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Patterns of beta-blocker use and dose optimization among ambulatory heart failure patients with reduced ejection fraction (HFrEF) attending public hospitals in Northeast Ethiopia: a multi-center cross-sectional study

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Abstract

Background Evidence-based beta-blockers are essential in managing heart failure with reduced ejection fraction (HFrEF) and are known to improve cardiovascular outcomes. Despite robust nascent guideline recommendations, studies indicate that beta-blockers are often underutilized or administered below target doses. This shivery issue is particularly relevant in Ethiopia, where comprehensive evaluations of beta-blocker utilization and dosing practices are limited. The Northeast region, specifically Dessie, remains underexplored in this context.

Objective This study aimed to evaluate the appropriate usage trend and dose optimization of beta-blockers among HFrEF patients attending ambulatory clinics of Dessie Comprehensive Specialized Hospital (DCSH) and Boru Meda General Hospital (BMH), Dessie, Ethiopia, 2024 G.C.

Methods A cross-sectional, multi-center study was conducted from February 1 to July 30, 2024, involving 200 randomly selected adult patients with confirmed HFrEF (120 from DCSH and 80 from BMH), who had at least 6-month regular follow-up visits at their respective ambulatory clinics. The study rigorously followed the latest (2022) American Heart Association (AHA) guideline recommendation. Patient's medical records was reviewed to gather the necessary data. A logistic regression analysis was performed to identify factors associated with beta-blocker use. Statistical significance was declared at p-value < 0.05.

Results Among the 200 patients, 88% were prescribed beta-blockers. About 15% of the patients were not receiving beta-blockers whereas they are indicated. Out of the total, 96.5% received guideline-recommended beta-blockers, with bisoprolol being the most common (65%), followed by metoprolol (29%) and carvedilol (3%). Only 13% of

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beta-blocker users were on optimal doses, with average daily doses of 27.9 mg for metoprolol succinate, 10.0 mg for carvedilol, and 4.8 mg for bisoprolol. Factors positively associated with beta-blocker use included Angiotensin Converting Enzyme Inhibitor use (AOR: 15.48, 95% CI: 2.11-113.54, $p=0.007$), and taking multiple medications (AOR: 7.12, 95% CI: 1.54–33.02, $p=0.012$), while ingestion of secondary prevention agents (AOR: 0.05, 95% CI: 0.01–0.98, $p=0.048$) and male gender (AOR: 0.08, 95% CI: 0.01–0.47, $p=0.005$) were negatively associated. Baseline ejection fraction of 25–40% (AOR: 5.44, 95% CI: 1.09–27.12, $P=0.039$) was a sole predictor for sub-optimal beta-blocker use.

Conclusion Although most patients with HFrEF were prescribed evidence-based beta-blockers, only a limited number reached the optimal dosing levels. It is crucial to align clinical practice with the latest guidelines, prioritize ongoing research, and enhance educational efforts for both healthcare providers and patients. By doing so, it is possible to significantly improve the effective utilization of beta-blockers, ultimately leading to better patient outcomes in this region.

Keywords HFrEF, Evidence-based beta-blocker, Utilization pattern, Dose optimization, Ethiopia

Introduction

Heart failure (HF) is a grievous public health problem causing prodigious mortality and morbidity, enormous health care expenditure, and trimmed quality of life [1, 2]. It is a complex progressive chronic cardiovascular disease characterized by structural or functional impairment of ventricular filling or ejection of blood [3]. Albeit the epidemiology varies by specific regions, HF affects more than 26 million people worldwide [1, 4]. Data on precise HF prevalence in Africa are currently lacking, however, the astounding burden of HF continues to pose a staggering threat across sub-Saharan Africa including Ethiopia [5, 6]. In the absence of pressing and ample actions, it is also predicted that the number will increase exponentially.

Based on left ventricular ejection fraction (LVEF), the latest international guidelines including the American Heart Association (AHA) [3], and the European Society of Cardiology (ESC) [7] categorize HF patients into three basic forms; HF with reduced EF (HFrEF: EF ≤ 40%), HF with preserved EF (HFpEF: EF ≥ 50%), and HF with mildly reduced EF (HFmEF: EF 40–49%). Implementing optimal guideline-directed medical therapy (GDMT) with the right drug selection, dosage, and target dose is a pivotal step in the management principles of HFrEF [8]. These nascent guidelines [3, 7, 9] highlighted that, in the absence of contraindications, patients with HFrEF should be treated with four frontline medication classes; Angiotensin Receptor Antagonist-Neprilysin Inhibitor (ARNI)/ Angiotensin Converting Enzyme Inhibitors (ACEIs)/ Angiotensin Receptor Blockers (ARBs), Mineralocorticoid Receptor Antagonist (MRA), Beta-blockers, and Sodium-Glucose Transporter-2 (SGLT2) inhibitors. Despite the presence of plenty of cardiovascular medications in today's global market, the utilization and attainment of optimal doses remain a thought-provoking issue [10–13].

