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Effect of Carvedilol, Ivabradine or their combination on exercise capacity in patients with Heart Failure (the CARVIVA HF trial)

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ABSTRACT

Aim: Patients with heart failure (HF) have reduced exercise capacity. The beneficial effect of beta-blocker on prognosis is not matched by an impact on exercise capacity and quality of life. We performed a randomised open blinded endpoint study to assess the effect of heart rate reduction with carvedilol, ivabradine, and their combination on exercise capacity in HF patients receiving maximal dose of ACE inhibitor.

Methods and results: After a run-in phase patients were randomly allocated to 3 groups: carvedilol up to 25 mg bid (n = 38); ivabradine up to 7.5 mg bid (n = 41); and carvedilol/ivabradine up to 12.5/7.5 mg bid (n = 42). The maximal dose of study treatment was more frequently tolerated in patients receiving ivabradine (36/41) than in those receiving carvedilol (18/38) or combination therapy (32/42) ($P<0.01$ ivabradine versus carvedilol). Heart rate was reduced in all three groups, but to a greater extent by the combination. The distance walked on the 6-min walking test and the exercise time on MVO_2 test significantly improved in the ivabradine and combination groups (both $P<0.01$ versus baseline), as did peak VO_2 and VAT ($P<0.01$ for ivabradine and $P<0.03$ for combination versus carvedilol, respectively). No changes in these parameters were found with carvedilol. The patients receiving ivabradine or the combination had better quality of life ($P<0.01$ versus baseline for ivabradine and $P<0.02$ for combination), versus no change with carvedilol.

Conclusion: Ivabradine alone or in combination with carvedilol is more effective than carvedilol alone at improving exercise tolerance and quality of life in HF patients.

Heart failure (HF) constitutes a major public health problem. It has a substantial clinical, social, and economic burden, notably due to significant functional limitations and the reduced quality of life of patients [1]. Several pathophysiological mechanisms underlie the progression of HF, including increased adrenergic tone, altered autonomic control of the cardiovascular system, activation of the renin-angiotensin-aldosterone system, and reduced peripheral blood flow [1]. Diuretics and angiotensin-converting enzyme (ACE) inhibitors are the mainstay of the management of HF [1]. Although the addition of beta-blockers is known to improve prognosis [2], they are often underused in clinical practise and are seldom prescribed at the doses proven to reduce events [3–6]. Moreover, the beneficial effect of beta-blockers on hard endpoints is not matched by their effect on exercise capacity or quality of life in HF [7].

It is well known that the altered haemodynamic homeostasis of HF patients is associated with an increased heart rate [8] and that the risk of adverse events in HF is closely related to heart rate [9,10]. In this context, the effect of beta-blockers on prognosis has been linked to their heart rate-reducing effect [11,12]. Heart rate reduction with the I_f inhibitor ivabradine improves event-free survival in HF patients with and without adequate beta-blockade [13]. Moreover, studies in patients with ischaemic heart disease have shown that a combination of ivabradine and beta-blocker is more effective than beta-blockade alone in improving exercise tolerance [14]. This raises the question of whether ivabradine would be an effective add-on treatment to ACE inhibitor and diuretics in HF, allowing uptitration of ACE inhibitors to optimal doses in HF.

We report the result of a prospective, randomised, open, blinded endpoint (PROBE) study in patients with chronic HF. The aim of the study was to assess the effect on exercise capacity, exercise duration, and quality of life of a therapeutic strategy aimed at optimising ACE inhibition and reducing heart rate using carvedilol, ivabradine, or their combination.

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1. Methods

1.1. Patients

Patients were recruited at three tertiary cardiology centres over a 4 month period. In order to obtain an applicability of the study results to the general population of patients with HF the inclusion criteria were broad. Eligible patients were aged 18 to 90 years, had been diagnosed with HF at least 12 months prior to selection (New York Heart Association [NYHA] functional class II to III), and had been clinically stable for the 3 weeks prior to selection or discharged in stable conditions. Patients were either not receiving beta-blockers, or were receiving beta-blockers but in combination with a suboptimal dose of ACE inhibitor. In the patients receiving sub-optimal beta-blockers, these drugs were gradually discontinued over 3 weeks by halving the dose every 7 days. Concurrently, ACE inhibitors were uptitrated to optimal doses recommended by the guidelines on heart failure of the European Society of Cardiology in all patients [1].

Patients with pacemakers set at heart rates >50 bpm were excluded, as well as those with an exercise capacity on the 6-min walking test <100 m or >400 m, or those with a variability of 10% or greater between the two 6-min walking tests at baseline. Patients with functional or orthopaedic limitations that could impair performance during cardiovascular functional tests were also excluded.

