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Optimization of heart rate lowering therapy in hospitalized patients with heart failure: Insights from the Optimize Heart Failure Care Program

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ABSTRACT

Background: Hospitalization is an opportunity to optimize heart failure (HF) therapy. As optimal treatment for hospitalized HF patients in sinus rhythm with heart rate ≥ 70 bpm is unclear, we investigated the impact of combined beta-blocker (BB) and ivabradine versus BBs alone on short and longer term mortality and rehospitalization.

Methods and results: A retrospective analysis was performed on 370 hospitalized HF patients with heart rate ≥ 70 bpm (150 BB + ivabradine, 220 BB alone) in the Optimize Heart Failure Care Program in Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Russia, Ukraine, and Uzbekistan, from October 2015 to April 2016.

Results: At 1 month, 3 months, 6 months and 12 months, there were fewer deaths, HF hospitalizations and overall hospitalizations in patients on BB + ivabradine vs BBs alone. At 12 months, all-cause mortality or HF hospitalization was significantly lower with BB + ivabradine than BBs (adjusted hazard ratio [HR] 0.45 (95% confidence interval [CI] 0.32–0.64, $P < 0.0001$). Significantly greater improvement was seen in quality of life (QOL) from admission to 12 months with BB + ivabradine vs BBs alone ($P = 0.0001$). With BB + ivabradine, significantly more patients achieved ≥50% target doses of BBs at 12 months than on admission (82.0% vs 66.6%, $P = 0.0001$), but the effect was non-significant with BBs alone.

Conclusions: Heart rate lowering therapy with BB + ivabradine started in hospitalized HF patients (heart rate ≥ 70 bpm) is associated with reduced overall mortality and re-hospitalization over the subsequent 12 months. A prospective randomized trial is needed to confirm the advantages of this strategy.

1. Introduction

Heart failure (HF) affects an estimated 26 million people worldwide [1] and places a significant economic burden on global healthcare systems due to repeated outpatient consultations and high hospitalization and readmission rates [2,3]. Indeed, in the US and Europe, HF is the

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leading cause of hospitalization [1], and rehospitalization rates approaching 30% have been reported at 60–90 days post-discharge [4]. The impact of HF on healthcare services is not limited to western countries; recent data from South East Asia showed a prevalence of HF that is similar to global values, with HF accounting for up to 20% of hospitalizations, and 30-day readmission rates of up to 15% [5].

Despite advances in treatment, HF mortality remains high, especially in patients requiring hospitalization [6–9]. Mortality is highest in the first 30 days after hospitalization [7], with reported all-cause mortality rates at 12 months ranging from 17.4% [8] to 30% [7]. Even at 18 months, a 3.5 fold increased risk of death has been reported for patients who are hospitalized for HF, compared to those who are not [9].

As hospitalization is an indication of worsening HF, it provides an opportunity to re-evaluate patient care, including optimization of current therapy and planning of longer-term management. Current European Society of Cardiology (ESC) recommendations for the treatment of symptomatic patients with HF with reduced ejection fraction (HFrEF) include angiotensin converting enzyme inhibitors (ACEI)/angiotensin receptor blockers (ARBs), beta blockers (BBs) and mineralocorticoid receptor antagonists (MRAs) [10]. A substantial proportion of patients hospitalized with HFrEF have a raised heart rate at discharge, despite treatment with BBs [11], and a heart rate ≥ 70 bpm is associated with increased risk of all-cause mortality or all-cause hospitalization in patients with HF [11,12]. For patients in sinus rhythm with a heart rate ≥ 70 bpm, current ESC guidelines recommend the addition of the I_f current inhibitor, ivabradine [10]. In the SHIFT study, ivabradine was shown to reduce a combined endpoint of mortality or hospitalization in HF patients with a heart rate over 70 bpm who were already on guideline-based therapy with ACEI/ARB, BB and/or MRA [12]. In this study, patients had been hospitalized for HF within the previous 12 months but not within the preceding 4 weeks, but there is a continuing need to identify the most effective approach for patients with a raised heart rate during hospitalization and/or at discharge. In the ETHIC-AHF study, co-administration of BB and ivabradine was shown to reduce heart rate and improve systolic function at 28 days and at four months in patients hospitalized with HF [13], but the question remains about whether this strategy can reduce the incidence of major clinical events in this potentially higher risk group of patients.

