Safety and efficacy of off-label use of ivabradine in patients with acute heart failure

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Background: **Ivabradine is approved to improve exercise tolerance and quality of life in patients with chronic heart failure; its use in acute heart failure (AHF) has not previously been studied.**

Methods: **Forty adult patients admitted with AHF were randomized into two groups; Group 1 patients were prescribed beta-blockers (BBs) and Group 2 patients were prescribed ivabradine. Both groups were given optimum anti-failure treatment for AHF. All patients were assessed for heart rate (HR), 6-minute walk test (6MWT), New York Heart Association (NYHA) classification, and Minnesota Living With Heart Failure Questionnaire (MLWHFQ) before and after 1 month of therapy.**

Results: **BBs or ivabradine among optimum medical therapy for AHF resulted in a significant improvement in all the studied parameters (NYHA class; 6MWT distance; HR and Borg scale dyspnea/fatigue score before and after the walk). The MLWHFQ was significantly worse during the follow-up in both groups. At the end of follow-up, there was a comparable beneficial effect attributed to the significant HR reduction observed in both groups.**

Conclusion: **The results of this pilot study demonstrated the safety of the early use of ivabradine alone versus BBs when tolerated in patients admitted with AHF (both acutely decompensated as well as *de novo*). Both groups achieved comparable reduction in HR with improvement in functional capacity and exercise tolerance.**

Keywords: Acute heart failure, Exercise tolerance, Functional capacity, Ivabradine

1. Introduction

Acute heart failure (AHF) refers to rapid onset or worsening of symptoms and/or signs of HF. It is a life-threatening medical condition requiring urgent evaluation and treatment, typically leading to urgent hospital admission. AHF may present as a first occurrence (*de novo*) or, more frequently, as a consequence of acute decompensation of chronic HF (CHF) and may be caused by primary cardiac dysfunction

Disclosure: Authors have nothing to disclose with regard to commercial support.

Received 15 March 2019; revised 22 May 2019; accepted 24 May 2019. Available online 12 June 2019

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1016-7315

Peer review under responsibility of King Saud University.
URL: www.ksu.edu.sa
https://doi.org/10.1016/j.jsha.2019.05.006

Production and hosting by Elsevier

or precipitated by extrinsic factors, often in patients with CHF [1]. Acute myocardial dysfunction (ischemic, inflammatory, or toxic), acute valvular insufficiency, or pericardial tamponade are among the most frequent acute primary cardiac causes of AHF. Decompensation of CHF can occur without known precipitant factors, but more often with one or more factors, such as infection, uncontrolled hypertension, rhythm disturbances, or non-adherence with drugs/diet [2]. The clinical presentation of AHF typically includes symptoms or signs related to congestion and volume overload rather than to hypoperfusion [3]. Identification of precipitants/causes leading to decompensation that needs urgent management (acute coronary syndrome, hypertensive emergency, rapid arrhythmias or severe bradycardia/conduction disturbance, acute mechanical cause, or acute pulmonary embolism) are crucial for the proper management of AHF.

Sympathetic hyperactivity and consequent increase in the heart rate (HR) are physiological responses to low cardiac output in patients with AHF. However, elevated HR may become inappropriate in these patients, increasing myocardial oxygen consumption/demand and decreasing diastolic filling time and might lead to hemodynamic deterioration, ventricular dysfunction (tachycardiomyopathy) and clinical deterioration. Ivabradine has shown to increase survival of patients with stable systolic CHF. Compared with beta-blockers (BBs), ivabradine has the advantage of ''pure'' negative chronotropic effect [increasing diastolic time through decrease of the spontaneous phase four depolarization in the sinoatrial node (SAN) action potential through blocking of the I_f channels present selectively in the SAN] [4], no effect on myocardial contractility [4], and has been validated as a therapeutic option in patients with CHF [5]. To the best of our knowledge, there are no studies published on the use of ivabradine in patients with AHF. Patients with HF have limited exercise tolerance; few pharmacological interventions have been proven effective in improving exercise capacity. Currently, there is conflicting evidence on the effectiveness of BBs on exercise capacity. Ivabradine has been shown to improve prognosis in patients with ischemic heart disease, left ventricular dysfunction, and HR $\geq$70 bpm [6]. The association of ivabradine and atenolol has been proven effective in increasing exercise tolerance in patients with ischemic heart disease [7].

