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RESEARCH ARTICLE

Effect of Ivabradine on recurrent hospitalization in patients with chronic systolic heart failure

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Abstract

Objectives: To detect the effect of treatment with Ivabradine on recurrent hospitalizations at Benha university hospital due to worsening heart failure.

Background: Heart rate is an important and easily accessible physiologic variable with prognostic and clinical importance. In chronic heart failure, changes in heart rate are even more important as myocardial performance is compromised. Control of heart rate with a β-blocker is important, further control of heart rate beyond and above that achieved with a β-blocker provides added value. The potential of Ivabradine, a pure heart rate lowering drug, in this context is therefore interesting and welcome.

Methods: This study involved 100 patients admitted during the preceding year, with decompensated congestive heart failure at the cardiology department at "Benha University hospital", who were randomized to either the specific heart rate–reducing agent Ivabradine, an I_f current inhibitor, or to placebo, on top of the best possible recommended heart failure therapy.

Results: Ivabradine was associated with significant reduction in the resting heart rate, left ventricular volumes ($p<0.001$), with significant increase in LVEF ($p<0.001$), and fewer total hospitalizations for worsening HF ($p<0.01$) during the 6 months follow up period.

Conclusion: heart rate reduction with Ivabradine in patients with CHF is associated with a better NYHA functional class with regression of left ventricular dimensions and volumes and significant reduction in the risk of repeated hospitalizations (and, thus, of total burden of hospitalizations) for worsening HF.

1.INTRODUCTION

Heart rate is a predictor of adverse outcomes in patients with chronic heart failure. Increased heart rate is associated with increased mortality, while reducing heart rate is associated with a reduction in adverse outcomes ***(Lanza et al., 2006).*** Despite current intensive multi-drug therapy, persons with heart failure (HF) are frequently admitted to hospital because of exacerbation of their symptoms and, once admitted, are often readmitted ***(Dunlay et al., 2009).*** Ivabradine is a heart rate lowering drug acts by selectively inhibiting the current in the sino-atrial (SA) node responsible for pacemaking, known as the 'funny current' (I_f) ***(Swedberg et al., 2010).*** The cardiac effects are specific to the SA node, with no effect on intra-atrial, atrioventricular (AV) or interventricular conduction times ***(DiFrancesco 2010).*** There is also no effect on myocardial contractility or ventricular depolarization at therapeutic

doses ***(Savelieva and Camm 2006).*** The rationale for adding Ivabradine to the optimal standard treatment (including β-blockers) in the management of patients with symptomatic CHF is to further reduce the hazards of excessive sympathetic stimulation primarily at the myocardial level in those patients who, despite therapy with a β-blocker, still have a relatively high resting HR.

2. Patients and Methods:

2.1. Study design:

This is a prospective, randomized, placebo-controlled study that was conducted at "Benha University hospital" and enrolled 100 patients from the attendants of the cardiology department who were admitted with decompensated congestive heart failure (CHF) during the period from December 2013 to December 2014, received optimal medical therapy and followed up for 6 months from the date of discharge. Included patients were in sinus rhythm with LVEF ≤35%, NYHA functional class II or III and a resting heart rate ≥ 77 b.p.m.

Patients who had recent MI (< 2 months), sick sinus syndrome or symptomatic hypotension were excluded plus patients with atrial fibrillation/flutter.

Eligible patients were randomly allocated to either placebo (50 patients) or Ivabradine (beginning with 5 mg b.i.d., which could be titrated to 7.5 or 2.5 mg b.i.d., or stopped, depending on heart rate and tolerability) (50 patients). At randomization and throughout the study, the selected patients were receiving the maximally tolerated doses of evidence-based medication for HF (including b-blockers) ***(Dickstein et al., 2008).***

2.2. Methods:

All included patients were subjected to complete and detailed medical history, thorough physical examination, laboratory investigations, resting standard 12 leads electrocardiogram and trans-thoracic echocardiography.

All the patients were followed up after six months of regular therapy.

2.3. Study end points:

- Heart rate response.
- Changes in NYHA functional class.
- Changes in echocardiographic parameters.
- Recurrent hospitalization.

2.4. Statistical Analysis:

The clinical and echocardiographic data obtained at day 0 and 180 days post-randomization were collected, verified, revised and then edited on the P.C. and analyzed by using statistical soft ware namely (SPSS 16) special package for special sciences.

