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**Original Research Article**

# Heart rate lowering agents in acute coronary syndrome

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## ABSTRACT

**Background:** Heart rate is a key indicator of cardiovascular mortality, with ACS having the highest mortality risk when heart rate is elevated. With a target heart rate of <70 bpm, it is crucial to evaluate the effects of medications that lowers heart rate.
**Methods:** In this prospective observational study, 45 patients with ACS were studied, and it was determined whether or not the patients' heart rates at discharge from the hospital were within goal range. Additionally, we looked at demographics, drug-related issues, vitals and then statistical tests were performed.
**Results:** The demographic of 45 patients showed mean adult age was 47 years and most observed ACS was STEMI (53.3%). Patients prescribed with HRLA showed lower mean HR, SBP and DBP at discharge. Evaluated Optimal HR ≤70 bpm with HRLA therapy at discharge of the inpatients was achieved in 26.6% (63.5±5.5 bpm).
**Conclusions:** The current study showed HRLA therapy effectively reduced the heart rate at hospital discharge, but despite being on HRLA only 1/4th of patients achieved the optimal heart rate.

**Keywords:** Acute coronary syndrome, ADR, Beta-blocker, Drug related problem, Ivabradine, Negative chronotropic

## INTRODUCTION

Heart rate (HR) is a most important determinant of myocardial oxygen consumption in patients with coronary artery disease, the relationship between heart rate and prognosis of myocardial ischemia has assumed major therapeutic importance. It is shown that sustained elevated heart rate is strongly predictive of a significantly higher incidence of death, compared with those in which the heart rate is persistently within the normal or a lower range.[1]

Numerous studies have been conducted to support the claim that heart rate is a reliable predictor of mortality. Tan Xu and a colleague also performed a meta-analysis on the subject of the connection between heart rate and mortality of patients with acute coronary syndromes in the era of coronary intervention, and they came to the conclusion that elevated heart rate may increase the mortality of ACS patients in the PCI era.[2] Heart rate at discharge following hospitalisation for myocardial infarction and long-term mortality was studied, and it was shown that heart rate at discharge was much more correlated with 3-year death than heart rate at admission.[3] Another study reported that HR has been an important independent risk predictor for all-cause and cardiovascular mortality, from all these studies, suggests a piece of strong evidence, and safe to say the evidence is established.[4] So, Heart rate (HR) monitoring is very important in post ACS patients, with a heart rate target at discharge <70 bpm to help reduce the mortality rate.[5,6]

Usually, beta-blocker drug (beta-1 selective blocker) has been used clinically to reduce the heart rate, other drugs may also include ivabradine and non-dihydropyridine calcium channel blockers. Due to their chronotropic

activities these drugs can be classified under heart rate lowering agents (HRLA).

## METHODS

A prospective and observational study was done for a period of 6 months from June 2022 to December 2022 in Bangalore Baptist Hospital a tertiary care hospital in Karnataka, India. Patients who matched the eligibility requirements were enrolled in the study. Forty-five patients with diagnosis as ACS were enrolled to the study, the method of collecting the data for the study involved checking the initial assessment of the patient which include basic demographic data like age, gender, diagnosis, comorbidities, history, heart rate at time of admission, blood pressure at time of admission, notes on daily progress of the patient, note on type of ACS, these were all the data collected in data collection form. In the medical chart, only HRLA were considered and daily heart rate and blood pressure were collected from the vital monitoring chart until the patient was discharged. Heart rate and length of hospital stay were recorded at the time of patient hospital discharge. All data were analysed for demographics, prescription pattern, drug related problems and success rate of the therapy. Patient data were collected with anonymity and privacy (Figure 1).