The present study aimed to assess the efficacy and safety of ivabradine versus BBs as a strategy of HR control to improve exercise tolerance and quality of life in patients with AHF.

Abbreviations

6MWD	6 minute walking distance
6MWT	6 Minute Walk Test
AHF	acute heart failure
ATS	American Thoracic Society
BB	beta-blockers
CHF	chronic heart failure
EF	Ejection fraction
HR	Heart rate
HRQOL	health related quality of life
HS	Highly significant
MLWHFQ	Minnesota Living with Heart Failure Questionnaire
NS	Non significant
NYHA	New York Heart Association
QOL	quality of life
S	Significant
SAN	sino-atrial node

2. Patients and methods

The approval of the Ain Shams University (Cairo, Egypt) Ethical Committee was obtained according to the ethical guidelines of the 1975 Declaration of Helsinki as revised in 2008. A simple, randomized, prospective, case-control design was used for this study (simple randomization based on a single sequence of random assignments is known as simple randomization. This technique maintains complete randomness of the assignment of a subject to a particular group) [8]. Patients admitted on Saturday, Monday, and Wednesday were categorized as Group 1, patients admitted on Sunday, Tuesday, and Thursday were categorized as Group 2. The study was conducted in Ain Shams University Hospitals (cardiac care units) from December 2017 through March 2018; it included patients with HR $\geq$80 bpm in sinus rhythm, hospitalized for AHF [patients with recent onset or worsening of symptoms and/or signs of HF typically leading to urgent hospital admission, patients may present as a first occurrence (*de novo*) or as a consequence of acute decompensation of CHF, and may be caused by primary cardiac dysfunction or precipitated by extrinsic factors, often in patients with CHF], New York Heart Association (NYHA) functional Class III or IV, and ejection fraction $\leq$40% [9]. The study excluded patients with systolic blood pressure $\leq$85 mmHg (cardiogenic shock), persis-

Table 1. Comparison between Groups 1 and 2 with regard to demographic data.

		Group 1 $n = 20$	Group 2 $n = 20$	Test value	p	Significance
Age (y)	Mean ± SD	60.85 ± 11.41	60.35 ± 11.08	0.141[b]	0.889	NS
	Range	40–86	31–87			
Sex	Males	16 (80.0)	14 (70.0)	0.533[a]	0.465	NS
	Females	4 (20.0)	6 (30.0)			
Smoking	Non-smoker	8 (40.0)	9 (45.0)	2.748[a]	0.253	NS
	Smoker	11 (55.0)	7 (35.0)			
	Ex-smoker	1 (5.0)	4 (20.0)			
DM	Negative	13 (65.0)	6 (30.0)	4.912[a]	0.027	S
	Positive	7 (35.0)	14 (70.0)			
HTN	Negative	11 (55.0)	10 (50.0)	0.100[a]	0.752	NS
	Positive	9 (45.0)	10 (50.0)			
CHF	Negative	12 (60.0)	14 (70.0)	0.440[a]	0.507	NS
	Positive	8 (40.0)	6 (30.0)			
Dyslipidemia	Negative	11 (55.0)	10 (50.0)	0.100[a]	0.752	NS
	Positive	9 (45.0)	10 (50.0)			
BMI, kg/m^2	Mean ± SD	28.80 ± 3.24	30.00 ± 4.40	−0.982[b]	0.332	NS
	Range	25–36	23–37			
EF eye-balling	Mean ± SD	31.25 ± 6.35	31.75 ± 5.85	−0.259	0.797	NS
	Range	19–40	18–40			
LVEDD, mm	Mean ± SD	60.50 ± 9.42	59.10 ± 9.21	0.475	0.637	NS
	Range	47–84	44–75			
LVESD, mm	Mean ± SD	48.05 ± 10.13	49.60 ± 9.54	−0.498	0.621	NS
	Range	36–72	36–68			
Serum creatinine, mg/dL	Mean ± SD	1.12 ± 0.34	1.42 ± 0.59	−1.975	0.056	NS
	Range	0.6–2	0.8–2.5			
INR	Mean ± SD	1.12 ± 0.15	1.30 ± 0.40	−1.871	0.069	NS
	Range	1–1.5	0.9–2.1			
HB, gm/dL	Mean ± SD	12.51 ± 2.19	11.62 ± 1.54	1.487	0.145	NS
	Range	7.5–16	9–14.7			

