

Utilization and Optimization of Beta-Blockers on Heart Failure Patients with Reduced Ejection Fraction (HFrEF) at Cardiac Clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: A Cross-Sectional Study

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Introduction: Optimal use of guideline-directed medical therapy (GDMT) is an important strategy in preventing cardiovascular morbidity and mortality from heart failure (HF). The use of beta blockers (BBs) is an important pillar of GDMT. The utilization and optimization of BBs are understudied in Ethiopia.

Patients and Methods: A hospital-based cross-sectional study was conducted at the cardiology clinic of Tikur Anbessa Specialized Hospital on the utilization and optimization of BBs in the management of HFrEF patients from August 2022 to October 2022 G.C. Patients with a baseline HFrEF diagnosis and who had follow up for at least six months were included in the study. Patients were recruited during their routine clinic visit using systematic random sampling and consent was obtained from all participants. A total of 271 participants were included in this study. The optimal dose of BBs was predefined according to the 2021 European Society of Cardiology HF guideline. Data were collected through patients interview and reviewing the patient's electronic medical records. The Collected Data was analysed using SPSS version 26.0.

Results: The study found BB utilization in 214 (79%) patients. Among the patients taking BBs only 102 (37.6%) participants were on guideline-recommended BBs. The other 41% of patients taking BBs were on Metoprolol tartrate (34.7%) and Atenolol (6.6%), which are not guideline-recommended BBs and these findings signify underutilization of guideline-recommended BBs. Duration of treatment follow-up for more than 1 year, absence of peripheral edema, presence of atrial fibrillation and diuretic use were positively associated with BB utilization.

Conclusion: Even though guideline-recommended BB at optimal doses exerts a clinical benefit, this study points out guideline-recommended BBs are underutilized and more importantly used at suboptimal doses among the study participants. To achieve the desired clinical benefit, physicians should attempt to provide guideline-recommended BBs at the optimum or maximum tolerable dose.

Keywords: heart failure, beta blocker, Tikur Anbessa Specialized Hospital, optimal therapy

Introduction

According to the 2021 universal definition of heart failure, HF is a clinical syndrome with cardinal symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated biomarkers (natriuretic peptide levels) and/or objective evidence of pulmonary or systemic congestion.¹ Heart failure is accompanied by progressive left ventricular dilatation and adverse cardiac remodelling. This process is the culmination of a complex series of transcriptional, signalling, structural, electrophysiological, and functional events occurring within the cardiac

myocyte.^{2,3} The diagnosis of HFrEF requires the fulfilment of the 2021 universal definition of HF and a reduced ejection fraction (LVEF $\leq$ 40%) that is most usually obtained by echocardiography.⁴

Globally, HF affects more than 26 million people, albeit the epidemiology varies by region.⁵ Sub-Saharan Africa lacks population-based incidence and prevalence. According to the published hospital prevalence studies, HF accounts for between 9.4% and 42.5% of all medical admissions and between 25.6% and 30.0% of admissions to cardiac units.⁶ There are no studies describing the prevalence or incidence of heart failure in Ethiopia's adult population.⁷ After pneumonia and tuberculosis, HF was the third most common reason for hospitalization, accounting for 16% of all admissions, according to a retrospective research on the pattern of admission and prognosis at Saint Paul's hospital.⁸

Significant morbidity and death, poor functional ability and quality of life, and high expenses are all characteristics of HF. According to the Framingham Heart Study, the death rate in USA after receiving a diagnosis of HF was approximately 10% after 30 days, 20–30% at 1 year, and 45–60% throughout the course of 5 years of follow-up.⁹ In Ethiopia, Non-communicable diseases (NCDs) account for 39% of all-cause of mortality of which, cardiovascular disease accounts for 16%.¹⁰ In a single-centre study in Ethiopia, the in-hospital mortality rate among patients admitted with acute heart failure was 21.29%.¹¹ A prospective observational study done at a tertiary care hospital in Ethiopia on treatment outcomes of acute heart failure showed in-hospital mortality of 17.2%.¹²

The goals of heart failure treatment are to improve their clinical condition, functional capacity, and quality of life, and to prevent the events of hospital readmissions and mortality. According to many guidelines for the treatment of heart failure, an important step in reducing morbidity and mortality from heart failure is to implement optimal guideline-directed medical therapy with the right drug selection, dosage, and target dose to be achieved in HF patients. Hence, unless contraindicated or not tolerated, individuals with HFrEF should be treated with suitable neurohormonal blockers at maximum tolerated doses.^{13–15}

