Original Research Article

Evaluation of β-blockers dosage regimen rationality in heart failure patients

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ABSTRACT

Background: β-Blockers are often associated with further cardiac function deterioration, ledding to them being often underused/underdosed by certain physicians in heart failure treatment, although they were seen to be beneficial in decreasing the rates of mortality and morbidity, duration of hospitalization in HFrEF patients, but data on their benefits in HFmEF and HFpEF patients is limited. Objective was to evaluate rationality of β-blockers' dosage regimen and its effectiveness in HF patients.
Methods: 43 HF patients have been enrolled. Data were collected from the medication chart (dose, route, frequency); dosage regimen was evaluated and compared to that of ESC guidelines for HF treatment. Heart rates pre/post drug treatments, ejection fraction (at admission & post-discharge) were recorded; effectiveness was evaluated through heart rate control, reduction in: duration of hospitalization, rehospitalization and mortality rate. Post-discharge updates of the patients were obtained through out-patient consultation reports.
Results: In All 43 patients dosage regimen of selected β-Blockers was found to be rational and following the ESC guideline for HF treatment. 65% of patients spent not more than 5 days in the hospital, 16% Re-hospitalized for cardiovascular diseases, and death rate was 4%.
Conclusions: The dosage regimen of selected β-Blockers was found to be as per that of ESC-guidelines HF treatment. β-Blockers have also been found to have reduced: hospitalization stay, frequency of rehospitalization, and death rate among patients under study.

Keywords: Rationality, Guidelines, β Blockers, Effectiveness, Mortality

INTRODUCTION

Heart Failure (HF) is a progressive disease. It is characterized by the Heart failing to pump sufficient blood to fulfill the requirements and metabolic demands of the body. It's a serious condition affecting 26 million people globally, hence requiring appropriate care and treatment, selection of appropriate(s) agent(s) and their rational use is critical for patient well-being.[1] Beta-blockers (βB), by binding to the β1-receptor on the heart, inhibit the binding of adrenaline or nor-adrenaline, preventing its action; βB exhibits negative inotropic as well as chronotropic impacts on the heart, ultimately leading to a reduction in heart rate and contraction force.[2] But their use in Hf patients has been debatable; although well known to decrease rates of morbidity and mortality in patients with HFrEF (heart failure with reduced ejection fraction), they are also feared due to possible deterioration of cardiac function and unwanted side effects, these may lead to their irrational use (underdosed, underutilized).[3-6] Data on their efficacy in HFmEF (Heart Failure with Mid-Range Ejection Fraction) is limited, and as for HFpEF (Heart Failure with Preserved Ejection Fraction) many trials concluded that no specific treatments reduce death rates in those patients.[7]

Toxicological reports on the agents include attempted suicides, accidental exposures and abuses; care must be taken to ensure their rational use by both prescribers as well as patients.[8]

WHO (World Health Organization) defines rational medication use as "patients receiving their medications in the right doses, times, in accordance with their clinical needs and at the lowest cost possible".[9] Like all medications, βB must be used following a suitable guideline. ESC (European Society of Cardiology) guidelines for HF treatment recommend the use of 4 beta-blockers in HFrEF treatment (cardio-selective: Bisoprolol, Metoprolol, and Nebivolol and non-selective: Carvedilol which has an additional alpha-blocking effect) with the following dose recommendations: Bisoprolol (initial dose 1.25mg PO OD, per oral; once a day; target dose 10 mg PO OD), Metoprolol (initial dose 12.5-25 mg PO OD; target dose 200 mg PO OD), Nebivolol (initial dose 1.25 mg PO OD; target dose 10 mg PO OD), Carvedilol (initial dose 3.125 mg PO BD; per oral; Twice a Day; target dose 25 mg PO OD or BD); treatment is to be initiated only on euvolemic hemodynamically stable HFrEF patients and the dose should start at its lowest then up-titrated till target dose or a well-tolerated dose is reached.[10] No specific initial dose/target dose was fixed by the guidelines for the treatment of HFpEF, HFmEF, and ADFH (acute decompensated heart failure), although the guideline recommends a cautious initiation of βB in all cases and the patient must be clinically stabilized first.[11]

Objectives

Primary objective was to evaluate the rationality of beta-blockers' dosage regimen in HF patients. Secondary Objective was to evaluate the effectiveness of beta-blockers in HF patients.