1.2. Study design

The design of this prospective, randomised, open, blinded endpoint (PROBE) [15] study is described in Fig. 1. In order to assure blinding of the PROBE study design two separate teams were responsible for patient management and supervision of the study assessments respectively. The screening visit involved clinical evaluation and assessment of inclusion and exclusion criteria. After giving written informed consent for participation in the study, which was approved by the local ethics committees, patients entered a 3 week phase for optimisation of ACE inhibitor dose and discontinuation of beta-blockers, where appropriate. At the end of this phase, patients were followed for 4 weeks at weekly intervals during run-in and underwent a baseline assessment at least 4 weeks after optimisation of the ACE-inhibitor dose. Baseline assessment included a full cardiology visit with a 6-min walking test, a cardiopulmonary exercise test (in compliant patients) and leg muscle strength, electrocardiogram (ECG), blood sampling for the assessment of laboratory parameters, assessment of quality of life, and echocardiography. In order to be included and randomised patients underwent a second 6-min walking test and a cardiopulmonary exercise test within 1 week from the baseline assessment. Only patients with reproducible (<10% variation) exercise tests were included. Patients were then started on outpatient cardiovascular rehabilitation including three sessions/week according to the guidelines of the European Society of Cardiology on Heart Failure [1] and were randomly allocated to three groups: carvedilol up to 25 mg bid; ivabradine up to 7.5 mg bid; and combination carvedilol/ivabradine up to 12.5/5 mg bid. Initial doses were carvedilol 12.5 mg bid, ivabradine 5 mg bid, or carvedilol/ivabradine 6.25/2.5 mg bid (half a tablet of carvedilol 12.5 mg and half a tablet of ivabradine 5 mg bid). Drug therapy was uptitrated after 2 weeks. During the treatment period, patients with resting heart rate <45 bpm were considered as treatment failure and analysed as intention to treat. In these patients, the dose of study treatment was readjusted in order to reach a target heart rate between 50 and 60 bpm. Patients were followed clinically during their rehabilitation programme. After 3 months of therapy, patients underwent a repeat of all the assessments performed at baseline. All tests were performed after an overnight fast and at a distance of at least 12 h from caffeine intake, 24 h from strenuous exercise, and 6 h from cigarette smoking. All patients were studied 2 h after the morning intake of their medical therapy.

1.3. Assessments

The primary endpoints of the study were the distance covered in the 6-min walking test and maximal oxygen consumption (MVO_2) on the cardiopulmonary exercise test. Secondary endpoints included quality of life and change in NYHA class. The 6-min walking test, the cardiopulmonary exercise test, and echocardiography were performed according to procedures discussed in detail elsewhere [16] and are described only briefly below.

The 6-min walking test was performed according to standardised procedure [16,17] at baseline, before inclusion (at least 1 week after baseline evaluation), and at the end of the study. Patients who had not done at least two tests in the past underwent two practice 6-min walking tests at least 3 days apart. Results are expressed in terms of both distance walked (metres) and as a percentage of predicted values in healthy subjects using Enright's equation. The test was supervised by a physical therapist. Patients were asked to walk at their own maximal pace a 100 m long hospital corridor. At the beginning of the last (6th) minute of the test a standard phrase of encouragement was told. Patients were allowed to stop if signs or symptoms of significant distress occurred (dyspnea, angina), through they were instructed to resume walking as soon as possible.

Functional capacity was assessed by means of a cardiopulmonary exercise test with a bicycle ergometer with gas exchange monitoring (Vmax 29C, SensorMedics) [16]. Peak oxygen consumption was defined as the MVO_2 observed during exercise and the respiratory exchange ratio (RER) was calculated at the same time-point. The slope of ventilation/carbon dioxide (VE/VCO_2) and the ventilatory anaerobic threshold (VAT) were calculated [16]. A 12-lead ECG and systolic and diastolic blood pressures (SBP and DBP) were recorded continuously.

Leg muscle strength was assessed as described elsewhere using a computer-based multifunctional dynamometer system (REV 9000, Technogym, Gambettola, Forlì, Italy) in the seated position [16,18]. Isometric strength was defined as the highest force developed by the patients in three, 5-s maximal voluntary contractions (MVC) separated by 1 min rest. Isokinetic strength was assessed by evaluating the highest peak torque achieved in a five maximal repetition test of concentric knee extension/flexion performed at 90°/s (PTmax). Quadriceps muscle fatigue was expressed as the fatigue index (work performed last repetition/work performed first repetition × 100).

Echocardiography (two-dimensional, M-mode, and Doppler) was performed by the same physicians unaware of clinical and study data, according to recommendations of the American Society of Echocardiography [19], using an Acuson Sequoia equipped with a 2.5–4.25 MHz wide-angle phased-array transducer. Left ventricular volumes were measured from the apical 4- and 2-chamber views, and left ventricular ejection fraction (LVEF) was calculated as described elsewhere [16].

Quality of life was evaluated using both a visual analogue scale and the MacNew QLMI questionnaire (27 items in three domains [physical, emotional, and social] with a global score for quality of life in the previous 2 weeks). The established minimal importance difference (MID) for the MacNew is 0.5 points on the 7-point scoring scale.