Large-scale randomized clinical trials and meta-analysis [14–16] have provided unambiguous evidence that individuals with HFrEF benefit clinically from optimal use of evidence-based beta-blockers including symptom improvement, reduction in hospitalizations, morbidity and mortality, induction in LV reverse remodeling, and increased survival and quality of life. Notwithstanding, the only evidence-based beta-blockers having such cardiovascular mortality and survival benefits are Carvedilol, Metoprolol succinate, and Bisoprolol. Recommended target doses in clinical trials include 200 mg of Metoprolol Succinate, 10 mg of Bisoprolol, and 50 mg of Carvedilol [3].

In the management principles of HFrEF, beta-blockers should be initiated at a low dose, and slowly titrated till the desired target doses are achieved. In special situations where target doses cannot be attained, maintaining the highest tolerated dose is strongly advocated [17, 18]. Nonetheless, to obtain the maximum prognostic benefit from this class of drugs, adequate and timely titration is required and thus a doubling of the dose every 2 weeks is mandatory [19, 20].

Although extensive data and professional practice guidelines support the use of beta-blockers in patients with HFrEF, clinicians prescribe these agents to less than 30% of patients who could benefit from them [21]. Furthermore, patients who do receive them sometimes receive a lower dose than shown to be effective in definitive clinical trials [22, 23]. Surprisingly, many healthcare practitioners still seem reluctant to use beta-blockers to their full potential, especially in the presence of comorbidities that are neither cardiovascular nor non-cardiovascular [21]. Underuse and sub-optimal dosing of beta-blockers compromise its cardiovascular morbidity and mortality reduction role, eventually leading to clinical apparent dire consequences [20].

To date, few observational studies [8, 10–12] have explored the utilization and dose optimization of beta-blockers across various regions in Africa, notably in Ethiopia. These studies demonstrated that longer duration of treatment, absence of peripheral edema, presence

of comorbidities, prior hospitalization, and diuretic use were either positively or negatively associated with beta-blocker use. However, the Northeast Amhara region of Ethiopia remains unexplored in this context, lacking any prior investigations. Existing studies are predominantly single center with limited sample sizes and focus on sociodemographic variables, omitting various disease and treatment-related variables affecting under-utilization. Hence, this study adopts a multi-center approach to specifically address these gaps and provide a comprehensive analysis. In view of addressing these knowledge gaps, this study assessed the patterns of beta-blocker use and dose optimization practices, as well as their influencing factors, among patients with HFrEF at the ambulatory clinics of DCSH and BMH. This evaluation was conducted in light of the latest AHA guidelines recommendation and took place in Dessie, Northeast Amhara, Ethiopia.

Method

Study setting, study design, and study period

A hospital-based cross-sectional multi-center study was conducted from February 01 to July 30, 2024, at the ambulatory care clinics of DCSH and BMH, Dessie, Northeast Ethiopia. Dessie is a town located in the Amhara region of northeast Ethiopia, 400 km away from Addis Ababa. The total population of the town is estimated to be 151,094, of which 78,203 are females. In Dessie town, there are 8 public health centers, one comprehensive specialized hospital, and one district hospital serving nearly 9 million people annually. Both DCSH and BMH feature a range of wards and outpatient clinics, including dedicated outpatient chronic care clinics that offer a broad spectrum of healthcare services [24]. These clinics provide comprehensive treatment and follow-up care. Specifically, the ambulatory clinics at DCSH and BMH deliver cardiac services mostly twice a week (DCSH on Mondays and Thursdays; BMH on Mondays and Wednesdays). On average, the clinics accommodate approximately 30 HFrEF patients daily at DCSH and 20 patients daily at BMH for follow-up visits.

Population

All adult patients with HFrEF attending the ambulatory care clinics at DCSH and BMH constituted the source population. Within this group, those who met the specified inclusion criteria at each hospital were considered the study population.

Eligibility criteria

Adult patients aged ≥ 18 years with an echocardiographically confirmed diagnosis of HFrEF (EF ≤ 40%) who had been on regular follow-up for at least 6 months were included in the study. Patients with precautions and contraindications to the utilization of beta-blockers including bradycardia, hypotension, peripheral vascular diseases, second and third-degree atrioventricular-block, and decompensated HF, chronic obstructive pulmonary disease (COPD), patients with critical illness, and incomplete medical records were excluded.

Sample size calculation and sampling technique

The sample size was determined using a single population proportion formula, incorporating a 95% confidence level, a 5% margin of error, and an estimated 21% proportion of beta-blocker underuse derived from a previous study conducted at Tikur Anbessa Specialized Hospital [10]. This calculation yielded a required sample size of 255 HFrEF patients. Proportional allocation was then executed based on the distribution of patients with HFrEF at each participating hospital during the study period, with 1440 patients at DCSH and 960 patients at BMH. Consequently, 153 patients were selected from DCSH and 102 from BMH. Of the 255 patients initially approached, 55 were excluded from each hospital due to contraindications to beta-blockers (28 from DCSH and 17 from BMH) or incomplete medical records (10 from DCSH and 5 from BMH). Thus, the final analysis included 200 patients, comprising 120 from DCSH and 80 from BMH. A simple random sampling technique was employed to select study participants who fulfilled the stated inclusion criteria. The sampling framework for the study was established using the Medical Referral Clinic (MRC) registration logbook from DCSH and the nursing appointment logbook from BMH. Patients were recruited randomly based on these frameworks.