Angiotensin receptor-neprilysin inhibitors (ARNIs), angiotensin receptor blockers (ARBs), angiotensin convertase enzyme inhibitors (ACEIs), beta-blockers, mineral corticoid receptor antagonists, and sodium-glucose co-transporter 2 inhibitors are the four drug classes that makeup GDMT for HFrEF.¹⁶ The beta-adrenergic receptors are G-protein coupled receptors that have a variable distribution. There are three known types of beta receptors, known as beta1 (β_1), beta2 (β_2), and beta3 (β_3). These receptors are activated by norepinephrine and epinephrine. The beta-adrenergic receptors are found in the myocardium and their activation has detrimental effects in patients with chronic HF.^{17,18} BBs reduce morbidity and improve cardiac function. Carvedilol, Metoprolol succinate, and Bisoprolol have been shown to improve survival in multiple randomized trials.^{19–23} The mechanisms of β -blocker effects in heart failure are cardiac protection from β_1 -adrenoceptor overstimulation, antiarrhythmic effects, reduction in heart rate, and positive energetic effects or a combination thereof.²⁴

The use of BB is the cornerstone in the management of HFrEF and one of the three BBs (Carvedilol, Metoprolol succinate, and Bisoprolol) should be initiated in all patients with HFrEF unless contraindicated or not tolerated.¹⁶ In HFrEF beta-blockers should be initiated at a low dose, and titration should be made to achieve the target doses of the beta-blockers. Titration can be made as frequently as 1 to 2 weeks. Achieving the target doses has shown to be effective and tolerable in several clinical trials.^{16,25} Recommended target doses in clinical trials include 200 mg of Metoprolol Succinate, 10 mg of Bisoprolol, and 50 mg of Carvedilol.^{13,19–23} If a target dose is not tolerated, then the highest tolerated dose should be maintained.²⁶

The optimal use of beta blockers has significant mortality and morbidity benefits as shown in several clinical trials.^{19–23} On the other hand, suboptimal use of beta-blockers has been associated with poor treatment outcomes in HF patients.²⁷ Despite having significant morbidity and mortality benefits, beta-blockers are often not seen being utilized in Ethiopia and there is a paucity of data on the standard and optimal use of guideline-recommended beta-blockers in our country. This study looked at the practice of optimal use of beta blockers among patients with HFrEF and remedies the gaps identified.

Materials and Methods

Study Design and Study Setting

We conducted a cross-sectional study at the cardiac referral clinic in Tikur Anbessa Specialized Hospital (TASH) among patients with heart failure with reduced ejection fraction on follow-up from August 2022 to October 2022 G.C. TASH is a university teaching hospital affiliated with Addis Ababa University. It is the largest referral hospital in the country. It provides specialized clinical services through its several departments.

Study Participants

Inclusion Criteria

- Age ≥ 18 years.
- Diagnosis of HF with a baseline left ventricular ejection fraction $< 40\%$.
- On Follow-up for ≥ 06 months.

Exclusion Criteria

- Patients with precautions and contraindications to the use of beta-blockers including:
 - ✓ Hypotension ($< 90/60$ mmHg).
 - ✓ Bradycardia (< 60 beats per minute).
 - ✓ 2nd and 3rd degree AV-block.
 - ✓ Asthma/COPD.
 - ✓ Decompensated heart failure:
- Patients with incomplete medical records.
- Critically ill patients.
- Who cannot provide written consent.

A sample of 294 was calculated by using single population proportion formula based on the results of a study conducted at Jimma University Hospital which revealed 34.2% beta-blocker utilization among patients with HF,²⁸ 95% confidence level, 5% margin of error, and 10% of contingency for nonresponse rate. From a total of 294 participants approached, 23 patients were excluded from the study due to precaution/contraindication to beta-blockers (15), declined consent (3) and incomplete medical record (5).

Data Collection Procedure

Patients were recruited into the study during their routine clinic visit using systematic random sampling. After explaining the purpose of the study, written informed consent was obtained from all study participants. Data were collected through both patient interviews and a review of patient's medical records. Face-to-face interviews were used to gather socio-demographic information and clinical and treatment-related information was gathered from electronic medical record.

Operational Definitions

Guideline-recommended beta-blocker therapy is defined as when HFrEF patients are prescribed Carvedilol, Metoprolol Succinate, or Bisoprolol. Non-guideline recommended beta-blocker therapy is defined as when patients are prescribed beta-blockers other than Carvedilol, Metoprolol Succinate, or Bisoprolol. Underutilization of beta-blocker is defined as when guideline-recommended beta blockers are not used in the absence of contraindication. Suboptimal use is defined as when the optimal dose of guideline-recommended beta blocker is not used in the absence of contraindication. The optimal use of beta-blocker is defined as when the optimal dose of guideline-recommended beta-blocker is used. Guideline recommended daily target doses were defined as 200mg for Metoprolol Succinate, 50mg for Carvedilol and 10mg for Bisoprolol 10mg/day. This is based on 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure guideline.