METHODS

This was prospective observational study. The study was conducted in the In-patient (IP) ward: cardiac care unit (CCU), high intensive unit (HICU), general medicine and in the out-patient (OP) ward at Bangalore Baptist hospital (a tertiary care hospital). The study was conducted over a period of 10 months, from January 1st to September 30th 2022.

Inclusion and exclusion criteria

All heart failure patients initiated on a Beta-blocker medication were included. Pregnant women and pediatric patients were excluded.

A prospective observational study was conducted in the department of cardiology, HICU, and general medicine, patients over 18 years of age, presented with heart failure and initiated on a beta-blocker medication were interviewed; patients undergoing βB therapy willing to participate were recruited in the study; primary outcome

was to evaluate the dosage regimen of beta-blockers in HF patients and compare it to that recommended by the ESC guidelines.
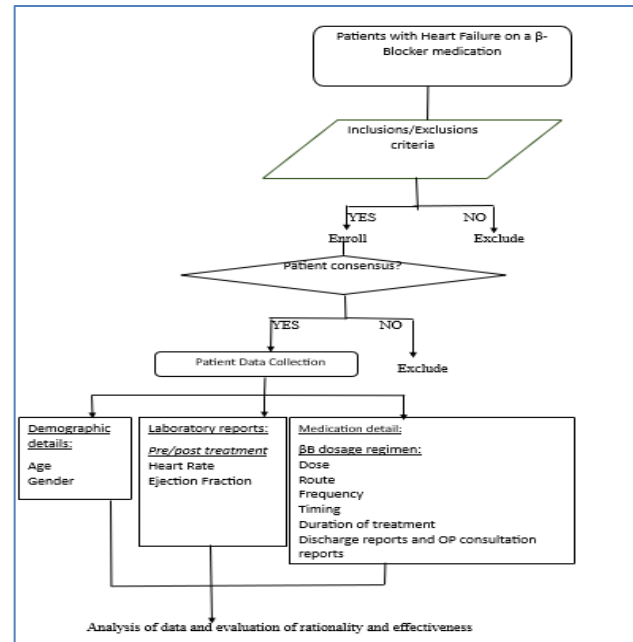

Figure 1: Methodology.

Patients' consensus to the study was obtained, those consenting were enrolled, and those non-willing were excluded. Using a self-designed case report form, data on patients were collected from Patients' case records (demographic details, HF type, disease comorbidities) and medication charts (name, dose, route, frequency of the drug and number of days on βB drug treatment), daily update of patients were done through physicians and nurses notes (patient daily assessment and progress notes) and by interviewing the patients. Dosage regimen was then evaluated and compared to that recommended by ESC guidelines for HF treatment. Secondary outcome was to evaluate the effectiveness of beta-blockers in HF patients for that data from Electrocardiogram (ECG) reports (heart rates pre/post βB administration), ejection fraction (at time of admission and post-discharge), number of days spent in hospital, frequency of rehospitalization and mortality rate were recorded; heart rate pre/post drug treatment, and ejection fraction value at admission and post-discharge were analyzed, effectiveness was then evaluated through efficacy in rate control, reduction in hospitalization duration, Reduction in rehospitalization frequency, and mortality. Post-discharge updates of the patients were obtained through OP consultation reports.

Statistical analysis

All data recorded were entered and analyzed using the MS Excel program. Statistical analysis of pre/post treatment heart rate and ejection fraction values, duration of hospitalization, frequency of rehospitalization; for any cardiovascular disease (CV), and the mortality rate was

carried out using analytical softwares: MS excel and JASP 0.16.04. Comparisons between (pre-treatment vs post-treatment) heart rates; ejection fractions (at-admission vs. post-discharge) were carried out utilizing a student's t test: Paired with 2 samples for means. All analyses were two-sided; a significant statistical difference was established for a p value ≤0.05.

RESULTS

A total of 43 HF patients from CCU, HICU and general medicine of the hospital were enrolled. Patients' demographics, types of heart failure, comorbidities details, and βB medications distributions can be observed in (Table 1).

Table 1: Patient's demographic details, diagnosis, comorbidities, and β-blocker medications distributions.