Study variables

Dependent variables (1) Beta-blocker utilization (2) Dose optimization of Beta-blocker.

Independent variables: Socio-demographic characteristics: age, sex, and residence. Disease-related characteristics: causes of HF, stages of HF, NYHA classification of HF, duration of HF, family history, presence and type of comorbidities, hospitalization history, and baseline and follow-up blood pressure and pulse rate values. Treatment-related characteristics: duration since starting HF therapy, total number of prescribed medications, and medication types.

Data collection procedures

The medical record number (MRN) of HFrEF patients who had regular follow-up visits at least for the last 6 months was retrieved from the logbooks of each hospital and taken to the respective hospitals' card room to be traced by the experienced staff of the card room. Patients' medical records were thoroughly reviewed to gather necessary sociodemographic, disease, and treatment-related data. A data abstraction checklist designed after

reviewing related pertinent literatures and guidelines was used to collect the data by two master (MSc) holder clinical pharmacists.

Data analysis

Initially, the data were entered into and cleaned in Epi Info version 4.6.0.2. Subsequently, the data was exported and analyzed in Statistical Package for the Social Sciences (SPSS) version 27. Frequencies and percentages were performed for all categorical variables, while mean ± standard deviation and/or median with interquartile range (IQR) for all continuous variables, as appropriate. First, multicollinearity was ascertained to test the correlation among the predictor variables using the variance inflation factor (VIF). For precluding collinearity, a VIF < 10 was implemented as a cut point. A binary logistic regression analysis was conducted to assess the association between beta-blocker use and all the predictor variables and to identify potential candidates for multivariable analysis. All predictor variables with p-value < 0.25 in the univariable binary logistic regression analysis were re-entered into a multivariable binary logistic regression model to identify predictors of beta-blocker use. Statistical significance was declared at p-value < 0.05.

Operational definitions

Guideline-recommended beta-blocker therapy is considered if patients with HFrEF are prescribed either of these three beta-blockers: Metoprolol Succinate/ Carvedilol/ Bisoprolol. Non-guideline recommended beta-blocker therapy is defined if patients with HFrEF are prescribed beta-blockers other than Metoprolol Succinate or Carvedilol or Bisoprolol. Beta-blocker underutilization is conceived if guideline-recommended beta-blockers are not used in the absence of contraindication. Suboptimal use of beta-blockers is exhibited by HFrEF patients if the optimal dose of guideline-recommended beta blocker is not used in the absence of contraindication while optimal use of beta-blockers is delineated if the optimal dose of guideline-recommended beta-blocker is used. Beta-blocker use can be considered appropriate if administered in the absence of contraindications, and its absence is deemed appropriate when contraindications are present. The guideline recommended daily target doses were defined as 200 mg for Metoprolol Succinate, 50 mg for Carvedilol, and 10 mg for Bisoprolol. This recommendation is based on the latest AHA guideline (2022) for the diagnosis and treatment of acute and chronic heart failure [3].

Results

Baseline socio-demographic and clinical-related characteristics of HFrEF patients

In total, 200 HFrEF patients (120 patients from DCSH, and 80 patients from BMH) were included in the study. The majority of the patients (68.5%) were less than 65 years of age. Out of the total studied patients, 105(52.5%) were males, and 119(59.5%) visited the respective hospital clinics from areas outside Dessie. Roughly, more than half of the patients (56.5%) had NYHA class III HF at baseline. The most frequently reported underlying causes of HF were dilated cardiomyopathy (46.5%), and coronary artery disease (40.5%). About 178(89%) patients presented with one or more comorbid medical conditions. Of these, ischemic heart disease (53.5%) and hypertension (36.5%) took the lion's share (Table 1).

Pertinent baseline laboratory findings of HFrEF patients

Roughly, 179 (89.5%) patients' EF was within the range of 25–40%, with a mean of 34.8%. About 171(85.5%) patients had a pulse rate value between 55 and 100 beats per minute. The majority of the patients had a baseline systolic blood pressure (SBP) of less than 120mmHg (43.5%) and a diastolic blood pressure (DBP) of less than 80mmHg (49.0%) (Table 2).

Treatment-related characteristics of HFrEF patients

Approximately half of the HFrEF patients (52.5%) were taking five or more medications. The top three frequently prescribed classes of medications besides beta-blockers utilized by HFrEF patients were other pertinent drugs including secondary prevention agents like statins, aspirin, and warfarin (82.0%), ACEIs (78.0%), and loop diuretics (72.0%) (Table 3).

Utilizations of beta-blocker in HFrEF patients

Out of the total, 88% of the patients took beta-blockers. About 15% of the patients were not receiving beta-blockers whereas they are indicated. Among those who received beta-blockers, about 170(96.5%) were on guideline-recommended beta-blockers. Of patients who utilized beta-blockers, roughly two-thirds of them (65%) received Bisoprolol followed by Metoprolol (29%), and Carvedilol (3%). Of those who received Metoprolol, 4% were put on unspecified types of Metoprolol and the rest were on Metoprolol succinate (96%). Amidst beta-blocker users, changing of beta-blocker was encountered at least once in 35% of patients in between follow-ups (Table 4).