Data Analysis

The collected data was verified, cleaned, and checked for quality before the analysis. The IBM SPSS Statistics software package version 26.0 was used for the entry of statistical data and analysis. Descriptive statistics was used as a statistical data analysis method and was expressed as frequencies and numbers (percentages %) for categorical variables. The results were summarized by using tables, and figures. Continuous variables were represented as means, standard deviations, and minimum and maximum values, and categorical variables as frequencies. Multicollinearity was assessed among independent variables using the variance inflation factor (VIF) and none was collinear. Univariable logistic regression analysis was performed to determine the association of each independent variable with the utilization of beta-blockers. Furthermore, a multivariable binary logistic regression model was done to identify predictors of beta-blockers

utilization. P-values less than 0.05 are considered to determine the statistical significance of the association and an odds ratio with a 95% confidence interval is used to determine the presence, strength, and direction of association between covariates and the outcome variable.

Ethics Approval and Informed Consent

The ethical clearance of the present study was obtained from the institutional review board department of internal medicine, AAU, CHS. And permission was also obtained from the cardiology unit. Participants including data collectors were also asked for their willingness to participate in the study after explaining the objectives of the study. We fully explained the purpose and protocol of the study to all participants included in the study and written informed consent was obtained from each participant. All the information obtained was held with confidentiality and used only for the intended purpose. Participants' identities will remain confidential. The obtained data was documented and analyzed anonymously. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Results

Sociodemographic Profiles

The mean [$\pm$ standard deviation] age of the participants was $54.1 \pm (13.5)$ with minimum and maximum ages of 18 and 84, respectively. One-third of patients were above the age of 60. Two-thirds participants were male. The majority (83%) of the participants were urban dwellers and 73.8% resided in Addis Ababa.

The Sociodemographic data are shown in [Table 1](#) and [Figure 1](#).

Clinical Characteristics

The majority of participants were having New York Heart Association (NYHA) functional class II (39.1%) and class III (34.7%). About a third, (36%) of patients had had a history of hospitalization and 48 (18%) patients had 2 or more admissions in the past year.

The most common rhythm disturbance was atrial fibrillation, which was found in 33 (12.2%) participants. Three participants had atrial flutter. Ventricular tachycardia (VT) and supraventricular tachycardia (SVT), each identified in 2 participants and 6 participants had documented premature ventricular complexes (PVCs).

Ischemic heart disease (IHD) was the commonest etiology identified in 204 (75.3%) followed by dilated cardiomyopathy (DCM) in 64 (23.6%) participants. Peripartal cardiomyopathy was identified in 3 participants. Documented left ventricular apical thrombus was found in 6 patients among IHD patients during the study period. Degenerative valvular heart disease was found in 13 (5%) and Rheumatic heart disease was found in a single participant.

Table 1 Sociodemographic Characteristics of Study Participants at Cardiac Clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, August 2022 – October 2022

Characteristics		Number (n)	Percentage (%)
Age Category (in years)	18–30	12	4.4
	30–45	63	23.2
	45–60	109	40.2
	>60	87	32.1
Sex	Male	175	64.6
	Female	96	35.4
Residence	Urban	225	83
	Rural	46	17

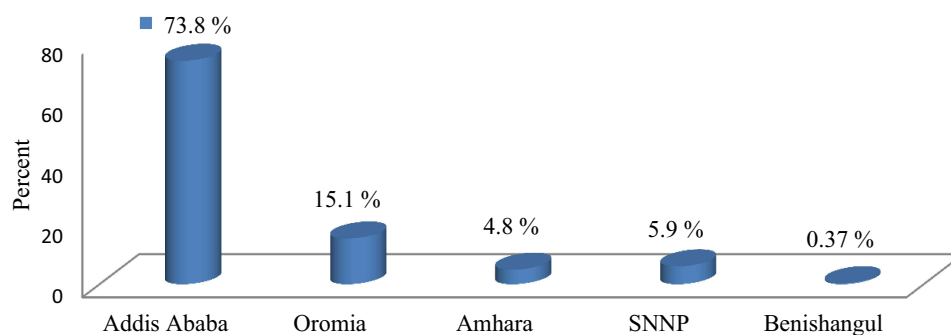


Figure 1 Region distribution of study participants at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, August 2022 – October 2022.