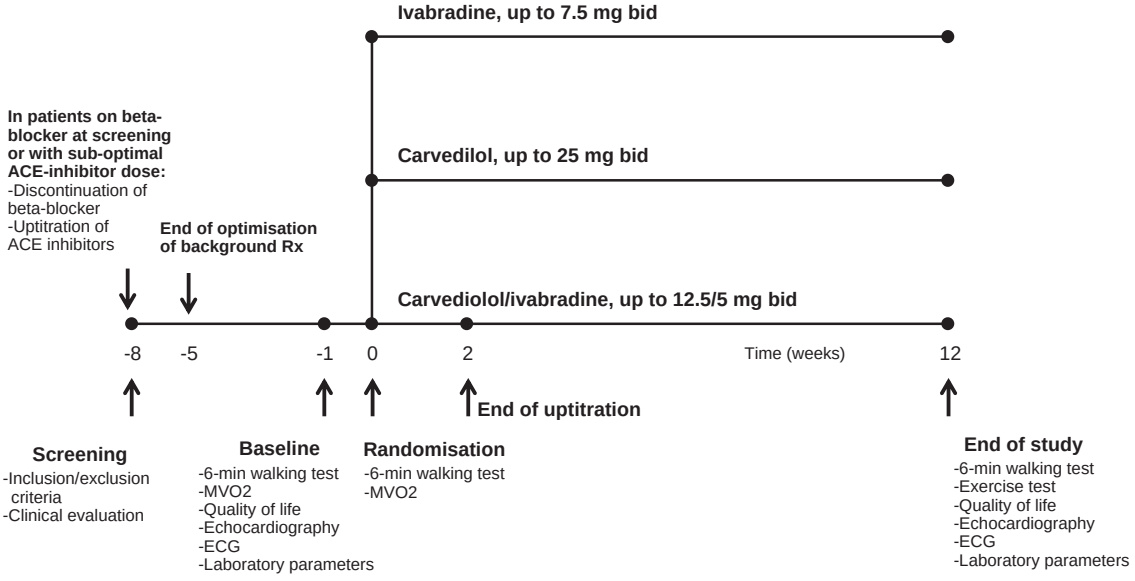

Fig. 1. Study design. ACE = angiotensin-converting enzyme. ECG = electrocardiogram. MVO_2 = cardio-pulmonary exercise test. NYHA = New York Heart Association.

1.4. Statistical analysis

Data were collected using a dedicated anonymous clinical report form. The database was kept in duplicate at the Department of Pharmacology at the Italian Institute of Health. Analysis was conducted on both intention to treat and per protocol patients. The sample size for the study was calculated on the basis of an exploratory analysis conducted on the effect of ivabradine in patients with HF of ischaemic origin in whom beta-blockers were contraindicated, which showed that a 2-month treatment was associated with a 25% relative increase in exercise capacity versus the pretreatment period, as well as a meta-analysis on the effect of beta-blockers showing a neutral effect on exercise capacity [7]. We estimated that 100 patients were required to obtain a similar effect size with 85% power and 5% significance assuming a dropout rate of 15%; we included 123 patients to increase the power of our results. All data were tested for normal distribution using the Kolmogorov–Smirnov test. Baseline characteristics between treatment groups were compared using unpaired Student *t* test for normally distributed variables or the Whitney *U* test for not normal or ordinal. Dichotomous variables were compared with Fisher's exact test. Within-group analyses were performed by paired *t* test for normally distributed variables and by Wilcoxon signed rank test for non-normal variables. Adjustment for multiple comparisons was performed using the Bonferroni test. Correlations between variables were tested by linear regression. Pearson coefficient and Spearman's rank correlation coefficient were calculated respectively for normally distributed and non-normally distributed or ordinal data. A two-tailed $P<0.05$ was considered statistically significant. All analyses were performed using a commercially available statistical package (SPSS for Windows 12.0, Chicago, Ill).

2. Results

Of the 186 patients screened, 123 met the inclusion criteria. Reasons for exclusion were 16 renal failure with creatinine clearance <60 mg/dL (n = 16), an orthopaedic or neurological condition that would have impaired performance of functional tests (n = 22), pacemaker (n = 11), and a >10% difference between the baseline and inclusion 6-min walking tests (n = 14). Two patients (1 in the carvedilol and 1 in the carvedilol/ivabradine groups) discontinued the study early after randomization because of willingness to leave the study and, since they did not undergo a functional assessment on therapy, they were excluded from the statistical analysis.

Baseline characteristics of 121 the patients included in the study are reported in Table 1. No significant difference between the treatment groups was found. At inclusion most of the population (155 patients, 95%) were on ACE inhibitors, and only 6 patients (5%) were on angiotensin receptor antagonists due to ACE inhibitor side effects; 101 patients (83%) were on diuretics, 49 (40%) antialdosterone agents, and 40 (33%) cardiac glycosides. Sixty-six patients (55%) were on beta-blockers but with suboptimal dose of ACE inhibitors at selection visit. In these patients, beta-blocker discontinuation and uptitration of ACE inhibition was well tolerated, and in no case led to a worsening of either symptoms or exercise capacity (Fig. 2).