Dose optimization of beta-blockers in HFrEF patients

Out of the total 170 patients who were on guideline-recommended beta-blockers, only 13(7.6%) patients received the guideline-recommended target dose. The

Table 1 Baseline socio-demographic and clinical related characteristics among HFrEF patients in Northeast Ethiopia, from February 1-July 30, 2024 ($n=200$)

Variables	Category	Frequency	Percent
Sex	Male	105	52.5
	Female	95	47.5
Age	< 65	137	68.5
	≥ 65	63	31.5
Residence	Dessie	81	40.5
	Outside Dessie	119	59.5
Baseline NYHA Class of HF	Class II	23	11.5
	Class III	113	56.5
	Class IV	64	32.0
Underlying Causes of HF	Dilated Cardiomyopathy	93	46.5
	Coronary Artery Disease	81	40.5
	CRVHD	17	8.5
	Hypertensive Heart Disease	4	2.0
	Congenital Heart Disease	4	2.0
	Others*	1	0.5
Hx of Hospitalization in the past 1year	No	96	48.0
	Yes	104	52.0
No of Hospitalization in the past 1year	Never	96	48.0
	Once	80	40.0
	Two or More	24	12.0
Presence of Comorbidity	No	22	11.0
	Yes	178	89.0
Type of Comorbidity	Hypertension	73	36.5
	Ischemic Heart Disease	107	53.5
	Atrial Fibrillation	39	19.5
	Valvular Heart Disease	26	13.0
	Kidney Disease	26	13.0
	Thyroid Disease	13	6.5
	Diabetes Mellitus	12	6.0
	Stroke	5	2.5
	Neurologic Disorder	4	2.0
	Others**	52	26.0

NYHA: New York Heart Association, HF: Heart Failure: CRVHD; Chronic Rheumatoid Valvular Heart Disease, Hx: History, No: Number, Others*: Corpulmonale, Others**: Dyslipidemia, HIV/AIDS, Cancer

Table 2 Baseline pertinent laboratory findings among HFrEF patients in Northeast Ethiopia, from February 1-July 30, 2024 ($n=200$)

Variables	Category	Frequency	Percent
Baseline Ejection Fraction [34.79 ± 5.83]	≤ 25%	21	10.5
	25–40%	179	89.5
Baseline Pulse Rate Category	55–100 beat/minute	171	85.5
	≥ 100 beat/minute	29	14.5
Baseline Systolic Blood Pressure Category	< 120 mmHg	87	43.5
	120–129 mmHg	34	17.0
	130–139 mmHg	22	11.0
	≥ 140 mmHg	57	28.5
Baseline Diastolic Blood Pressure Category	< 80 mmHg	98	49.0
	80–89 mmHg	60	30.0
	≥ 90 mmHg	42	21.0

Table 3 Baseline treatment-related characteristics among HFrEF patients in Northeast Ethiopia, from February 1-July 30, 2024 ($n=200$)

Variables	Category	Frequency	Percent
Duration Since Start of HF Treatment	≤ 2years	160	80.0
	> 2years	40	20.0
Total Number of Prescribed Medications	< 5	95	47.5
	≥ 5	105	52.5
Class of Medication Received Other Than Beta-blockers	ARBs	11	5.5
	ACEIs	156	78.0
	Diuretics	144	72.0
	MRAs	122	61.0
	Other pertinent drugs*	164	82.0

ARBs: Angiotensin Receptor Blockers, ACEIs: Angiotensin Converting Enzyme Inhibitors, MRAs: Mineralocorticoid Receptor Antagonists, Other pertinent drugs*: secondary prevention agents like statin, aspirin, clopidogrel, warfarin, digoxin etc

target dose was achieved only in patients utilizing bisoprolol. The mean daily doses of metoprolol succinate, carvedilol, and bisoprolol that were taken by the patients were 27.9 mg, 10.0 mg, and 4.8 mg, respectively (Table 5).

Factors affecting beta-blocker utilization in HFrEF patients

Before conducting a multivariate binary logistic regression, bivariate binary logistic regression was performed on selected socio-demographic, clinical, and treatment-related characteristics to ascertain variables candidate for multivariate binary logistic regression. Overall, 13 variables were found to be candidates at a *P*-value of ≤ 0.25. However, in the final multivariate regression model, only four variables were found to have a statistically significant association with beta-blocker utilization. These included male sex, ACEI use, taking multiple medications, and use of other pertinent drugs. Gender-wise, male patients were 92% less likely to use beta-blockers as compared to their counterparts [AOR: 0.08, 95% CI: 0.01–0.47, $p=0.005$]. Patients who were taking ACEIs had 15 times higher odds of utilizing beta-blockers as compared to patients not taking ACEIs [AOR: 15.48, 95% CI: 2.11-113.54, $p=0.008$)]. Moreover, patients who were taking other pertinent drugs (including secondary prevention agents) were 95% less likely to utilize beta-blockers than those who were not ingesting other pertinent drugs [AOR: 0.05, 95% CI: 0.01–0.98, $p=0.048$)]. Patients who were taking 5 or more prescribed medications had 7 times higher odds of utilizing beta-blockers as compared to patients taking less than 5 medications [AOR: 7.12, 95%CI: 1.54–33.02, $p=0.012$] (Table 6).

