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Article

Outcomes in acute decompensated chronic heart failure patients discharged with and without ivabradine: Advantages beyond heart rate control

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Abstract: Background and Aim: Ivabradine is indicated in chronic heart failure (HF) and reduced ejection fraction (EF) of < 35% and resting heart rate (HR) of > 70 bpm. However, role of Ivabradine in acute decompensated chronic HF (ADCHF) is not well known. The aim of this study was to evaluate one-year outcomes of ADCHF patients discharged with and without Ivabradine. **Materials and Methods:** This is a prospective observational cohort study of ADCHF patients from January 2016 to January 2018. Main exclusion criteria was new onset de-novo acute HF, those with EF > 50% and atrial fibrillation. Data were analysed from 130 patients who were discharged with (62 patients) or without Ivabradine (68 patients). The primary end points were one-year re-hospitalization and cardiovascular mortality between two groups. **Results:** The mean age of patients were 56 ± 15 years and 61 ± 17 years between Ivabradine and Non-ivabradine groups. EF upon discharge was 37.48% ± 5.34% vs 40.01% ± 8. 12%, with *p*-value of 0.036. At discharge, higher HR was noted in patients with Ivabradine 84 ± 13 bpm compared to 77.84 ± 12. 13 bpm in patients without Ivabradine (*p*-value = 0.006). After a year, HR in Ivabradine group was low compared to non-Ivabradine group, but was not statistically significant, 66.15 ± 8 vs. 69.29 ± 11.3 bpm, respectively. In the Ivabradine group 27.4% of patients visited emergency room (ER) more than once compared to 60.2 % without Ivabradine (*p*-value = 0.0001). 9.7% of patients in Ivabradine group required one readmission compared to 55.9% without Ivabradine (*p*-value = 0.0001). **Conclusions:** In ADCHF patients there was significant reduction in ER room visit and re-admission rate in patients discharged with Ivabradine. Hence Ivabradine therapy may be considered in patients with ADCHF with EF < 50% and HR > 70 bpm to prevent re-hospitalization and save hospitalization costs.

Keywords: ivabradine; heart failure; re-hospitalization

1. Introduction

Heart failure (HF) in the Middle-East including Oman is a very serious cardiac problem [1–3]. In the published Gulf HF registry data from Oman, there was high 1-year re-hospitalization (50%) and mortality (26%) among acute HF(AHF) patients in Oman [3]. Acute HF may present as de- novo HF or acute decompensation of chronic HF (ADCHF) and may be either HF with reduced ejection fraction < 40% (HFrEF) or HF with preserved EF > 50% (HFpEF). A new class of HF was introduced in 2016 called HF with mid-range EF (HFmEF) i.e., 41% to 49% by both European and American guidelines [4,5].

Ivabradine is a specific inhibitor of the I*f* channel in the sinoatrial node which causes decrease in the HR that in turn increases diastolic filling thus reducing myocardial oxygen demand with no other significant hemodynamic effects [6–9]. Randomized trials using Ivabradine have shown that reducing HR is associated with

reduced hospitalization and mortality in patients with HFrEF [6–8]. Both American and European guidelines recommend Ivabradine in patients with chronic HFrEF with EF < 35%, sinus rhythm and resting heart rate (HR) of> 70 bpm [3–4]. However, it is not recommended in HFpEF with EF > 50 % or in acute HF. There is lack of enough data in the use of Ivabradine in patients with presenting with ADCHF who are already on guideline directed medical therapy (GDMT). Intriguing question is whether addition of Ivabradine in those patients with ADCHF who are already on GDMT will reduce hospitalization or mortality.

We designed this prospective study to find any benefit of Ivabradine in chronic HFrEF patients who were already on GDMT and who presented with decompensated HF. The aim of this study was to evaluate long-term outcomes of ADCHF patients who were discharged with and without Ivabradine.

