Adv Ther
DOI 10.1007/s12325-015-0185-5

ORIGINAL RESEARCH

Addition of Ivabradine to β-Blocker Improves Exercise Capacity in Systolic Heart Failure Patients in a Prospective, Open-Label Study

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Received: October 27, 2014

ABSTRACT

Introduction: Difficulties initiating and uptitrating β-blockers due to tolerability can complicate management of heart failure. Among other actions, β-blockers reduce heart rate, which is an important cardiovascular risk factor in heart failure. A new therapeutic strategy is ivabradine, which reduces resting heart rate and is associated with improved outcomes.

Methods: A 5-month, prospective, open-label, nonrandomized single-center study was performed in 69 patients. All patients had chronic heart failure with left ventricular systolic dysfunction in sinus rhythm, each were initiated on 3.125 mg twice daily (bid) carvedilol alone ($n = 36$) or 3.125 mg bid carvedilol/5 mg bid ivabradine ($n = 33$), on top of background therapy including angiotensin-converting enzyme inhibitor (88%), diuretics (86%), antiplatelet agents (91%), and statins (90%). Dosages were uptitrated every 2 weeks to 25 mg bid carvedilol in both groups and 7.5 mg bid ivabradine maximum in the carvedilol/ivabradine group. Uptitration of carvedilol lasted 1.9 ± 0.4 months with carvedilol/ivabradine and 2.8 ± 0.6 months with carvedilol alone ($P < 0.05$).

Results: The patients receiving ivabradine had lower resting heart rate at 5 months (61.6 ± 3.1 versus 70.2 ± 4.4 bpm, $P < 0.05$). Adding ivabradine to carvedilol in patients with heart failure was associated with increases in the 6-min walk test and ejection fraction (all $P < 0.05$). Treatment tolerability was satisfactory. Patients receiving ivabradine and carvedilol had lower heart rates and better exercise capacity than those on carvedilol alone.

Conclusion: Adding ivabradine to carvedilol in patients with chronic heart failure improves the uptitration of β-blocker. The results merit further verification in a prospective double-blind study.

Electronic supplementary material The online version of this article (doi:10.1007/s12325-015-0185-5) contains supplementary material, which is available to authorized users.

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Published online: 21 February 2015

Keywords: Heart rate; Heart failure; Ivabradine; Carvedilol; β-blockers

INTRODUCTION

The management of chronic heart failure has improved substantially in recent years [1, 2]. However, there remain a number of difficulties in clinical practice, notably the uptitration of β-blockers, which can be complicated due to tolerability problems. Indeed, uptitration can be a lengthy process, and may involve numerous visits to the physician. Many patients therefore receive suboptimal dosages. Observational data in Europe suggest that the target dose laid out for patients with chronic heart failure is reached in only 37% of patients receiving carvedilol and 21% of patients receiving bisoprolol or metoprolol [1, 3, 4]. Even in selected populations in randomized controlled trials, a substantial percentage of patients are unable to maintain the recommended β-blocker dose over a long period of time [5].

One of the beneficial actions of β-blockers is the reduction of heart rate. Despite this, it appears that heart rate is not optimally controlled in many heart failure patients [6, 7]. This is of concern since elevated heart rate is an important cardiovascular risk factor in chronic heart failure, and heart rate reduction is a recognized therapeutic target [8]. Moreover, as further uptitration of β-blockers is clearly not achievable in many patients, there is an urgent need for complementary therapeutic strategies to reduce heart rate.

Ivabradine, which acts by pacemaker current (I_f) inhibition in the sinus node, represents a new therapeutic opportunity [9]. Ivabradine produces a rapid reduction in resting heart rate, and is associated with a reduction in major cardiovascular events in heart failure [10]. Indeed, in SHIFT (Systolic Heart Failure Treatment with the I_f inhibitor ivabradine Trial, ISRCTN70429960), treatment with ivabradine in patients with systolic heart failure, heart rate $\geq$70 bpm, and in sinus rhythm was associated with a 26% reduction in risk for heart failure mortality ($P = 0.014$) and a 26% reduction in hospitalization for worsening heart failure ($P < 0.0001$) [10].

