Utilisation and optimisation of beta-adrenergic receptor blockers over a 6-month period among chronic heart failure patients with reduced ejection fraction

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Background. Beta-adrenergic receptor blocker (BARB) drugs are a wide range of medicines that are used in various conditions, including chronic heart failure (HF). Several studies have reported a wide-ranging inappropriate use of evidence-based beta-blockers (EBBBs) in chronic HF in both inpatients and outpatients.
Objectives. To assess the utilisation and optimisation of EBBBs among patients with HF who presented with a reduced ejection fraction (HFrEF).
Methods. A hospital-based retrospective cross-sectional study was carried out at the Adult University Teaching Hospital (AUTH), in Lusaka, Zambia, where patient medical files for the period of 1 July 2018 to 31 July 2021 were reviewed. Patient information, including file number, age, sex, type of BARB and the dose used, was recorded on the developed and validated checklist. Multivariable regression analysis was performed to identify factors associated with utilisation of BARBs.
Results. Of the 173 medical records reviewed, BARBs were utilised in 101 (58.4%) patients. Among the patients who utilised BARBs, 96 (95.0%) were taking EBBBs, while the rest (*n*=5, 5.0 %) were taking atenolol, which is a non-EBBB. Among the patients who were on EBBBs, none of them received the optimal dose. Age ≥65 years (adjusted odds ratio (aOR) 0.3, 95% confidence interval (CI) 0.17 - 0.64), previous hospitalisation (aOR 0.3, 95% CI 0.13 - 0.51) and furosemide dose ≥40 mg (aOR 0.4, 95% CI 0.21 - 0.64) were significantly associated with lower likelihood of BARB utilisation. New York Heart Association (NYHA) class II (aOR 3.4, 95% CI 1.08 - 10.7), NYHA class III (aOR 4.8, 95% CI 1.65 - 13.7) and patients using at least 5 medications (aOR 5.0, 95% CI 2.91 - 8.77) were independent predictors of BARB utilisation.
Conclusion. This study showed that 95.0% of chronic HF patients were utilising EBBBs, and none received the optimal dose as recommended in the guidelines. Pharmacotherapy with EBBBs should be optimised among patients with chronic HfrEF, as these drugs reduce both morbidity and mortality.

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Heart failure (HF) continues to be a worldwide growing problem owing to an increasing elderly population and comorbidity.[1] HF affects >26 million people worldwide, and significantly contributes to the global burden of cardiovascular disease.[1,2] The burden of HF has been growing in sub-Saharan African countries over the past decades, and Zambia has not been exempted.[3,4] Despite the associated morbidity and mortality, there have been notable advances in the management of HF.[5,6] The growing body of knowledge has shown a decrease in HF-associated morbidity and mortality after implementation of evidence-based guidelines for management of HF.[5,7] However, HF remains a major cause of morbidity and mortality owing to a number of factors such as polypharmacy, comorbidities, advanced age and lack of proper titration of doses of evidence-based beta-blockers (EBBBs) in line with recommended guidelines.[5]

Beta-adrenergic receptor blocker drugs (BARBs) are a class of drugs that are used to prevent the binding of epinephrine and norepinephrine with the beta-adrenergic receptors,[8,9] and are among the mainstays in the management of chronic HF presented with a reduced ejection fraction (HFrEF).[10,11] These drugs have proven to help reduce morbidity and mortality in randomised clinical trials of HF patients.[10,12] In patients who have systolic HF, EBBBs such as carvedilol, metoprolol and bisoprolol have proven to reduce hospitalisation, reverse adverse effects of neurohormonal activation and help in left ventricular function.[13,14] However, even with this proven evidence, there is underutilisation of these drugs by clinicians, coupled with wrong dosing.[15,16] EBBBs in patients with HFrEF should be started at low doses, and the doses increased slowly to the maximum tolerable doses as evidenced in the randomised clinical trials.[17] One study revealed that 34.2% of patients received EBBBs according to guideline recommendations, while 65.8% were taking atenolol, which is a non-EBBB. The study further revealed that among the patients who received EBBBs, only 3% were taking optimal doses.[18] In another study, it was discovered that of the patients whose targeted heart rate was not achieved in relation to the use of BARBs, 72.3% received less than the target dose of beta-blocker.[19] Even with high rates of EBBBs target doses being achieved in clinical trials, target dose attainment in clinical practice remains low, resulting in poor desired patient outcomes.[20,21]

At the time our research was conducted, utilisation and optimisation of EBBBs among HF patients at the University Teaching Hospital in Lusaka, Zambia, had not yet been established and published. Therefore, this study aimed at investigating the utilisation and optimisation of EBBB therapy in the management of patients with chronic HF.

