patients who were on maximally tolerated doses of these medications, and it also asses factors associated with it.

Out of the total, 254 patient 96.1% of the patients were using ACEIs/ARBS while Betablockers and MRAs were used by 88.97% and 85.82% of patients respectively which goes in. But on the contrary only 8.7% of the patients were using SGL2 inhibitors. The usage ACEIs/ARBS and B blockers is comparable to that of in **QUALIFY-HF study.**(45)

This rate of prescription was slightly higher for ACEIs/ARBS and B blockers and there is also significantly improved rate of prescription of MRAs as compared a prospective multinational **ASCIAN-HF registry study** where the rate of prescription of ACEIs/ARBS, B blockers and MRA was 87.2%, 86.7and 69.3% respectively.(46) And the difference may be due to the different time gap of research conduction. In this similar study **(ASCIAN-HF registry study)**, Cost was not reported as a reason for not achieving the guideline recommended dose, but in our study among patient who did not reach target dose, drug cost is reason for 18.5% of patients taking B blockers and 7.5% and 5.7% of patients taking MRAs and ACEIS/ARBS respectively. and 22.4 % of patients did not start on SGL2 inhibitors due to drug cost. This clearly shows that implementing subsidy programs or financial assistance to patients can help to reduce the burden of drug costs, making it more feasible to reach target doses in substantial portion of the patients.

Among them maximum tolerated dose is achieved in 38.2% of ACEIs/ARBS,20.5% of MRAs and 20.1% of B blockers respectively and only target dose of drug is achieved for 29.9% of ACEIs/ARBS, 12.6% of MRAs and 3.5% of B blockers. Which is slightly higher as compared to similar study done at black lion tertiary hospital.(33) but rate of target dose target dose achievement is lower for b blockers and MRAs but higher to that of ACEIs/ARBS as compared

to **ASCIAN-HF registry study**(46). And the difference may be due to difference in socioeconomic difference and difference in setup.

Among patients prescribed but did not reach their target dose of ACEIS/ARBS, there is no known reason for not achieving it in about three forth patients. while 18% of patients did not reach target dose due to development of drug side effect or intolerance and around 5% found the drug expensive.

Similarly, there is no known reason for not reaching target dose in nearly half of patient's taking B blockers in dose that is less that the recommended target dose, while most of the remaining patients failed to achieve target dose due to Cost of the drug (27.9%) and drug intolerance (21.5%).

There is also no known reason for not achieving target dose of spironolactone in 79.9% of patients while drug intolerance is the reason in 13.9% of patients. And approximately two third of patients were not offered SGL2 inhibitors and one fourth of patients did not start SGL2 inhibitors due to drug cost.

So as there is no clear reason for not achieving target doses in majority of the patients, which might indicate that other reason like physician factors is contributing, which can be used us an opportunity to improve quality and further studies.

Use of all four pillar drugs of HFrEF at optimal dose (i.e. **optimization of GDMT**) occurs only in 4.7% of the participants. Which is twice as high as similar study conducted in tertiary hospital of northern Nigeria . The difference may be due to difference in sociodemographic characteristics of patients.(35)

Optimization of GDMT is associated with leaving in rural area (AOR: 3.9, 95%CI:1.98-15.50), probably due to better insurance coverage in rural dwellers as compared to urban and also having comorbidities like hypertension (AOR: 10.62, 95%CI: 1.14-8.37), and having diabetes mellites (AOR:7.73, 95%CI:3.85-19.86) were significantly associated with optimization of GDMT. This may be due to the fact that raised blood pressure gives room to escalate drug, and physicians tend to prescribe SGL2 inhibitors to diabetes patients as compared to non-diabetes.

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Limitations of the study

- The fact that the study is single center will affect its generalizability
- Physician related factors was not studied
- Because most of the information is collected from secondary data incompleteness of the data might affect the result.
- The study did not assess the adherence of patients to the prescribed medication so that the result cannot predict the outcome.

Strength of the study

- The research highlights the primary barrier to achieving target dosages, providing insights into areas of improvement in patient care.
- It highlights areas where more investigation is needed.

CHAPTER SEVEN: CONCLUSION AND RECOMMENDATION

7.1 Conclusion

Conclusion: With the exception of SGL2 inhibitors, HFrEF patients have a high adoption rate for guideline-directed medical therapy, despite the fact that dose up titration is still a major problem. But patient having hypertension or diabetes mellitus have better optimization of GDMT.

7.2 Recommendation

- It is important to implement subsidy programs or financial assistance to patients in order to reduce the burden of drug costs and improve drug optimization.
- To improve the outcomes of heart failure patients, we need to establish a multidisciplinary HF clinic focusing on up-titrating to optimal doses for greatest benefits is necessary, as is increasing the use of guideline-directed medical therapy (GDMT
- So as there is no clear reason for not escalating GDMT in majority of the patients, which might indicate that other reason, like physician related factors might play role which necessitates further study.

