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Effect of Combining Ivabradine and β-Blockers: Focus on the Use of Carvedilol in the SHIFT Population

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Key Words
β-Blockers · Chronic systolic heart failure · Heart rate

Abstract
Objectives: We explored the prescription of β-blockers with ivabradine in patients with systolic heart failure, focusing on the most frequently coprescribed β-blocker, carvedilol. ***Methods:*** We analyzed outcomes in SHIFT patients with systolic heart failure who were prescribed β-blockers (carvedilol, bisoprolol, metoprolol, or nebivolol) with ivabradine or placebo. Analysis was by intention to treat in patients prescribed a β-blocker at the time of the event. ***Results:*** Data were available for 2,596 patients receiving carvedilol, 1,483 bisoprolol, 1,424 metoprolol, and 197 nebivolol. Mean treatment duration was 19 months. There was no difference in the effect of ivabradine on the primary composite endpoint of cardiovascular death or heart failure hospitalization between the various β-blockers [hazard ratios (HR) for risk reduction, 0.75–0.89; p for interaction = 0.86]. Patients prescribed carvedilol with ivabradine had lower rates of primary composite endpoint (HR 0.80, 95% CI: 0.68–0.94), heart failure hospitalization (HR 0.73, 95% CI: 0.61–0.88), and cardiovascular hospitalization (HR 0.80, 95% CI: 0.69–0.92) versus carvedilol with placebo. The dosage of carvedilol had no detectable effect and there were no unexpected safety issues. ***Conclusions:*** Whatever β-blocker was coprescribed with ivabradine, there were improvements in cardiovascular outcomes in patients with systolic heart failure, especially with the most prescribed β-blocker – carvedilol.

Introduction

The management of heart failure has evolved tremendously in recent decades. Renin-angiotensin system (RAS) inhibitors and β-blockers are now widely used and have contributed to major therapeutic advances in heart failure. Despite this, the prognosis of patients with heart failure remains poor, with a median survival of 4.2 years without any discernible improvement over time [1]. There is clearly still room for improvement in management strategies and a relatively new agent, ivabradine, is a viable candidate for change in the management of systolic heart failure. Ivabradine acts via I_f inhibition in the

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sinoatrial node and reduces resting heart rate without altering other cardiac currents or hemodynamic parameters as well as without a negative inotropic effect [2, 3].

In 2010, the SHIFT (Systolic Heart Failure Treatment with the I_f Inhibitor Ivabradine Trial) investigators demonstrated that adding ivabradine to neurohormonal blockade improves mortality and morbidity in patients with systolic heart failure in sinus rhythm with a heart rate ≥70 bpm [4]. Treatment with ivabradine was associated with a significant 18% reduction in the primary composite endpoint of cardiovascular death or hospitalization for worsening heart failure, a 26% reduction in hospitalization for worsening heart failure, and a 26% reduction in heart failure death. Since the SHIFT results were published, ivabradine has been granted the new indication and has become an increasingly important component in the management of chronic systolic heart failure [5], and has been included in international guidelines for the treatment of chronic heart failure, alongside other evidence-based therapies such as β-blockers and RAS inhibitors [5].

The large majority of the 6,505 patients in the SHIFT population were taking a background β-blocker at baseline (89%) [4]. The SHIFT investigators have previously explored the effect of β-blocker dosage on outcomes [6]. They concluded that it was the heart rate reduction obtained with a β-blocker plus ivabradine – rather than the β-blocker dosage – that primarily determined the effect on outcomes. In the analysis described here, we set out to explore the effect of different individual β-blockers in combination with ivabradine on top of other evidence-based therapies in the SHIFT population, with a particular focus on the most frequently prescribed β-blocker – carvedilol [7].

Methods

Study Design and Outcomes

The design of the SHIFT trial has been described in great detail elsewhere [4, 8]. Briefly, SHIFT was an event-driven randomized double-blind placebo-controlled trial carried out in 677 centers in 37 countries. Participants had moderate-to-severe heart failure (NYHA class II–IV) with left ventricular ejection fraction ≤35%; they were in sinus rhythm and had a resting heart rate ≥70 bpm (12-lead electrocardiography). Patients had to be on stable background treatment for ≥4 weeks at entry, according to heart failure guidelines in force at the time the trial was performed [9]. Background treatment had been uptitrated as far as contraindications and tolerability would allow, and there was a particular emphasis on optimizing β-blocker dosage as close to the target as possible for each patient before initiation of study treatment. Against this background treatment, patients were randomly allocated to receive ivabradine (initiated at 5 mg b.i.d., which could be adjusted up or down to 7.5 or 2.5 mg b.i.d., according to resting heart rate and/or symptoms of bradycardia at 14 or 28 days, and then at every 4-month visit thereafter) or matching placebo.

