Safety profile and efficacy of ivabradine in heart failure due to Chagas heart disease: a post hoc analysis of the SHIFT trial

Edimar Alcides Bocchi¹*, Salvador Rassi², Guilherme Veiga Guimarães¹ and Argentina, Chile, and Brazil SHIFT Investigators

¹Heart Institute (InCor), São Paulo University Medical School (HC-FUMSP), Rua Dr Melo Alves 690, 4o andar, Bairro Cerqueira Cesar, São Paulo, São Paulo, CEP 014170-010, Brazil; ²Medical School, Federal University of Goiás, Goiânia, Goiás, Brazil

Abstract

Aims The SHIFT trial showed that ivabradine reduced heart rate (HR) and the risk of cardiovascular outcomes. Concerns remain over the efficacy and safety of ivabradine on heart failure (HF) due to Chagas disease (ChD). We therefore conducted a post hoc analysis of the SHIFT trial to investigate the effect of ivabradine in these patients.

Methods and results SHIFT was a randomized, double-blind, placebo-controlled trial in symptomatic systolic stable HF, HR ≥ 70 b.p.m., and in sinus rhythm. The ChD HF subgroup included 38 patients, 20 on ivabradine, and 18 on placebo. The ChD HF subgroup showed high prevalence of bundle branch right block and, compared with the overall SHIFT population, lower systolic blood pressure; higher use of diuretics, cardiac glycosides, and antialdosterone agents; and lower use of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker or target daily dose of beta-blocker. ChD HF presented a poor prognosis (all-cause mortality at 2 years was ~60%). The mean twice-daily dose of ivabradine was 6.26 ± 1.15 mg and placebo 6.43 ± 1.55 mg. Ivabradine reduced HR from 77.9 ± 3.8 to 62.3 ± 10.1 b.p.m. (P = 0.005) and improved functional class (P = 0.02). A trend towards reduction in all-cause death was observed in ivabradine arm vs. placebo (P = 0.07). Ivabradine was not associated with serious bradycardia, atrioventricular block, hypotension, or syncope.

Conclusions ChD HF is an advanced form of HF with poor prognosis. Ivabradine was effective in reducing HR in these patients and improving functional class. Although our results are based on a very limited sample and should be interpreted with caution, they suggest that ivabradine may have a favourable benefit–risk profile in ChD HF patients.

Keywords Chagas disease; Heart failure; Ivabradine; SHIFT trial; Heart rate; Chagasic cardiomyopathy

Introduction

The cardiomyopathy caused by Chagas disease (ChD) is a major cause of morbidity and mortality in Latin America.¹ Also, ChD has become a global health issue mainly owing to migration. Despite the substantial burden to the healthcare system, there is uncertainty regarding the efficacy and safety of standard guideline-oriented pharmacological interventions for treating heart failure (HF) in patients with ChD.² The current guidelines recommend the use of non-chagasic HF treatments for ChD HF, although no robust evidence supports this practice.³–⁶ In addition, the specific etiological treatment for
chronic ChD produces frequent side effects or it seems to be not effective.⁷,⁸ Patients with HF due to ChD face a worse prognosis in comparison with other aetiologies.⁹ Many of the pathogenic and remodelling mechanisms involved in ChD HF might render chagasic HF patients unresponsive to usual treatment,¹⁰ and this may also explain the high mortality.

Thus, new evidences of novel therapeutic approaches for the treatment of ChD HF are crucial. Iverapin, a specific inhibitor of the I_{f} current in the sinoatrial node was associated with reduction of cardiovascular death or hospitalization for worsening HF in the SHIFT study.¹¹ Effects of ivabradine in ChD HF were not reported. In this post hoc analysis of SHIFT, we explored the effects of ivabradine in patients with ChD HF.

Methods

Study design

The SHIFT study was described in detail previously.¹¹ Briefly, this randomized, double-blind, placebo-controlled, parallel-group, multinational clinical trial included 6505 patients with moderate to severe chronic HF and documented left ventricular (LV) systolic dysfunction (LV ejection fraction ≤ 35%). Eligible patients were in sinus rhythm with a resting heart rate (HR) of ≥70 b.p.m. on 12-lead electrocardiography; they had been clinically stable for ≥4 weeks and had been admitted to the hospital for worsening HF within the previous 12 months. All participants were receiving guideline-based background therapy for HF, including maximized beta-blocker therapy, if tolerated. Other inclusion and exclusion criteria have been described previously. After a 2-week run-in period, patients were randomly assigned to receive either ivabradine (5 mg b.i.d.) or placebo. Ivabradine or placebo therapy was initiated with 5 mg b.i.d. At subsequent visits at 14 days, at 28 days, and every 4 months thereafter (or at any other time if necessary), the dosage of blinded study medication could be adjusted upward (7.5 mg b.i.d.) or downward (2.5 mg b.i.d.) depending on resting HR. The ethics committee approved the trial, and all subjects gave written informed consent to participate in the trial.

Objective of this analysis

A post hoc analysis of SHIFT was performed to explore the safety profile and efficacy of ivabradine in patients with systolic HF due to ChD in sinus rhythm, with resting HR ≥ 70 b.p.m. All primary and secondary endpoints of SHIFT were analysed. Main adverse events during the study also were studied.