Methods

Study design, setting and population

This hospital-based retrospective cross-sectional study was conducted between August 2021 and October 2021 at the AUTH. The University Teaching Hospital (UTH) is the biggest referral teaching health institution in Lusaka, Zambia, which provides both inpatient and outpatient services to the entire population. It is located in the capital city Lusaka, about 4 km east of the city, with a bed capacity of ~1 655.

The population of interest comprised chronic HF patients aged ≥18 years with an ejection fraction of <40% who were taking at least a BARB with or without other drugs during the period 1 July 2018 through 31 July 2021. Patients with precautions and contraindications to the use of BARBs, including asthma, decompensated HF, hypotension (<90/60 mmHg), bradycardia (<60 bpm), as well as those with incomplete medical records, were excluded from this study.

Sample size

We used the Single population formula ($n= z^2p\ (1 - p)/d^2$) to estimate the sample size, where n = sample size, z = 95% confidence level at 1.96, d = margin of error ($n=1.96^2 \times 0.5\ (1 - 0.5)/0.05^2$, $n=3.8416 \times 0.5(0.5)/0.0025$, and therefore, n=384 patients. The expected population of patients with HF manifest by a HFrEF taking BARBs during the study period was 280. Thereafter, since the total patient population was <10 000, the adjustment reduction formula was used to determine the minimal final sample size. Using the correction formula ($nf = (n*N)/(n+N)$, where nf = minimum required sample size, ni = reduced sample size (385) and N = total number of our respondents (280), a corrected sample size of 173 was obtained.

Study procedure

A data collection sheet was developed for purposes of collecting relevant research data. A systemic random sampling technique was used to select patient files for review. Information was obtained using the data abstraction checklist that contained patient information such as sex, age and type of BARB used. The patient files were reviewed to obtain more information about whether the medicine doses were up titrated to a target dose or maximum tolerable dose.

Study definition and outcome

The optimum use of EBBBs was decided according to evidence-based guidelines.[11,22] The primary outcome of this study was utilisation and optimisation of BARBs in HFrEF. Patients were considered as having used EBBBs therapy if they received a prescription of carvedilol, bisoprolol or metoprolol and they were considered as having used non-EBBBs if they received a prescription of BARBs not recommended in the guidelines. The dose of EBBBs was considered optimum if it was prescribed at maximum tolerable dose according to the recommended guidelines, while the dose was considered suboptimal if the patient received EBBBs below the maximum tolerable dose in the absence of contraindications for up-titration. The optimal dose for metoprolol was considered as 200 mg daily, and carvedilol if the patient received 50 mg daily, as shown Table 1.

Data analysis

The data were checked and cleaned on a daily basis during collection and before analysis. Stata version 15.1 (StataCorp, USA) was used to analyse the collected data. Descriptive statistics such as means, frequencies and percentages were determined. For parametric data, the mean and standard deviation (SD) were computed, while median and interquartile range (IQR) were computed for non-parametric data. The Shapiro-Wilk test was used to test for normality, and continuous variables with p>0.05 were considered to be normally distributed. We further performed a bivariate logistic regression analysis to determine the association of each independent variable with utilisation of EBBBs. All independent variables with p<0.2 in bivariate analysis were incorporated in the multivariable logistic regression model to identify factors independently associated with EBBBs utilisation. A p-value <0.05 was considered statistically significant in all analyses. Findings from data analysis are presented in tables, figures and text.

Ethical clearance

This research received ethical clearance from the University of Zambia Health Sciences Research Ethics Committee (UNZAHSREC) (ref. no. 202112030065) with the Adult University Teaching Hospital (AUTH) management. The personal information was handled in a confidential and ethical manner, and all research was performed in accordance with the approved institutional guidelines.

Results

Sociodemographic characteristics

A total of 173 patient files were reviewed in this study. The majority of patients reviewed were female (n=99, 57.2%), and 135 (78.0%) of them were aged <65 years. The mean age of the patients was 51.4 years (SD 15.03) and the majority (n=150, 86.7%) were from urban areas. More than half (n=96, 55.5%) of the patients had attained secondary education, and the majority were married (n=115, 66.5%) (Table 2).