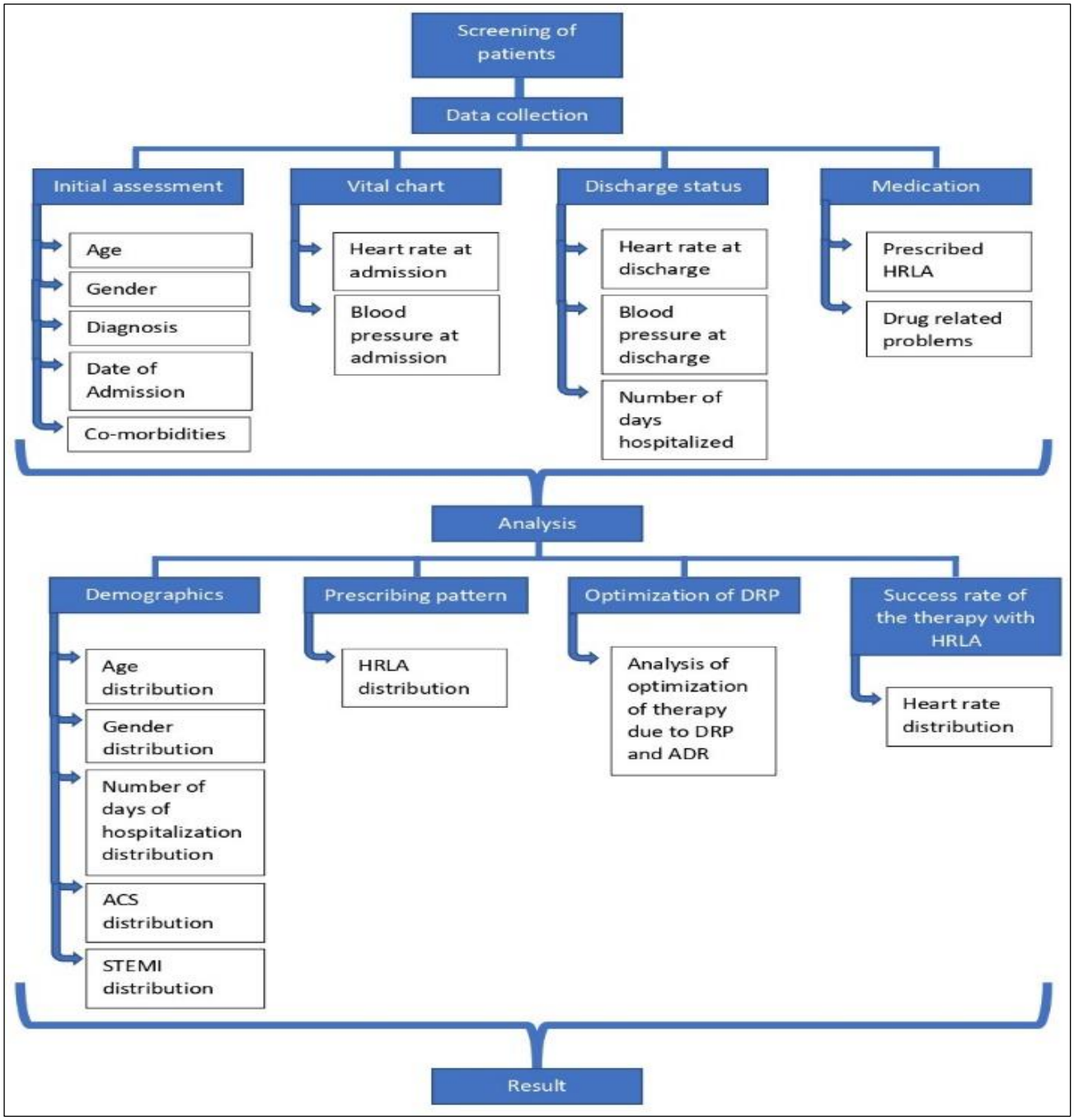


**Figure 1: Research design.**

### *Statistical analysis*

The data obtained were entered in a Microsoft excel sheet, and statistical analysis was performed using Jeffreys's Amazing Statistics Program 0.14.1v. The results are presented as Mean±SD, counts or percentages. If the variables are normally distributed (tested with Shapiro wilk test for normality), Comparison of two variables were performed using paired sample t test, if data are not normally distributed Wilcoxon signed rank test was performed. For all tests, significant was achieved at $p<0.05$.

## RESULTS

The age distribution within the study population with subjects admitted with ACS was categorized into two: adults between 18-59 years old and elderly with age above 59 years old.