Baseline characteristics	N (%)
Gender	
Males	27 (63)
Females	16 (37)
Total	43 (100)
Age group (years)	
20-40	3 (7)
41-60	15 (35)
61-80	22 (51)
81-90	3 (7)
Mean age (years) with SD	63.093±13.437
Heart failure types	
ADHF	20 (46)
HFpEF	10 (23)
HFmEF	8 (19)
HFrEF	5 (12)
Comorbidities details	
Hypertension	25 (29)
Diabetes mellitus	26 (31)
IHD	12 (14)
CKD	10 (12)
AKI	3 (3)
ACS	9 (11)
Beta-blocker medications	
Bisoprolol	29 (67)
Metoprolol	9 (21)
Nebivolol	2 (5)
Carvedilol	3 (7)

AKI: Acute Kidney Injury; ACS: Acute Coronary Syndrome; CKD: Chronic Kidney Disease; IHD: Ischemic Heart Disease; SD: Standard Deviation.

A total of 29 patients were on tablet bisoprolol. Of those 29; 9 patients (31%) were newly initiated on the drug with a starting dose of 1.25mg (OD/BD) (Table 2). The remaining 20 patients (61%) were already on the medication at the time of admission (2.5mg OD/BD) (Table 3-4). At discharge, dose up-titration was observed in 6(20%) patients (P3; P5; P7; P8; P9; P26) out of the 29 patients, a dose reduction was also observed in 4(13%) patients (P10; P18; P19; P21) and finally 3 (10%) patients were initiated on other Beta-Blockers (P2; P15; P17) (Table 2, 3&4). Post-discharge bisoprolol was discontinued and substituted by another βB in 4 patients (12%) (Table 5).

In the carvedilol and nebivolol groups, a total of 3 and 2 patients were treated with the agents respectively, at initial doses as per ESC guidelines for the treatment of heart failure (Table 6). At discharge, one patient (33%) in the Carvedilol group was initiated on Bisoprolol (P3); and in the nebivolol group both patients (100%) were initiated on bisoprolol and metoprolol tablets respectively (Table 6). Post-discharge, the substitution rate in the Carvedilol group was (66%); no change was observed in the group of Nebivolol (Table 5).

In the metoprolol group: 2 patients (22%) were newly initiated on the drug (P3; P4) at initial doses of 12.5mg BD and 25mg BD respectively; at discharge dose up-titration was observed in one patient (11%) (P3), while 2 patients (22%) (P6 & P9) were initiated on other βB (Table 7).

Post-discharge no change in dose nor substitution by another βB was observed (Table 5). In the ADHF group: only 30% of patients stayed for more than 5 days in the hospital, and CV rehospitalization in that group was 20%, no death was recorded and finally recovery rate was 5%; in the HFpEF group: only 20% of the patients stayed for more than 5days in the hospital only 20% were re-hospitalized for CV diseases; no death has occurred in that group either. Finally, in the HFmEF and HFrEF groups: death rates were 12.5% and 20%, respectively; and in both groups 12.5% and 60% stayed in the hospital for more than 5 days respectively, and no CV rehospitalization occurred in both groups (Table 8).

At last mean ejection fraction values of the patients at admission and discharge were respectively: 45.09% ±10.82, (95% CI-48.42, 41.76) and 48.13%±11.29, (95% CI-51.61, 44.66), p value=0.08; and mean heart rates pre/post-treatment were found to be (78.67 bpm±15.59; 75.41 bpm±14.54 (p value=0.0003) respectively (Table 9).

Table 2: 1.25 mg OD/BD Bisoprolol dosage regimen.

Patient No	HF type	NYHA class	Newly initiated on βB?	βB used	Dose and Freq	Timing	Time spent at hospital (days)	βB dose and Freq discharge	Timing
P1	ADHF	IV	yes	Bisoprolol	1.25 mg OD	8 am	9	Bisoprolol 1.25 mg OD	8 am

Continued.