In the post hoc analysis described here, we explored outcomes in SHIFT patients in subgroups divided according to the type of β-blocker they received at baseline (carvedilol, bisoprolol, metoprolol succinate or tartrate, or nebivolol). The outcome of interest was the primary endpoint, which is a composite of cardiovascular death and hospitalization for worsening heart failure. For the patients receiving the most frequently used β-blocker, carvedilol, we also investigated the following secondary endpoints: the individual components of the primary endpoint, heart failure death, cardiovascular hospitalization, and all-cause hospitalization, as well as safety data.

Statistical Methods

Baseline characteristics are presented according to treatment group (β-blocker in combination with ivabradine or placebo) using means ± SD for continuous variables and numbers of patients (%) for categorical variables. Baseline characteristics were compared using a Kruskal-Wallis test (continuous variables) or a χ^2 test (categorical variables).

The effect of the β-blocker in combination with ivabradine was analyzed in all randomized patients who received the combination of β-blocker with ivabradine or placebo at randomization. The analysis of events was performed exclusively while on the combination; in other words, only events that occurred between the first and last (+2 days) concomitant intake of the β-blocker and the study treatment were taken into account. Hazard ratios (HRs) were estimated between treatment groups (β-blocker in combination with ivabradine versus β-blocker in combination with placebo) based on an adjusted Cox's proportional hazards model with prognostic factors at baseline as covariates (NYHA class II/III or IV, left ventricular ejection fraction, ischemic etiology of heart failure, age, systolic blood pressure, heart rate, and creatinine clearance), and are presented with associated 95% CI. The associated p values were given for the comparison between carvedilol in combination with ivabradine versus carvedilol in combination with placebo. Differences between β-blocker subgroups were tested using a likelihood ratio test for heterogeneity, comparing the model including the interaction term with the model not including the interaction term, to produce a p value for interaction. Treatment effect was also explored in patients receiving different dosages of carvedilol; the dose retained for each patient was that used for the longest time during the study. Due to the low size of these dosage subgroups, only the number of events and incidence were calculated.

Safety was assessed while on the combination in patients who had had at least one intake of carvedilol and randomized treatment during the study. Safety data were compared using two-sided Fisher's exact tests. Due to the exploratory nature of this analysis, no correction for multiplicity was applied. All statistical analyses were performed by the Biostatistics Division of the Institut de Recherches Internationales Servier using SAS® Software version 9.2.

Results

We analyzed 2,596 patients on carvedilol (45% of all patients receiving a β-blocker), 1,483 patients (26%) on bisoprolol, 1,424 (25%) on metoprolol (tartrate and/or

Table 1. Baseline characteristics in 2,596 patients receiving carvedilol in combination with ivabradine or placebo at randomization

	Carvedilol + ivabradine (n = 1,318)	Carvedilol + placebo (n = 1,278)	p
Demographic characteristics			
Age, years	59.7±11.3	59.2±11.8	0.41
Male	1,018 (77)	973 (76)	0.51
Ethnic origin			
Caucasian	1,171 (89)	1,141 (89)	0.83
Black	25 (2)	26 (2)	
Asian	73 (6)	61 (5)	
Other	49 (4)	50 (4)	
Current smoker	191 (14)	215 (17)	0.25
BMI, kg/m^2	28.1±5.2	27.9±5.0	0.41
Cardiac parameters			
Heart rate, bpm	79.5±9.2	80.0±9.3	0.15
Systolic blood pressure, mm Hg	119.9±16.0	119.7±15.5	0.70
Diastolic blood pressure, mm Hg	75.1±9.9	75.0±9.7	0.46
Left ventricular ejection fraction, %	28.1±5.4	28.2±5.5	0.56
Creatinine clearance, ml/min/1.73 m^2	74.8±23.0	75.3±24.4	0.80
NYHA class			
Class II	709 (54)	695 (54)	0.53
Class III	598 (45)	567 (44)	
Class IV	11 (<1)	16 (1)	
Medical history			
Duration of heart failure, years	3.6±4.3	3.7±4.3	0.50
Primary cause of heart failure			
Ischemic	800 (61)	761 (60)	0.55
Nonischemic	518 (39)	517 (40)	
Myocardial infarction	640 (49)	617 (48)	0.89
Hypertension	819 (62)	798 (62)	0.87
Diabetes	414 (31)	406 (32)	0.84
Stroke	89 (7)	110 (9)	0.08
Atrial fibrillation and/or flutter	93 (7)	96 (8)	0.66
Treatment at randomization			
ACE inhibitor	1,009 (77)	993 (78)	0.49
Angiotensin II receptor blocker	213 (16)	184 (14)	0.21
Diuretics	1,156 (88)	1,108 (87)	0.44
Mineralocorticoid receptor antagonist	928 (70)	891 (70)	0.70
Digitalis	345 (26)	336 (26)	0.95
At least one device	56 (4)	65 (5)	0.31
Implanted ICD	49 (4)	55 (4)	0.45
Implanted CRT	16 (1)	22 (2)	0.28