One-third 73 (27%) of the participants do not have identified comorbidities and about one-quarter of participants have more than one comorbidity. Hypertension was the commonest comorbidity identified in 120 (44.3%) patients followed by diabetes in 87 (32%). Fifty-two (19%) patients have both diabetes and hypertension. CKD and cancer of any type were found in 18 and 15 participants, respectively.

The mean [$\pm$ standard deviation] Ejection fraction (EF) of the participants was $28.6\% \pm 7.3$ and the leading proportion (69.4%) of participants were having EF below 30%. Only 31 (11.4%) participants had a pulse rate of above 100. The mean [$\pm$ standard deviation] Mean arterial pressure (MAP) of the participants was 89.9 ± 11.6 . Edema was found in 51 (18.8%) patients.

The clinical characteristics are shown in Table 2.

Treatment-Related Characteristics

The mean ($\pm$ SD) duration of follow-up for the management of HF was $4.36 (\pm 4.6)$ years and about two-thirds of patients were on follow-up for more than one year. One hundred and sixty-three (60.1%) patients were taking 5 or more drugs. RAAS-blockers are the most commonly used drugs in 233 (86%) patients followed by Beta-blockers in 214 (79%)

Table 2 Clinical Characteristics of Study Participants at Cardiac Clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, August 2022 – October 2022

Characteristics		Number (n)	Percentage (%)
NYHA class	I	58	21.4
	II	106	39.1
	III	94	34.7
	IV	13	4.8
Hospitalization	No	174	64.2
	Yes	97	35.8
Rhythm Disturbances	Atrial fibrillation	33	12.1
	Atrial flutter	3	1.1
	PVCs	6	2.2
ECHO Findings	IHD	204	75.3
	DCM	64	23.6
	PPCM	3	1.1
	VHD	15	5.5

(Continued)

Table 2 (Continued).

Characteristics		Number (n)	Percentage (%)
Mean EF (SD)		28.63 ± 7.29	
Ejection fraction category	10–15%	20	7.4
	15–30%	168	62
	30–40%	83	30.6
Mean MAP (SD)		89.95 ± 11.64	
Comorbidities	Hypertension	120	44.3
	Diabetes	87	32.1
	CKD	18	6.6
	Cancer, if any	15	5.5
Pulse rate category	60–100bpm	240	88.6
	> 100bpm	31	11.4
Edema	No	220	81.2
	Grade- I	19	7.1
	Grade- II	28	10.3
	Grade- III	4	1.5
	Grade- IV	0	0

and MRA in 159 (58.7%). Among RAAS-blockers Enalapril was a commonly used drug in 212 patients and only 3 participants were on ARNI. SGLT2i was used in 14 (5%) cases. More than three-quarters of the patients were receiving antiplatelet and/or anticoagulants. About three-quarters of participants were on a statin and 155 (57.2%) were taking diuretics. About two-thirds (61.6%) of the patients were taking Aspirin and 21 (7.7%) patients were taking DAPT.

The treatment-related characteristics are shown in. [Table 3](#) and [Figures 2 and 3](#)

Utilization of Beta-Blocker Among Patients with HFrEF

Among 214 (79%) participants taking beta-blocker, only 102 (37.6%) were on guideline-recommended beta-blocker. Among guideline-recommended beta-blockers, Metoprolol succinate was the most commonly used beta blocker in 79 (29.2%). Carvedilol and Bisoprolol were used by 13 and 10 participants, respectively. Ninety-four (34.7%) participants were getting Metoprolol tartrate and 18 (6.6%) were on Atenolol. Among patients receiving guideline-recommended beta-blockers (102), 16 (15.7%) were taking the optimal dose. Among patients who took the optimal dose of guideline-

Table 3 Treatment-Related Characteristics of Study Participants at Cardiac Clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, August 2022 – October 2022

Characteristics		Number (n)	Percentage (%)
Mean Duration of HF (SD)		4.36 ± 4.56	
Number of Drugs	< 5	108	39.9
	≥ 5	163	60.1

(Continued)

Table 3 (Continued).

Characteristics		Number (n)	Percentage (%)
Drugs	Beta-blockers	214	79
	ACEIs	215	79.3
	ARB	15	5.5
	ARNI	3	1.1
	MRA	159	58.7
	Furosemide	148	54.6
	Statin	202	74.5
	ASA	167	61.6
	DAPT	21	7.7

recommended beta-blocker 12 patients were taking Metoprolol succinate, 1 was on Carvedilol, and 3 were getting Bisoprolol. The mean daily doses of Metoprolol succinate, Carvedilol, and Bisoprolol were 72.18 mg, 18.75 mg, and 5.75 mg, respectively.