Clinical characteristics

In this study, a majority (n=127, 73.4%) of the patients were in the New York Heart Association (NYHA) class III, followed by class II

Table 1. Initial and maximum doses for evidence-based beta-blockers in heart failure patients

Beta-blocker	Initial dose (mg)	Maximum tolerable dose (mg)
Carvedilol	3.125 mg twice daily	50
Metoprolol	12.5 mg twice daily	200
Bisoprolol	1.25 mg once daily	10
Nebivolol	1.25 mg daily	10

Table 2. Sociodemographic characteristics of heart failure patients (N=173)

Variable	*n* (%)
Gender	
Female	99 (57.2)
Male	74 (43.8)
Age, years	
<65	135 (78.0)
≥65	38 (22.0)
Residence	
Rural	23 (13.3)
Urban	150 (86.7)
Education level	
Illiterate	9 (5.2)
Primary	24 (13.9)
Secondary	96 (55.5)
Tertiary	44 (25.4)
Marital status	
Married	115 (66.5)
Single	20 (11.5)
Divorced	3 (1.7)
Widowed	35 (20.3)

(*n*=69, 18%). More than half of the patients had been hospitalised in the previous year (*n*=123, 71.0%). A total of 104 (60.2%) patients had <2 comorbidities, while the rest had either ≥2. Hypertension (*n*=111, 64.2%) and dilated cardiomyopathy (*n*=94, 54.3%) were the most common comorbid diseases that were noted. The systolic mean (SD) blood pressure (BP) was 125 (19.5) mmHg, while the diastolic mean (SD) BP was 82 (14) mmHg. The mean (SD) heart rate was 89 (14), and the mean (SD) ejection fraction was 30 (7) (Table 3).

Treatment-related characteristics of chronic heart failure patients

The study revealed that 105 (60.7%) of the patients were taking ≥5 medications, the common ones being furosemide (*n*=156, 90.4%) with a mean (SD) dose of 77.2 (51.5) mg, spironolactone (*n*=132, 76.0%) with a mean (SD) dose of 25.9 (4.6) mg, anti-platelets (*n*=112, 64.7%), angiotensin-converting enzyme inhibitors (*n*=259, 67.5%) (median dose 5 mg, IQR 2.5 - 10 mg) and digitalis glycosides (*n*=87, 50.3%) with a mean (SD) dose of 0.128 (0.02) mg. Moreover, 67 (38.7%) patients were on angiotensin-converting enzyme inhibitors and beta-blocker combination therapy (Table 4).

Utilisation and dosing of BARBs in HF patients

Of the 173 participants, 101 (58.4%) were on beta-blockers, and of these 96 (95%) were taking EBBBs, while the rest (*n*=5, 5%) were taking atenolol, which is a non-EBBB used in chronic HF. Among the 96 patients who were taking EBBBs, none received the optimal dose, while only 5 (5%) reached at least ≥50 - <100% of the guideline recommended target dose (Table 5).

Table 3. Clinical characteristics of heart failure patients (*N*=173)

Characteristic	*n* (%)*
NYHA class	
I	15 (8.7)
II	31 (17.9)
III	127 (73.4)
Hospitalisation	
No	50 (29.0)
Yes	123 (71.0)
Duration of hospitalisation, weeks	
<2	145 (83.8)
≥2	28 (16.2)
Systolic BP, mean (SD)	125 (19.5)
Diastolic BP, mean (SD)	82 (14)
Heart rate, mean (SD)	89 (14)
Ejection fraction, mean (SD)	30 (7)
Age, median (IQR), years	52 (39 - 63)
Comorbidities, *n*	
<2	104 (60.2)
≥2	69 (39.8)
Common comorbidities	
Ischaemic heart disease	9 (5.2)
Hypertension	111 (64.2)
Diabetes mellitus	14 (8.1)
Chronic kidney disease	11 (6.4)
Dilated cardiomyopathy	94 (54.3)
Rheumatic heart disease	3 (1.7)
Stroke	3 (1.7)
Atherosclerosis	3 (1.7)

NYHA = New York Heart Association; BP = blood pressure; SD = standard deviation; IQR = interquartile range.
*Unless otherwise indicated.

Multivariate and bivariate logistic regression factors associated with utilisation of beta-blockers

In the unadjusted logistic regression model, age ≥65 years, (crude odds ratio (COR) 0.3, 95% onfidence interval (CI) 0.16 - 0.44) previous hospitalisation (COR 0.4, 95% CI 0.24 - 0.62) and furosemide dose ≥40 mg (COR 0.4, 95% CI 0.25 - 0.61) were significantly associated with underutilisation of beta-blockers. However, NYHA class III (COR 2.1, 95% CI 1.04 - 4.53), and patient ≥5 medications (COR 3.3, 95% CI 2.61 - 5.07) were significantly associated with BARB utilisation.