Current study shows that most subjects admitted with ACS were between age 18-59 years old. Adult patients admitted with ACS were 53.3% and had mean age of 47±9.37 years, while elderly patients admitted with ACS were 46.6% with mean age of 69.8±8.84 (Table 1). Male participants were admitted with ACS at a higher rate than female subjects, with 71.1% of the study population being male (Table 1). Most patients in the study group (71.7%) were admitted for 2 to 4 days, and those admitted with ACS and receiving HRLA were more likely to stay for 3 days (33.3%) (Table 1). ACS distribution of study population shows 53.3% were admitted with STEMI, followed by 28.8% with NSTEMI and 11.1% with UA. Within the study population, 6.6% admitted with the ACS did not specify type of ACS in the initial assessment chart. In our study population most subjects admitted with STEMI had AWMI (46%) followed by IWMI (37%) and LWMI (17%) (Table 1). Besides ACS, subjects admitted had previous history of DM (64.4%) followed by HTN (48.8%), dyslipidemia (8.8), HF (6.6%), hypothyroidism (4.4%) and asthma (2.2%) of the study population (Table 1).

**Table 1: Patients demographic.**

| Baseline characteristics | HRLA therapy (n=45) | |
|---|---|---|
| **Age in years with mean and SD** | **N (%)** | **Mean±SD** |
| Adults: 18-59 | 24 (53.3) | 47±9.37 |
| Elders: >59 | 21 (46.6) | 69.8±8.84 |
| **Gender** | **N (%)** | |
| Male | 32 (71.1) | |
| Female | 13 (28.8) | |
| **Number of days hospitalized (length of stay-LOS)** | **Number of days** | **N** |
| | 1 | 1 |
| | 2 | 7 |
| | 3 | 15 |
| | 4 | 13 |
| | 5 | 3 |
| | 6 | 1 |
| | 7 | 1 |
| | 8 | 1 |
| | 9 | 1 |
| | 10 | 2 |
| **ACS distribution** | **N (%)** | |
| UA | 5 (11.1) | |
| NSTEMI | 13 (28.8) | |
| STEMI | 24 (53.3) | |
| Unspecified | 3 (6.6) | |
| **STEMI distribution** | **N (%)** | |
| AWMI | 11 (24.4) | |
| IWMI | 9 (20) | |
| LWMI | 4 (8.8) | |
| **Comorbidities** | **N (%)** | |
| Hypertension | 22 (48.8) | |
| Type 2 DM | 29 (64.4) | |
| Dyslipidemia | 4 (8.8) | |
| Heart failure | 3 (6.6) | |
| Hypothyroidism | 2 (4.4) | |
| Asthma | 1 (2.2) | |

**Table 2: Descriptive statistics of vitals.**

| Vitals | Mean±SD | Mean difference | P value |
|---|---|---|---|
| **Admission heart rate (bpm)** | 96.9±17.1 | 21 | <0.001 |
| **Discharge heart rate (bpm)** | 75.9±9.5 | | |
| **Admission systolic blood pressure (mmHg)** | 133.3±29.4 | 22.2 | <0.001 |
| **Discharge systolic blood pressure (mmHg)** | 111.1±13.7 | | |
| **Admission diastolic blood pressure (mmHg)** | 78.5±18.4 | 9.2 | <0.001 |
| **Discharge diastolic blood pressure (mmHg)** | 69.3±8.5 | | |

The HR, SBP, and DBP showed a mean difference between hospital admission and discharge. Between admission and discharge, the HR indicated a mean difference of 21 bpm (Table 2), which corresponded to a 21.67% decrease in heart rate. SBP showed similar patterns, with a mean difference of 22.2 mmHg (Table 2), or a 16.65% decrease from the baseline value to the discharge value. The DBP exhibited a mean difference of 9.2 mmHg (Table 2), which

was 11.71% decrease from the initial value to the discharge value.