The following tests were used:

1. Mean.
2. Standard deviation (SD).
3. Number and percentage.
4. Student T test for independent samples.
5. Paired T test.
6. Chi square test (X^2).

Significance of results:

- Non significant: *P* value > 0.05.
- Significant: *P* value < 0.05.
- Highly significant: *P* value <0.001.

3. Results

The baseline characteristics of the study population showed that the mean age was 53±13.4 years (range from 22 to 82 years). Seventy percent were males, 46% were hypertensives, 37% had history of DM, 44% were smokers, 8% were obese (BMI > 30), 64% had history of IHD with 48% had history of myocardial infarction and 11% had history of AF and/or atrial flutter with mean duration of HF 3.5±1.5 years.

Between groups, analysis showed no statistically significant difference between Ivabradine group and placebo group as regards the baseline demographic criteria, risk factors, medical history, NYHA functional class, Hemodynamic data or Echocardiographic parameters at randomization.

These data are showed in *(Table 1)*.

Table (1): Baseline characteristics of the study population:

			All patients (100)		Ivabradine group (50)		Placebo group (50)		P value
			No	%	No	%	No	%	
demographic criteria	**Age (years)**	**Mean ±SD(%)**	**53±13.4**		**52.8±13.8**		**53.2±13.1**		**>0.05(NS)**
	Sex	**Male**	70	70%	34	68%	36	72%	>0.05(NS)
risk factors	**Hypertension**		46	46%	24	48%	22	44%	>0.05(NS)
	DM		37	37%	19	38%	18	36%	>0.05(NS)
	Smoking (current)		44	44%	21	42%	23	46%	>0.05(NS)
	Obesity		8	8%	5	10%	3	6%	>0.05(NS)
medical history	**History of IHD**		64	64%	31	62%	33	66%	>0.05(NS)
	History of MI		48	48%	22	44%	26	52%	>0.05(NS)
	History of AF and/or atrial flutter		11	11%	6	12%	5	10%	>0.05(NS)
NYHA functional class	**NYHA class (II)**		37	37%	15	30%	22	44%	>0.05(NS)
	NYHA class (III)		63	63%	35	70%	28	56%	>0.05(NS)

NS: non-significant, DM: diabetes mellitus, IHD: Ischemic heart disease, MI: myocardial infarction, AF: atrial fibrillation, LVEF: left ventricular ejection fraction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume.

All the patients were evaluated as regards their clinical status after 6 months with emphasis on NYHA functional class, heart rate, echocardiographic parameters and total number of hospitalization in both groups.

3.1. Change in heart rate and NYHA functional class of both groups after 6 months:

This study showed a clearly evident significant reduction in the resting heart rate by a mean of 21bpm in the Ivabradine group ($p<0.001$), without a significant change in blood pressure *(Table 2).* There was also a trend towards improvement in the NYHA functional class in the Ivabradine group as compared to the placebo, which did not reach statistical significance *(Table 3 & figure 1)*.

Table (2): Heart rate changes in both groups at baseline and after 6 months.