Data are presented as n (%), mean ± SD, or range.
BMI = body mass index; CHF = chronic heart failure; DM = diabetes mellitus; EF = ejection fraction; HB = hemoglobin; HS = highly significant; HTN = hypertension; INR = international normalized ratio; LVEDD = left ventricular end diastolic diameter; LVESD = left ventricular end systolic diameter; NS = non-significant; S = significant.
[a] Chi-square test.
[b] Independent t test.

tent need of positive inotropes, acute myocarditis, primary valvular disease requiring surgery, atrial fibrillation/flutter, second/third-degree atrioventricular blockade, long QT syndrome, severe pulmonary disease, hepatic failure, creatinine ≥2.5 mg/dL, hemodialysis, or pregnancy/lactation.

Group 1, 50% of the study patients, were prescribed BBs up titrated, as tolerated, to the guideline recommended doses according to the type of BBs together with other anti-failure treatment. Group 2, 50% of the study patients, were prescribed ivabradine 5 mg twice daily with other anti-failure treatment. BBs were started when patients were weaned off intravenous (IV) inotropes, the lungs were dry, and HR was ≥80 bpm. Ivabradine was started once the patient was admitted with HR of ≥80 bpm and weaned off IV vasopressors (if any were used).

All study patients were subjected to 12-lead surface electrocardiogram. Echocardiographic assessment was performed by an expert blinded of the patient allocation in the study groups (using a GE Vivid S5N (HORTEN, NORWAY) version 10.3.0b.114 machine with an RS3 probe). Each patient was assessed for left ventricular ejection fraction using two-dimensional eye balling, left ventricular dimensions, segmental wall motion abnormalities, and diastolic function).

2.1. Functional capacity assessment

2.1.1. 6-minute walk test (6MWT)

The test was performed according to American Thoracic Society statement 2002 [10] before treatment and after 1 month of follow-up. Prior to the test, the patient was advised to sit on a chair near

Table 2. Difference between two groups at baseline with regard to NYHA class, MLWHFQ, 6MWT distance, HR and Borg scale before and after 6MWT.

Baseline		Group 1	Group 2	Test value[a]	*p*	Significance
NYHA class	3	14 (70.0)	14 (70.0)	0.000	1.000	NS
	4	6 (30.0)	6 (30.0)			
MLWHFQ total score	Mean ± SD	21.35 ± 26.52	13.45 ± 22.14	1.023[b]	0.313	NS
	Range	0–70	0–70			
HR before, bpm	Mean ± SD	94.25 ± 13.31	94.50 ± 12.13	−0.062[b]	0.951	NS
	Range	80–130	80–130			
Borg dyspnea before	Median (IQR)	4 (3–5)	3 (3–4)	−2.307[c]	0.021	S
	Range	2–7	2–5			
Borg fatigue before	Median (IQR)	4 (3–5)	3 (3–4)	−2.307	0.021	S
	Range	2–7	2–5			
6MWT distance, m	Mean ± SD	138.00 ± 66.54	135.50 ± 60.91	0.124	0.902	NS
	Range	30–280	20–230			
Premature termination of 6MWT	Negative	17 (85.0)	16 (80.0)	0.173[a]	0.677	NS
	Dyspnea	3 (15.0)	4 (20.0)			
HR after, bpm	Mean ± SD	120.50 ± 13.17	120.75 ± 15.75	−0.054[b]	0.957	NS
	Range	100–150	100–150			
Borg dyspnea after	Median (IQR)	8 (6–8)	7 (6–8)	−0.140[c]	0.889	NS
	Range	4–10	5–10			
Borg fatigue after	Median (IQR)	8 (6–8)	7 (6–8)	−0.140[c]	0.889	NS
	Range	4–10	5–10			