Factors affecting sub-optimal use of beta-blockers

A total of ten variables were found to be candidates at a *P*-value of ≤ 0.25 in bivariate logistic regression. However,

Table 4 Beta-blocker utilization pattern among HFrEF patients in Northeast Ethiopia, from February 1-July 30, 2024

Variables	Category	Frequency	Percent
Overall Beta-blocker Usage Trend (*n* = 200)	No	24	12.0
	Yes	176	88.0
Beta-blocker Category (*n* = 176)	Guideline Recommended	170	96.5
	Non-Guideline Recommended	6	34.0
Appropriateness of Beta-blocker Use (*n* = 200)	Appropriate	171	85.5
	Inappropriate	29	14.5
Type of Beta-Blocker Received (*n* = 176)	Bisoprolol	114	65.0
	Metoprolol	51	29.0
	Carvedilol	5	3.0
	Atenolol	4	2.0
	Propranolol	2	1.0
Type of Metoprolol (*n* = 51)	Unspecified	2	4.0
	Metoprolol Succinate	49	96.0
Frequency of Beta-Blocker Change (*n* = 176)	Never	115	65.0
	Once	48	27.0
	Two and more	13	7.4

Table 5 Dose optimization of beta-blockers among HFrEF patients in Northeast Ethiopia, from February 1-July 30, 2024

Variables	Evidence-Based Beta-Blocker Type		
	Metoprolol Succinate	Carvedilol	Bisoprolol
Number of patients on medication (%) [*n* = 170]	51(30)	5(3)	114(67)
Mean (SD) daily dose (mg/d)	27.94 ± 13.36	10.00 ± 8.38	4.81 ± 2.21
Minimum dose used (mg/d)	12.5	6.25	2.5
Maximum dose used (mg/d)	50	25	10
Number of patients on optimal/target dose (%)	0(0)	0(0)	13(11)
Number of patients on 50-<100 target dose (%)	0(0)	1(20)	65(57)
Number of patients on < 50% target dose (%)	51(100)	4(80)	36(32)

Key: Target dose of Metoprolol Succinate ≥ 200 mg, Bisoprolol ≥ 10 mg and Carvedilol ≥ 50 mg

in the final multivariate regression model, only one variable was found to have a statistically significant association with beta-blocker sub-optimal use. This variable was baseline ejection fraction of 25–40% [AOR: 5.44, 95% CI: 1.09–27.12, $P = 0.039$)]. Patients with baseline ejection fraction of 25–40% had five times higher odds of developing sub-optimal beta-blocker use compared to those who presented with a baseline ejection fraction of ≤ 25% (Table 7).

Discussion

This is one of the few observational studies conducted in Ethiopia and the first of its kind in the region encompassing a multicenter approach that assessed the utilization pattern and dose optimization practice of beta-blockers along with its multifaceted socio-demographic, clinical, and treatment-related determinants.

The present study found 88% beta-blocker utilization and 15% of patients who were indicated for beta-blockers were not receiving them. This finding is higher compared to the two studies conducted in France reporting [65%] [25] and [69%] [26], a study done in Zambia [58.4%] [11], previous studies carried out in Jimma [67%] [12], and Addis Ababa [79%] [10], Ethiopia. The distinction of beta-blocker utilization among various studies could be attributed to differences in the study settings and population. The possible reason behind the higher beta-blocker use in this study could be a result of physician's better adherence to recommended clinical practice guidelines within the institution. Furthermore, it could be a result of improved drug availability and healthcare access. Although beta-blockers are pivotal drugs in the treatment of HFrEF, unless contraindicated, 12% of the patients in this study did not receive beta-blockers. Similarly, many studies [10, 25, 26] have shown that beta-blockers are undeniably underutilized. Among those patients who took beta-blockers, precisely 96.6% were on guideline-recommended beta-blockers. This result is in line with a study done in Lusaka, Zambia [11] that underscored 95% utilization of guideline-recommended beta-blockers, but it is higher than the two studies conducted in Jimma and Addis Ababa [10, 12], Ethiopia reporting 34.2%, and 16.2%, respectively. The higher magnitude rate noted in this study could be ascribed to adequate physician knowledge regarding the prodigious impact of prescribing evidence-based beta-blockers and strict adherence to the clinical practice guidelines.

In this study, 2% of the patients were receiving atenolol, which is not guideline recommended beta-blocker. This result is lower than the study conducted in Lusaka, Zambia which unveiled 5% use of Atenolol [11], studies from Jimma [12] and Addis Ababa [10] revealing 65.8% and 8.4%. Likewise, this difference could be explained by the eminent availability of the guideline-recommended beta-blockers at affordable prices for patients residing in the study setting. Additionally, this study found a 1% propranolol utilization which is unique from the previously conducted studies [10, 16] in Ethiopia. The main justification behind this issue may be related to the presence of compelling comorbidity like thyrotoxicosis amidst patients, driving physicians to preferably prescribe non-selective beta-blockers in view of ameliorating adrenergic symptoms caused by the disease.