Utilization of beta blockers among patients with HFrEF is shown in Table 4 and Figure 4

Factors Associated with Beta-Blocker Utilization

Table 5 shows the logistic regression analysis of factors associated with beta-blocker utilization and odds ratio and a 95% confidence interval was used to measure the degree of association between the independent variables and beta-blocker utilization. Multicollinearity was assessed among independent variables using the variance inflation factor (VIF), and none was collinear. Initially, bivariate binary logistic regression was performed on selected sociodemographic, clinical, and treatment-related characteristics to identify variables candidate for multivariate binary logistic regression and a total of 8 variables were found to be candidates at a P -value of ≤ 0.2 . These include age greater than 60 (Crude odd ratio (COR) 1.590, 95% confidence interval (CI) 0.817–3.095), residence in Addis Ababa (COR 1.558, 95% CI: 0.827–2.934), duration of treatment follow-up for more than 01 year (COR 3.152, 95% CI: 1.728–5.750), presence of atrial fibrillation (COR 4.658, 95% CI: 1.080–20.086), diuretic use (COR 4.272, 95% CI: 2.269–8.044), ejection fraction $\leq 15\%$ (COR 6.435, 95% CI: 0.811–51.045) and absence of edema (COR 5.037, 95% CI: 2.596–9.773). However, in the final multivariate regression model, only 4 variables were found to have a statistically significant association with beta

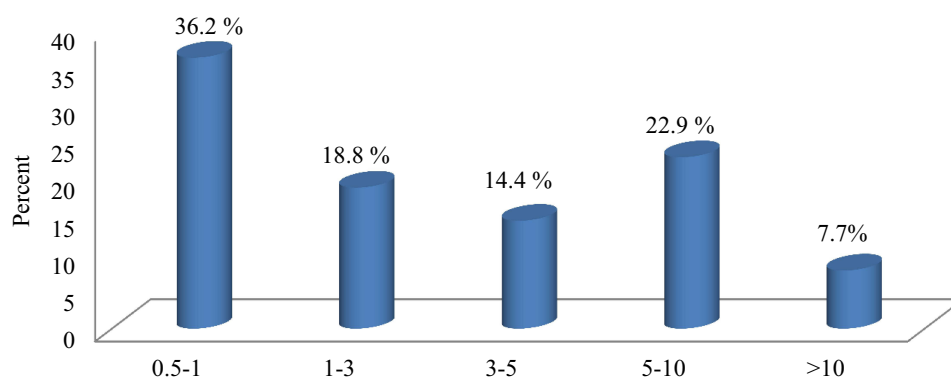


Figure 2 Distribution of duration of follow up in year among patients with HFrEF at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, August 2022 - October 2022.

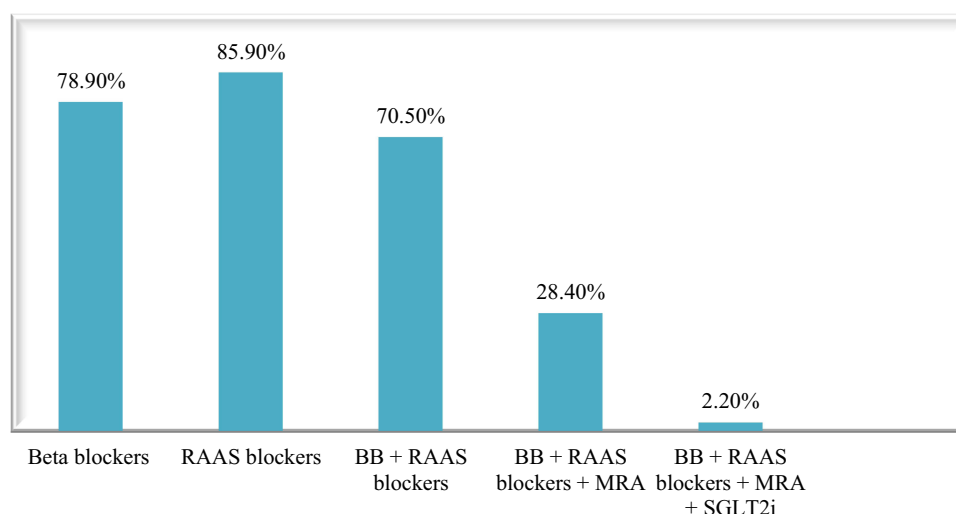


Figure 3 Distribution of utilization guideline medical therapy in patients with HFrEF at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, August 2022 – October 2022.

blocker utilization at a P -value of ≤ 0.05 . These included having duration of treatment follow-up for more than 01 year, presence of atrial fibrillation, diuretic use, and absence of edema.