This paper describes a prospective open-label, nonrandomized single-center study performed to explore the effect of ivabradine on the exercise capacity, hemodynamics, and left ventricular (LV) function in patients with chronic heart failure with LV systolic dysfunction in sinus rhythm initiated on the β-blocker carvedilol.

METHOD

Study Design

This prospective open-label, nonrandomized single-center study was performed in patients attending the Cardiology Department of Donetsk Medical University, Ukraine. The first patient was recruited on 6 April 2011 and the last patient visit was on 22 December 2011. All procedures followed were in accordance with the ethical standards of the responsible committee (institution and nation) and with the Helsinki Declaration of 1975, as revised in 2006 and 2008. Informed consent was obtained from all patients for being included in the study.

Patients and Treatments

Male and female stable patients were eligible for inclusion if they had congestive heart failure in New York Heart Association (NYHA) class II or

III, LV systolic dysfunction (ejection fraction <40%), were in sinus rhythm, and had resting heart rate ≥70 bpm. Patients who had previously received ivabradine were excluded, as were those who received β-blockers in the 2 months prior to entry to the study. Patients could have received β-blockers more than 2 months previously, but had to have stopped due to tolerability or adherence issues. All patients had had a myocardial infarction between 1 and 8 years before study initiation.

The study design is presented in Fig. 1. Carvedilol 3.125 mg bid (6.25 mg/day) was initiated in all patients at entry to the study on top of standard therapy, and doubled every 2 weeks up to 25 mg bid (50 mg/day) or until the maximum tolerated dose was reached. The standard uptitration schedule for carvedilol was followed (i.e., initiation at 3.125 mg bid and then doubling the dose every 2 weeks to 25 mg bid according to tolerability). Ivabradine 5 mg bid (10 mg/day) was initiated 1 to 2 days after carvedilol, and uptitrated to 7.5 mg bid (15 mg/day) 1 month later if resting heart rate ≥70 bpm. The decision to initiate ivabradine was left to the investigator's judgment, though the protocol advised to start it in every other patient. Ivabradine was not initiated on the same day to leave time to check hemodynamic response to carvedilol. Ivabradine was down-titrated (from 7.5 to 5 or from 5 to 2.5 mg bid) in patients presenting with resting heart rate <55 bpm. All patients continued to receive standard therapy for management of their heart failure [e.g., angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker, statin, mineralocorticoid receptor antagonist, and diuretic].

Evaluations

Dosages of carvedilol and ivabradine were recorded at every routine patient visit (at 2, 4, and 6 weeks, and then 3 and 5 months), along with resting heart rate (by electrocardiogram), blood pressure (measurement by