To start to address this question, we carried out a retrospective analysis of the effects of in-hospital coadministration of BB and ivabradine versus BB alone on mortality, rehospitalization and quality of life in hospitalized patients taking part in the Optimize Heart Failure Care Program. This Program is a global initiative to improve prescription of guidelines-recommended drug therapies, patient education and engagement, and post-discharge planning for patients hospitalized with HF [14].

2. Material and methods

For this retrospective analysis, we identified hospitalized patients with HF aged 18 years or older with sinus rhythm, heart rate ≥ 70 bpm and left ventricular ejection fraction (LVEF) <40%, who participated in the international multicenter Optimize Heart Failure Care program in Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Russia, Ukraine, and Uzbekistan from October 2015 to April 2016. The design and rationale of the program (www.optimize-hf.com), which is currently operating in 45 countries, have been described previously [14]. All participating hospitals were provided with examples of best practice protocols developed for optimizing HF management based on the recommendations from the ESC Guidelines, pre- and post-discharge checklists, and 'My HF Passport' — an education aid (available in print form and as a smart phone application) to improve patient understanding of HF and encourage involvement in care and treatment adherence.

Best practice protocols for optimizing HF management included ESC recommendations for pharmacological therapy, such as ACEI/ARBs, BBs, MRAs and ivabradine. Physicians participating in the Program were free to choose their own strategy of in-hospital administration of BB alone or with ivabradine. Patient characteristics and data on the use of ACE/ARBs, BBs, MRAs and diuretics on admission and at 12 months follow up were analyzed according to administration strategies for BB ± ivabradine. Mortality and hospitalization data for patients at admission, one, three, six and 12 months were compared according to use of BB ± ivabradine.

Patient quality of life (QOL) was evaluated using the Minnesota Living with Heart Failure Questionnaire (MLHFQ).

The survey was conducted according to the rules of the declaration of Helsinki and was approved by relevant ethical committees and/or regulatory bodies in all eight participating countries. All patients gave written informed consent to participate, in accordance with national and local regulations.

2.1. Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS version 17.0, SPSS Inc., Chicago, IL, USA) and Microsoft Office Excel 2013. Normal distribution of the data was tested by means of the Kolmogorov–Smirnov test. Continuous variables were analyzed using the Student *t*-test to determine the difference between the groups. Categorical variables were expressed as absolute frequencies (n) and compared by chi-square test when there was a sufficient number of observations, and by Fisher's exact test when this was not the case. Continuous variables are presented as mean ± standard deviation and categorical variables as number and percentage (%). Time to event curves were estimated using the Kaplan–Meyer method, with adjustment for baseline differences in covariates. Last observation carried forward (LOCF) analysis of QOL changes was applied to minimize survival bias in the data. Two-sided $P < 0.05$ was required for statistical significance.

3. Results

Three hundred and seventy patients were included in the analysis (220 treated with BB alone, 150 with BB + ivabradine combinations) (Table 1). Baseline characteristics, including age, sex, comorbidities and New York Heart Association (NYHA) classification, were similar for the two groups, with the exception of heart rate. Mean heart rate in the BB alone group was 80.0 ± 13.3 bpm, compared to 89.2 ± 14.5 bpm in the BB + ivabradine group ($P = 0.0001$).

Table 1
Baseline characteristics of hospitalized patients with heart failure.