More patients achieved maximal dose of study treatment in the ivabradine group (36 patients, 88%) than in the carvedilol group (18 patients, 47%) or the combination group (32 patients, 76%) ($P<0.001$ for ivabradine versus carvedilol; $P<0.003$ for combination therapy versus carvedilol). The most frequent reason for suboptimal uptitration was excessive blood pressure lowering for the carvedilol group and pronounced (<50 bpm) heart rate reduction for the ivabradine and combination groups. Worsening HF requiring hospitalisation occurred during the trial in 3 patients receiving carvedilol and in 1 patient receiving combination therapy.

Heart rate was reduced by a similar extent by ivabradine and carvedilol and significantly more by combination therapy (Table 2). No significant changes in blood pressure were noted in patients receiving ivabradine (SBP, 3.0 ± 6.5 mm Hg, 95% confidence interval [CI] 0.7 to 5.1 mm Hg; DBP, 1.1 ± 6.1 mm Hg, 95% CI 0.22 to 2.5 mm Hg), while both groups of patients receiving carvedilol had significant falls in SBP (−4.7 ± 7.3 mm Hg, 95% CI −6.8 to −0.2 mm Hg for combination; and −9.4 ± 9.2 mm Hg, 95% CI −16.8 to −1.2 mm Hg for carvedilol) and in DBP (−2.1 ± 3.3 mm Hg, 95% CI −3.8 to −0.4 mm Hg for combination, and −6.4 ± 4.3 mm Hg, 95% CI −9.2 to −1.2 mm Hg for carvedilol). A nonsignificant improvement in LVEF was observed in both ivabradine and combination therapy groups versus no change in the carvedilol group (data not shown). NYHA class improved significantly more in patients receiving ivabradine and combination therapy compared with those allocated to carvedilol (Fig. 3).

At study end, the distance walked on the 6-min walking test and the exercise time on MVO_2 test improved significantly versus baseline in the ivabradine and combination groups, but not in the carvedilol group (Fig. 4). Significant differences were also detected between patients receiving ivabradine or the combination and those receiving carvedilol ($P<0.01$ ivabradine versus carvedilol, $P<0.02$ combination versus carvedilol). When patients receiving suboptimal dose of carvedilol were included in the analysis, a marginal improvement in distance walked on the 6-min walking test versus baseline was noted in this group. However, even when analysed by intention-to-treat, the significant differences in exercise performance between ivabradine

Table 1
Clinical characteristics and treatment at inclusion in study patients. No significant differences in clinical features nor in background therapy was detected between groups. Data are number, (%) or means (SD). ACE = angiotensin-converting enzyme. NYHA = New York Heart Association.

	All patients (n = 121)	Ivabradine (n = 41)	Carvedilol (n = 38)	Carvedilol/ivabradine (n = 42)
Demographics				
Age (years)	66.8 (9.5)	67.2 (9.5)	66.7 (10.1)	66.5 (9.2)
Sex (female)	39 (32%)	13 (32%)	12 (32%)	14 (33%)
Body mass index (kg/m^2)	26.7(3.1)	27 (3.3)	26.8 (3.2)	26.4 (3.0)
Concomitant diseases				
Dyslipidaemia	98 (81%)	32 (78%)	31 (82%)	35 (83%)
Hypertension	89 (74%)	31 (76%)	30 (79%)	28 (67%)
Cigarette smoking	37 (31%)	14 (34%)	10 (26%)	13 (31%)
Diabetes/impaired glucose metabolism	65(54%)	23 (56%)	21 (55%)	21 (50%)
Heart failure characteristics				
Duration of heart failure (weeks)	52.2(25.3)	50.8 (26.4)	48 (25.3)	57.3 (24.1)
Ischaemic heart failure	98 (81%)	33 (80%)	32 (84%)	33 (79%)
Non-ischaemic heart failure	23 (19%)	8 (20%)	6 (16%)	9 (21%)
NYHA Class II	63 (52%)	20 (49%)	22 (58%)	21 (50%)
NYHA Class III	58 (48%)	21 (51%)	16 (42%)	21 (50%)
Cardiac parameters				
Heart rate (bpm)	77.5 (12.2)	79.6 (11.2)	76.7 (12.8)	75.7 (12.5)
Systolic blood pressure (mm Hg)	124.6 (13.5)	123.7 (12.8)	125.4 (15.2)	124.8 (12.9)
Diastolic blood pressure (mm Hg)	74.3 (9.9)	79.6 (11.2)	74.8 (9.1)	71.9 (8.6)
Left ventricular ejection fraction (%)	27% (4.9)	26.4 (4.7)	26 (5.0)	28 (4.8)
Treatment at inclusion				
Beta-blocker	66 (55%)	21 (51%)	22 (58%)	23 (55%)
ACE inhibitor	115 (95%)	38 (93%)	38 (100%)	39 (93%)
Angiotensin receptor blocker	6 (5%)	2 (5%)	1 (3%)	3 (7%)
Non-antialdosterone diuretics	101 (83%)	34 (83%)	32 (84%)	35 (83%)
Antialdosterone agents	49 (40%)	16 (39%)	14 (37%)	19 (45%)
Cardiac glycosides	40 (33%)	13 (32%)	12 (32%)	15 (36%)
Antiplatelet/anticoagulant	116 (96%)	39 (95%)	37 (97%)	40 (95%)
Statins	85 (70%)	27 (66%)	29 (76%)	29 (69%)
Beta-blocker at inclusion				
Bisoprolol	19 (16%)	6 (15%)	7 (18%)	6 (14%)
Mean daily dose (mg/day)	5.5 (2.3)	6.7 (2.7)	5.4 (2.9)	5 (2.6)
Carvedilol	35 (29%)	12 (29%)	10 (26%)	13 (31%)
Mean daily dose (mg/day)	25.7 (16.9)	24.5 (17)	23.7 (18.8)	25.5 (16)
Metoprolol	12 (10%)	3 (2%)	5 (13%)	4 (10%)
Mean daily dose (mg/day)	66.7 (26.8)	58.3 (28.8)	70 (35.6)	56.2 (31.4)