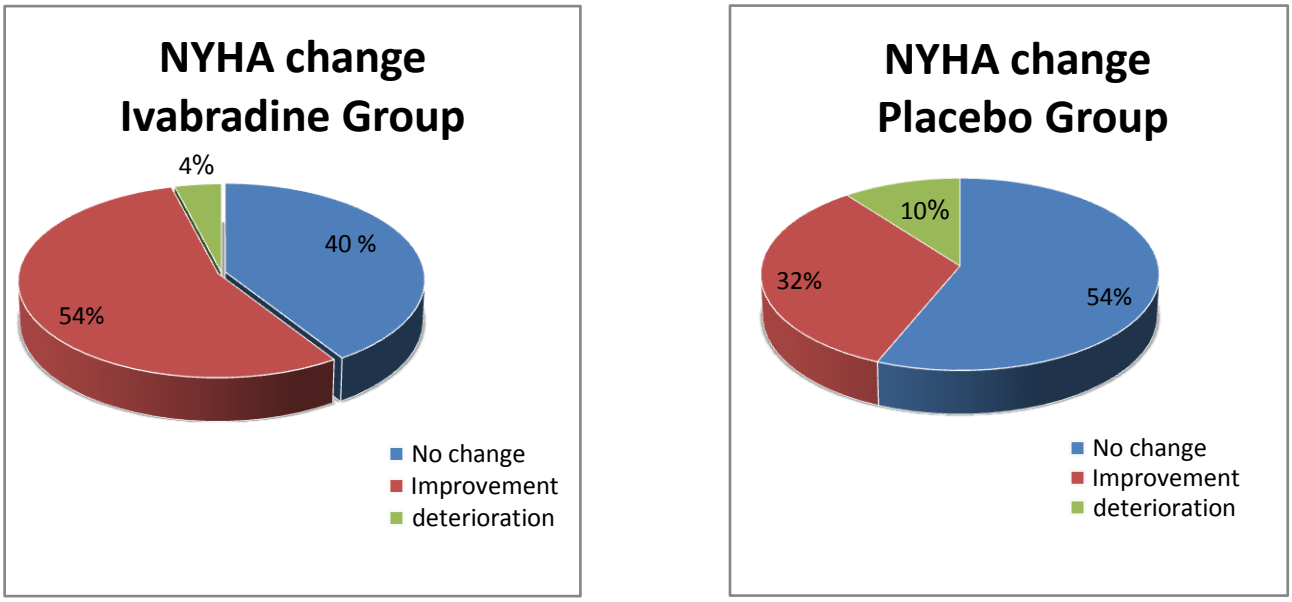
Heart rate (bpm)	Baseline	6 months	Change from baseline	p-value
Ivabradine group	91.3±7.4 bpm	70.2 ± 6.4 bpm	-21.1±5.9 bpm	<0.001(S)
Placebo group	91.6±7.3 bpm	90.3 ± 5.3bpm	-1.3±4.6 bpm	>0.05(NS)

S: significant, NS: non-significant, values are expressed as mean ± SD (%).

Table (3): Distribution of patients according to their NYHA functional classes in each group after 6 months.

	Ivabradine group (50)		Placebo group (50)		P value
	No	%	No	%	
NYHA class (I)	7	14.3%	6	12.5%	P>0.05(NS)
NYHA class (II)	27	55.1%	21	43.8%	
NYHA class (III)	14	28.6%	17	35.4%	
NYHA class (IV)	1	2%	4	8.3%	

NS: non-significant, values are expressed as mean ± SD (%).



(p>0.05)

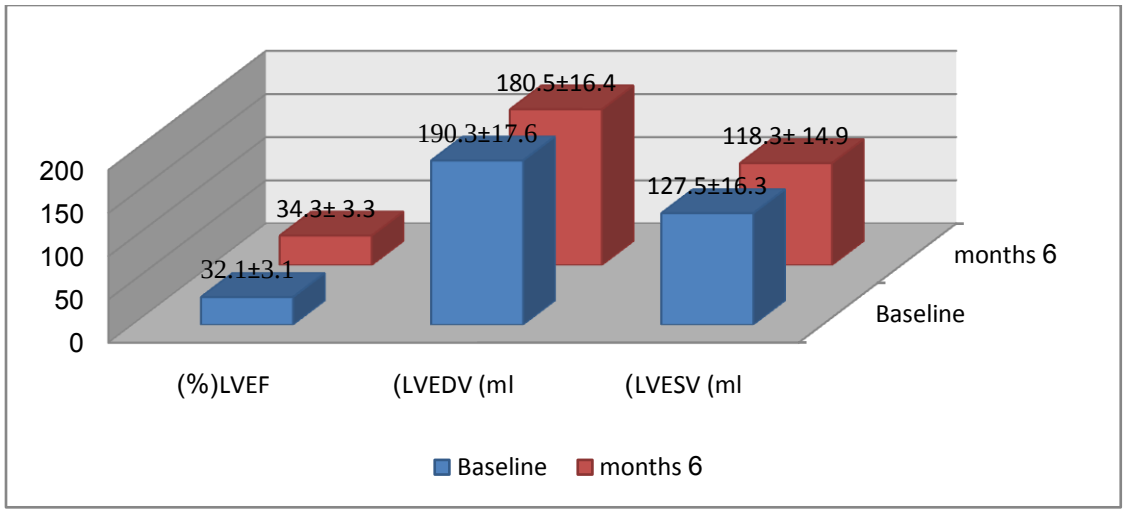
Figure (1) Pie charts showing distribution of patients with NYHA functional class change after 6 months of randomization in both groups.