Prescribing pattern seeks to monitor, evaluate, and suggest modifications in practitioners prescribing habits to make medical care more rational. In our current study, patient were prescribed with monotherapy, combination therapy and HRLA changed for optimization of therapy, all HRLA drugs which were exposed to patient were recorded and we observed most HRLA were prescribed was bisoprolol (68.6%), followed by Ivabradine (17.6%), metoprolol (9.8%), carvedilol (1.9%) and nebivolol (1.9%) (Figure 2).

Type A ADR was mostly observed in current study population, leading to the optimization of therapy. Most ADR observed was hypotension + bradycardia (50%) followed by hypotension (40%) and bradycardia (10%) (Table 3).

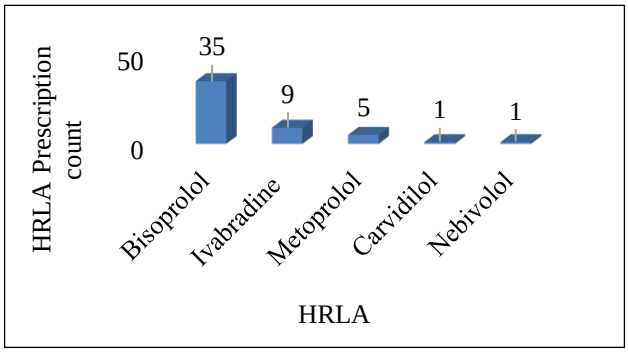


**Figure 2: Prescribing pattern of HRLA treated in study population.**

**Table 3: Optimization of drug related problems associated with HRLA therapy.**

| Drug related problems | Action taken to optimize | | | | ADR n=10 | Drug causing ADR |
|---|---|---|---|---|---|---|
| | Switching from one HRLA to another HRLA (n) | Medication dechallenge and rechallenge (n) | Frequency change (n) | Discontinuation of therapy (n) | | |
| **Bradycardia + hypotension** | 2 | 1 | 1 | 1 | 5 | Bisoprolol |
| **Hypotension** | 1 | 2 | | 1 | 4 | Bisoprolol |
| **Bradycardia** | - | | | 1 | 1 | Bisoprolol |
| **Other Reasons** | 2 | - | - | 1 | - | - |

**Table 4: Admission HR of subjects in study population before HRLA therapy.**

| Heart rate at discharge (bpm) | Number of subjects n (%) | Mean±SD |
|---|---|---|
| **≤70** | 2 (4.44) | 66.5±2.1 |
| **71-80** | 5 (11.1) | 79±1.1 |
| **81-90** | 14 (31.11) | 86.8±2.8 |
| **>90** | 24 (53.3) | 109±13.787 |

**Table 5: Discharge HR of subjects in study population treated with HRLA therapy.**

| Heart rate at discharge (bpm) | Number of subjects n (%) | Mean±SD |
|---|---|---|
| **≤70** | 12 (26.6) | 63.5±5.5 |
| **71-80** | 18 (40) | 75.8±2.1 |
| **81-90** | 13 (28.8) | 85.1±3.3 |
| **>90** | 2 (4.4) | 92±0 |

***Success rate of the therapy***

Hospital admission vs discharge heart rate of subjects in study population treated with HRLA therapy showed 4.44% vs 26.6% had HR <70 bpm (mean HR 66.5±2.1 bpm vs 63.5±5.5 bpm), 11.1% vs 40% had HR 71-80 bpm (mean HR 79±1.1 bpm vs 75.8±2.1 bpm), 31.1% vs 28.8% had HR 81-90 bpm (mean HR 86.8±2.8 bpm vs 85.1±3.3 bpm) and 53.3% vs 4.4% had HR >90 bpm (mean HR 109±13.7 bpm vs 92 bpm) (Table 4, Table 5).