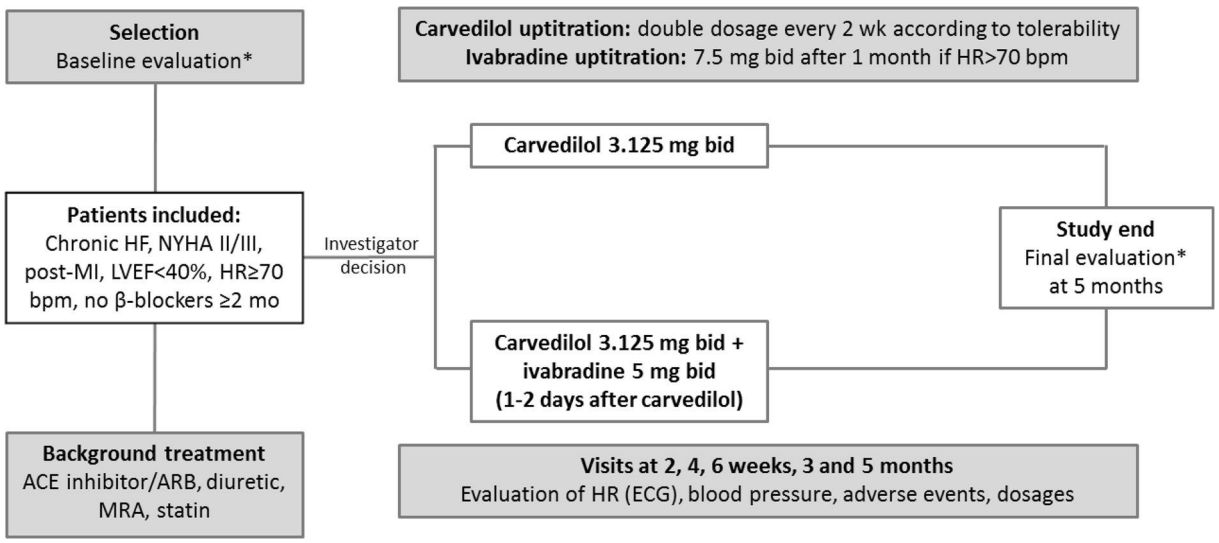

Fig. 1 Study design. *Baseline and final evaluations: laboratory tests, electrocardiography (ECG), echocardiography (ECHO), 6-min walking test, New York Heart Association (NHYA) class. *HF* heart failure, *HR* heart rate, *MI* myocardial infarction, *LVEF* left ventricular ejection fraction, *ACE* angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *MRA* mineralocorticoid receptor antagonist, *Bid* twice daily, *Mo* month

sphygmomanometer, standard protocol), and safety and tolerability as part of the routine physical examination. A 6-min walking test and echocardiography were performed at baseline and 5 months. Patients with and without ivabradine were compared for performance on the 6-min walking test at 5 months (primary endpoint) and echocardiographic parameters at 5 months (LV ejection fraction, LV end-diastolic diameter, LV end-systolic diameter, and left atrial dimension).

Statistical Methods

Baseline characteristics are presented for the whole population and for the two treatment groups separately as descriptive statistics, with mean ± SD for continuous variables and numbers and percentages for categorical variables. Safety and tolerability are also presented using descriptive statistics. Between-group differences in heart rate, carvedilol dosage, systolic blood pressure (SBP), 6-min walking test, and echocardiographic parameters were analyzed using a Wilcoxon's test. A P value of <0.05 was considered as statistically significant. Statistics were performed by the Donetsk Medical University, Ukraine, using NCSS-2007 program (NCSS LLC, 329 North 1000 East, Kaysville, USA).

RESULTS

A total of 76 patients were selected, and 69 patients were included and completed the planned 5-month follow-up with 36 patients receiving carvedilol alone and 33 patients receiving carvedilol/ivabradine (Fig. 2). There were no withdrawals during the study.

The baseline characteristics of the patients receiving carvedilol alone were similar to those

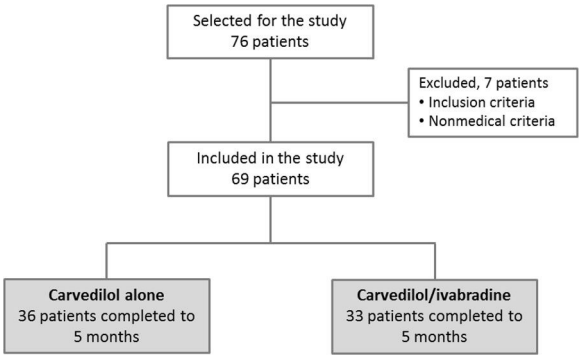

Fig. 2 Trial profile

receiving carvedilol/ivabradine (Table 1). All patients were in sinus rhythm. Angina of varying severity was present in 55 patients (80%). In patients with chronic renal insufficiency, levels of glomerular filtration rate were within the range 30–60 mL/min/1.73 m^2. The large majority of patients were receiving ACE inhibitors (88%), diuretics (86%), antiplatelet agents (91%), and statins (90%). There were no significant differences between the two treatment groups, with the exception that there were fewer patients with hypertension in the carvedilol/ivabradine group ($P < 0.05$). There were also more patients with previous percutaneous coronary intervention, statistically non-significant (P = NS), in the group receiving carvedilol/ivabradine.