2. Methods

Single center prospective observational cohort study was done on 130 patients with ADCHF patients from January 2016 to January 2018 who were discharged with and without Ivabradine. Royal Hospital Scientific Research Committee approval was obtained (No. SRC#109/2018) Inclusion criteria was ADCHF patients above 18 years who were prior to index admission already diagnosed with chronic HFrEF, investigated and were being treated with GDMT. Information regarding use of GDMT medications and the dose prescribed at discharge and at one year was documented. The dose of 2 GDMT class of medications for HFrEF was converted to the equivalent of the following medications: (https://globalrph.com/drug-comparisons/) for angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), all doses were converted to equivalence of captopril; and for beta blockers, all doses converted to equivalence of carvedilol. The available medications during the study period which were prescribed were Captopril 6.25 to 50 mg TID, Lisinopril 2.5 to 20–35 mg OD, Valsartan 40 to 160 mg BD, Bisoprolol 1.25 mg to 10 mg OD and Carvedilol 3.125 to 25 mg BD. Spironolactone 25 mg was used in all patients as standard dose.

European Society of Cardiology (ESC) criteria for acute HF was used to define HF [5] and all other definitions were as per Oman HF registry study [3].

Exclusion criteria included patients with new onset de-novo acute HF, EF > 50%, HF patients who were discharged from the emergency room (ER) without admission, history or ECG evidence of atrial fibrillation or flutter, history of untreated sick sinus syndrome/second or third degree atrio-ventricular block, those who have a Pacemaker, those on hydralazine/isosorbide dinitrate combination or digoxin and lastly those with no clinical, EF or medication data at discharge or 1-year follow-up visit.

The primary end points are one-year re-hospitalization and cardiovascular mortality in HF patients on Ivabradine (Cohort 1) when compared to those not on Ivabradine (Cohort 2). The secondary end points are one-year HR, ER visits and New York Heart Association (NYHA) class.

3. Statistical analysis

Demographic information, patient's characteristics, current and follow up medications, vital signs, causes of HF, number of ER visits, admissions and one year mortality were recorded on the data sheet then transferred to EPIDATA software.

The data was analyzed using SPSS software. For the baseline variables frequencies and proportions for categorical variables and means and SD for continuous variables. The patient characteristics were compared using Fisher's exact test for categorical outcomes and t-tests for continuous variables, as appropriate. Differences between groups in terms of proportions were tested using χ^2 tests. All P values were two-sided. A *p*-value of <0.05 was considered to be statistically significant.

4. Results

Total number of 521 patients with diagnosis of ADCHF were screened, 130 patients met our inclusion and exclusion criteria. 78 patients were male which counted for 60% of total patients. A total number of 62 patients were in Ivabradine group and 68 of patients in non-Ivabradine group. **Table 1** shows the clinical characteristics of ADCHF patients.

Table 1. Clinical characteristics of patients with acute decompensated chronic heart failure.

	Study type	**Number**	**Mean**	**Std. Deviation**	***P*-value**
Age in years	With Ivabradine	62	55.82	14.887	0.087
	Without Ivabradine	68	60.71	17.153	
HR at discharge	With Ivabradine	62	84.03	13.092	0.006*
	Without Ivabradine	68	77.84	12.134	
HR at 1 year	With Ivabradine	62	66.15	8.008	0.071
	Without Ivabradine	66	69.29	11.331	
Systolic BP at discharge	With Ivabradine	62	125.06	15.798	0.055
	Without Ivabradine	68	130.72	17.295	
Diastolic BP at discharge	With Ivabradine	62	75.85	12.092	0.390
	Without Ivabradine	68	73.99	12.589	
Systolic BP at 1 year	With Ivabradine	62	127.21	14.197	0.350
	Without Ivabradine	66	129.53	13.787	
Diastolic BP at 1 year	With Ivabradine	62	76.68	9.363	0.068
	Without Ivabradine	66	73.30	11.325	

HR, heart rate; BP, blood pressure; EF, ejection fraction; *, *p*-value significant.