Patient No	HF type	NYHA class	Newly initiated on βB?	βB used	Dose and Freq	Timing	Time spent at hospital (days)	βB dose and Freq discharge	Timing
P2	ADHF	NA	yes	Bisoprolol	1.25 mg OD	9 am	2	Carvedilol 3.125 mg BD	9 am-9 pm
P3	ADHF	II-IV	yes	Bisoprolol	1.25 mg OD	8 am	4	Bisoprolol 2.5 mg OD	8 am
P4	HFrEF	NA	yes	Bisoprolol	1.25 mg OD	8 am	6	Bisoprolol 1.25 mg OD	8 am
P5	HFrEF	III-IV	yes	Bisoprolol	1.25 mg BD	8 am-8 pm	7	Bisoprolol 2.5 mg BD	8 am-8 pm
P6	HFmEF	NA	yes	Bisoprolol	1.25 mg BD	8 am-8 pm	16	Bisoprolol 1.25 mg BD	8 am-8 pm
P7	HFpEF	NA	yes	Bisoprolol	1.25 mg BD	9 am-9 pm	5	Bisoprolol 2.5 mg BD	9 am-9 pm
P8	HFpEF	II-IV	yes	Bisoprolol	1.25 mg BD	11 am-11 pm	4	Bisoprolol 2.5 mg BD	11 am-11 pm
P9	HFpEF	NA	yes	Bisoprolol	1.25 mg BD	8 am-8 pm	3	Bisoprolol 2.5 mg BD	8 am-8 pm

ADHF: Acute Decompensated Heart Failure; HFrEF: Heart Failure with Reduced Ejection Fraction; HFpEF: Heart Failure with Preserved Ejection Fraction; HFmEF: Heart Failure with Mid-Range Ejection Fraction; βB: Beta-Blocker; OD: Once Daily; BD: Bis (Twice) Daily; NYHA: New York Heart Association; Freq: Frequency; No: Number; NA: Not Available

Table 3: 2.5 mg OD/BD Bisoprolol dosage regimen.

Patient No	HF type	NYHA class	Newly initiated on βB?	βB Used	Dose & Freq	Timing	Time spent at hospital (days)	βB dose and Freq discharge	Timing
P10	ADHF	NA	No	Bisoprolol	2.5 mg OD	9am	7	Bisoprolol 1.25 mg OD	9am
P11	ADHF	NA	No	Bisoprolol	2.5 mg OD	8am	4	Bisoprolol 2.5 mg OD	8am
P12	ADHF	NA	No	Bisoprolol	2.5 mg OD	8am	6	Bisoprolol 2.5 mg OD	8am
P13	ADHF	NA	No	Bisoprolol	2.5 mg OD	8am	2	Bisoprolol 2.5 mg OD	8am
P14	ADHF	II-III	No	Bisoprolol	2.5 mg OD	8am	3	Bisoprolol 2.5 mg OD	8am
P15	ADHF	NA	No	Bisoprolol	2.5 mg OD	8am	4	Metoprolol 25 mg OD	8am
P16	ADHF	NA	No	Bisoprolol	2.5 mg OD	9pm	3	Bisoprolol 2.5 mg OD	9pm
P17	ADHF	II-IV	No	Bisoprolol	2.5 mg OD	8am	3	Metoprolol 25 mg OD	8am
P18	ADHF	NA	No	Bisoprolol	2.5 mg OD	8am	3	Bisoprolol 1.25 mg OD	8am
P19	ADHF	NA	No	Bisoprolol	2.5 mg OD	8am	4	Bisoprolol 1.25 mg OD	8am

Table 4: 2.5 mg OD/BD Bisoprolol dosage regimen.

Patient No	HF type	NYHA class	Newly initiated on βB?	βB Used	Dose & Freq	Timing	Time spent at hospital (days)	βB dose and Freq discharge	Timing
P20	ADHF	NA	No	Bisoprolol	2.5 mg OD	8am	3	Bisoprolol 2.5 mg OD	8am
P21	HFrEF	II-III	No	Bisoprolol	2.5 mg OD	8am	3	Bisoprolol 1.25 mg OD	8am
P22	HFrEF	NA	No	Bisoprolol	2.5 mg OD	9am	6	Bisoprolol 2.5 mg OD	9am

Continued.