The mean dosage of ivabradine at 5 months was 12.2 ± 2.1 mg/day. Uptitration of carvedilol lasted 1.9 ± 0.4 months in the carvedilol/ivabradine group and 2.8 ± 0.6 months in the group on carvedilol alone ($P < 0.05$). Patients receiving carvedilol/ivabradine achieved higher dosages of carvedilol over the study (37.8 ± 13.9 mg/day) than the group receiving carvedilol alone (30.9 ± 15.3 mg/day) ($P = 0.049$) (Fig. 3a). The proportion of patients reaching at least 50% of the target carvedilol dosage of 50 mg/day was 23 (70%) in

Table 1 Baseline characteristics

	Whole population ($n = 69$)	Carvedilol ($n = 36$)	Carvedilol/ivabradine ($n = 33$)
Demographic characteristics			
Age (years)	62.9 ± 12.1	62.1 ± 11.4	63.2 ± 12.3
Male	46 (67%)	25 (69%)	21 (64%)
Body mass index, kg/m^2	28.4 ± 4.1	27.6 ± 4.0	28.9 ± 3.8
Cardiovascular history			
Left ventricular ejection fraction (%)	37.0 ± 5.9	36.9 ± 6.1	37.4 ± 6.3
Heart rate (bpm)	82.4 ± 11.2	83.1 ± 10.6	82.7 ± 11.3
Systolic blood pressure (mm Hg)	132.5 ± 13.8	131.4 ± 13.6	133.6 ± 12.7
Diastolic blood pressure (mm Hg)	76.6 ± 9.6	75.4 ± 10.1	77.3 ± 9.4
Angina			
CCS class I	14 (20%)	8 (22%)	6 (18%)
CCS class II	37 (54%)	19 (53%)	18 (55%)
CCS class III	4 (6%)	2 (6%)	2 (6%)
Heart failure			
NYHA class II	28 (41%)	15 (42%)	13 (39%)
NYHA class III	41 (59%)	21 (58%)	20 (61%)
Arterial hypertension	39 (57%)	24 (67%)	15 (46%)
Previous stroke/TIA	9 (13%)	4 (11%)	5 (15%)
Prior CABG	13 (19%)	7 (19%)	6 (18%)
Prior PCI	26 (38%)	12 (33%)	14 (42%)
Time from last myocardial infarction (years)	2.0 ± 1.5	2.3 ± 1.9	2.1 ± 0.8
Medical comorbidities			
Diabetes mellitus	17 (25%)	10 (28%)	7 (21%)
Current or former smoker	39 (57%)	22 (61%)	17 (52%)
Chronic renal insufficiency	24 (35%)	13 (36%)	11 (33%)
Current medications[a]			
Angiotensin-converting enzyme inhibitors	61 (88%)	31 (86%)	30 (91%)
Angiotensin II receptor blockers	8 (12%)	5 (14%)	3 (9%)
Digoxin	25 (36%)	14 (39%)	11 (33%)
Loop/thiazide diuretics	59 (86%)	31 (86%)	28 (85%)
Aldosterone antagonists	42 (61%)	21 (58%)	21 (64%)
Aspirin/P2Y12 inhibitors	63 (91%)	34 (94%)	29 (88%)

Table 1 continued

	Whole population ($n = 69$)	Carvedilol ($n = 36$)	Carvedilol/ivabradine ($n = 33$)
Warfarin	6 (9%)	2 (6%)	4 (12%)
Statins	62 (90%)	34 (94%)	28 (85%)

Values are mean ± SD or *n* (%)

CCS Canadian Cardiovascular Society, *NYHA* New York Heart Association, *TIA* transient ischemic attack, *CABG* coronary artery bypass graft, *PCI* percutaneous coronary intervention

[a] According to the inclusion criteria, none of the patients had received β-blockers in the 2 months before the study