3.2. Echocardiography:

All patients had a full echo evaluation at 6 months.

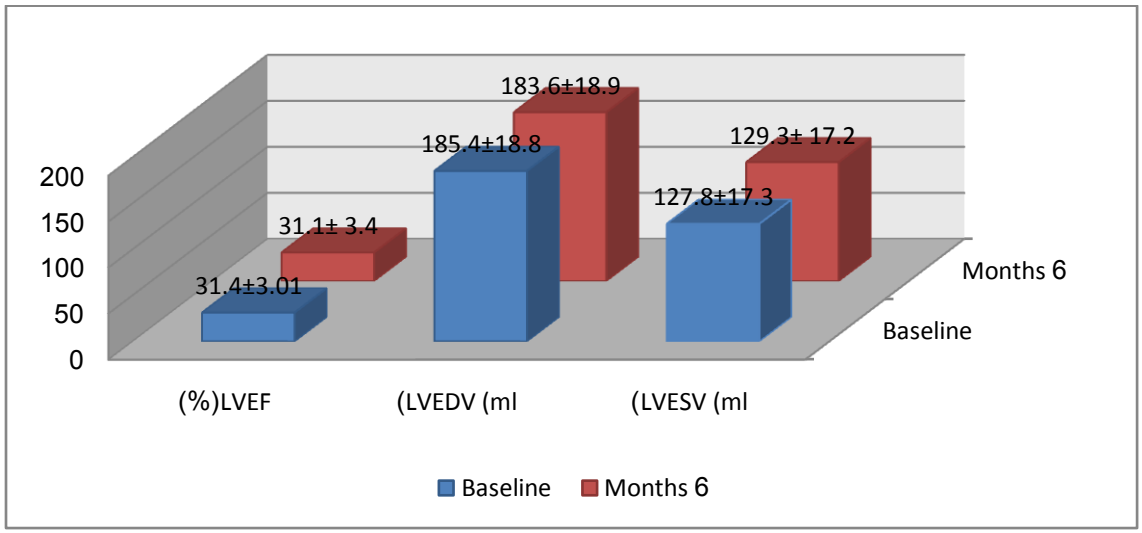
In Ivabradine group, there were significant reduction in LVEDV and LVESV from the baseline measurements (p<0.001), with a significant improvement in LVEF by 2.2% ± 2.1% (p<0.001). The details are shown in *figure (2)*.

In placebo group, there were no significant changes from the baseline measurements in the echocardiographic parameters (p>0.05). The details are shown in *figure (3)*.



Values are expressed as mean ± SD

Figure (2) Echocardiographic parameters of Ivabradine group at baseline and after 6 months follow up.



Values are expressed as mean ± SD

Figure (3): Echocardiographic parameters of Placebo group at baseline and after 6 months follow up.

3.3. Recurrent hospitalization:

In total, 31 of the 100 randomized patients experienced at least one HF hospitalization during the study. Of these 31 patients, 14 suffered at least a second HF hospitalization and 6 experienced a third *(figure 4).*

When compared with the effect of placebo, Ivabradine was associated with fewer total hospitalizations for worsening HF (19 events with Ivabradine vs. 32 events with placebo), ($P<0.01$) during a median follow-up of 6 months *(figure5).*