Data are number of patients (%) or means ± SD. ACE = Angiotensin-converting enzyme; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter defibrillator.

succinate), and 197 (3%) on nebivolol. There were 107 patients receiving other β-blockers who were not included in our analysis. The baseline characteristics of the largest subgroup, the 2,596 patients on the most prescribed β-blocker, carvedilol, are presented in table 1. No statistical difference was shown between the patients allocated to ivabradine or placebo in any of the β-blocker subgroups (data not shown). Notably, the population was treated according to international guidelines. In the carvedilol subgroup, most patients received RAS inhibi-

Table 2. Effect of β-blockers in combination with ivabradine vs. β-blockers in combination with placebo on the composite enpoint of cardiovascular death or hospitalization for worsening heart failure in patients receiving different β-blockers

	Patients, n		Events, n (%)		HR (95% CI)	p for interaction (heterogeneity)
	β-blocker + ivabradine	β-blocker + placebo	β-blocker + ivabradine	β-blocker + placebo		
Carvedilol	1,318	1,278	268 (20)	319 (25)	0.80 (0.68–0.94)	0.86
Bisoprolol	720	763	112 (16)	137 (18)	0.89 (0.69–1.15)	
Metoprolol	696	728	97 (14)	132 (18)	0.75 (0.58–0.97)	
Nebivolol	100	97	19 (12)	22 (16)	0.77 (0.41–1.45)	

HR based on an adjusted Cox proportional hazards model with prognostic factors as covariates.

Table 3. Effect of treatment with carvedilol in combination with ivabradine (n = 1,318) vs. carvedilol in combination with placebo (n = 1,278) on cardiovascular outcomes

	Events, n (%)		HR (95% CI)	p
	Carvedilol + ivabradine	Carvedilol + placebo		
Cardiovascular death or hospitalization for worsening heart failure composite endpoint	268 (20)	319 (25)	0.80 (0.68–0.94)	0.008
Cardiovascular death	98 (7)	93 (7)	1.04 (0.79–1.39)	0.77
Heart failure hospitalization	194 (15)	253 (20)	0.73 (0.61–0.88)	0.001
Cardiovascular hospitalization	345 (26)	413 (32)	0.80 (0.69–0.92)	0.002
All-cause hospitalization	445 (34)	481 (38)	0.89 (0.78–1.02)	0.084
Death from heart failure	14 (1.1)	15 (1.2)	–	–

HR based on an adjusted Cox proportional hazards model with prognostic factors as covariates.

tors (77% on an angiotensin-converting enzyme inhibitor and 15% on an angiotensin II receptor blocker), diuretics (87%), and mineralocorticoid antagonists (70%). The mean duration of coprescription of carvedilol in combination with ivabradine or placebo was 19.2 ± 9.0 months.

After 28 days and after 1 year, heart rates were 63.8 ± 10.7 and 64.3 ± 11.1 bpm, respectively, for patients receiving carvedilol in combination with ivabradine versus 75.2 ± 11.8 and 74.4 ± 12.6 bpm, respectively, for those receiving carvedilol in combination with placebo. Mean heart rate reduction at 28 days and at 1 year was –15.7 ± 10.5 and –14.9 ± 11.7 bpm in patients receiving carvedilol in combination with ivabradine, respectively, compared with –4.7 ± 10.2 and –5.3 ± 12.1 bpm in patients receiving carvedilol in combination with placebo.