	Beta-blockers alone ($n = 220$)	Beta-blocker + ivabradine combinations ($n = 150$)	*P* value
Age (years)	60.7 ± 12.1	62.9 ± 12.8	0.74
Women (%)	24.1	28.7	0.43
History of MI (%)	21.8	20.0	0.54
Hypertension (%)	34.1	35.3	0.71
Diabetes (%)	17.7	16.0	0.5
Anemia (%)	16.8	18.0	0.67
COPD (%)	21.8	24.0	0.48
Etiology of heart failure (%):			
• Ischemic	62.2	61.3	0.60
• Idiopathic	17.8	16.7	0.67
• Hypertensive	20.0	22.0	0.56
NYHA functional class	2.8 ± 0.6	2.7 ± 0.6	0.40
BMI, kg/m^2	30.4 ± 4.0	29.6 ± 3.4	0.61
SBP, mm Hg	123.0 ± 18.9	128 ± 24.5	0.06
DBP, mm Hg	78.0 ± 10.9	80.8 ± 15	0.10
HR, bpm	80.0 ± 13.3	89.2 ± 14.5	0.0001
LVEF (%)	29.7 ± 7.7	28.9 ± 7.2	0.26
Creatinine, μmol/L	104.4 ± 32.7	100.0 ± 28.4	0.20

MI — myocardial infarction; COPD — chronic obstructive pulmonary disease; NYHA — New York Heart Association; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; HR — heart rate; LVEF — left ventricular ejection fraction.

At 12 months follow up, significant changes were seen in mean NYHA class, heart rate, LVEF and use of ACEI/ARBs, BBs, MRAs and diuretics compared with on-admission status in both the BB alone and BB + ivabradine treatment groups (Table 2). Pairwise comparison for those who survived to 12 months is shown in the Supplementary Table.

Mean dose of ivabradine at 12 months was 9.9 ± 4.2 mg, compared with 9.6 ± 3.5 mg at discharge. The majority of patients included in the analysis received bisoprolol (46%) and metoprolol succinate (33%). The mean doses of bisoprolol at discharge in the BB + ivabradine group and BB alone group were 3.1 ± 1.3 mg and 3.6 ± 1.8 mg, and increased to 5.6 ± 1.3 mg and 3.8 ± 2.3 mg at 12 months, respectively. Similarly, mean doses of metoprolol succinate increased from 75 ± 25.7 mg at discharge to 100 ± 42 mg at 12 months in the BB + ivabradine group, compared to an increase from 45.0 ± 12 mg to 65 ± 23.5 mg, in the BB alone group.

At 12 months, a greater reduction in heart rate was seen in the BB + ivabradine than the BB group (19.2 bpm vs 8.2 bpm; $P = 0.0001$). In the BB + ivabradine group, significantly more patients achieved ≥50% target doses of BBs at 12 months than on admission (82.0% vs 66.6%, $P = 0.0001$), but the effect was non-significant in the BB alone group (Table 2).

A comparison of 12-month follow up data for drug dosing showed that a higher proportion of patients in the BB + ivabradine group achieved ≥50% target doses of ACEI/ARBs, BBs and MRAs compared to the BB group (68% vs 58%, $P = 0.05$, 82% vs 55.5%, $P = 0.001$, 86.6% vs 77.2%, $P = 0.05$ respectively).

At all stages following discharge (1 month, 3 months, 6 months and 12 months), there were fewer deaths, HF hospitalizations and overall hospitalizations in patients on combination treatment with BB + ivabradine than in those in the BB group (Table 3). Kaplan–Meier curves adjusted for age, gender, heart rate, systolic blood pressure, serum creatinine, and NYHA class at baseline show that the probability of all-cause mortality or heart failure hospitalizations was significantly lower in the BB + ivabradine group than in the BB alone group (adjusted hazard ratio [HR] 0.45 (95% confidence interval [CI] 0.32–0.64, $P < 0.0001$) (Fig. 1). Unadjusted HR is 0.41 (95% CI 0.29–0.57, $P < 0.0001$).