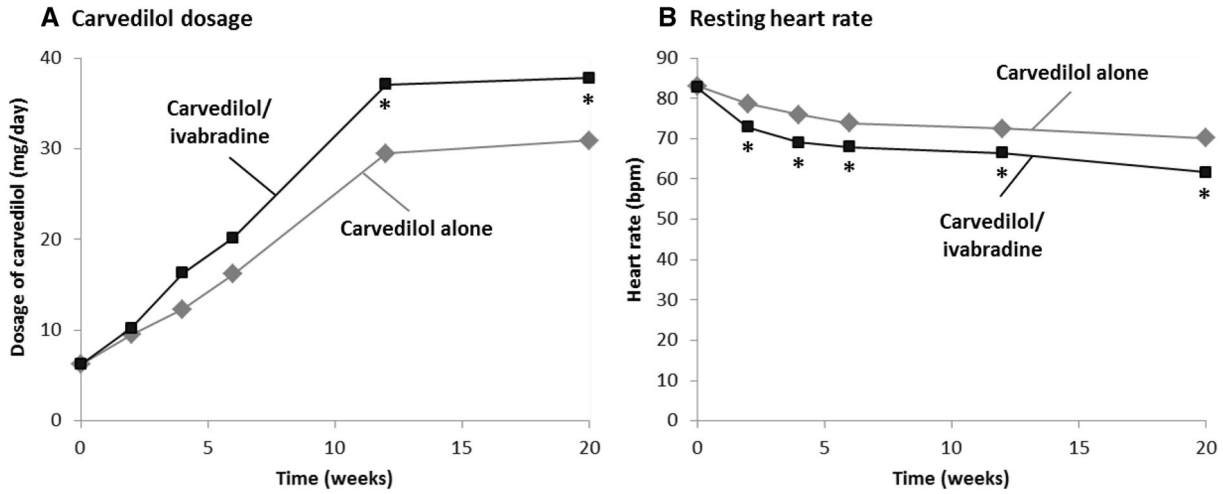

Fig. 3 Mean dosage of carvedilol **a** and mean resting heart rate **b** according to treatment group. *$P < 0.05$ versus patients on carvedilol alone

the group with carvedilol/ivabradine versus 13 (36%) in the group receiving carvedilol alone.

The patients in the carvedilol alone group had lower β-blocker dosage than the patients in the carvedilol/ivabradine group ($P < 0.05$) (Table 2). In addition, the patients in the carvedilol alone group had lower systolic blood pressure ($P < 0.001$). The patients receiving ivabradine had lower resting heart rate of 61.6 ± 3.1 bpm at 5 months versus 70.2 ± 4.4 bpm at 5 months in the group on carvedilol alone ($P < 0.001$) (Fig. 3b).

In both groups of patients, there were improvements in LV ejection fraction and LV volumes over the 5-month treatment period (Table 3). The increase in LV ejection fraction and reduction LV volume was more pronounced in the group with carvedilol/ivabradine, with significant differences for LV end-systolic diameter ($P < 0.001$) and left atrial dimension ($P < 0.001$). The distance reached in 6-min walking test was significantly longer in the carvedilol/ivabradine group than in the carvedilol alone group. ($P < 0.001$) (Table 3).

Adding ivabradine to carvedilol in patients with heart failure was associated with a range of significant beneficial effects with a greater reduction in heart rate, an increase in the distance walked in the 6-min walk test, and an increase in the LV ejection fraction (all

Table 2 Mean dosages of carvedilol and ivabradine, heart rate, and systolic blood pressure doses of carvedilol, and ivabradine during the study

	Carvedilol alone ($n = 36$)			Carvedilol/ivabradine ($n = 33$)			
	Carvedilol dosage, mg/day[a]	Heart rate (bpm)	SBP (mm Hg)	Carvedilol dosage, mg/day[a]	Ivabradine dosage, mg/day[a]	Heart rate (bpm)	SBP (mm Hg)
Baseline	6.25	83.1 ± 10.6	131.4 ± 13.6	6.25	10	82.7 ± 11.3	133.6 ± 12.7
2 weeks	9.5 ± 3.2	78.7 ± 8.4	127.4 ± 13.5	10.2 ± 3.1	10	72.9 ± 6.9*	129.3 ± 12.0
4 weeks	12.3 ± 6.4	75.9 ± 6.7	120.7 ± 10.3	16.3 ± 6.9	10.6 ± 1.7	69.1 ± 4.5*	125.2 ± 11.8
6 weeks	16.2 ± 8.7	73.8 ± 5.1	114.6 ± 7.8	20.2 ± 11.7	10.9 ± 1.9	67.9 ± 3.6*	124.5 ± 9.6*
3 months	29.5 ± 14.7	72.5 ± 4.6	112.5 ± 8.1	37.1 ± 17.2*	11.1 ± 2.1	66.4 ± 3.5*	123.8 ± 7.1*
5 months	30.9 ± 15.3	70.2 ± 4.4	116.4 ± 7.8	37.8 ± 16.3*	12.2 ± 2.1	61.6 ± 3.1*	123.5 ± 5.7*