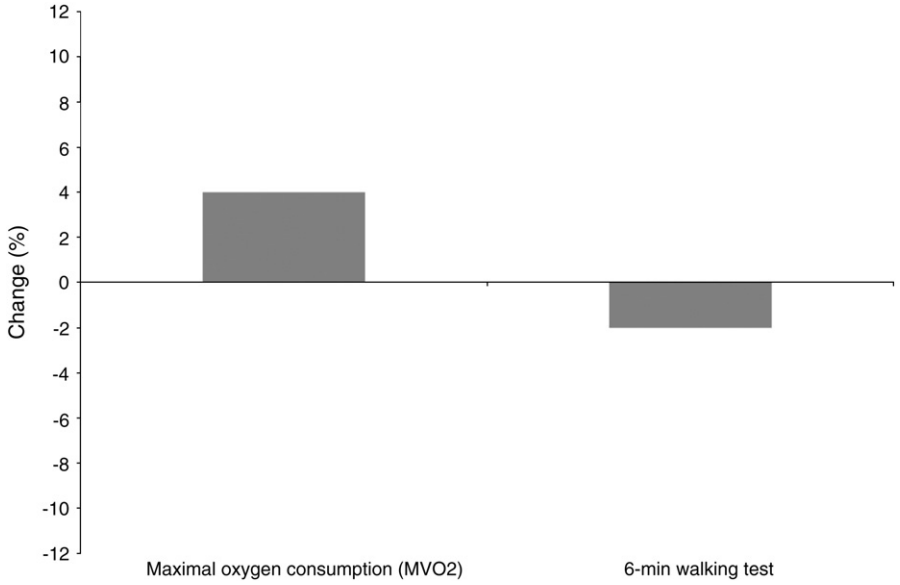

Fig. 2. Percentage change in exercise capacity (peak oxygen consumption [MVO_2] and 6-min walking test) between inclusion and baseline tests in patients undergoing optimisation of ACE inhibitor dose and discontinuation of beta-blockers (66 patients).

and combination therapy versus carvedilol persisted. A trend towards a longer distance walked on the 6-min walking test and on exercise time on MVO_2 was noted between patients receiving ivabradine and those receiving the combination (Table 3). All differences between ivabradine and combination therapy on exercise capacity and duration disappeared when patients were analysed in the intention to treat.

At 3 months, peak VO_2 and VAT significantly improved in patients receiving ivabradine and the combination, but remained unchanged in the carvedilol group ($+3.8\pm2.0$, $+2.3\pm1.7$, and -0.6 ± 1.2 mL/kg/min, respectively; $P<0.01$ for ivabradine and $P<0.03$ for combination versus carvedilol respectively). The slope VE/VCO_2 significantly decreased and peak workload increased in the ivabradine and combination group, whereas no significant changes were detected in the carvedilol group (Table 3). Also for the assessment of MVO_2 results when patients receiving suboptimal dose of carvedilol were included in the analysis, a trend towards an improvement in VAT and VE/VCO_2 was noted in this group. Even when analysed by intention-to-treat, the significant differences in exercise performance between ivabradine and combination therapy versus carvedilol persisted. However, in the intention to treat analysis ivabradine and combination therapy led to a similar improvement of exercise parameters.