In the current study, approximately two-thirds of patients (67%) received Bisoprolol then followed by Metoprolol (29%). This finding is higher compared to the study done in Addis Ababa spotlighting lower Bisoprolol (5%) and higher Metoprolol (81%) utilization [10].

Table 6 Factors affecting beta-blocker utilization among HFrEF patients in Northeast Ethiopia, from February 1-July 30, 2024 ($n=200$)

Variables	Category	Beta-blocker use		COR, 95%CI	*P*-value	AOR, 95%CI	*P*-value	X^2 (*P*-value*)
		No n(%)	Yes n(%)					
Sex	Female	5(20.8)	90(51.1)	1	1	1	1	**7.777 (0.005)**
	Male	19(79.2)	86(48.9)	0.25 (0.09–0.70)	0.009	0.08 (0.01–0.47)	**0.005**	
Presence of AF	No	22(91.7)	139(79)	1	1	1	1	2.166 (0.141)
	Yes	2(8.3)	37(21)	0.36 (0.66–13.01)	0.158	3.70 (0.49–27.44)	0.201	
Presence of VHD	No	19(79.2)	155(88.1)	1	1	1	1	1.480 (0.224)
	Yes	5(20.8)	21(11.9)	0.52 (0.17–1.52)	0.231	0.28 (0.06–1.26)	0.097	
Comorbidity	No	14(58.3)	134(76.1)	1	1	1	1	0.415 (0.519)
	Yes	10(41.7)	42(23.9)	0.44 (0.18–1.06)	0.067	0.73 (0.04–15.16)	0.839	
Baseline NYHA Class	Class II	5(20.8)	18(10.2)	1	1	1	1	3.386 (0.184)
	Class III	10(41.7)	103(51.5)	2.86 (0.88–9.35)	0.082	3.95 (0.53–29.48)	0.180	
	Class IV	9(37.5)	55(31.3)	1.69 (0.50–5.73)	0.394	1.95 (0.25–15.46)	0.529	
ACEIs Use	No	13(54.2)	31(17.6)	1	1	1	1	16.44 (< 0.001)
	Yes	11(45.8)	145(82.4)	5.53 (2.27–13.48)	0.000	15.48 (2.11–113.5)	**0.007**	
ARBs Use	No	19(79.2)	170(96.6)	1	1	1	1	12.337(< 0.001)
	Yes	5(20.8)	6(3.4)	0.13 (0.37–0.48)	0.002	0.37 (0.02–6.33)	0.492	
MRAs Use	No	14(58.3)	64(36.4)	1	1	1	1	4.285 (0.038)
	Yes	10(41.7)	112(63.6)	2.45 (1.03–5.83)	0.043	1.59 (0.35–7.12)	0.547	
Other Pertinent Drug Use	No	1(4.2)	35(19.9)	1	1	1	1	3.536 (0.060)
	Yes	23(95.8)	141(80.1)	1.75 (0.02–1.34)	0.094	0.05 (0.01–0.98)	**0.048**	
Baseline pulse rate (beat per minute) category	55–100	23(95.8)	148(84.1)	1	1	1	1	2.439 (0.125)
	≥ 100	1(4.2)	28(15.9)	4.35 (0.56–33.55)	0.158	8.33 (0.45–153.7)	0.154	
Baseline systolic blood pressure category (mmHg)	< 120	10(41.7)	77(43.8)	1	1	1	1	5.284 (0.152)
	120–129	1(4.5)	33(18.8)	4.29 (0.53–34.85)	0.174	6.83 (0.38–122.2)	0.192	
	130–139	5(20.8)	17(9.7)	0.44 (0.13–1.46)	0.180	0.47 (0.05–4.48)	0.513	
	≥ 140	8(33.3)	49(27.8)	0.79 (0.29–2.15)	0.653	0.55 (0.04–7.66)	0.654	
Baseline diastolic blood pressure category (mmHg)	< 80	11(45.8)	87(49.4)	1	1	1	1	2.795 (0.247)
	80–89	5(20.8)	55(31.3)	1.39 (0.46–4.22)	0.560	1.06 (0.14–8.18)	0.953	
	≥ 90	8(33.3)	34(19.3)	0.54 (0.19–1.45)	0.220	0.74 (0.06–9.27)	0.814	
Number of medications	< 5	18(75)	77(43.8)	1	1	1	1	8.271 (0.004)
	≥ 5	6(25)	99(56.3)	3.86 (1.46–10.18)	0.006	7.12 (1.54–33.02)	**0.012**	

AF: Atrial Fibrillation, VHD: Valvular Heart Disease, NYHA: New York Heart Association, ACEI: Angiotensin Converting Enzyme Inhibitors, ARB: Angiotensin Receptor Blocker, MRA: Mineralocorticoid Receptor Antagonist, X2: Pearson chi-square, P-value*: p-value for the chi-square test

This may be owing to the ease of availability and lower price of Bisoprolol than Metoprolol. This study revealed that among patients who were on Metoprolol, 96% were on Metoprolol succinate. This result is higher than the study done in Addis Ababa which revealed 46% of Metoprolol succinate utilization [10]. Moreover, roughly 4% of the patients in this study were on an unspecified type of Metoprolol in which we could not distinguish whether it was succinate or tartrate.