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ANNEXES

6.1 Data collection check list

Instructions: write the required information or circle the number

NOTE: If the information is not available on the chart of the patient (if not recorded, or the investigation was not done/missed) leave the space provided empty or do not circle the No**.**

Date: _____/_____/_____ Code no: _____

I. Socio-demographic characteristics			
Code	**Variable**	**Response**	**Skip**
	Age	_____years	
	Sex	1. Male 2. Female	
	Residence	1. Urban 2. Rural	
	Do you have health insurance	1**.Yes 2. No**	
	Highest level of Education achieved	**1. No Formal education** **2. Primary school** **3. Secondary school** **4. Highschool** **5. College/ university diploma or degree** **6. Other**	
	Marital status	**1. Single** **2. Married** **3. Divorced** **4. Widowed** **5. Other**	
	Occupation	**1. Merchant** **2. Government employee** **3. Farmer** **4. Private employee** **5. Unemployed** **6. Daily laborer** **7. Retired** **8. Other**	

	Average Monthly family income	**1. <3,100(low)** **2. 3,100-12,100(low middle)** **3. 12,100-37,600(high middle)** **4. >37,600(high)**	
II. Clinical characteristics			
	Height	**----------in meterrs**	
	Weight	**_____in kg**	
	Respiratory rate		
	Systolic BP	**_____mmhg**	
	Diastolic BP	**_____mmhg**	
	Heart rate	**_____mmhg**	
	Underlying cardiac cause for Heart Failure	**1. ischemic heart disease** **2. Cardiomyopathy** **3. Hypertensive heart disease** **4. VHD** **5. Other…….**	
	Duration of HF	**_____in years**	
	Ejection fraction **at Diagnosis**	_____%	
	Recent Echo done	1.**Yes 2. No**	
	If yes for **Q18** recent **EF**	1._____%	
	NO of previous admissions with HF	1. Once 2. Twice 3. More than twice 4. No history of admission	
	If yes for q 15 Mean tine since last hospitalization	_ _----------in years	
	Presence of risk factors /comorbidity	1.**Yes 2. No**	
	If yes **FOR Q 18** Type of comorbidity	1. Renal dysfunction 2. HTN 3. DM 4. Asthma 5. COPD	6. CKD 7. RVI 8. Atrial fibrillation 9. other_____

	Smoking history	**1. none smoker** **2. current smoker** **3. former smoker**	10.
	Is the patient being on treatment of **HF**	1.**Yes 2. No**	
	If yes to **Q 20**, specify the name/names of the drug/drugs	**1. ACEI/ARBs/ARNI** **2. Beta blockers** **3. MRAs** **4. SGL2 Inhibitors** 5. Calcium channel blockers 6. Nitrates 7. Statin 8. Asprin	9. Diuretics 10. Digoxin 11. Oral glucose lowering agent 12. anticoagulants 13. Insulin 14. 10.Other (specify)----------
	If the patient is taking **ACEI/ARBs/ARNI** what is the **type of the medication** and the dose	1. Type of medication……. 2. Dose……	
	If the patient is not taking target the dose of ACEIs /ARBS/ ARNI assess reason for not escalation	1. I don't know, I am taking as per the order 2. I have developed unwanted symptoms /side effect related to the drug 3. The drug was expensive don't know the reason 4. Other	
	Asses for ACEI/ARBs/ARNI related **side effect**	1.**Yes 2. No**	
	If Yes to **Q 29**what's the side effect	1. cough 2. Angioedema 3. Renal dysfunction 4. hyperkalemia	5. Hypotension 6. Others (specify)_____
	If the patient is taking BB what's the name of the BB he is taking and the recent dose	1. NAME ……. 2. Dose……	
	If the patient is not taking target the dose of BB assess reason for not escalation	1. I don't know, I am taking as per the order 2. I have developed unwanted symptoms /side effect related to the drug 3. The drug was expensive don't know the reason 4. Other	
	Beta Blocker associated side effects	1.**Yes 2. No**	