When variables with $p<0.2$ in the unadjusted logistic regression model were analysed in the adjusted logistic regression model, age ≥65 years (adjusted odds ratio (aOR) 0.3, 95% CI 0.17 - 0.64), previous hospitalisation (aOR 0.3, 95% CI 0.13 - 0.51) and furosemide dose ≥40mg (aOR 0.4, 95% CI 0.21 - 0.64) were significantly associated with lower likelihood of BARB use. NYHA class II (aOR 3.4, 95% CI 1.08 - 10.7), NYHA class III (aOR 4.8, 95% CI 1.65 - 13.7) and patient on multiple medications (aOR 5.0, 95% CI 2.91 - 8.77) were determinants of beta-blocker utilisation (Table 6).

Discussion

Despite being underutilised, many studies have proven that EBBBs consistently reduce morbidity and mortality in chronic HF patients with an ejection fraction <40%.[18] Optimisation and utilisation of EBBBs have proven to be a significant intervention in HF for the present and future, hence the reason for the study.[23]

In this study, the age of the patients during the period under review ranged from 18 to 89 years, the majority (78.0%) being <65 years. The median (IQR) age was 52 (39 - 63) years. The percentage

Table 4. Treatment characteristics of heart failure patients (*N*=173)

Characteristic	*n* (%)
Medications	
<5	68 (39.3)
≥5	105 (60.7)
Frequently used medications	
Beta-blockers	101 (58.4)
Angiotensin-converting enzyme inhibitors (enalapril)	117 (67.5)
Angiotensin-converting enzyme inhibitors and beta-blockers	67 (38.7)
Angiotensin channel blockers (losartan)	40 (23.1)
Spironolactone	132 (76.0)
Furosemide	156 (90.2)
Anti-platelets	
Aspirin	112 (64.7)
Clopidogrel	6 (3.4)
Aspirin and clopidogrel	3 (1.7)
Anticoagulants	
Warfarin	3 (1.7)
Warfarin and enoxaparin	6 (3.5)
Calcium channel blockers	
Amlodipine	7 (4.0)
Nifedipine	6 (3.5)
Others	
Digitalis glycosides (digoxin)	87 (50.3)
Statins (atorvastatin)	17 (9.8)

Table 5. Type and dose of beta-adrenergic receptor blocker utilised in heart failure patients (*n*=101)

	Medication			
Variable	**Carvedilol**	**Bisoprolol**	**Nebivolol**	**Atenolol**
Patients on medication, *n* (%)	89 (88.0)	4 (4.0)	3 (3.0)	5 (5.0)
Patients on optimal/target dose, *n*	0	0	0	-
Patients on ≥50 - <100% target dose, *n* (%)	0	5 (5.0)	0	-
Minimum dose used, mg	3.125	5	2.5	50
Maximum dose used, mg	12.5	5	2.5	100

Table 6. Unadjusted and adjusted binary logistic regression models examining the factors associated with utilisation of beta-blockers

		Unadjusted			Adjusted		
Variable	**Category**	**COR**	**95% CI**	***p*-value**	**aOR**	**95% CI**	***p*-value**
Gender	Female	1					
	Male	1.3	0.87 - 1.96	0.197*	1.1	0.67 - 1.91	0.626
Age, years	<65	1					
	≥65	0.3	0.16 - 0.44	0.0001*	0.3	0.17 - 0.64	0.001**
Previous hospitalisation within the year	No	1					
	Yes	0.4	0.24 - 0.62	0.0001*	0.3	0.13 - 0.51	0.0001**
Duration of hospitalisation, weeks	<2	1					
	≥2	1.4	0.79 - 2.41	0.255	-	-	-
NYHA classification	Class I	1					
	Class II	1.3	0.57 - 3.10	0.507	3.4	1.08 - 10.7	0.036**
	Class III	2.1	1.04 - 4.53	0.040*	4.8	1.65 - 13.7	0.004**
Comorbidities, *n*	<2	1					
	≥2	0.7	0.47 - 1.08	0.109*	0.9	0.49 - 1.53	0.618
Medications, *n*	<5	1					
	≥5	3.3	2.16 - 5.07	0.0001*	5.0	2.91 - 8.77	0.0001**
Daily dose of furosemide, mg	<40	1					
	≥40	0.4	0.25 - 0.61	0.0001*	0.4	0.21 - 0.64	0.0001**
Ischaemic heart disease	No	1					
	Yes	0.82	0.32 - 2.11	0.683	-	-	-