In both groups, there were significant improvements in QOL from admission to 12-month follow up, but this was significantly greater in the BB + ivabradine group (Table 2). The mean values for MLHFQ were 56.9 ± 18.2 and 49.9 ± 22.3 at baseline ($P = 0.06$) in the BB alone group and the BB + ivabradine group, respectively. At 12-month follow up, these values improved significantly to 48.5 ± 15.8 ($P = 0.01$) and 29.5 ± 15.3 ($P = 0.0001$), respectively. The difference between the groups at 12 months was also significant ($P = 0.0001$) (see Supplementary Table for pairwise comparisons of only those who survived to 12 months).

4. Discussion

Despite the current beta-blocker therapy, many patients hospitalized with HFrEF have an elevated raised discharge heart rate, which is associated with higher mortality and hospitalization rates [11,15]. In this context, the search for optimal strategies of heart rate control in HF patients becomes an important therapeutic task [16].

In this first study of its kind in these eight countries of the post-Soviet area, we demonstrated that the addition of ivabradine to BB therapy was associated with a reduction in all-cause mortality or HF rehospitalization in patients hospitalized with HF, in sinus rhythm, with heart rate ≥ 70 bpm and LVEF < 40%, compared to BBs alone. We also showed that this treatment strategy was associated with greater improvement in QOL for patients with HF.

The beneficial outcomes of the combination BB + ivabradine strategy were seen in the early post-discharge phase when HF patients are typically most vulnerable to readmission or death and continued throughout the 12-month follow up. These early and sustained effects build on findings from the SHIFT study in HF patients with a heart rate ≥ 70 bpm [12], which included a post hoc analysis of the effects of the addition of ivabradine to ACEI/ARB, BB and MRA treatment on early readmissions in patients hospitalized for HF [17]. This analysis showed that ivabradine was associated with fewer all-cause hospitalizations at one month [incidence rate ratio (IRR) 0.70, 95% confidence interval (CI) 0.50–1.00, $P < 0.05$], two months (IRR 0.75, 95% CI 0.58–0.98, $P = 0.03$), and three months (IRR 0.79, 95% CI 0.63–0.99, $P = 0.04$) [17]. A trend towards a reduction in cardiovascular and HF hospitalizations was also observed in ivabradine-treated patients.

The significantly greater improvement in quality of life seen with the BB + ivabradine strategy also reinforces the beneficial effects seen with ivabradine in previous clinical research. In the SHIFT study, ivabradine significantly improved Kansas City Cardiomyopathy Questionnaire (KCCQ) overall and clinical summary scores (placebo-corrected, $P < 0.01$ and $P = 0.02$ respectively), with the magnitude of heart rate reduction related to the extent of improvement in health related QOL [18].

In the prospective, open-label, multicentre, INTENSIFY study, addition of ivabradine to standard HF treatment with ACEI/ARB, BB and MRA was associated with an improvement in mean QOL EQ-5D (European quality of life-5 dimensions) sum score index from 0.64 ± 0.28 at baseline to 0.79 ± 0.21 at 4-month follow up [19]. In this study of nearly 2000 patients with chronic HF, the mean baseline heart rate of 85.0 ± 11.8 bpm was comparable to that seen in HF patients in the Optimize Heart Failure Care Program, and highlights the challenge of this known risk factor for increased mortality and hospitalization in daily clinical practice.

Participation in the Optimize Heart Failure Care Program appears to have had beneficial effects on drug administration and up-titration towards target doses, especially in the BB + ivabradine group. The most pronounced effect was observed for BBs, with ≥50% of target doses having been achieved in 82.0% of patients in the BB + ivabradine group vs. 55.5% in the BB alone group ($P = 0.0001$). A similar improvement in achievement of BB target doses was demonstrated in a study by Bagriy et al. [20], which analyzed the addition of ivabradine to carvedilol

Table 2
Patient characteristics and drug administration on admission and in those, who survived to 12 months after discharge. Pairwise comparison for those who survived to 12 months is shown in the Supplementary Table.