## DISCUSSION

In the total of 45 patients, analysis of age, gender, number of days hospitalized, diagnosis and vitals were performed. Paired sample t-test was conducted between admission and discharge vitals. The total mean age of adult was 47 years±9.37 (53.3%), and mean age of elderly was 69.2 years±8.84 (46.6%). The total mean age of study population is 57.6 years±14.4, this was consistent with the study conducted by Sidhu et al with mean age of 56.06 years ±11.29.[7] The total percentage of males in the present study population is 71.1 % and females is 28.8%. it was compared with study conducted by Sidhu et al with 75.8% of patients were male.[7] The study was consistent with the previous study with male being most admitted with ACS and treated with HRLA. Regarding the length of hospitalization (Table 1), the patients were mostly hospitalized for 2-4 days which accounts for 77.7% of total cases (N=45), specifically most hospitalized was for 3 days (N=15, 33.3%). The study was compared with previous study conducted by Tickoo S et al with mean length of stay (LOS) 5.5 days and median of 4 days.[8] The present study showed mean LOS was less and almost

similar compared to the previous study conducted by Tickoo et al in 2016.[8] Regarding the diagnosis of the patients with ACS, the most cases were STEMI (53.3%), then NSTEMI (28.8%) and the least cases were unstable angina (11.1%) in total sample. Subject with unspecified on type of ACS were about 6.6%. In the STEMI mostly observed was AWMI (24.4%) followed by IWMI (20%) and LWMI (8.8%) in total study population. Previous study conducted by Sidhu et al observed 61.9% of patients were admitted with STEMI, similar to our study with most admitted with STEMI. Regarding comorbidities in ACS patients, most seen comorbidities were type 2 diabetes (61.6%) and hypertension (48.3%).[7] Previous study conducted by Sidhu et al observed patients admitted with ACS had history of comorbidities like hypertension (39%), diabetes (37%) and dyslipidemia (34.6%).[7] The proportion of various comorbidities in the current study did not match that in earlier investigations. When the difference between admission heart rate and discharge heart rate was analysed in subject with HRLA therapy, it was found that they had lower mean heart rate at discharge (95% confidence interval [CI], 75.9 9.5 vs 96.9 17.1, P=0.0001), lower systolic blood pressure (95% confidence interval [CI], 111.1 13.7 vs 133.3 29.4, P=0.0001), and lower diastolic blood pressure (95% confidence interval [CI], 69.3 ± 8.5 vs 78.5±18.4, P<0.003) (Table 2). The current study observed a total of 10 ADR, accounting for 22.2% of HRLA therapy. Most ADR observed was hypotension + bradycardia (50%) followed by hypotension (40%) and bradycardia (10%) (Table 3). According to textbook De sutter et al and review article in Boudonas GE both included beta blocker ADR as bradycardia and hypotension being most common side effect.[9,10] Thus, current study consistent with previous studies. When HRLA is administered, the current study showed 28% of inpatients therapy were optimized and 8.8% of the time led to discontinuation of the drug. 20% of the patients were intolerant to HRLA therapy and needed a optimization of therapy (Table 3). This study is consistent with the previous studies conducted by De Stefano et al where out of 370 ACS patients 84 were intolerance to beta blockers which was about 22.7% of the patients treated with beta blockers, study also concluded that the intolerance of beta blockers was associated to non-previous use of statin and Killip class II and had a high risk of death within 6 months.[11]

**Table 6: Previous studies and their inferences.**

| Study | Year conducted | Year published | Most HRLA used (%) | Mean HR | Total Sample size | Target heart rate | Target achieved (%) | Inference on target HR |
|---|---|---|---|---|---|---|---|---|
| **Herman et al[14]** | 2007 | 2009 | Metoprolol atenolol | 74 | 300 | 50-60 bpm | 5.3 | Not achieved |
| **Irani et al[15]** | 2007 | 2012 | Metoprolol (62.9) atenolol | 67.1±6.9 | 279 | <60 bpm | 19 | Improved with ACS pathway |
| **Gabriel steg[16]** | 2010 | 2012 | Bisoprolol (34) | 67.6 | 33438 | <60 bpm | 22.1 | Further HR lowering possible |
| **Balode et al[17]** | 2010 | 2014 | Metoprolol (47.9) bisoprolol, nebivolol carvedilol | 67.7±9.5 | 120 | <60 bpm | 25 | Insufficiently controlled |
| **Daly et al[18]** | 2003 | 2010 | Metoprolol, bisoprolol, carvedilol and atenolol | 73 | 3779 | <70 bpm | 47.7 | Inadequate control |
| **Gabriel steg[16]** | 2010 | 2012 | Bisoprolol (34) | 67.6 | 33438 | <70 bpm | 59 | Further HR lowering possible |
| **Current study with ≤70 bpm** | 2021 | NA | Bisoprolol metoprolol | 75.9±9.5 | 45 | ≤70 bpm | 26.6 | NA |