Values are mean ± SD
Bid twice daily, *SBP* systolic blood pressure
* $P < 0.05$ versus patients on carvedilol alone
[a] Initiating dosages were carvedilol 3.125 mg bid carvedilol and 5 mg bid ivabradine. Target dosage of carvedilol was 50 mg/day (25 mg bid); target dosage of ivabradine was 7.5 mg bid

Table 3 Echocardiographic data and distance in the 6-min walking test in patients taking carvedilol or carvedilol/ivabradine

	Carvedilol ($n = 36$)		Carvedilol/ivabradine ($n = 33$)	
	Baseline	5 months	Baseline	5 months
LV ejection fraction (%)	36.9 ± 6.1	38.7 ± 6.8	37.4 ± 6.3	41.3 ± 6.9
LV end-diastolic diameter (cm)	6.8 ± 0.4	6.7 ± 0.3	6.8 ± 0.3	6.5 ± 0.3
LV end-systolic diameter (cm)	4.7 ± 0.3	4.6 ± 0.3	4.6 ± 0.3	4.4 ± 0.2*
Left atrial dimension (cm)	4.2 ± 0.2	4.0 ± 0.3	4.1 ± 0.3	3.8 ± 0.2*
6-mi walking test (m)	465.3 ± 87.6	527.2 ± 90.6	458.4 ± 93.2.6	574.4 ± 102.3*

Values are mean ± SD
LV = left ventricular
* $P < 0.05$ versus patients on carvedilol alone

$P < 0.001$) (Fig. 4a–c). Significantly, more patients in the carvedilol/ivabradine group (58%) had an improvement of at least one NYHA class than in the carvedilol alone group (36%) ($P < 0.05$) (Fig. 4d).

Treatment tolerability was satisfactory in all patients. In eight cases, there were side effects of carvedilol, including six cases of muscle/general weakness and two cases of transient bronchial obstruction. Observed side effects were mild, and drug withdrawal was not deemed necessary in any of the cases. The side effects generally reversed using a slower uptitration schedule or reducing dosage. The use of ivabradine in combination with carvedilol was associated with a reduction in resting heart rate to levels in the range of 40–50 bpm in three cases without the development of syncope or