Mean age for patients with Ivabradine was 55.82 ± 14.88 years and for patients without Ivabradine was 60.71 ± 17.15 years. EF upon discharge showed significant difference between patients on Ivabradine and patients without Ivabradine 37.48% ± 5.34% vs. 40.01% ± 8.12%, with P value of 0.036. However, after 1 year follow up there was some improvement in the EF of patients with Ivabradine to 42.9% ± 7.46% and patients without Ivabradine remained almost the same at 40.47% ± 8.26%, but was not statistically significant. In regards to HR upon discharge, higher HR was noted in

patients with Ivabradine 84.03 ± 13 bpm comparted to 77.84 ± 12.13 bpm in patients without Ivabradine which was statistically significant with a *p*-value of 0.006. However, after a year, HR in Ivabradine group was low compared to non-Ivabradine group, but was not statistically significant, 66. 15 ± 8 vs. 69.29 ± 11.3 bpm, respectively. There were no statistically significant changes in systolic and diastolic BP upon discharge or after 1 year follow up.

Table 2 shows the difference between ACEi/ARBs and β blockers in terms of total dose used.

Table 2. Average dose of ACE inhibitors, ARBs and β blockers medications. The doses of each class of medications were calculated and reported as mean dose equivalent for Captopril (ACE inhibitors/ARBs), and Carvedilol (beta blockers).

Dose equivalent	Ivabradine use	Patients No	Total dose	*P* value
ACEi/ARBs upon discharge	With	62	50.76 ± 77.05	0.138
	Without	68	71.61 ± 73.10	
ACEi/ARBs at 1 year	With	62	60.40 ± 85.93	0.007
	Without	68	103.12 ± 79.32	
Beta blockers upon discharge	With	62	15.02 ± 11.07	0.308
	Without	68	17.99 ± 23.17	
Beta blockers at 1 year	With	62	16.79 ± 15.61	0.003
	Without	68	23.32 ± 16.62	

ACEi/ARBs and β blockers dosage at 1 year were used significantly more in those without Ivabradine. In terms of etiology of Heart failure, **Figure 1** shows the different etiologies of Heart failure wherein DCM was more common in Ivabradine group which was statistically significant with *p*-value of 0.042.

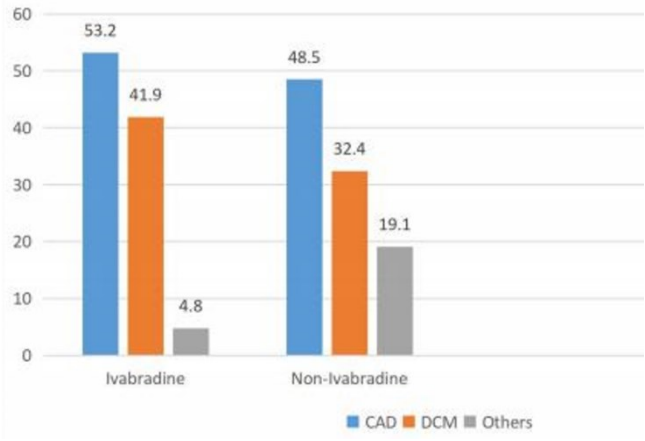

Figure 1. Etiology of heart failure.

CAD, coronary artery disease; DCM, dilated cardiomyopathy; **P*-value = 0.042 for DCM.

Table 3 shows ER visits difference between the two groups where in majority of patients without Ivabradine had frequent ER visits which was highly statistically significant with *p*-value of 0.0001 using Chi-Square Test.

Table 3. No of emergency room visits within 1 year.

	No of Emergency Room visits					
Number of Patients	**0**	**1**	**2**	**3**	**4**	***P* Value**
With Ivabradine %	45 72.6	6 9.7%	10 16.1%	1 1.6%	0 0.0%	0.0001
Without Ivabradine %	27 39.7%	10 14.7%	14 20.6%	15 22.1%	2 2.9%	
Total %	72 55.4%	16 12.3%	24 18.5%	16 12.3%	2 1.5%	

Table 4 shows readmission rates among the two groups.

Table 4. No of in-hospital re-admission with heart failure within a year.

Number of Patients	**No of in-Hospital re-admission**					
	0	**1**	**2**	**3**	**Total**	***P*-Value**
With Ivabradine %	56 90.3	6 9.7%	0 0.0%	0 0.0%	62 100%	0.0001
Without Ivabradine %	30 44.1%	32 47.1%	3 4.4%	3 4.4%	68 100%	
Total %	86 66.2%	38 29.2%	3 2.3%	3 2.3%	130 100%	

Few patients were re-admitted to hospital within one year in the Ivabradine group compared to many patient admissions in the non Ivabradine group, with P-Value of 0.0001 which is very much statistically different.