The favorable effect of β-blockers in combination with ivabradine compared with β-blockers in combination with placebo on the composite endpoint of cardiovascular death or hospitalization for worsening heart failure was consistent whatever the β-blocker (HRs 0.75–0.89, p for interaction = 0.86; table 2). Patients prescribed carvedilol in combination with ivabradine had lower rates of the composite endpoint of cardiovascular death or hospitalization for worsening of heart failure (HR 0.80, 95% CI: 0.68–0.94), heart failure hospitalization (HR 0.73, 95% CI: 0.61–0.88), and cardiovascular hospitalization (HR 0.80, 95% CI: 0.69–0.92) versus those prescribed carvedilol in combination with placebo (table 3). There was no difference in the rate of cardiovascular death (HR 1.04, 95% CI: 0.79–1.39). There were 14 heart failure deaths (1.1%) in the group on carvedilol in combination with ivabradine versus 15 (1.2%) in the group on carvedilol in combination with placebo, which precluded any relevant conclusion with regard to this endpoint.

Of the 2,596 patients on carvedilol in combination with ivabradine or placebo, carvedilol dosages were evenly distributed throughout the dose range up to the recom-

mended maximal target of 50 mg/day [9]. A total of 417 (16%) patients received 6.25 mg/day, 626 (24%) received 12.5 mg/day, 587 (23%) received 25 mg/day, and 676 (26%) received 50 mg/day. The remaining 290 (11%) patients received other dosages of carvedilol, which were generally between the lowest and highest of these four dosages. Carvedilol dosage was relatively stable during the study, and 88% of patients continued on the same dosage for the duration of coprescription (89% of the group on carvedilol in combination with ivabradine and 86% of the group on carvedilol in combination with placebo). In the 12% of patients who did change carvedilol dosage, most did so only once during the study. Whatever the dosage of carvedilol, ivabradine dosage was also relatively stable, with 25% patients receiving 5 mg b.i.d. and 75% patients receiving 7.5 mg b.i.d.

In all the carvedilol dosage subgroups, there were fewer cardiovascular deaths or hospitalization for worsening heart failure events with carvedilol in combination with ivabradine than carvedilol in combination with placebo [carvedilol 6.25 mg/day, 67 (29.1%) vs. 69 (36.9%) events, respectively; carvedilol 12.5 mg/day, 67 (22.3%) vs. 85 (26.2%) events; carvedilol 25 mg/day, 63 (20.4%) vs. 57 (20.5%) events, and carvedilol 50 mg/day, 48 (14.2%) vs. 65 (19.2%) events]. The low number of events in the individual dosage subgroups precluded any formal statistical analysis.

The safety of carvedilol in combination with ivabradine appeared to be in accordance with previous findings (table 4). There was no evidence for a relevant difference between the different dosages of carvedilol (data not shown).

Table 4. Safety: selected emergent adverse events expected with carvedilol and ivabradine in patients who had taken at least one dose of the combination

	Events, n (%)		p
	Carvedilol + ivabradine (n = 1,383)	Carvedilol + placebo (n = 1,361)	
All emergent adverse events	1,036 (75)	984 (72)	0.13
Heart failure	331 (24)	388 (29)	0.007
Atrial fibrillation	118 (9)	85 (6)	0.024
Bradycardia	67 (3)	8 (<1)	<0.001
Phosphenes	33 (2)	6 (<1)	<0.001
Hypotension	30 (1)	41 (3)	0.12
Fatigue	14 (1)	7 (<1)	0.19
Asthenia	11 (<1)	4 (<1)	0.12
Hypertension	9 (<1)	17 (1)	0.12
Second- or third-degree AV block	7 (<1)	8 (<1)	0.80
Blurred vision	5 (<1)	2 (<1)	0.45
Hyperglycemia	2 (<1)	3 (<1)	0.69
QTc interval prolongation	1 (<1)	0	1.00
Heart rate decrease	80 (6)	13 (1)	<0.001

AV = Atrioventricular.

Discussion

Our findings in the SHIFT population show that the coprescription of a β-blocker and ivabradine in patients with systolic heart failure is associated with an improvement in cardiovascular outcomes, regardless of the individual β-blocker coprescribed with ivabradine. This is in line with another analysis in this population [6], which reported that the effect on outcomes is determined primarily by the magnitude of heart rate reduction with β-blockers and ivabradine, as opposed to the actual dosage of the β-blocker. Our analysis takes this one step further by analyzing the effect of individual β-blockers, notably carvedilol. Carvedilol was the most frequently used β-blocker in patients with systolic heart failure in the SHIFT study. It was also the most widely prescribed β-blocker in a European registry including nearly 9,000 patients with systolic heart failure, in which 57% of patients were receiving carvedilol [7]. Similar rates of prescription of carvedilol were reported in the USA in a registry of about 6,000 patients with heart failure [10], as well as in the ESC-HF Pilot Survey, in which carvedilol was prescribed to 43% of patients in 12 European countries [11]. In our analysis, prescription of carvedilol in combination with ivabradine for a mean duration of 19 months was associated with an improvement in cardiovascular outcomes (a composite endpoint of cardiovascular death or hospitalization for worsening of heart failure, hospitalization for heart failure, cardiovascular hospitalization, and all-cause hospitalization) compared with carvedilol in combination with placebo.