Data are presented as *n* (%) or mean ± SD and range.
6MWT = 6-minute walking test distance; HR = heart rate; HS = highly significant; IQR = interquartile range; MLWHFQ = Minnesota Living with Heart Failure Questionnaire; NS = non-significant; NYHA = New York Heart Association; S = significant.
[a] Chi-square test.
[b] Independent *t* test.
[c] Fisher exact test.

the starting position where blood pressure/pulse was measured, baseline dyspnea/overall fatigue was recorded using the Borg scale [11] (Appendix 1), and the worksheet was filled (Appendix 2). The scale was forwarded to the patient and the patient was asked to record his level (score) of shortness of breath and level (score) of fatigue using the scale. At the end of the exercise, the patient was reminded of the breathing score and fatigue score that he chose before the exercise and he was asked to grade both again. We used a 30-m walking corridor with marks on the wall every 3 m. The patient had to turn around at the end of the 30 m to complete one lap of 60 m at the starting line, which marks the beginning and end of each 60-m lap, and was marked on the floor using a tape [11].

2.1.2. Minnesota Living With Heart Failure Questionnaire (MLWHFQ)

The MLWHFQ is a self-administered disease-specific questionnaire for patients with HF [12], comprising 21 items rated on 6-point Likert scales, representing different degrees of impact of HF on health-related quality of life (HRQOL), from 0 (none) to 5 (very much). It provides a total score (range 0–105, from best to worst HRQOL) as well as scores for two dimensions, physical (8 items, range 0–40), and emotional (5 items, range 0–25). The other eight items (of the total of 21) are only considered for the calculation of the total score [13]. Participating patients were asked to complete the MLWHFQ at baseline and at the end of the study. For each of the 21 questions, the patients were asked to indicate how much a possible effect of HF prevented them from living as they wanted during the past month (it is important to explain beforehand to patients that they should consider the past month to answer the questionnaires). The score of the physical dimension corresponds to the sum of eight questions (# 2–7, 12, and 13) related to dyspnea and fatigue. The score of the emotional dimension is formed by five questions (# 17–21). The remaining questions (# 1, 8–11, and 14–16) plus the physical and emotional dimensions determined the total score. Higher scores indicate worse HRQOL (Appendix 3).

2.1.3. NYHA classification

(1) No limitation of physical activity, (2) slight limitation of physical activity, (3) marked limitation of physical activity, and (4) unable to carry on any physical activity without discomfort. (Symptoms of HF at rest) [14].

2.2. Statistical analysis

Data were collected, revised, coded, and entered to the statistical package for social science (SPSS version 17; SPSS Inc., Chicago, IL, USA). Qualitative data were presented as *n* (%), whereas quantitative data were presented as mean, standard deviations, and ranges. The comparison between two groups with qualitative data was done by using Chi-square test, and Fisher exact test was used only when the expected count in any cell was less than five. The comparison between two paired groups with quantitative data and normally distributed data was done by using paired sample *t* test. The confidence interval was set at 95%, and the margin of error accepted was set at 5%. The *p* value was considered significant as the following: $p > 0.05$, non-significant; $p < 0.05$, significant; $p < 0.01$, highly significant.

3. Results

Male patients represented 80% and 70% of the study population in Groups 1 and 2, respectively ($p = 0.89$). As shown in Table 1, demographics and baseline characteristics were matching in both groups, with exception of the prevalence of diabetes mellitus that was significantly higher in Group 2 ($p = 0.03$).

At baseline, there were no significant differences between both groups regarding the NYHA class, MLWHFQ, and the distance covered in the 6MWT with the assessment before and after the walk for the HR and Borg scale dyspnea/fatigue score, with the exception of Borg scale dyspnea/fatigue score before that showed significantly worse results in Group 1 ($p = 0.02$; Table 2).

There was no significant difference comparing length of hospital stay between both groups during the index admission. There were no recorded readmissions for enrolled patients during the period of follow-up; the length of stay for patients receiving BB (Group 1) was 6.85 ± 1.98 days (range, 4–10 days) and that for patients receiving ivabradine (Group 2) was 6.65 ± 2.25 days (range, 4–11 days), $p = 0.617$.