MVC was similar in the three treatment groups at baseline. MVC increased significantly in both ivabradine (29%) and combination groups (23%) versus a decrease in the carvedilol group (−14%) with a trend towards significance. The between-group difference in change in MVC was significant for the ivabradine ($P<0.001$) and combination ($P<0.01$) groups versus the carvedilol group. The isokinetic torque of the quadriceps was similar in the three treatment groups at baseline, and significantly improved in the ivabradine and combination therapy groups (+19 and +11 Nm), while it remained unchanged in the carvedilol group (+3 Nm). Total work increased in the ivabradine and combination groups (14 and 8 J) and decreased in the carvedilol group (−3 J) ($P<0.02$ and $P<0.05$ ivabradine and combination therapy versus carvedilol respectively). No significant change in power was detected in any of the groups over the study.

The fatigue index significantly improved in patients randomised to ivabradine or combination (ivabradine, $-36.4\pm12.1\%$, $P<0.03$ versus baseline; and combination $-26.5\pm9.5\%$, $P<0.05$ versus baseline, respectively), whereas there was no significant change with carvedilol with a trend towards a worsening ($-7.1\pm4.9\%$, $P=0.06$ versus baseline).

In patients receiving ivabradine or combination, the change in heart rate between baseline and study end inversely correlated with improvement in peak VO_2 ($r=-0.49$, $P=0.03$ for ivabradine, $r=-0.45$, $P=0.46$ for combination) and distance reached in the 6-min walking test ($r=-0.46$, $P=0.03$ for ivabradine, $r=-0.37$, $P=0.04$ for combination). No correlation between heart rate and changes in exercise capacity was noted in patients receiving carvedilol. Worsening HF requiring hospitalisation occurred in 3 patients receiving carvedilol and in 1 patient receiving combination therapy.

Table 2
Heart rate at baseline and at study end in patients allocated to Carvedilol, Ivabradine or combination therapy. Heart rate detected from resting electrocardiogram. Data for per protocol and for intention to treat patients are reported. *$P<0.05$ versus carvedilol.

	Heart rate at baseline (bpm)	Heart rate at follow-up (12 weeks) (bpm)	
		Per protocol	Intention to treat
All patients	77.5	62.5	67.2
Carvedilol	76.7	64.8	68.3
Ivabradine	79.6	62.4	62.7
Combination	76.7	57.2*	61.4

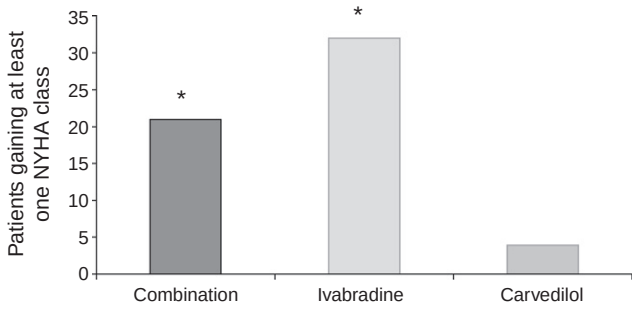

Fig. 3. Number of patients with an improvement by at least one New York Heart Association (NYHA) class according to treatment allocation (carvedilol, ivabradine, or combination carvedilol/ivabradine). *$P<0.001$ ivabradine versus carvedilol, $P<0.003$ carvedilol versus carvedilol.

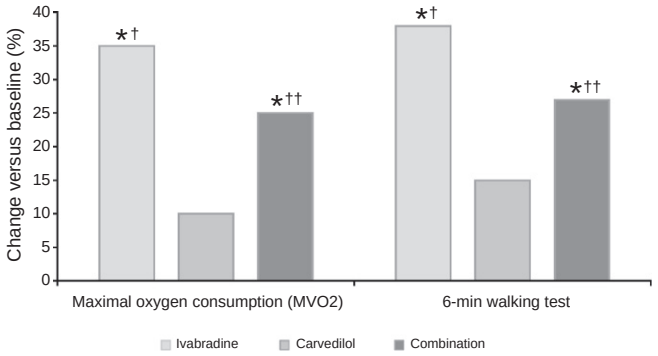

Fig. 4. Effect of carvedilol, ivabradine, and their combination on percentage change in exercise capacity (peak oxygen consumption [MVO_2] and result on 6-min walking test) over the 3 months of the study. *$P<0.01$ versus baseline. †$P<0.01$, ††$P<0.02$ versus carvediolol.

The overall assessment of quality of life showed an improvement in patients receiving ivabradine or the combination (from 4.3 ± 0.5 to 6.7 ± 0.9, $P<0.01$) versus baseline for ivabradine, and from 4.7 ± 0.8 to 6.1 ± 0.6, $P<0.02$ for combination, while no changes were detected in patients receiving carvedilol (from 4.6 ± 0.8 to 4.1 ± 0.6, $P=$NS). This trend was more evident in the per protocol analysis. The physical and social domains of the MacNew QLMI scale improved in patients receiving ivabradine and the combination but not in those allocated to carvedilol (physical domain: $36\pm11\%$, $27\pm9\%$, and $-7\pm4\%$, respectively, $P<0.01$ ivabradine and combination versus carvedilol; social domain: $41\pm8\%$, 32 ± 12, and $-9\pm5\%$, respectively, ivabradine and combination versus carvedilol, $P<0.01$).