Beta-blocker use among participants who had a follow-up for more than 1 year was more than 3 times as compared to patients who had to follow up for less than 1 year (Adjusted odds ratio (AOR 3.601), 95% CI: 1.707–7.597, $p=0.001$). The presence of atrial fibrillation increases the chance of beta-blocker utilization more than 5 times as compared to its absence (AOR 5.629, 95% CI: 1.063–29.817, $p=0.042$). Patients taking diuretics had increased the use of beta-blockers by more than 4 times as compared to patients not taking diuretics (AOR 4.498, 95% CI: 2.030–9.970, $p=0.0002$). Beta-blocker utilization among participants without edema was more than 9 times as compared to the presence of edema (AOR 9.588, 95% CI: 3.948–23.286, $p<0.0001$).

Discussion

Heart failure is a progressive disease associated with significant morbidity and mortality and disease-modifying agents are important in halting this process. Guideline-directed medical therapy is endorsed by most international guidelines and beta blockers are one of the four pillars of GDMT. The use of guideline-recommended beta-blockers (Metoprolol succinate, Bisoprolol, and Carvedilol) is associated with decreased adverse cardiovascular events, cardiovascular

Table 4 Beta-Blocker Type and Dosage of Study Participants at Cardiac Clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, August 2022 – October 2022

Characteristics	Metoprolol Succinate	Carvedilol	Bisoprolol
Number of patients (%)	79 (77.5)	13 (12.7)	10 (9.8)
Minimum daily dose (mg/day)	12.5	6.25	2.5
Maximum daily dose (mg/day)	200	50	10
Mean (SD) daily dose (mg/day)	72.18 ± 50.16	18.75 ± 12.24	5.75 ± 3.13
Patients on target dose (%)	12 (11.8)	1 (1)	3 (2.9)
Patients on $\geq 50\% < 100\%$ of target dose (%)	25 (24.5)	5 (4.9)	4 (3.9)
Patients on $< 50\%$ of target dose (%)	42 (41.2)	7 (6.9)	3 (2.9)

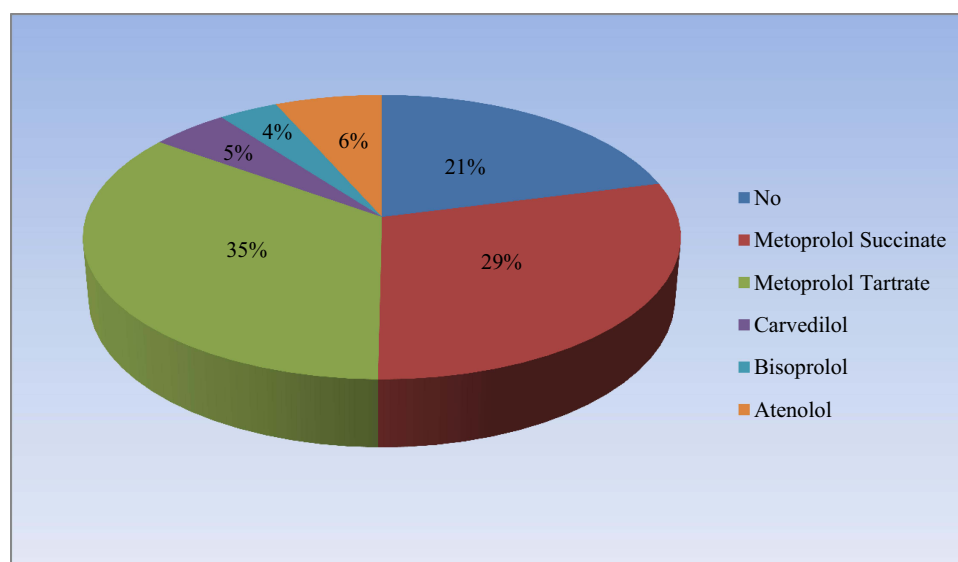


Figure 4 Types of beta-blockers used in patients with HFrEF at cardiac clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, August 2022 – October 2022.

mortality, and all-cause mortality.^{19–23} Although these benefits have been demonstrated by many randomized controlled trials, different studies showed underutilization of these important components of GDMT.^{28–30}

Our study found beta-blocker utilization in 214 (79%) patients, a figure that is comparable with the result of two France studies that showed a beta-blocker utilization rate of 65% and 70%.^{29,30} This result is higher as compared to

Table 5 Bivariate and Multivariate Regression to Assess Factors Associated with Beta Blocker Utilization of Study Participants at Cardiac Clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, August 2022 – October 2022