When used, BB up-titrated as part of optimum medical therapy for AHF resulted in a significant improvement in all the studied parameters (NYHA class; 6MWT distance; HR and Borg scale dyspnea/fatigue score before and after the walk), except for the premature termination of the 6MWT that did not reach statistical significance (Table 3).

When ivabradine 5 mg twice a day dose was used as part of optimum medical therapy for AHF resulted in a significant improvement in all the studied parameters (NYHA class; 6MWT distance; HR and Borg scale dyspnea/fatigue score

Table 3. Effect of BB therapy with regard to NYHA class, 6MWT distance, HR and Borg scale before and after 6MWT.

Group 1		Baseline	End of follow-up	Test value	*p*	Significance
NYHA class	1	0 (0)	8 (42.1)	35.264	<0.001	HS
	2	0 (0)	10 (52.6)			
	3	14 (70.0)	1 (5.3)			
	4	6 (30.0)	0 (0)			
HR before, bpm	Mean ± SD	94.25 ± 13.31	69.47 ± 6.85	8.981	<0.001	HS
	Range	80–130	60–80			
Borg dyspnea before	Median (IQR)	4 (3–5)	2 (1–2)	3.890	<0.001	HS
	Range	2–7	0–4			
Borg fatigue before	Median (IQR)	4 (3–5)	2 (1–2)	3.890[c]	<0.001	HS
	Range	2–7	0–4			
6MWT distance, m	Mean ± SD	138.00 ± 66.54	278.95 ± 107.44	7.813[b]	<0.001	HS
	Range	30–280	80–400			
Premature termination of 6MWT	Negative	17 (85.0)	19 (100.0)	3.243[a]	0.072	NS
	Dyspnea	3 (15.0)	0 (0.0)			
HR after, bpm	Mean ± SD	120.50 ± 13.17	93.95 ± 10.35	7.245[b]	<0.001	HS
	Range	100–50	80–120			
Borg dyspnea after	Median (IQR)	8 (6–8)	4 (4–5)	3.856[c]	<0.001	HS
	Range	4–10	3–8			
Borg fatigue after	Median (IQR)	8 (6–8)	4 (4–5)	3.856[c]	<0.001	HS
	Range	4–10	3–8			

Data are presented as *n* (%), mean ± SD, or range.
6MWT = 6-minute walking test distance; BB = beta-blockers; HR = heart rate; HS = highly significant; IQR = interquartile range; MLWHFQ = Minnesota Living with Heart Failure Questionnaire; NS = non-significant; NYHA = New York Heart Association; S = significant.
[a] Chi-square.
[b] independant t test.
[c] Fisher exact test.

Table 4. Effect of ivabradine therapy with regard to NYHA class, 6MWT distance, HR and Borg scale before and after 6MWT.

Group 2		Baseline	End of follow-up	Test value	*p*	Significance
NYHA class	1	0 (0.0)	7 (36.8)	35.264[a]	<0.001	HS
	2	0 (0.0)	11 (57.9)			
	3	14 (70.0)	1 (5.3)			
	4	6 (30.0)	0 (0.0)			
HR before	Mean ± SD	94.50 ± 12.13	72.37 ± 6.53	8.340[b]	<0.001	HS
	Range	80–130	60–85			
BORG dyspnea before	Median (IQR)	3 (3–4)	2 (1–2)	3.919	<0.001	HS
	Range	2–5	1–3			
BORG fatigue before	Median (IQR)	3 (3–4)	2 (1–2)	3.923[c]	<0.001	HS
	Range	2–5	1–3			
6MWT distance	Mean ± SD	135.50 ± 60.91	254.21 ± 6.21	10.899[b]	<0.001	HS
	Range	20–230	150–360			
Premature termination of 6MWT	Negative	16 (80.0)	19 (100.0)	4.234[a]	0.039	S
	Dyspnea	4 (20.0)	0 (0.0)			
HR after	Mean ± SD	120.75 ± 15.75	88.42 ± 9.73	7.843[b]	<0.001	HS
	Range	100–150	70–110			
Borg dyspnea after	Median (IQR)	7 (6–8)	5 (4–6)	3.750[c]	<0.001	HS
	Range	5–10	3–7			
Borg fatigue after	Median (IQR)	7 (6–8)	5 (4–6)	3.750[c]	<0.001	HS
	Range	5–10	3–7			