3. Discussion

The present study shows that ivabradine alone or in combination with carvedilol is more effective than carvedilol alone in improving exercise capacity and quality of life in HF patients receiving recommended doses of ACE inhibitors. The study also shows that patients allocated to ivabradine-based therapy are more likely to reach target therapeutic doses than patients receiving carvedilol alone.

It is well established that elevated heart rate is associated with increased total mortality and cardiovascular events in patients with coronary artery disease [20–24] and in those with HF [9,25,26]. Although it has been suggested that the threshold for increased risk should be heart rate >70 bpm [21], population studies along with the results of interventional studies suggest that heart rate must be considered as a continuous variable and that target heart rate is important in determining benefits of treatment with drugs with heart rate-reducing effect [10,12,20,22–24,27–31]. More recently, the SHIFT study showed a progressive protective effect of ivabradine with lowering heart rate [25], with best event-free survival in those with heart rate <60 bpm. Previous meta-analyses had suggested that the beneficial long-term effect of beta-blockers is related to their heart rate-reducing effect and that the survival benefit was greater in those studies where the heart rate reduction was more pronounced [32,33]. Therefore, at the time of the design of our study, and in the absence of specific guidance from scientific guidelines, data from literature suggested that target heart rate in patients with coronary artery or HF should be between 50 and 56 bpm.

The importance of reducing heart rate in patients with coronary artery disease became clear when studies comparing beta-blockers and non-dihydropyridine calcium channel blockers found that target heart rate was related to improvement in exercise-induced myocardial ischaemia [34]. Elevated heart rate was long considered a compensatory mechanism in HF. However, following the demonstration that the increased sympathetic tone was related to clinical conditions, strategies aimed at reducing heart rate have been implemented usually with beta-blockade. On the other hand, beta-blockers are often prescribed at suboptimal dosages because of blood pressure-lowering effects and the haemodynamic instability of HF patients [3–6]. Moreover, because of the understanding of a prognostic benefit, beta-blockers are often implemented in therapy before target ACE inhibition has been achieved. The CIBIS III study failed to show non-inferiority of implementation of "beta-blockers first" versus "ACE inhibitor first" strategy and showed that implementation of beta-blockers before optimisation of ACE inhibition is associated with increased risk of HF hospitalisation [12,30]. Several surveys have indicated that, like beta-blockers, ACE inhibitors are not used optimally in many patients with HF or coronary artery disease [3–6], most likely due to concerns over hypotension, particularly if they are used concurrently with other agents with a haemodynamic action. Therefore, strategies for effective control of heart rate and optimisation of ACE inhibitors are needed. The present study addresses this need by demonstrating that, in patients receiving ACE inhibition without beta-blockade, or beta-blockade with inadequate ACE inhibition, ivabradine alone or in combination with carvedilol is superior to carvedilol alone in improving exercise capacity and quality of life. Regarding the possible concern of reducing or stopping beta-blockers in HF patients, in our study, these drugs were only stopped in order to optimise ACE inhibition, on the understanding that ACE inhibition should be implemented before

Table 3
Physiological and functional parameters at baseline and at study end in patients allocated to Carvedilol, Ivabradine or combination therapy. Exercise capacity improved significantly more in patients allocated to Ivabradine compared to those receiving Carvedilol or Carvedilol/Ivabradine. SBP = systolic blood pressure. DBP = diastolic blood pressure. MVO_2 = maximal oxygen consumption. VE/VO_2, ventilation/carbon dioxide. VAT = ventilatory anaerobic threshold. MVC = maximal voluntary contractions. PTmax, peak torque. *$P<0.01$, †$P<0.03$ versus baseline/carvediolol.

	Ivabradine (n = 41)		Carvedilol (n = 38)		Carvedilol/ivabradine (n = 42)	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
SBP, mm Hg	122.8 ± 11.7	124.1 ± 14.2	125.3 ± 13.9	115.6 ± 12.6	123.6 ± 11.7	118.3 ± 9.1
DBP, mm Hg	74.8 ± 8.3	76.2 ± 8.4*	74.4 ± 8.9	68.3 ± 7.6	71.1 ± 8.1	69.4 ± 7.8
Resting heart rate, bpm	78.6 ± 9.8	62.8 ± 7.1	75.6 ± 11.8	64.3 ± 6.2	76.3 ± 12.8	58.1 ± 5.4
MVO_2, mL/kg/min	12.05 ± 2.1	15.8 ± 1.9*†	12.3 ± 2.6	12.9 ± 2.4	12.4 ± 2.5	14.7 ± 1.6
VE/VCO_2 slope	31.8 ± 4.7	26.3 ± 4.3*†	32.2 ± 5.4	31.2 ± 8.3	32.4 ± 4.9	28.8 ± 5.1
AT, mL/kg/min	7.6 ± 2.1	6.8 ± 3.1*†	8.3 ± 2.6	7.8 ± 4.6	7.9 ± 2.8	7.3 ± 2.7*†
Distance on 6-min walking test, m	346.7 ± 112.0	474.8 ± 127.3*†	379.0 ± 96.3	435.7 ± 121.3	358.2 ± 107.6	453.1 ± 87.4
MVC, N	114.3 ± 21.2	147.5 ± 34.1*†	116.9 ± 32.4	103.3 ± 26.7	119.9 ± 26.7	147.5 ± 36.6
PTmax, Nm	73.2 ± 16.2	92.4 ± 21.6*†	72.9 ± 18.3	76 ± 22.1	75.8 ± 23.8	77.1 ± 27.3