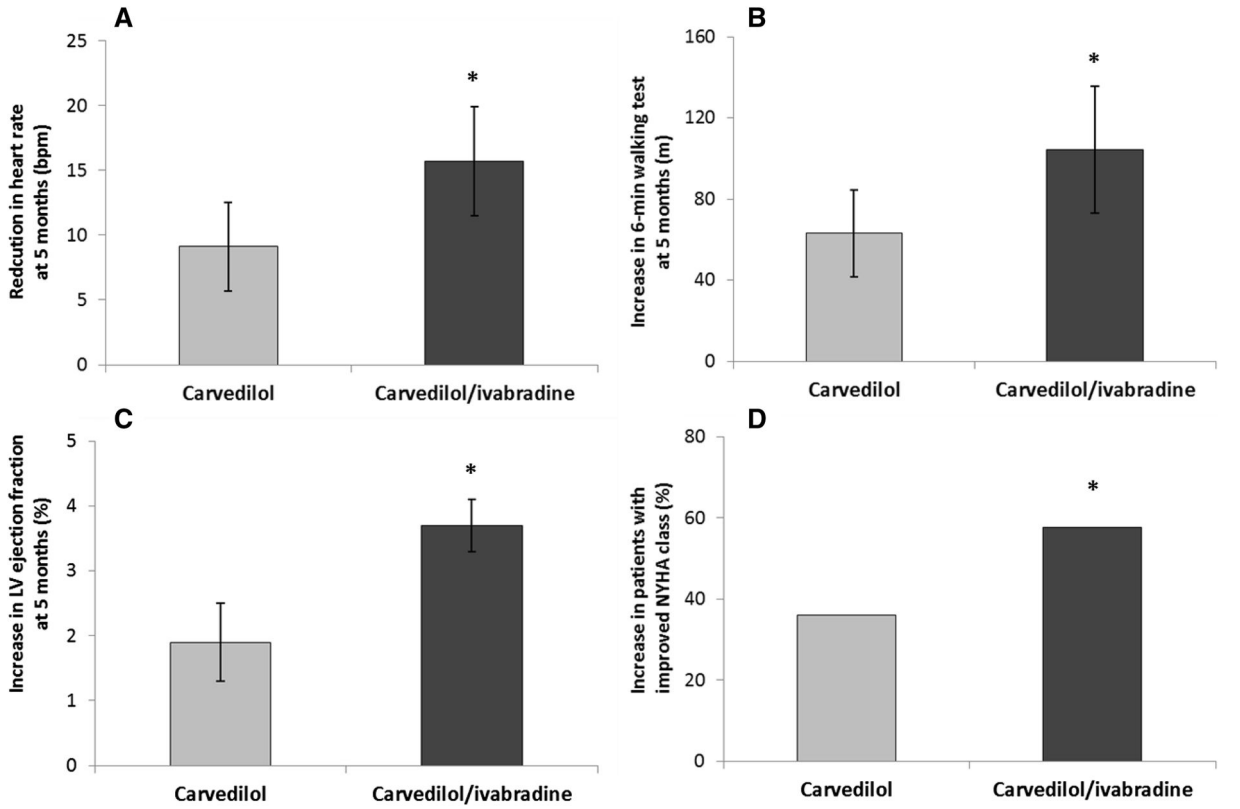

Fig. 4 Change in heart failure parameters between baseline and 5 months for (**a**) resting heart rate, (**b**) distance walked in the 6-min walking test, (**c**) left ventricular (LV) ejection fraction, and (**d**) percentage of patients with an improvement of at least one New York Heart Association (NYHA) in the carvedilol ($n = 36$) and carvedilol/ivabradine ($n = 33$) groups. *$P < 0.01$ versus patients on carvedilol alone

changes in sinoatrial, atrioventricular, and intraventricular conduction on electrocardiography. These episodes of bradycardia were also mild and transient, and could be eliminated by reducing the dose of ivabradine (from 7.5 to 5 mg bid in two patients, and from 5 to 2.5 mg bid in one patient) and never led to withdrawal of ivabradine. Two patients on ivabradine had mild and transitory visual effects (blurred vision) without the need for drug withdrawal.

DISCUSSION

The addition of ivabradine shortly after initiation of carvedilol in patients with chronic heart failure and in sinus rhythm was associated with significantly greater reduction in heart rate, and significantly improved LV ejection fraction and exercise capacity (6-min walking test). The results are in line with the recent results of an open-label multicenter study in nearly 2000 patients with heart failure, which reported that ivabradine effectively reduced heart rate and improved symptoms over 4 months [11]. The addition of ivabradine in our study also appeared to facilitate the uptitration of the β-blocker, with more patients in the carvedilol/ivabradine group reaching ≥50% target dose of β-blocker than in the group on carvedilol alone.

Since the mode of action of ivabradine does not affect parameters other than heart rate, ivabradine does not have negative inotropic

effect and does not carry the risk for hypotension; it also improves systemic hemodynamics and exercise tolerability [12–14]. In clinical terms, this translates into increased stroke volume and preserved cardiac output in patients on ivabradine, and better exercise tolerance and ultimately a better quality of life for patients with chronic heart failure [15–17]. In line with this, even though the patients in the study who received ivabradine reached higher dosages of carvedilol, they had significantly higher levels of SBP at the end of the study (123.5 ± 5.7 versus 116.4 ± 7.8 mm Hg, $P < 0.05$). This constitutes a considerable advantage insofar as low SBP limits the use of many other heart failure therapies and is associated with increased risk for all-cause, heart failure, and cardiovascular mortality, as well as hospitalization for cardiovascular reasons or heart failure [18–21].

The improved efficacy of the combination in comparison with β-blocker alone can be rationalized pathophysiologically by the complementary modes of action of β-blocker and ivabradine. By contrast to β-blocker, since ivabradine does not have negative inotropic and lusitropic effects [22, 23], it reduces heart rate without affecting cardiac output, and it has no impact on blood pressure. This explains the differences in the impact on hemodynamic profile with ivabradine versus that with β-blocker and the absence of many of the limitations associated with β-blockers. Results from a study in which patients with advanced heart failure received an acute intravenous administration of ivabradine indicate that the heart rate reduction achieved with ivabradine maintains cardiac output due to an increase in stroke volume [24]. These data are consistent with a recent analysis in the SHIFT trial which demonstrated that improved ventricular–arterial interaction caused by heart rate reduction seems to contribute to the increase in stroke volume and improved cardiac efficiency, thereby preserving cardiac output of patients receiving ivabradine [17]. Therefore, heart rate reduction with ivabradine does not have any of the detrimental effects that might occur in the beginning of uptitration of β-blockers complicating the achievement of target doses. Globally, the differences in hemodynamic profile in ivabradine-treated patients may have two effects: it makes patients more likely to exercise in everyday life and activity, as has been demonstrated in other studies [25]; and it facilitates the uptitration of β-blockers. There are a number of possible mechanisms for the improved exercise capacity with the combination of ivabradine with carvedilol, including better coronary perfusion, improvement of left ventricular contraction, and better peripheral blood flow.