Data are presented as *n* (%), mean ± SD, or range.
6MWT = 6-minute walking test distance; HR = heart rate; HS = highly significant; IQR = interquartile range; MLWHFQ = Minnesota Living with Heart Failure Questionnaire; NS = non-significant; NYHA = New York Heart Association; S = significant.
[a] Chi-square test.
[b] Independent *t* test.
[c] Fisher exact test.

Table 5. Difference between two groups at the end of follow-up with regard to NYHA class, MLWHFQ, 6MWT distance, HR and Borg scale before and after 6MWT.

End of follow-up		Group 1	Group 2	Test value[a]	*p*	Significance
NYHA class	1	8 (42.1)	7 (36.8)	0.114	0.944	NS
	2	10 (52.6)	11 (57.9)			
	3	1 (5.3)	1 (5.3)			
MLWHFQ total score	Mean ± SD	30.68 ± 13.70	25.79 ± 11.66	1.186[b]	0.243	NS
	Range	15–55	12–55			
HR before	Mean ± SD	69.47 ± 6.85	72.37 ± 6.53	−1.333[b]	0.191	NS
	Range bpm	60–80	60–85			
Borg dyspnea before	Median (IQR)	2 (1–2)	2 (1–2)	−0.159[c]	0.874	NS
	Range	0–4	1–3			
Borg fatigue before	Median (IQR)	2 (1–2)	2 (1–2)	−0.315[c]	0.753	NS
	Range	0–4	1–3			
6MWT distance	Mean ± SD	278.95 ± 107.44	254.21 ± 56.21	0.889	0.380	NS
	Range m	80–400	150–360			
Premature termination of 6MWT	Negative	20 (100.0)	19 (100.0)	NA	NA	NA
HR after	Mean ± SD	93.95 ± 10.35	88.42 ± 9.73	1.696[b]	0.099	NS
	Range bpm	80–120	70–110			
Borg dyspnea after	Median (IQR)	4 (4–5)	5 (4–6)	−1.526[c]	0.127	NS
	Range	3–8	3–7			
Borg fatigue after	Median (IQR)	4 (4–5)	5 (4–6)	−1.526[c]	0.127	NS
	Range	3–8	3–7			

Data are presented as *n* (%), mean ± SD, or range.
6MWT = 6-minute walking test distance; HR = heart rate; HS = highly significant; IQR = interquartile range; MLWHFQ = Minnesota Living with Heart Failure Questionnaire; NS = non-significant; NYHA = New York Heart Association; S = significant.
[a] Chi-square test.
[b] Independent *t* test.
[c] Fisher exact test.

before and after the walk) including the premature termination of the 6MWT (Table 4). The MLWHFQ was significantly worse during the follow-up in both groups.

At the end of follow-up for 1 month, one case was missed to follow-up in each group. There were no recorded mortalities in both groups at the end of the study period. There were no significant differences between both groups regarding the NYHA class, MLWHFQ, and the distance covered in the 6MWT with the assessment before and after the walk for the HR and Borg scale dyspnea/fatigue score (Table 5).

We did not observe any significant bradycardia, re-worsening of HF, arrhythmias, or drug-related significant side effects (including phosphines in the ivabradine arm).

4. Discussion

To the best of our knowledge, this study was the first published work to compare ivabradine versus BB in AHF. The present study demonstrated that ivabradine administration was as effective as BB administration in patients with AHF.

The present study demonstrated that there was a significant reduction in resting HR after 4 weeks of treatment in both groups. The degree of reduction in resting HR in our study was comparable to the data from the The Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial (SHIFT study) subgroup (17.5 bpm reduction at 28 days in the sub-group with baseline resting HR $\geq$75 bpm) [5].