Variables	Beta-Blocker Use		COR (95% CI)	P value	AOR (95% CI)	P value
	Yes	No				
Residences of the study participants						
Addis Ababa	162	38	1.558 (0.827–2.934)	0.170	1.737 (0.796–3.791)	0.166
Out of Addis Ababa	52	19	1	1		
Age of the study participants (Year)						
<= 60	141	43	1	1		
> 60	73	14	1.590 (0.817–3.095)	0.172	1.504 (0.683–3.313)	0.311
Duration of treatment follow-up (Year)						
0.5–1	65	33	1	1		
> 1	149	24	3.152 (1.728–5.750)	0.000182	3.601 (1.707–7.597)	0.001
Presence of AFIB						
No	183	55	1	1		
Yes	31	2	4.658 (1.080–20.086)	0.039	5.629 (1.063–29.817)	0.042
Number of drugs						
< 5	81	27	1	1		
>= 5	133	30	1.478 (0.820–2.663)	0.194	0.754 (0.353–1.609)	0.465

(Continued)

Table 5 (Continued).

Variables	Beta-Blocker Use		COR (95% CI)	P value	AOR (95% CI)	P value
	Yes	No				
Diuretics Use						
No	76	40	I	I		
Yes	138	17	4.272 (2.269–8.044)	0.000007	4.498 (2.030–9.970)	0.0002
Presence of Edema						
No	187	33	5.037 (2.596–9.773)	0.000002	9.588 (3.948–23.286)	0.0003
Yes	27	24	I	I		
Ejection fraction						
<= 15	19	I	6.435 (0.811–51.045)	0.078	5.172 (0.544–49.159)	0.153
16–30	133	35	1.287 (0.693–2.391)	0.424	1.069 (0.502–2.275)	0.862
30–40	62	21	I	I		

Note: The bold values show significant associations of factors associated with beta-blocker utilization.

a previous study (67%) done in Jimma Hospital.²⁸ The variation in beta-blocker utilization rates among the various studies done could be due to differences in sample characteristics. The higher rate of beta-blocker utilization in our study could be due to increased healthcare access and drug availability since most of the study participants reside in the urban area and the study was conducted in the country's highest hospital. In this study, RAAS blockers are the most commonly used drug in 86% of patients, which is in line with two studies conducted in France and one from Jimma, which showed RAAS-blocker use in 80%, 92%, and 82.6%, respectively. More than one-third (69.7%) of the participants were taking both RAAS-blocker and beta-blocker, which was 61% and 58% in France and Jimma studies, respectively.^{28–30}

Despite the proven benefit of β -blockers in HFrEF, they are often underutilized in current clinical practice and this has been shown by different studies.^{28–31} It is also demonstrated by this study, 21% of the study participants were not taking beta-blockers. Among the patients taking beta-blockers only 102 (37.6%) participants were on guideline-recommended beta-blockers. The other 41% of patients taking beta-blockers were on Metoprolol tartrate (34.7%) and Atenolol (6.6%), which are not guideline-recommended beta blockers. The possible reasons for the higher prescription rate of Metoprolol tartrate and Atenolol might be due to the high local cost of guideline-directed beta-blockers (Metoprolol succinate, Carvedilol, and Bisoprolol), lack of patient awareness in differentiating between succinate and tartrate preparations of Metoprolol, lack of knowledge on the different effects of succinate and tartrate preparations of Metoprolol by pharmacists (drug dispensers), and incomplete prescriptions without specifying the type of Metoprolol by physicians.

In this study, four variables were found to be independent predictors of beta-blocker utilization. Duration of treatment follow-up more than 1 year, the absence of peripheral edema, the presence of atrial fibrillation and diuretic use were positively associated with beta-blocker utilization were positively associated with beta-blocker utilization.

Beta-blocker utilization was 3 times higher in participants who had a treatment follow-up for more than 1 year as compared to patients who had a treatment follow-up for more than 1 year. A possible justification might be a shorter duration of follow-up prevents the patients to attend multiple clinic visits and the physicians to initiate and escalate the dose of beta-blockers. This finding is consistent with IMPROVE HF registry.³² Beta-blocker utilization was 5 times lower in patients who had peripheral edema as compared to patients without edema. This could be due to lower physician inertia in prescribing beta-blockers in these patients. The presence of atrial fibrillation was significantly associated with beta-blocker utilization as compared to its absence. This could be due to the increased use of beta-blockers for rate control in these patients. The use of diuretics was significantly associated with beta-blocker utilization as compared to those patients not taking diuretics. This could be due to the use of diuretics decreasing congestion, which is one of the reasons not to prescribe beta-blockers or to escalate their doses. This finding is consistent with the Jimma study.²⁸

None of the socio-demographic characteristics, underlying etiology, and comorbidities such as ischemic heart disease and hypertension were found to be significant predictors of beta-blocker utilization.