beta-blockade. ACE inhibitors are known to modulate sympathetic tone and we found that downtitration of beta-blockade and uptitration of ACE inhibition was not associated with any significant change in heart rate, unfavourable changes in exercise capacity, or worsening HF, suggesting that this therapeutic strategy can be safely implemented in stable HF patients.

The results of this study are in agreement with previous observations that beta-blockers do not improve exercise capacity in HF patients. As reported by Olsson et al.[7], only 3 of 20 comparative studies including 15 placebo-controlled trials of beta-blockers showed an improvement in 6-min walking test distance, when only large multicentre trials only one of five comparisons showed an improvement in exercise capacity with beta-blockers.

This is the first study to compare the effects of beta-blockers and ivabradine on exercise capacity and quality of life. Our results imply that the better effect of ivabradine on exercise capacity is related not only to heart rate reduction, but also to differing effects of ivabradine and carvedilol on skeletal muscle performance. Previous studies have shown that beta-blockers impair the alpha-adrenergic-mediated dilation that occurs during exercise [35–37]. Unlike beta-blockers, ivabradine has been shown to preserve the exercise-induced vasodilation and increase blood flow [38]. The difference in the effects of ivabradine and carvedilol on exercise performance is therefore most likely related to a better muscular blood flow improving exercise performance. Our data are in agreement with a recent report that the combination of ivabradine and bisoprolol in patients with coronary artery disease was more effective at improving exercise capacity than doubling the bisoprolol dose, though that study did not assess the effect of ivabradine alone or the relative effect of the therapies since all patients were receiving bisoprolol 5 mg at baseline [39].

We assessed exercise capacity by the 6-min walking test and MVO_2, and a good concordance between the two methods was found in those patients who were compliant to MVO_2 measurement. Previous reports have shown a good concordance 107 of 139 (77%) comparisons, of which 85 showed neutral and 22 showed positive concordances [7]. It is well known that compliance with the MVO_2 test is poor in clinical practise. Nevertheless, in patients compliant with the MVO_2 test, we reached results similar to those obtained with the 6-min walking test, which implies the validity of our study.

There are a number of possible mechanisms for the improved exercise capacity with ivabradine and its combination with carvedilol, for example, better coronary perfusion, preservation of left ventricular contraction and relaxation, and better peripheral blood flow. Apart from a different effect of ivabradine and carvedilol on vasodilation on muscle perfusion, beta-blockers per se may have a detrimental effect on muscle strength.

Quality of life is an important endpoint for patients with chronic disabling diseases like HF. The observed effect on quality of life with ivabradine compared to carvedilol is likely to be related to the improved exercise capacity, reduction of the beta-blocker-related asthenia, and the well-known effect of beta-blockers on mood.

This is the first study to compare three therapeutic strategies that have been shown to be effective in improving survival in HF patients. The inclusion criteria were broad, which means that our results apply to the general population of patients with HF. The translation of our findings to routine clinical practise will depend on several factors. Because of the very well established role of beta-blockers in clinical practise and in absence of a head-to-head comparison between beta-blockers and ivabradine, it may be safe to recommend the implementation of combination therapy in patients who may tolerate beta-blockers, and ivabradine alone in all those patients in whom, after optimisation of ACE inhibitor dose, beta-blockers are not tolerated or are contraindicated or associated with side effects. It may also be safe to suggest that, in those patients in whom beta-blockers are associated with dose-related side effects or with adverse effect on quality of life, beta-blockers may be downtitrated and administered in combination with ivabradine.

In conclusion, the present study shows that ivabradine alone or in combination with beta-blockers is safe and effective in improving exercise capacity and quality of life in HF patients with optimised ACE inhibitor dose. Given the superiority of ivabradine over carvedilol on the functional parameters in this study and on the possibility of achieving more adequate therapeutic doses in clinical practise, studies to assess the comparative efficacy of ivabradine, beta-blockers, and their combination on hard cardiovascular endpoints in chronic stable HF are warranted.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [40].

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