In addition, our study assessed the effect of ivabradine on exercise tolerance and HR changes with exercise and showed significant beneficial effect of ivabradine on exercise HR. The present study confirmed favorable effects of ivabradine administration alone on functional capacity as there was a highly significant improvement in the NYHA class of the patients in the current study population (there was a shift of patients from NYHA classes III and IV to NYHA classes I and II). Clinical data supporting the effects of ivabradine in HF is provided by an improvement in physical performance and increase in exercise capacity with addition of ivabradine. The SHIFT trial has demonstrated the importance of HR reduction with ivabradine for improvement of clinical outcomes of HF symptoms [5]. ETHIC-AHF (Effect of early treatment with ivabradine combined with beta-blockers versus beta-blockers alone in patients hospitalized with heart failure and reduced left ventricular ejection fraction) study result showed a trend toward a better functional class observed in patients in the intervention group (ivabradine plus BB), versus the control group (BB only) who had NYHA class III or IV at 4 months [15].

In the present study, the 6MWT distance improved significantly in both groups after treatment indicating an improvement in the functional performance, the consequence of which is an enhancement of daily activity and that can be reflected on improvement in mortality as shown by Alahdab et al. [16]; they demonstrated that increasing the walking distance by 30 m was associated with reduced mortality risk of patients with HF irrespective of their age and NYHA class. According to LIVE:LIFE study, ivabradine was well tolerated and by 6 months, it was consistently associated with meaningful improvements in quality of life [17].

We observed a worsened MLWHFQ score in >50% of patients enrolled in the study; this was attributed to acute ischemic cardiomyopathy as an underlying etiology for their AHF. Interpretation of QOL questions was worse when compared with a month prior to their precipitating event. Nevertheless, there was a QOL improvement in patients who presented with acute on-top of CHF. Ivabradine provided an extra benefit as it lacks negative inotropic effect, which allowed earlier administration of therapy than BBs, which necessitates stable blood pressure and dry lung.

4.1. Limitations

This was a single-center study with a limited number of patients; however, the sample size was adequate for the study of the primary endpoint (efficacy and safety of ivabradine in AHF).

The relative predominance of male sex and the inclusion of all causes and precipitating factors of AHF in the study population may reduce the ability for generalising the results on AHF population.

BBs were used to the maximum tolerated dose, whereas dose of ivabradine was kept at 5 mg twice and was not up-titrated to the recommended 7.5 mg twice.

5. Conclusion

The present study demonstrated the safety of the early use of ivabradine alone versus BBs when tolerated in patients admitted with AHF (both acutely decompensated as well as *de novo*). Patients in both groups achieved comparable reduction in HR with improvement in functional capacity and exercise tolerance.

Conflicts of interest

The authors declare no conflict of interest.

Appendix 1. The Borg scale.

0	Nothing at all
0.5	Extremely weak (just noticeable)
1	Very weak
2	Weak (light)
3	Moderate
4	Somewhat strong
5	Strong (heavy)
6	
7	Very strong
8	
9	
10	Extremely strong (almost max)

Appendix 2. Worksheet used in the 6-minute walking test [10].

The following elements should be present on the 6MWT worksheet and report:

Lap counter: _____ _____ _____

Patient name: _____ Patient ID# _____

Walk # _____ Tech ID: _____ Date: _____

Gender: M F Age: ___ Race: ___ Height: __ ___ ___ meters

Weight: _____ lbs, ____kg Blood pressure: ____ / ____

Medications taken before the test (dose and time): _____

Supplemental oxygen during the test: No Yes, flow _____ L/min, type ____

	Baseline	End of Test
Time	__:__	__:__
Heart Rate	____	____
Dyspnea	___	___ (Borg scale)
Fatigue	___	___ (Borg scale)

Stopped or paused before 6 minutes? No Yes, reason: _____

Other symptoms at end of exercise: angina dizziness hip, leg, or calf pain

Number of laps: ___ (×60 meters) + final partial lap: ____ meters =

Total distance walked in 6 minutes: _____ meters

Appendix 3. Minnesota Living with Heart Failure Questionnaire

MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	No	Very Little				Very Much
1. causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

11/10/04

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