NYHA Classification at discharge and at one year is shown in **Figures 2** and **3**.

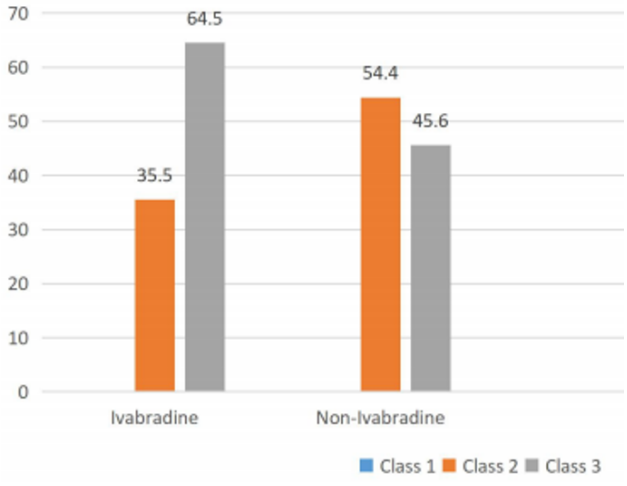

Figure 2. NYHA class at discharge in %.

NYHA, New York Heart Association; *p*-value = 0.003 for class 3.

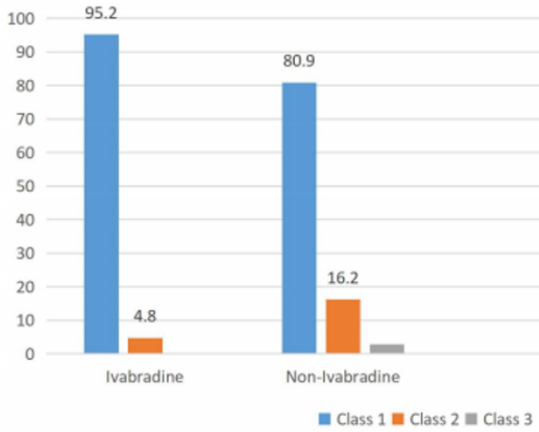

Figure 3. NYHA class at one year in %.
NYHA, New York Heart Association; *p*-value = 0.024 for class 2.

Most of the patients in both groups were NYHA class 2 or 3 at admission and at 1 year showed marked improvement in both groups to NYHA class 1. However, 4.8% of patients in the Ivabradine group were in NYHA class 2 when compared to 19.1% of patients in non-Ivabradine group in NYHA class 2/3 at one year (*p*-value = 0.024). Only one patient in the Ivabradine group had an adverse reaction which was not statistically significant with a *p*-value of 0.477. Non-cardiovascular mortality was higher in the Ivabradine group with 4 patients (6.5%), all due to pneumonia and sepsis. However, there was no cardiac deaths in Ivabradine group and 0.0% passed away in the group that never used Ivabradine at 1 year follow up. **Table 2** shows the ACE inhibitors and beta blockers dosage at discharge and at one year. Finally, the per day dose usage of Ivabradine at 1 year was 0 mg in 1 patient who stopped it and 4 patients used 5 mg and 57 patients used 10 mg of Ivabradine.

5. Discussion

The predominant finding from this study at our center is that in patients admitted with ADCHF who were discharged on Ivabradine, there was very significant reduction in emergency visit and re-admission rate in the Ivabradine group. No mortality benefit was noted.

In the observations from the Oman acute HF registry, 53% of patient of HF were re-admitted to the hospital within 12 months of discharge and Ivabradine was not available in the Ministry hospitals during that study [3]. This study results for re-hospitalization was similar to previous Oman registry at 55% in patients without Ivabradine. However, in those with Ivabradine there was markedly low readmission rate at 9.7%.

In the landmark SHIFT trial (Systolic Heart Failure Treatment with the IF Inhibitor Ivabradine Trial) Ivabradine significantly reduced readmission for worsening HFrEF, whereas mortality was not affected which is similar to our study of ADCHF patients where there was no cardiovascular mortality in either group [6]. This could be explained because of highly selected patients of ADCHF who were already on GDMT which demonstrates that patients getting GDMT in their target doses have mortality benefit in both groups.