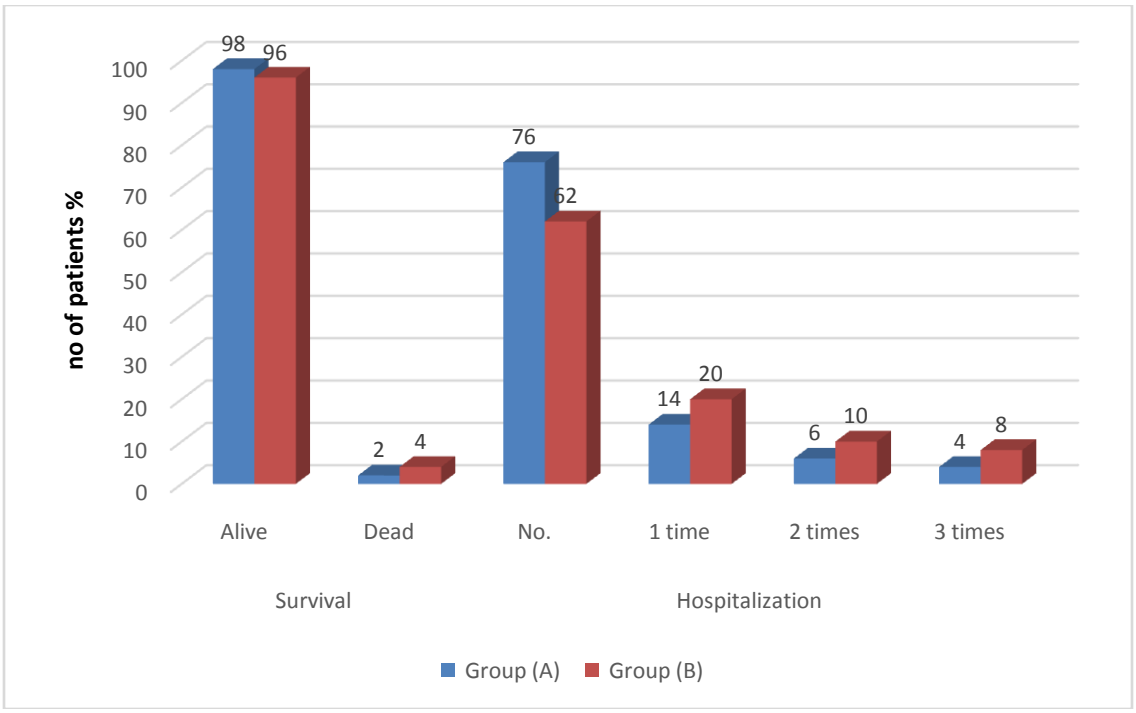


Figure (4) Distribution of patients according to their survival and number of hospitalization in each group after 6 months.

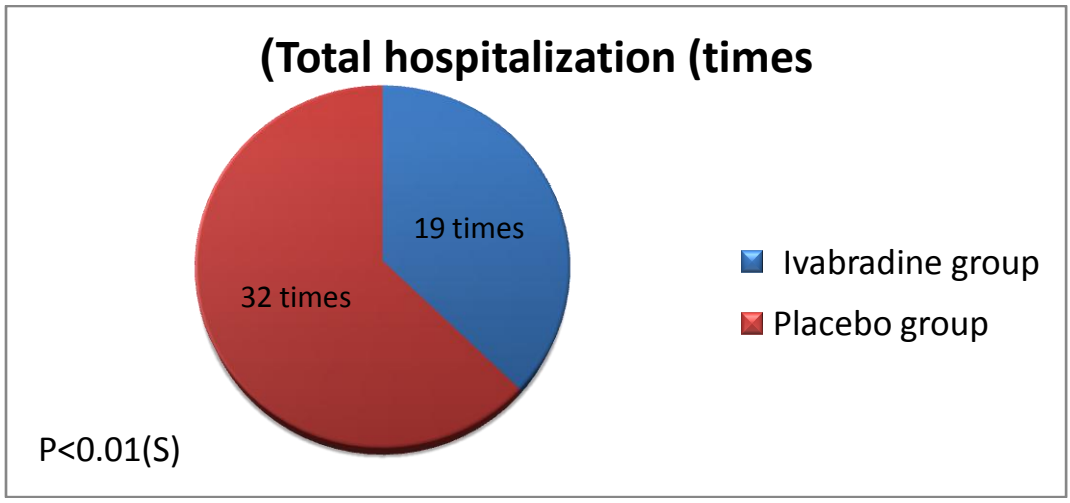


Figure (5) Total numbers of hospitalizations in each group during the 6 months follow up period.

3.4. Safety and side effects:

The incidence of adverse events though the work was low and generally similar to placebo in all treatment group. The only exception was symptomatic sinus bradycardia in two patients and minor visual disturbances considered likely to be drug related in only one patient observed in treatment group. No clinically important changes were found in the blood tests following Ivabradine, no significant effect of Ivabradine on the PR, QRS or QT intervals was found.

