International Journal of Cardiology 260 (2018) 113–117

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

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

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ARTICLE INFO

Article history:
Received 11 October 2017
Received in revised form 18 December 2017
Accepted 22 December 2017

Keywords:
Heart failure
Optimize
Mortality
Hospitalization
Ivabradine
Beta blockers

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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https://doi.org/10.1016/j.ijcard.2017.12.093
0167-5273/

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.