Despite all the recent therapeutic advances, both mortality and morbidity in patients with heart failure remain unacceptably high [1]. Accordingly, there is a need to identify new therapeutic targets and associated strategies. Heart rate is now recognized as both a risk factor and a therapeutic target in heart failure, and its reduction has become an integral part of the management of risk factors in chronic systolic heart failure [5, 12]. Reduction in resting heart rate is a common feature of the modes of action of both

β-blockers and ivabradine, though β-blockers have other cardiovascular effects, such as a detrimental impact on myocardial contractility and hemodynamics, while ivabradine has no influence on other cardiac parameters [13, 14]. Furthermore, registry data suggest that heart rate is not adequately controlled in a large majority of patients, despite therapy with β-blockers [15, 16]. In a large prospective observational study including 7,401 European patients with chronic heart failure, 56% had a resting heart rate ≥70 bpm, despite the fact that 89% of patients were receiving a β-blocker [16]. This might be related to difficulties uptitrating β-blockers in many patients due to tolerability issues; in addition, some patients might have poor response due to β-receptor polymorphisms [17]. This implies that other strategies may be necessary to improve heart rate control in these patients. This may explain why ivabradine further reduced major risk associated with heart failure when added to evidence-based therapies including β-blockers. The SHIFT trial results presented herein show that the addition of ivabradine to a β-blocker is safe and effective in patients with chronic systolic heart failure. Moreover, the patients receiving ivabradine appeared no more or less likely to change dosage of carvedilol during the study, which suggests that use of ivabradine does not affect the use of carvedilol – or vice versa – and is reassuring regarding the safety and tolerability of this combination.

Our results have a number of implications for clinical practice. First, β-blockers are widely used in patients with heart failure, forming the cornerstone of their management together with RAS inhibitors. Our results also imply that β-blocker dosages in heart failure remain stable since 82% of patients on carvedilol stayed on the same dosage throughout the study. On the other hand, many patients have inadequate heart rate control despite the use of β-blockers. Insofar as ivabradine provides additional significant benefits when added to β-blockers, this should be considered in patients with chronic systolic heart failure in sinus rhythm and with a heart rate ≥70 bpm in the presence of β-blockade as recommended by the latest heart failure guidelines [5]. Our analysis suggests that combination therapies may be applicable in heart failure, in particular a combination of carvedilol and ivabradine. One major advantage of combination therapies in chronic conditions is improved compliance [18], which implies better overall efficacy of treatment.

There are a number of limitations to our study. It suffers from all the limitations of a post hoc analysis, though the results are consistent with previous analyses of patients taking β-blockers in the SHIFT trial [6]. There was no randomized allocation of β-blockers, which were prescribed as a background treatment, using agents and dosages selected by the investigator. The relatively small size of the subgroups, notably for the various dosages of carvedilol, limited the power of the analysis and precluded any formal statistical analysis. In this exploratory analysis, no correction for multiplicity was applied.

Conclusion

Our findings suggest that the prescription of β-blocker in combination with ivabradine is associated with improvement in cardiovascular outcomes, regardless of the β-blocker used. In patients treated with carvedilol, the most frequently used β-blocker in the trial population, carvedilol in combination with ivabradine improved cardiovascular outcomes and was safe in patients with systolic heart failure in sinus rhythm with a resting heart rate ≥70 bpm.

Conflict of Interest

E.A.B. has received consulting fees from Baldacci and Servier; travel grants from Baldacci, Servier, Berlin Heart GmbH, and Novartis; fees for membership of steering committees from Servier and Novartis; fees for contracted research from Servier and Amgen, and honoraria from Servier. L.T. and I.F. received research grants and honoraria for conducting research as trial committee members sponsored by Servier. K.S. has received research support from Amgen and Pfizer. M.K. is a coprincipal investigator of the SHIFT trial and a member of the Speaker's Bureau for Servier. J.S.B. and K.S. are consultants to Servier and have received honoraria and fees from this company. K.S. is a consultant for Amgen, Novartis, Roche, and Vifor. M.B. has received consulting and speakers fees for Boehringer Ingelheim, Servier, and Medtronic.

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