3.5. Mortality:

Two patients died due to acute decompensated heart failure patient in group B, whereas one patient died with SCD in group A (P>0.05), *figure 4.*

4. DISCUSSION

Enhanced heart rate is generally observed in patients with congestive heart failure (CHF) due to increased sympathetic nervous activity. It is a double-edged weapon as it tends to preserve the cardiac output at the cost of impaired left Ventricular (LV) filling, increased myocardial 0_2 consumption, and reduced coronary perfusion time ***(Spinale et al., 1991).***

Among the new perspectives in heart failure management, pure heart rate reduction with Ivabradine offers a promising approach. The rationale for adding a pure HR-Lowering agent to a B-blocker is to further reduce the consequences of excessive sympathetic stimulation primarily at the myocardial level in those patients who despite therapy with a B-blocker still have a relatively high resting HR ***(Ferrari et al., 1999).***

In the current study, we prospectively assessed the efficacy of I_f channel blocker, Ivabradine as an add on therapy in patients with CHF on optimal medical therapy in a placebo-controlled trial through several parameters including assessment of NYHA functional class, clinical parameters (blood pressure and heart rate), various echocardiographic parameters and incidence of recurrent hospitalization before and six months after randomization to either Ivabradine or placebo.

In this study, there was a significant reduction in the resting heart rate in the study group as compared to placebo. This finding is supported by the results of the study conducted by ***De Ferrari et al*** on patients with advanced LV dysfunction in which there was a mean reduction in the heart rate by 24% in the group treated with IV infusion of Ivabradine ***(De Ferrari et al., 2006).***

Moreover, the reduction in the heart rate in the present study was similar to that achieved by Ivabradine in ischaemic patients with LV systolic dysfunction included in the BEAUTIFUL study (mean reduction of 7.2 bpm at 6 months in the Ivabradine group corrected for placebo) ***(Fox et al., 2008).***

The discrepancy in the mean change in resting heart rates from baseline measurements in the Ivabradine group (compared to placebo) between the current study (21.1 bpm) and the BEAUTIFUL study (7.2 bpm) can be explained by the fact that the magnitude of the heart rate slowing induced by the I_f current inhibitor, Ivabradine is proportional to the resting heart rate ***(Camm et al., 2007),*** where the mean resting heart rate at baseline in this study was 91.3±7.4 bpm compared to71.6±9.9 bpm in the BEAUTIFUL study**.**

As NYHA functional classification is the most commonly used system to quantify the degree of functional limitation imposed by HF, we studied the effects of Ivabradine versus placebo as regard the NYHA functional class of patient six months after randomization in relation to the baseline NYHA functional class of patients at randomization, there was a trend towards improvement in the NYHA functional class in the Ivabradine group as compared to the placebo, which did not reach statistical significance.

These results are consistent with a 6-month placebo-controlled study conducted by ***Sarullo et al*** which randomized 60 patients with NYHA class II and III CHF with EFs less than 40% were randomized to either Ivabradine or placebo therapy. Over the following 6 months, patients receiving Ivabradine reported improved quality of life and improvement in NYHA functional class; objectively, they were found to have improved exercise capacity, improved peak oxygen consumption, and a significant reduction in baseline N-terminal probrain natriuretic peptide levels ***(Sarullo et al., 2010).***

Echocardiography is a crucial diagnostic tool for the diagnosis of heart failure. Some echocardiographic parameters are associated with adverse outcome in patients with CHF, such as the presence of low ejection fraction, marked LV dilatation and moderate mitral regurgitation ***(Paulus et al., 2007)***.

In the present work, there was a significant reduction in LVEDV, LVESV and a significant improvement in LVEF 6 months after randomization in the Ivabradine group. This finding is supported by the results of a double-blinded placebo-controlled trial on 65 patients with coronary artery disease and moderate LV systolic dysfunction conducted by ***Jondeau et al.*** where there was a reduction in both EDV and ESV after 6 months of Ivabradine therapy ***(Jondeau et al., 2004).***

The significant changes in left ventricular volumes and dimensions after 6 months of being treated with Ivabradine suggest that long-term Ivabradine use may prevent LV remodelling as suggested by ***Mulder et al. 2004*** in a rat model after 90 days on Ivabradine.