	Beta-blockers alone			Beta-blockers + ivabradine			Comparison between 2 groups
	On admission ($n = 220$)	12 months ($n = 198$)	*P* value	On admission ($n = 150$)	12 months ($n = 146$)	*P* value	
NYHA	2.8(0.56)	2.3(0.56)	0.0001	2.7 (0.6)	2.1 (0.4)	0.0001	0.05
HR, bpm	80(13.3)	71.8(8.3)	0.001	89.2(14.5)	70.4(9.2)	0.0001	0.07
LVEF (%)	29.7(7.7)	32.4(8.7)	0.001	28.9(7.2)	34(7)	0.001	0.001
Diuretics, *n* (%)	218(99%)	178(89.9%)	0.05	139(92.2%)	136(89.4%)	0.07	0.6
ACEIs/ARBs, *n* (%)	198(90%)	180(81%)	0.05	133(88.7%)	140(95.8%)	0.06	0.001
ACEIs/ARBs, ≥50% of target dose, *n* (%)	110(55.5%)	100(58%)	0.08	86(64%)	96(68%)	0.07	0.05
BBs, ≥50% of target dose, *n* (%)	117(53%)	122(55.5%)	0.09	100(66.6%)	123(82%)	0.0001	0.0001
MRAs, *n* (%)	200(90.9%)	170(77.2%)	0.001	131(87.3%)	130(86.6%)	0.6	0.05
QOL score	56.9(18.2)	48.5(15.8)	0.01	49.9(22.3)	29.5(15.3)	0.0001	0.0001

Table 3
Deaths, HF hospitalization and all hospitalization from admission to 12-month follow up.

Beta-blockers alone ($n = 220$)	Admission	Discharge	1 month	3 months	6 months	12 months	Total
Death, *n* (%)	2 (0.9%)	0	5 (2.3%)*	0	10 (4.5%)*	5 (2.3%)	22
Hospitalization for HF, *n* (%)	0	0	6 (2.7%)*	13 (5.9%)*	23 (10.4%)*	26 (11.8%)*	68
All hospitalizations, *n* (%)	0	0	7 (3.1%)**	30 (13.6%)*	31 (14%)*	30 (13.6%)*	98
Beta-blockers + ivabradine (n = 150)							
Death, *n* (%)	0	0	0	1 (0.7%)	1 (0.66%)	2 (1.3%)	4
Hospitalization for HF, *n* (%)	0	0	2 (1.3%)	4 (2.6%)	5 (3.3%)	5 (3.3%)	16
All hospitalizations, *n* (%)	0	0	3 (2%)	8 (5.3%)	6 (4%)	9 (6%)	26

* $p < 0.0001$ vs. BB + ivabradine group.
** $p < 0.001$ vs. BB + ivabradine group.

in patients with chronic HF. Patients receiving carvedilol and ivabradine achieved higher dosages of carvedilol during the study, compared to those receiving carvedilol alone, and 70% of patients on combination treatment achieved >50% of target doses compared to 36% in the group receiving carvedilol alone. However, in our study, in comparison with the above-mentioned study [20], the mean baseline heart rate was significantly higher in the BB + ivabradine group compared with the patients receiving BBs alone. This could play a certain role in achieving higher BB doses, which could contribute to better outcomes in addition to the effects of ivabradine.

Under-dosing of key medications is a major issue in HF populations, as demonstrated in the international QUALIFY (QUality of Adherence to guideline recommendations for LIFe-saving treatment in heart failure surveY) survey, in which 15% of patients were at target dose for BBs at baseline and 52% at ≥50% of target dose [21]. A subsequent 6-month analysis of QUALIFY data showed that poor adherence to recommended doses was associated with significantly higher overall mortality ($P = 0.001$); CV mortality ($P = 0.003$); HF mortality ($P = 0.032$), combined HF hospitalization or HF death ($P = 0.024$) and CV hospitalization or CV death ($P = 0.013$) [22]. There was also a strong trend between poor adherence and HF hospitalization ($P = 0.069$).