The impact of treatment with beta-blockers in HFrEF, in terms of overall mortality, cardiovascular mortality, and HF hospitalization is selectively seen with Carvedilol, Bisoprolol, and Metoprolol Succinate when titrated up to the maximum tolerated dose and these agents are mostly tolerable upon titration.^{19–23,33} In this study, among patients receiving guideline-recommended beta-blockers, 15.7% were taking the optimal doses and 49% reached more than or equal to 50% of the target dose. Although this figure is higher than the Jimma study in which only 10.5% of patients were at the optimal dose, it is quite comparable with the FUTURE survey, 56%.^{28,34}

Even though the median dose achieved in major clinical trials for Metoprolol succinate, Carvedilol, and Bisoprolol was 159mg, 7.5mg, and 37mg, in this study the mean daily doses of Metoprolol succinate, Carvedilol, and Bisoprolol in this study are 72.18 mg, 18.75 mg, and 5.75 mg, respectively.^{21,22,30} The possible reason for sub-optimal dosing could be due to low physician inertia in up-titrating to the target dose, low awareness of dose titration among physicians, longer duration of clinic appointments, and patient refusal because of cost issues.

Conclusion

Even though the guideline-recommended beta-blocker at optimal doses exerts a clinical benefit, this study points out that beta-blockers are underutilized and more importantly used at suboptimal doses. Duration of treatment follow-up more than 1 year, the absence of peripheral edema, the presence of atrial fibrillation and diuretic use were positively associated with beta-blocker utilization and were positively associated with beta-blocker utilization. A significant association was not found for socio-demographic characteristics, underlying etiology, and comorbidities. To achieve the desired clinical benefit from beta-blockers physicians should attempt to provide guideline-recommended beta-blockers and should escalate to the optimum or maximum tolerable dose. Furthermore, factors associated with underutilization and sub-optimal dosing should be identified and modified by further studies.

Recommendation

This is a hospital-based study with a small sample size, thus a large-scale and prospective study with a longer duration of follow-up is needed for the determination of factors associated with underutilization and suboptimal dosing of guideline-recommended beta-blockers in HFrEF patients. Clinicians' knowledge and inertia in utilizing and optimizing beta-blockers should be determined in future studies.

Strengths and Limitations of the Study

The strength of this study is as it is a cross-sectional study, and data were collected over specified time duration and which enabled us to execute an accurate assessment of the descriptive and analytic analysis. This study is one of a few studies conducted both in TASH and Ethiopia. We believe this study will add more information regarding the current status of beta-blocker utilization, types, and dosages in the country's largest hospital and motivate the cardiology unit and department of internal medicine to assess factors associated with underutilization and suboptimal dosing and remedy the gap.

Although the pattern of beta-blockers used and factors associated with beta-blocker utilization are assessed, this study did not assess patient-related factors including financial and educational status and physician knowledge and inertia in initiating and titrating beta-blockers; therefore further study is required. Even though the finding of this study is similar to many studies, it cannot be generalized to the general population because this is a single-center study.

Abbreviations

AAU, Addis Ababa University; AHA, American Heart Association; ACC, American College of Cardiology; ACE-I, Angiotensin Converting Enzyme Inhibitor; ASA, Aspirin; ARBs, Angiotensin Receptor Blockers; ARNI, Angiotensin receptor-Neprilysin Inhibitor; BP, Blood Pressure; BB, Beta Blockers; β -blockers, Beta Blockers; BPM, Beats Per-Minute; CHS, College of Health Sciences; CKD, Chronic Kidney Disease; CVD, Cardiovascular Disease; DAPT, Double Anti-Platelet Therapy; DBP, Diastolic Blood Pressure; DCM, Dilated Cardiomyopathy; DM, Diabetes Mellitus; EF,

Ejection Fraction; ESC, European Society of Cardiology; GDMT, Guideline Directed Medical Therapy; HF, Heart Failure; HFrEF, Heart failure with reduced ejection fraction; HFpEF, Heart failure with preserved ejection fraction; IHD, Ischemic Heart Disease; LVEF, Left Ventricular Ejection Fraction; MRA, Mineralocorticoid receptor antagonist; NCD, Non-Communicable Diseases; PPCM, Peripartal Cardiomyopathy; PR, Pulse Rate; PVCs, Premature Ventricular Contractions; RAAS, Renin-angiotensin-aldosterone System; RCTs, Randomized controlled Trials; SBP, Systolic Blood Pressure; TASH, Tikur Anbessa Specialized Hospital; VHD, Valvular Heart Disease.

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Disclosure

The authors report no conflicts of interest in this work.

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