These results are also concordant with results from the ***SHIFT echocardiography substudy*** where 411 patients were randomly allocated to Ivabradine or placebo, superimposed on background therapy for HF. Complete echocardiographic data after 8 months showed that treatment with Ivabradine was associated with a significant reduction in LVESVI vs. placebo (- 7.0± 16.3 vs. - 0.9± 17.1 ml/m^2) and also in LVEDVI (- 7.9±18.9 vs. - 1.8±19.0 ml/m^2 in placebo) with significant improved LVEF (%) (2.4±7.7 vs. - 0.1± 8.0 in placebo) ***(Tardif et al., 2011).***

This also goes with the hypothesis of the lower the heart rate, the better; suggesting that the heart rate reduction can be a therapeutic target in patients with CHF and LV dysfunction. This is consistent with the results of the pilot study performed by ***Logeart et al.*** on patients with LV dysfunction who were pacemaker-dependant (>90% paced QRS) who

were followed up for 3 months, where pacing rate was set at either 55 or 75 b.p.m. Compared with 75 b.p.m., pacing at 55 b.p.m. was associated with a higher LVEF [+4.7% (2.6-6.7), P < 0.001], lower B-type natriuretic peptide levels [-91 pg/mL (-148 to -33), P < 0.01], and lower NYHA class (2.2 +/- 0.6 vs. 2.6 +/- 0.5, P = 0.03) ***(Logeart et al., 2009).***

Chronic HF is common and is associated with frequent exacerbations that often result in hospitalization and death ***(Dickstein et al., 2008).*** Worsening HF is one of the most common causes of hospitalization in patients with HF and is often recurrent. Even though the rate of hospitalization for worsening HF has declined over several decades, it remains relatively high ***(Chen et al., 2011).*** HF hospitalizations are also powerful predictors of subsequent HF mortality ***(Abrahamsson et al., 2009).*** Thus, a reduction in HF admissions contributes to a reduction in the overall burden of HF on patients and to a reduction in the risk of subsequent hospitalizations and death. For all these reasons, the development of therapeutic strategies that can prevent recurring hospital admissions can provide important clinical benefit.

In our study, heart rate reduction was associated with significant decline in total hospitalizations for worsening HF (19 events with Ivabradine vs. 32 events with placebo, *P<0.01*) 6 months after randomization, this finding is supported by data from the ***SHIFT*** (Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial), presented in the Heart Failure Congress 2011 ***(Borer et al., 2012).***

Our results are also consistent with the most recent guidelines from the European Society of Cardiology for the management of HF, ***(McMurray et al., 2012)*** which recommend Ivabradine for the reduction in risk for HF hospitalization. The reduction in total hospitalizations for worsening HF with Ivabradine is consistent with data reported from other clinical trials, including rennin–angiotensin system inhibitors ***(Carson et al., 2003)*** and B-blockers ***(Lane et al., 2007).*** Randomized cardiac resynchronization therapy trials have also consistently reported a reduction in admissions for worsening HF, including recurrent events ***(Goldenberg et al., 2011)***.

However, in the subgroup of patients in ***Shift study*** receiving at least half the recommended maximum dose of a beta-blocker (56% of the patients included in the trial), there was no statistically significant difference between the Ivabradine and placebo arms in terms of either overall mortality or the primary outcome, which combined cardiovascular mortality and hospitalization for worsening heart failure ***(Borer et al., 2012).***

This opens the question about the benefits of Ivabradine for heart failure patients in whom beta-blockers are tolerated and not contraindicated because of clinical status and heart rate?

5. Study Limitations

① The relatively limited number of patients included could limit the strength of results and conclusion obtained from this study.

② Being a single-center study; it is possible that unique characteristics of the patients, the physicians, or the institution may limit the generalizability of these results.

③ Follow up period was relatively short in comparison with other studies.

④ Effect of Ivabradine on hospitalizations for causes other than worsening HF could not be evaluated in our study.

6. Conclusion

Heart rate reduction with Ivabradine in patients with symptomatic CHF who are in sinus rhythm with an EF ≤35% is associated with a better NYHA functional class and a regression in left ventricular dimensions and volumes with improvement in EF as well as a pronounced reduction in the risk of repeated hospitalizations (and, thus, of total burden of hospitalizations) for worsening HF.

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