Out of 5 patients, 2 patients were switched to a different class of HRLA (ivabradine), while the remaining 3 patients were switched to a different beta blocker. Ivabradine and metoprolol were prescribed as HRLA combination, however after the patient's stability, the combination was modified to a single HRLA medication. The trends observed in the ADR suggest a risk of beta blocker intolerance. The intolerance may have multiple factors, these factors may increase possibility of ADR to occur, which may include: age group, gender, multiple drugs, and disease state, history of ADR or allergy, genetic

factors, large doses. The drug interaction may be one of the major cause of beta blocker intolerance, there are studies and expert consensus document from European society of cardiology suggesting multiple drug in standard treatment affect the beta blocker.[12,13] The drug interaction study for HRLA drug with standard treatment medication was not investigated under current study, so it is important to consider for future study on beta blocker drug interaction with the standard treatment and find the dose optimization with the therapy.

In the current study only 26.6% (63.5±5.5 bpm) of the inpatients was able to achieve heart rate ≤70 bpm with HRLA therapy at time of discharge. Maximum number of patients seen with discharge heart rate was between 71-80 bmp which accounted for 40% (75.8±2.1 bpm) of inpatients with the HRLA therapy (Table 5). Previous studies like Herman et al conducted their study 2007 and published in 2009 used HRLA metoprolol and atenolol and observed to have mean HR 74 in total of 300 sample size.[14] The study was kept with target HR of 50-60 bpm. The study concluded having observed only 5.3% achieving target HR and inferred target HR not achieved. Like Michael Herman study, Irani et al conducted a study on the same HRLA as Michael Herman study, with more preference to metoprolol with 62.9% use.[15] The study showed mean HR as 67.1±6.9 bpm and 19% achieved target HR with study inference as can achieve more with improved ACS therapy pathway. Gabriel et al conducted a study in 2010 with HRLA and 34% was treated with bisoprolol; the study observed mean HR to be 67 bpm and number of sample were 33,438; this study showed 22.1% achieved the target HR <60bpm with study inference as further HR lowering possible.[16] Balode et al conducted study in 2010 with HRLA and 47.9% was treated with metoprolol, followed by bisoprolol, carvedilol and atenolol in 120 patients; the study showed mean HR 67.7±9.5 bpm with target HR <60 bpm, 25% achieved the target HR with study inference as insufficiently controlled.[17] Present study was conducted with target HR of <70 bpm based on multiple evidence on mortality rate showing higher cardiovascular event risk with HR >70bpm. Previous study conducted by Daly et al treated patients with metoprolol, bisoprolol, carvedilol and atenolol in 3779 subjects; the study observed mean HR 67.6 bpm; with target HR <70 bpm, the study achieved target HR with 59% and inferred further HR lowering possible.[18] In Gabriel et al study if target HR <70 bpm was considered, then 59% of the patients would have achieved target HR<70 (Table 6).[16] Comparison with previous study showed further HR lowering possible, the effects of HRLA in present study might have not shown its full potential due to multiple factors like length of stay, drug interaction, ADR.

The present study had some limitations. The study was carried out over a relatively short period, which involved a reduced number of subjects, lacked control groups for proper comparison and was conducted solely within the Critical Care Unit (CCU) department, limiting detailed understanding of efficacy, safety profiles.

## CONCLUSION

The current study showed that even though we observed significant reduction in mean HR between admission and discharge, only 1/4$^{th}$ of the patients treated with HRLA achieved target heart rate. Hypotension and bradycardia were most observed ADR, and the reason for drug-related problem leading to further optimization of therapy. All ADR observed was type A (augmented) ADR caused by bisoprolol. Due to increased risk of ADR, one must look at another add on therapy or optimize dose, to achieve target heart rate.

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