In the ETHIC-AHF study [9], a comparative, randomized study of acute HF in patients with an left ventricular EF < 40%, HR at 28 days (64.3 ± 7.5 vs. 70.3 ± 9.3 bpm, $p = 0.01$) and at 4 months (60.6 ± 7.5 vs. 67.8 ± 8 bpm, $p = 0.004$) after discharge were significantly lower in the Ivabradine with B blocker group compared to only B blocker group. In contrast, in the current study Ivabradine with B blocker (B blocker dose was optimal) had lower HR at 1 year though statistically not significant (mean HR of 66.15 ± 8 and 69.29 ± 11.3 bpm) indicating that in ADCHF patients already on optimal B clocker dose with low HR, Ivabradine may have additional actions like improve regional myocardial blood flow, save cardiac potential energy, indirectly improve contractile function reversing LV remodeling with no negative inotropic effect which is seen with B blockers [10]. This is hypothesis generating reasoning which needs to be addressed in large trials.

In the SHIFT Chinese study, at the follow up period of 1.5 yrs., the percentage of patients with improvement in NYHA class (53.8% vs. 34.5%, $P = 0.006$) was significantly higher in the Ivabradine group than in the placebo group [11]. In the current study, there was marked improvement to NYHA class I at one-year which is similar to ETHIC-AHF study and the SHIFT Chinese sub-study [9,11].

A pooled analysis of individual patient data from SHIFT and the Morbidity-Mortality Evaluation of the I(f) Inhibitor Ivabradine in Patients with Coronary Disease and Left Ventricular Dysfunction (BEAUTIFUL) trial showed that Ivabradine improved outcomes in LV systolic dysfunction patients, whether HF etiology was ischemic or non-ischemic and across the spectrum of LVEFs and NYHA classes as noted in our current study [6,12].

A post hoc study of the SHIFT showed that among 272 patients with severe HF and a HR ≥ 75 bpm, Ivabradine reduced HF hospitalizations by 30% ($p = 0.042$) and cardiovascular death by 32% ($p = 0.034$). Though in our study there was no mortality benefit seen as mortality events were very low, 55% reduction in hospitalization was seen [13].

In a prospective cohort study similar to our study among patients with chronic HF receiving Ivabradine there was reduction in the hospitalization rate (23% before treatment vs. 5% with therapy) and was associated with a significant improvement in NYHA class, and less frequent signs of decompensation (36% to 8%). These improvements in clinical status was accompanied by an increase in LVEF (+ 5.1% at 1 year). However in the current study there was marked reduction in hospitalization and improvement in NYHA class, though there was trend towards lower EF in the Ivabradine group [14].

Furthermore, to the best of our knowledge this is only study which has shown significant reduction in ER visits in those patients on Ivabradine with ADCHF though the limitation was low sample size as many patients were excluded due to missing data during admission and at one year follow up as well as loss to follow-up. The ongoing study, efficacy of early initiation of Ivabradine treatment in patients with acute heart failure, SHIFT-AHF trial may confirm our findings [15].

6. Conclusions

In patients admitted with ADCHF who were on maximum GDMT on presentation, there was very significant reduction in emergency visit and re-admission rate in those patients discharged with Ivabradine. Hence Ivabradine therapy may be considered in patients with ADCHF with EF < 50% and resting heart rate > 70 bpm to prevent re-hospitalization and save hospitalization costs. Large scale studies are needed to confirm our findings.

Author contributions: Conceptualization, PP and AAA; methodology, PP and AAA; software, AAA; validation, IAS, AAA and PP; formal analysis, AAA; investigation, AAA; resources, AAA and IAS; data curation, AAA; writing—original draft preparation, PP; writing—review and editing PP, IAS and AAA; visualization, PP; supervision, AAA; project administration, AAA and IAS; funding acquisition, AAA. All authors have read and agreed to the published version of the manuscript.

Ethical approval: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Royal Hospital Muscat Oman with IRB No. SRC#109/2018.

Conflict of interest: The authors declare no conflict of interest.

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