Patient No	HF type	NYHA class	Newly initiated on βB?	βB Used	Dose & Freq	Timing	Time spent at hospital (days)	βB dose and Freq discharge	Timing
P23	HFrEF	NA	No	Bisoprolol	2.5 mg OD	8am	3	NA	NA
P24	HFpEF	NA	No	Bisoprolol	2.5 mg OD	8am	2	Bisoprolol 2.5 mg OD	8am
P25	HFpEF	NA	No	Bisoprolol	2.5 mg OD	8am	5	Bisoprolol 2.5 mg OD	8am
P26	HFmEF	NA	No	Bisoprolol	2.5 mg BD	8am-8pm	5	Bisoprolol 5mg BD	8am-8pm
P27	HFpEF	NA	No	Bisoprolol	2.5 mg BD	9am-9pm	7	Bisoprolol 2.5 mg BD	9am-9pm
P28	HFmEF	III	No	Bisoprolol	2.5 mg BD	9am-9pm	16	Bisoprolol 2.5 mg BD	9am-9pm
P29	HFmEF	NA	No	Bisoprolol	2.5 mg BD	8am-8pm	5	Bisoprolol 2.5 mg BD	8am-8pm

Table 5: Post-discharge medication updates.

Drug	Dose up-titration N (%)	Dose Reduction N (%)	Drug substitution N (%)
Bisoprolol	1 (3)	1 (3)	4 (12)
Carvedilol	NA	NA	2 (66)
Nebivolol	NA	NA	NA
Metoprolol	NA	NA	NA

Table 6: Carvedilol and Nebivolol dosage regimen.

Patient No	HF type	NYHA class	Newly initiated on βB?	βB Used	Dose & Freq	Timing	Time spent in hospital (days)	βB dose and Freq. discharge	Timing
P1	ADHF	II-IV	No	Carvedilol	3.125 mg BD	8am-8pm	4	Carvedilol 3.125 mg BD	8am-8pm
P2	ADHF	NA	No	Carvedilol	3.125 mg BD	8am-8pm	6	Carvedilol 3.125 mg BD	8am-8pm
sP3	HFpEF	I-III	No	Carvedilol	3.125 mg BD	9am-9pm	8	Bisoprolol 1.25 mg BD	9am-9pm
P1	ADHF	NA	Yes	Nebivolol	2.5 mg OD	9am	7	Bisoprolol 1.25 mg OD	9am
P2	ADHF	II-III	Yes	Nebivolol	2.5 mg OD	9am-9pm	3	Metoprolol 25 mg OD	9am

Table 7: Metoprolol dosage regimen.

Patient No	HF type	NYHA class	Newly initiated on βB?	βB used	Dose & Freq	Timing	Time spent in hospital (days)	βB dose and Freq discharge	Timing
P1	ADHF	II-IV	NO	Metoprolol	25 mg OD	8am	6	Metoprolol 25 mg OD	8am
P2	ADHF	IV	NO	Metoprolol	25 mg BD	9am-9pm	5	Metoprolol 25 mg BD	9am-9pm
P3	HFmEF	NA	Yes	Metoprolol	12.5 mg BD	9am-9pm	10	Metoprolol 25 mg BD	9am-9pm
P4	HFmEF	NA	Yes	Metoprolol	25 mg BD	9am-9pm	20	Metoprolol 25 mg BD	9am-9pm
P5	HFmEF	III-IV	NO	Metoprolol	25 mg OD	9am	1	NA	NA
P6	HFpEF	NA	NO	Metoprolol	25 mg BD	8am-8pm	4	Bisoprolol 2.5 mg OD	8am

Continued.

Patient No	HF type	NYHA class	Newly initiated on βB?	βB used	Dose & Freq	Timing	Time spent in hospital (days)	βB dose and Freq discharge	Timing
P7	HFpEF	NA	NO	Metoprolol	25 mg OD	8am	3	Metoprolol 25 mg OD	8am
P8	HFpEF	NA	NO	Metoprolol	50 mg BD	9am-9pm	3	Metoprolol 25 mg BD	9am-9pm
P9	HFmEF	NA	NO	Metoprolol	50 mg BD	10am-10pm	1	Carvedilol 3.12 mg BD	10am-10pm

Table 8: Evaluation of beta-blockers medications effectiveness.