*p<0.2 in unadjusted model.
**p<0.05 in adjusted model.
1 = reference category; COR = crude odds ratio; CI = confidence interval; aOR = adjusted odds ratio; NYHA = New York Heart Association.

of those <65 years old correlates with that in a study carried out in Ethiopia (74.7%) on the utilisation and optimisation of beta-blockers.[18] However, the number of female patients (57%) in this study was similar to that in a study in South Africa, where females constituted 58% of study participants.[24] This is in contrast with a study in Ghana that showed that more males than females suffered from HF.[25] The most common comorbidities in this study were hypertension (64.1%) and dilated cardiomyopathy (54.2%), similar to the study conducted in Ghana.[25]

In our study, BARB utilisation was at 58.4%, which was lower than the percentage that was noted in a similar study in Ethiopia, with 67% use of BARBs.[18] The observed low use of BARBs may be attributed to the lack of adherence to recommended treatment guidelines for HF in the institution. However, this could also be a result of drug availability and accessibility factors. The rate of BARB utilisation in the current study was higher than what was observed (41%) in a study conducted in the USA.[26] Despite BARBs being the recommended drugs for the management of HFrEF, unless in cases where they are contraindicated, 41.6% of the patients in the current study were not receiving BARBs. Similarly, studies have shown that BARBs are indeed underutilised in HFrEF.[18,25,27] The variance in the rate of BARB utilisation could be due to the difference in study settings and population, non-compliance with recommended guidelines and patient factors. Of the patients who received BARBs in this study, the majority (95%) were using EBBBs comprising carvedilol, nebivolol and bisoprolol. This is higher than the percentages observed in the USA and Ethiopia, where EBBB utilisation was at 23% and 34.2%, respectively.[18,26] The high utilisation of EBBBs in our study could be attributed to more awareness regarding the benefits of EBBBs in HFrEF than in the previous two studies.

In our study, previous hospitalisation and high furosemide dose (≥40 mg) were significantly associated with a lower utilisation rate of BARBs. This is consistent with results of a study done in Ethiopia, which revealed that previous hospitalisation and high doses of furosemide affected the utilisation of BARBs in patients with chronic HF.[18] Furthermore, low utilisation of BARBs was observed in patients with advanced age (≥65 years), a finding that was consistent with the fact that advanced age is an independent predictor of beta-blocker utilisation in the management of chronic HF.[28] We are not certain whether physicians in the current study perceived advanced age as a risk factor for BARB intolerance, which resulted in underutilisation of EBBBs observed in this age group. On the contrary, BARBs have been shown to be well tolerated in the elderly with chronic HF and, therefore, their utilisation should be optimised.[17] NYHA class II and III as well as polypharmacy (≥5 medications) were independent predictors of a high rate of BARB utilisation in our study.

In this study, none of the patients was on optimised doses of EBBBs (reached maximum tolerable doses), as observed from suboptimal EBBBs doses. In another study conducted in Africa, only 3% of patients received the optimal doses.[18] This finding demonstrates inappropriate practice of dose titration of EBBBs. It has been reported that while health practitioners may have adequate knowledge on EBBBs use, they may not be aware of how to titrate their dose to their recommended maximum doses.[5] If EBBBs are to provide the maximum clinical benefit, health practitioners should give the maximum tolerable doses for the best clinical outcomes.[23] This has been observed in most clinical trials where patients received optimal doses of EBBBs.[29-31] However, despite this evidence, our study showed that none of the patients received optimal doses of EBBBs.

Study strengths and limitations

A strength of this study was that there was full access to patient files in order to collect all the information needed. Also, this study is the first to have full information on the utilisation and optimisation of beta-blockers in Zambia; hence, it could be used for future interventions in HF patients.

The weakness of study is that this research was limited to AUTH; hence, there is a need for similar studies to be conducted in all tertiary hospitals in Zambia. If this study is to be extrapolated to other parts of the country, this should done with caution owing to differences in participant characteristics and variation in distribution of experienced health practitioners who are specialised in the management of chronic HF patients at the institutions.

Conclusion

EBBBs were underutilised and not optimised for patients who presented with chronic HFrEF. Medication utilisation reviews should be performed in patients on EBBBs with chronic HFrEF. More effort, knowledge and practice are needed by health practitioners to know and master the art of utilising and up titrating EBBBs to maximum tolerable doses for better clinical outcome.

Declaration. None.

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Author contributions. MK and PM conceptualised the research, collected data, participated in data analysis and write-up; WM and AH participated in conceptualisation, editing and review; JH was involved in formal analysis, write-up and review of the research.

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