4.1. Limitations

All observational studies such as this analysis of data from the Optimize Heart Failure Care Program carry a possibility for bias, leading to overestimation or underestimation of treatment effects. As centres involved in the Program were selected by a national coordinator, selection bias cannot be excluded. Participating physicians were free to choose between BB alone and BB + ivabradine strategies and the baseline difference in heart rate suggests physicians were more likely to combine BB with ivabradine in those with a higher heart rate (and thus higher risk). Despite this baseline higher risk, mortality and HF hospitalization rates were lower in this group than in those selected for the strategy of heart rate control with BB alone. Adjusting the survival analysis for the small differences in baseline characteristics made little difference to the comparison between the two groups, with substantial reduction in risk of mortality or HF hospitalization in the combined strategy group. Also, despite the higher mortality in the BB alone group, potentially removing the sickest patients (informative censoring) from follow-up, the improvement in QOL and reduction in HF hospitalization was more marked in those selected for the combined BB + ivabradine strategy. The pairwise comparison of QOL for those who were alive at 12 months confirms this effect.

A higher baseline heart rate not only influenced the choice of combined BB + ivabradine strategy, but also could be an incentive for more active up-titration of BBs in HF patients. This, in turn, could determine the contribution of achieved higher doses of BBs to improved outcomes in the combined strategy group. However, this assumption requires confirmation in a separate study.

Although the Program is underway in 45 countries, the current analysis has been carried out in eight post-Soviet countries and results may not be representative of those in other geographic areas. However, it does provide valuable insights into the optimization of heart rate

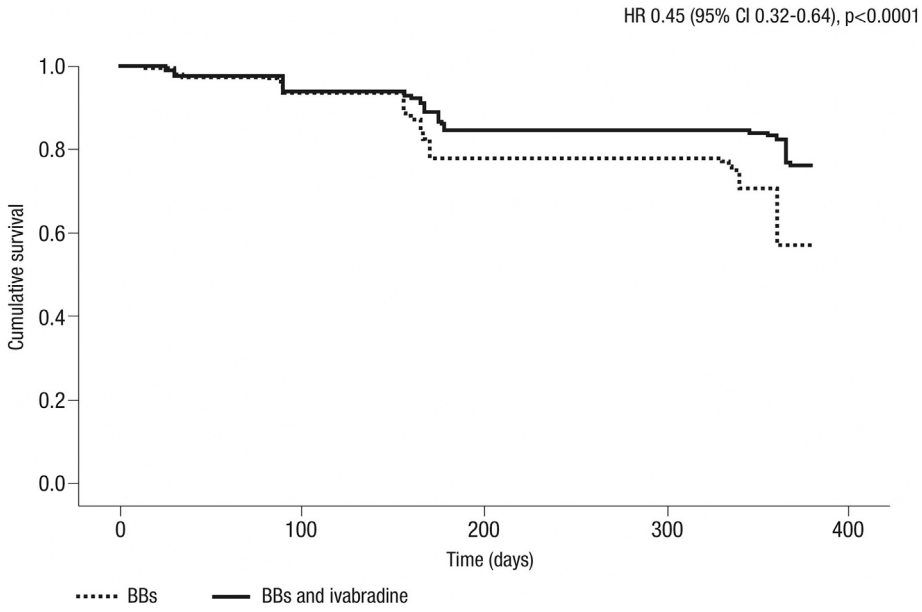

Fig. 1. Kaplan–Meier curves for the probability of all-cause mortality or heart failure hospitalizations, adjusted for baseline differences in age, gender, heart rate, systolic blood pressure, serum creatinine, and NYHA class.

lowering therapy in hospitalized patients with HF in a region with little previous clinical data, and our findings are in line with those seen in other studies (SHIFT, ETHIC-AHF and QUALIFY) in other parts of the world [12,13,21].

5. Conclusions

Heart rate lowering therapy with BB + ivabradine combination treatment started in hospitalized patients with HF, with heart rate ≥ 70 bpm, was associated with a substantial reduction in overall mortality and re-hospitalization. A large clinical trial is needed to confirm the advantages of this strategy in hospitalized patients with HF.

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Conflict of interest

Yuri M Lopatin has received speaker fees and has provided consultancy advice to Servier.

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