	If yes to **Q 27** what's the side effect,	1. Hypotension 2. Worsening of Heart Failure symptoms **3. Hypotension**	4. Bradycardia 5. Other ----------
	If the patient is taking **MRA** Type and dose of MRA	1. Type of MRA_____ 2. Dose…….	
	If the patient is not taking target the dose of MRAs assess reason for not escalation	1. I don't know, I am taking as per the order 2. I have developed unwanted symptoms /side effect related to the drug 3. The drug was expensive don't know the reason 4. Other	
	IS the patient taking **SGLUT inhibitor**	1.**Yes 2. No**	
	If **yes for Q 28 type and dose SGLUT inhibitor**	1. Type of SGLUT inhibitor _____ 2. Dose_____	
	If NO **for Q 37 assess reason for not initiation**	1. I was not offered 2. The drug is expensive 3. I couldn't find the drug 4. fear of the side effect 5. disbelief in the effectiveness 6. Other	
	offer Sgl2is after telling benefit and side effect of the drug and check patient response	1. ok I will start the drug 2. I cannot afford the medication 3. I need time to think about it 4. I don't want to take it, it seems risky	
	Have you ever discussed with your doctor or pharmacist about the benefits of increasing the doses of your medication	1. Yes 2. NO	
	Does your income cover all your medication cost	1. Yes 2. NO	
	Do you have health insurance	1. Yes 2. NO	
	How do you get your medication cost covered	1. Mostly by health insurance 2. Some by in pocket money and some by health insurance 3. Mostly by in pocket money 4. Searching fund from relatives	

		5. Other	
	Current NYHA class	**I II III IV**	
III. Laboratory results			
	Recent update in hgb, cbc or cr level (with in 6month)	**1. Yes** **2. NO**	
	Hg level	**_____%**	
	Serum K		
	Serum Creatinine (recent)	**_____mg/dl**	

6.2 INFORMATION SHEETAND INFORMED VOLUNTARY CONSENT FORM FOR HEAD JUMC

My name is _____ I am working as a data collector for the study be conducted in this hospital by Dr. Kidus Tesfaye (Internal medicine Resident) who is conducting a study for the requirement of specialty in Internal Medicine at Jimma University, College of Health and Medical Sciences. I kindly request you to lend me your attention to explain to you about the study and why your institution being selected as the study setting.

1. The study/project title:

Optimization of Guideline directed Medical Therapy and associated factors among adult patients with heart failure with reduced ejection fraction having follow up at Jimma University Medical Center chronic follow up clinic, Jimma, Southwest Ethiopia; a Cross-sectional Study.

The findings of this study will be important to identify the areas of improvement in the care of stroke patients. It also helps to inform the hospital administration about importance of improving work force, diagnostic modalities and establishing stroke unit with interdisciplinary stroke rehabilitation team.

The data from this research will inform the regional health administration about the burden of stroke in the region and helps them to develop effective health education programs for the community about the risk factors, symptoms of stroke, and the importance of seeking medical care within the golden window.

The finding on the current research can also serve as baseline for a future research. Moreover, the aim of this study is to write a thesis as a partial requirement for the fulfillment of Internal medicine specialty.

2. Procedure and duration:

We will fill Secondary data from medical record chart of each patient for 25 minutes. Then we will collect medical records from hospital card room with permission.

3. Risks and benefits:

The risk of taking secondary data from the patients file is minimal, but the findings from this research may reveal important information for the hospital, providers and for the patients.

4. Confidentiality:

The information provided will kept confidential. There will be no information that will identify the participants in particular. The findings of the study will be general for the study community and will not reflect anything particular of individual persons. Code is given to the questionnaires to a avoid sowing names.

5. Rights:

The hospital/card room has the right to get the medical chart of the patients at any time.

6. Contact address:

If there is any questions or enquires any time about the study or the procedures, please contact:
Dr, Kidus Tesfaye (principal investigator)
Phone numbers **+251920197780**
Email address- **kdstesfaye@gmail.com**
Contact address of Institutional Health Research Ethics Review Committee (IHRERC)
Office phone ----------
P.O. Box -----, Jimma

7. Declaration of informed voluntary consent:

I have read the participant information sheet. I have clearly understood the purpose of the research, the procedures, the risks and benefits, issues of confidentiality, the rights to get the patients file at any time and the contact address for any queries. I had given the opportunity to ask questions for things that may have been unclear. I am informed; the

Hospital has the right to stop this study if any misdeeds and unethical procedures observed during the data collection process in the Hospital's premises. Therefore, I declare my voluntary consent on behalf of JUMC management to allow conducting the study in the Hospital with my initials.

Name and Signature of Head of the JUMC: _____

Name and Signature of Data Collector: _____

6.3 APPROVAL SHEET SCHOOL OF GRADUATE STUDIES JIMMA UNIVERSITY

Submitted by:

_____	_____	_____
Name of student	Signature	Date

Approved by:

1. _____	_____	_____
Name of Advisor 1	Signature	Date
2. _____	_____	_____
Name of Advisor 2	Signature	Date
3. _____	_____	_____
Name of Advisor 3	Signature	Date