According to this study, despite the massive utilization rate, only 13(7.6%) patients were on optimized doses. This result is congruent with the report of the European Heart Journal [13] which highlighted that 12% of the patients were at the recommended target doses of beta-blockers. However, this finding is lower compared to the study conducted in France [25] and Addis Ababa [10] which unveiled 18% and 15.7% dose optimization practices, respectively. In fact, it is higher than the study done in Zambia and Jimma which found 0% and 3% dose optimization of beta-blockers [11, 12].

The findings of this study spotlighted that nearly one-third of patients encountered frequent changes in beta-blockers in between follow-ups. This could be a hindering factor in applying standardized dose titration protocols and dose optimization. It has been reported that while health practitioners may have adequate knowledge of beta-blocker use, they may not be aware of how to titrate their dose to their recommended maximum doses [27]. If beta-blockers are to provide the maximum clinical benefit, health practitioners should render the optimal doses [28]. This has been observed in most clinical trials [29] where patients received optimal doses of beta-blockers. Nonetheless, despite this evidence, our study showed that only 7.6% of patients received optimal doses.

The current study found four variables as predictors for the utilization of beta-blockers which include male

Table 7 Factors affecting sub-optimal beta-blocker use among HFrEF patients in Northeast Ethiopia, from February 1-July 30, 2024 ($n=171$)

Variables	Category	Beta-blocker use		COR, 95%CI	*P*-value	AOR, 95%CI	*P*-value
		Optimal n(%)	Sub-optimal n(%)				
Age	< 65	12 (92.3)	103 (65.2)	1	1	1	1
	≥ 65	1 (7.7)	55 (34.8)	6.41 (0.81–50.58)	0.078	4.14 (0.46–37.56)	0.206
Residence	Dessie	3 (23.1)	65 (41.1)	1	1	1	1
	Outside Dessie	10 (76.9)	93 (58.9)	0.43 (0.11–1.62)	0.212	0.27 (0.05–1.41)	0.121
Presence of AF	No	8 (61.5)	127 (80.4)	1	1	1	1
	Yes	5 (38.5)	31 (19.6)	0.39 (0.12–1.28)	0.120	0.44 (0.08–2.28)	0.325
Baseline NYHA Class	Class II	3 (23.1)	15 (9.5)	1	1	1	1
	Class III	7 (53.8)	93 (58.9)	2.66 (0.62–11.42)	0.189	3.33 (0.38–29.02)	0.276
	Class IV	3 (23.1)	50 (31.6)	3.33 (0.61–18.27)	0.165	5.49 (0.43–70.85)	0.192
Ejection Fraction	≤ 25%	6 (46.2)	28 (17.7)	1	1	1	1
	25–40%	7 (53.8)	130 (82.3)	3.98 (1.24–12.75)	0.020	5.44 (1.09–27.12)	**0.039**
BB Change	No	6 (46.2)	105 (66.5)	1	1	1	1
	Yes	7 (53.8)	53 (33.5)	0.43(0.14–1.35)	0.150	0.38 (0.09–1.65)	0.197
ARBs Use	No	11 (84.6)	154 (96.5)	1	1	1	1
	Yes	2 (15.4)	4 (2.5)	0.14 (0.02–0.87)	0.035	0.093 (0.01–2.94)	0.178
MRAs Use	No	1 (7.7)	60 (38.0)	1	1	1	1
	Yes	12 (92.3)	98 (62.0)	0.14 (0.02–1.07)	0.058	0.18 (0.02–2.23)	0.183
Other Pertinent Drug Use	No	7 (53.8)	28 (17.7)	1	1	1	1
	Yes	6 (46.2)	130 (82.3)	5.42 (1.69–17.35)	0.004	1.93 (0.12–31.41)	0.644
No of Prescribed Medications	< 5	8 (61.5)	64 (40.5)	1	1	1	1
	≥ 5	5 (38.5)	94 (59.5)	2.35 (0.74–7.51)	0.149	1.11 (0.09–13.98)	0.953

BB: Beta-blockers, ARB: Angiotensin Receptor Blocker, MRA: Mineralocorticoid Receptor Antagonist, No: Number, AF: Atrial Fibrillation, NYHA: New York Heart Association