Heart failure type	Duration of hospitalization		Cardiovascular Rehospitalization	Patient's health status at the end of the study	
	Duration (days)	N (%)	N (%)	Health Status	N (%)
ADHF (N=20)	1-5	14 (70)	4 (20)	Recovering	15 (75)
	6-10	6 (30)		Recovered	1 (5)
	11-15	0		Dead	0
	< 15	0		Unknown	3 (15)
HFpEF (N=10)	1-5	8 (80)	2 (20)	Recovering	5 (50)
	6-10	2 (20)		Recovered	0
	11-15	0		Dead	0
	<15	0		Unknown	5 (50)
HFmEF (N=8)	1-5	4 (50)	1 (12.5)	Recovering	5 (62.5)
	6-10	1 (12.5)		Recovered	0
	11-15	0		Dead	1 (12.5)
	<15	3 (37.5)		Unknown	2 (25)
HFrEF (N=5)	1-5	2 (40)	0	Recovering	2 (40)
	6-10	3 (60)		Recovered	0
	11-15	0		Dead	1 (20)
	<15	0		Unknown	2 (40)

Table 9: HR & EF mean, standard deviation pre/post-treatments.

Part	Parameters	Mean±SD	P value	95% CI
A	HR (bpm)			
	Pre-Treatment	78.67±15.59	0.0003	83.47-73.87
	Post-Treatment	75.41±14.54		79.89 -70.94
B	EF (%)			
	At-admission	45.09±10.82	0.08	48.42-41.76
	Post-discharge	48.13±11.29		51.61-44.66

DISCUSSION

The dosage regimen of β-blockers for treatment of HFrEF was found to be following that of ESC guidelines for treatment of HF, patients newly initiated on the drug received the appropriate starting dose of the medications as per the guideline, and in ADHF, HFpEF, HFmEF patients, we observed that βB was prescribed following the same recommendations as in those with HFrEF and the drug were found to have had great outcomes in the management of the disease.In the bisoprolol and metoprolol groups events of bradycardia and hypotension occurred which led to their discontinuations and substitutions by other agents of the same class, in the nebivolol group the drug was substituted at discharge by bisoprolol and metoprolol respectively and in the carvedilol group as well, drug was substituted by bisoprolol at discharge and post-discharge during OP consultation respectively, yet no unwanted ADRs had occurred during hospitalization in none of the patients in those 2 groups, these substitutions were mainly due the preference of bisoprolol and metoprolol over nebivolol and carvedilol, since not only they were prescribed the most but some studies have also proven the superiority of bisoprolol in HF treatment and as well in better antagonism of β-adrenergic hormone; though the same studies didn't see much difference in superiority of metoprolol compared to the other two.[12,13]

Overall rational use of the four agents (in that particular hospital) in the treatment of the above 4 types of heart failure could be confirmed; we also observed that minimal adverse events had occurred, potency of the drugs were observed and there was no urge to withdraw either of them completely, this also implied that a strict abiding to the recommendations of the guidelines helps in reducing the so feared unwanted effects of β-blocker medications.[14]

The majority of patients didn't receive dose up-titration even after months of being treated with the agents; thus it could be that physicians often aim towards a target heart rate/ or a well-tolerated dose rather than up-titrating till the target dose is reached.[15] No significant difference was observed between patients' mean ejection fraction values at admission and discharge; though our finding wasn't significant other larger-scale trials had found a minimal association between βB and further cardiac function deterioration.[16] We did observe a significant difference in mean heart rates pre/post treatments with the agents (78.67 ± 15.59 & 75.41 ± 14.54, $p=0.0003$) and also, we observed that out of those 45 patients majority (65%) spent not more than 5 days in hospital and only a few were readmitted for cardiovascular diseases (16%) in the course of the study and mortality rate was low among the study participants (4%), these results reflected the effectiveness of β-blocker medications in reducing the duration of hospitalization, frequency of readmission for CV diseases and reduction in death rate in all 4 types of heart failure under study, these results also corroborate with those found.[17]

Limitations

Limitations were a larger study would have been ideal to draw noticeable and more clinically significant data. Due to its short and limited time, the study period didn't allow comparative effectiveness study among the drugs under study.

CONCLUSION

The dosage regimen of beta-blockers under study was found to have followed that of ESC-guidelines for HF treatment, hence their rational use in that particular hospital could be confirmed. Beta-blockers were found to have had a significant impact on heart rate control and reduction in: duration of hospitalization, frequency of rehospitalization, and death among the patients under study.

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