All current registries consistently report under dosing of β-blockers in many patients with heart failure [1, 3, 4]. This is believed to be related to a range of factors such as undesired side effects, patients' fears, and multiple comorbidities, all of which could limit uptitration. The phenomenon has even been observed in clinical trial conditions: even in selected patients with heart failure who did not have intolerance or contraindications to β-blockers, a large proportion of patients (two-thirds) could not reach target dose [5].

A recent analysis of prospective multicenter screening in 15,148 outpatients with chronic systolic heart failure from Germany [25] demonstrated that, despite uptitration of β-blockers, resting heart rate was frequently inadequately controlled. Even though 86% of the population were currently on β-blocker and 88% had been diagnosed more than 6 months earlier (leaving sufficient time for uptitration),

the mean heart rate was 73 bpm, and 42% of the population presented with heart rate ≥75 bpm. Increased heart rate was documented irrespective of the achieved mean or maximally tolerated β-blocker dose: those receiving <50% of target dose of β-blocker (34% of the population) had a mean heart rate of 72 bpm, those receiving between 50% and 100% of target dose (49%) had mean heart rate of 73 bpm, and those receiving ≥100% (17%) of target dose had mean heart rate 74 bpm [25].

There is now a large volume of data highlighting the unmet medical need for guideline-oriented pharmacological optimization of resting heart rate in chronic systolic heart failure. Resting heart rate is currently integrated in the algorithm of management of patients with heart failure and LV systolic dysfunction to guide the choice of therapy. In addition to demonstrating the beneficial impact of ivabradine in chronic heart failure, the results of the SHIFT trial have led to a greater understanding of importance of heart rate in the management of heart failure patients [10]. Recent data from a heart failure registry indicate that 5-year event-free survival was significantly lower among heart failure patients with heart rates ≥70 bpm compared with those with <70 bpm despite optimal therapy with β-blockers [6]. This analysis underlines the necessity of rigorous heart rate control, even in patients considered to be receiving optimal pharmacotherapy [5].

The main limitation of the study is that it is open-label, unblinded study that was not randomized, and performed in a small population of 69 patients, and these features should be taken into consideration when interpreting the results. On the other hand, the design implies that the results reflect what actually happens in real-life clinical practice. Another possible limitation is that information on the possibility of prescribing ivabradine first and then adding a β-blocker later was not collected. Finally, the possibility of selection bias cannot be excluded, as inclusion in the study was left to the decision of the investigator, as well as a possible bias due to the motivation of the patient with regard to exercise tolerance.

CONCLUSION

The results indicate that adding ivabradine to carvedilol in patients with chronic heart failure results in lower heart rates and better exercise capacity, and patients treated with ivabradine achieved higher dosages of β-blocker more rapidly than patients without ivabradine. The results merit further verification in a prospective double-blind study.

ACKNOWLEDGMENTS

Article processing charges for this paper were funded by Servier International, Suresnes, France. No funding was received for the study, which was independently conducted. All named authors meet the ICMJE criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Conflict of interest. Andrey Bagriy has given lectures for Servier, Pfizer, Astra Zeneca, Takeda, and Sanofi. E. V. Schukina, O. V. Samoilova, O. A. Pricolota, S. I. Malovichko, A. V. Pricolota, E. A. Bagriy declare no conflicts of interest.

Compliance with ethics guidelines. All procedures followed were in accordance with the ethical standards of the responsible

committee (institution and nation) and with the Helsinki Declaration of 1975, as revised in 2006 and 2008. Informed consent was obtained from all patients for being included in the study.

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