gender, ACEI use, taking multiple medications, and ingesting other pertinent drugs. The fact that ACEI use is associated with beta-blocker use is in keeping with the study conducted in Germany and by Chang et al.. which revealed that the use of ACEIs/ARBs increased the likelihood of using beta-blockers, and vice versa [30, 31]. On the other hand, being male negatively affects the utilization of beta-blockers as evidenced by the findings of this study. This is consistent with a recent AHA report that revealed that female patients with HFrEF had lower use across every GDMT class and lower use of optimal GDMT at each time point of follow-up [32]. Notwithstanding, this result is contrary to a nascent analysis from the REPORT-HF registry [29] that demonstrated lower rates of beta-blockers, MRAs, and RAAS inhibitor use at discharge among female patients with HFrEF. In a longitudinal study of young US veterans with HFrEF, Dhruva et al. [33], displayed those female patients had 46% lower odds of receiving at least one HF medication at follow-up. Furthermore, the lower utilization habit observed in this study among patients taking other pertinent drugs like secondary prevention agents (aspirin, clopidogrel, and warfarin) could be colligated to lesser progression of the disease slowing the clinicians urge of prescribing cardiovascular drugs having survival benefits. Additionally, the fact that ingesting 5 or more medications have a positive association with beta-blocker utilization may be due to the presence of comorbidities that eventually acts as a compelling indication to use of polypharmacy incorporating beta-blockers in the regimens. Concerning contributing factors associated with beta-blocker under use, the present study revealed three predictors including female gender, ACEI use, and ingesting five or more prescribed medications which are negatively associated.

The current study demonstrated that a baseline ejection fraction of 25–40% is positively associated with sub-optimal beta-blocker use. The association between a baseline EF of 25–40% and sub-optimal beta-blocker use can be attributed to several factors. EF < 25% is often perceived as indicative of more severe heart failure, prompting clinicians to prioritize aggressive treatment, including optimized beta-blocker use. In contrast, patients with EF between 25 and 40% may be considered at lower immediate risk, leading to less intense management and possible underuse or suboptimal dosing of beta-blockers. Clinical guidelines may offer clearer recommendations for severe heart failure, while intermediate EF ranges receive less definitive guidance, contributing to variability in treatment. Additionally, physicians may have greater comfort in managing more severe cases, and individualized treatment plans for moderate EF patients might focus more on other therapies. Tolerability concerns and regional practice variations also influence prescribing patterns,

further supporting the trend of sub-optimal beta-blocker use in this group.

This study acknowledges some important limitations that should be taken into account. First, the lack of digitization and organization of the patients' medical records posed significant challenges in gathering all the necessary information. As a result, critical patient-related factors, such as educational background, body mass index, marital status, employment, and economic conditions, were not adequately captured. Second, while the study was conducted in a multi-center setting, the political unrest in the region led to a reduced number of patients with HFrEF being available for analysis during the study period. Third, although the research aimed to evaluate various factors influencing the use of beta-blockers, it did not investigate healthcare professionals' knowledge regarding beta-blocker administration and dose adjustment. Consequently, the reasons behind the failure to initiate or appropriately increase doses of guideline-recommended beta-blockers were not identified. Fourth, due to the cross-sectional design of the study, establishing definitive cause-and-effect relationships for many of the observed associations is not feasible. Finally, caution should be exercised when extrapolating the findings of this study to other countries, as variations in study characteristics, disease prevalence, healthcare systems, and methodologies may affect the results. Despite these limitations, this study contributes valuable insights into the patterns of beta-blocker utilization and dose optimization in patients with HFrEF in the region.

Conclusion

Although most patients with HFrEF were prescribed evidence-based beta-blockers, only a limited number reached the optimal dosing levels. ACEIs use and taking multiple medications were positively associated with beta-blocker use while the ingestion secondary prevention agents, and male gender were negatively associated with beta-blocker use. An EF of 25–40% is positively associated with sub-optimal beta-blocker use. It is crucial to align clinical practice with the latest guidelines, prioritize ongoing research, and enhance educational efforts for both healthcare providers and patients. By doing so, it is possible to significantly improve the effective utilization of beta-blockers, ultimately leading to better patient outcomes in this region. Continuous engagement and collaboration among all stakeholders will be vital in bridging the gap between current practices and optimal care standards.

Abbreviations

BMH	Boru Meda General Hospital
DCSH	Dessie Comprehensive Specialized Hospital
EF	Ejection Fraction
GDMT	Guideline Directed Medical Therapy
HF	Heart failure
HFrEF	Heart Failure with Reduced Ejection Fraction
LVEF	Left Ventricular Ejection Fraction
MRC	Medical Referral Clinic
NYHA	New York Heart Association
RAAS	Renin Angiotensin Aldosterone System

Supplementary Information

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Supplementary Material 1

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Author contributions

M.H, O.S.M., and M.Y.G. conceptualized and designed the study, wrote the original manuscript, and performed analysis and interpretation of data. T.K.E, N.A.T, M.B.D., T.F.W, and T.S assisted in data analysis and manuscript evaluation. M.H. edited and wrote the final version of the manuscript. All authors have made an intellectual contribution to the work and have approved the final version of the manuscript for submission.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval

Ethical approval was sought from the Ethical Review Board (ERB) of the School of Pharmacy, College of Medicine and Health Sciences (CMHS), Wollo University (16/01/2024; Reference Number: CMHS 964/20/2024). Subsequent permissions were granted from DCSH and BMH administration and related concerned bodies before commencing actual data collection by using letter of cooperation. Informed consent was obtained from each participant. The study protocol was performed in accordance with the Declaration of Helsinki. All obtained data were treated confidentially.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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