Statistical analysis

Baseline characteristics are presented as numbers and percentages for categorical variables and means (±SD) for continuous variables. Because this study is a post hoc analysis of SHIFT data, the statistical methods employed also were selected post hoc, although they are standard for analyses of this type of data. The Graphpad Prism 5.0 was used for statistical analysis. Survival analyses were performed on a time-to-first-event basis with an intention-to-treat principle. Time-to-event curves were estimated with the Kaplan–Meier method. Groups were compared with log-rank test and Breslow (generalized Wilcoxon). The percentages of patients improving their New York Heart Association (NYHA) functional class from baseline to last evaluation were compared with a χ² test. Intra-group HR comparisons from baseline to last evaluation were performed by a paired t-test.

Role of sponsor of the SHIFT trial

The first author, who was a member of the Steering Committee of the SHIFT study, requested the sponsor of SHIFT to provide the data of ChD HF patients included in the SHIFT study. The first author was the investigator of this post hoc analysis; neither the sponsor of SHIFT nor the executive committee of the trial participated in the analysis of data or in any activity related to manuscript except for data sharing.

Results

From 6505 patients randomized in SHIFT, 20 patients with HF due to ChD HF were randomized to receive ivabradine and 18 patients to placebo. Sixteen patients (42%) were randomized in Argentina, 21 (55%) in Brazil, and 1 (3%) in Chile. The mean studied follow-up for ChD HF patients was 13 ± 7 months and concluded on 31 March 2010. Baseline characteristics of ChD HF are given in Table 1. The characteristics of this substudy population were similar to those of the population of the main study (Table 1) except for lower percentages of men, NYHA functional class III patients, hypertension, diabetes, history of atrial arrhythmias, and device indication; longer duration of symptoms; and lower systemic blood pressure. The ChD HF subgroup showed high prevalence of bundle branch right block. In contrast to other SHIFT patients, ChD HF patients more frequently received antialdosterone agents and lower doses of beta-blockers. Hypotension was the most frequent reason for failing to reach target dose of beta-blocker: 68% vs. 45% in main study (Table 2). The mean ivabradine dose prescribed after the titration phase for ivabradine was 6.26 ± 1.15 mg and for placebo 6.43 ± 1.55 mg twice daily.
Heart rate effects of ivabradine

**Figure 1A** shows changes in HR. In comparison with baseline HR at 28 days and 12 months after randomization, the HR reduced in the ivabradine group (−12 ± 7 and −11 ± 10 b.p.m.) and in the placebo group (−8 ± 11 and −6 ± 16 b.p.m.). From the baseline to post-randomization last evaluation, the HR reduced from 77.9 ± 3.8 to 62.3 ± 10.1 b.p.m. (−16 ± 9 b.p.m.) in the ivabradine group (P = 0.005), while in the placebo group, the HR was 78.8 ± 10.6 b.p.m. at baseline and 79.6 ± 13.7 b.p.m. in the last evaluation (1 ± 16 b.p.m. in comparison with baseline) (**Figure 1B**).

**Functional class**

**Figure 2** shows the NYHA functional class from baseline to 12 months and at last post-randomization evaluation. The

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**Table 1** Baseline characteristics of patients with Chagas disease heart failure enrolled in the SHIFT trial

| Baseline characteristics | SHIFT trial (n = 6505) | ChD HF n = 38 | ChD HF Iva n = 20 | ChD HF Pla n = 18 |
|--------------------------|------------------------|---------------|-------------------|-------------------|
| Age (years)              | 60.9 ± 11.6            | 60 ± 12       | 62 ± 11           | 58 ± 13           |
| Sex (male), n (%)        | 4970 (76.4%)           | 26 (68.4%)    | 13 (65%)          | 13 (72%)          |
| Ethnic origin, n (%)     | White (Caucasian) 5771 (88.7%) | 31 (81.5%) | 17 (85%) | 14 (78%) |
| Black                    | NR 3 (7.8%)            | 0             | 3 (17%)           | 1 (6%)            |
| Other                    | 202 (3.1%)             | 4 (10.5%)     | 3 (15%)           | 1 (6%)            |
| Current smoking          | NR 3 (7.8%)            | 1 (5%)        | 2 (11%)           |                   |
| BMI (kg/m²)              | 25.8 ± 2.4             | 25.5 ± 5.2    | 26 ± 6.5          | 25 ± 4            |

**Cardiac parameters**

| Heart rate (b.p.m.)      | 79.9 ± 9.6             | 78.3 ± 7.2    | 77.9 ± 3.8        | 78.8 ± 10.6       |
| SBP (mmHg)               | 121.7 ± 16             | 111 ± 15.5    | 112 ± 16          | 110 ± 15          |
| DBP (mmHg)               | 75.7 ± 9.5             | 70 ± 8.5      | 71 ± 9            | 69 ± 8            |
| LVEF (%)                 | 29 ± 5.2               | 27.5 ± 5.5    | 28 ± 5            | 27 ± 6            |
| Bundle branch block right | NR 9 (23.6%)          | 4 (20%)      | 5 (28%)           |                   |
| Bundle branch block left | 912 (14%)              | 6 (15.7%)     | 2 (10%)           | 4 (22%)           |

**NYHA, n (%)**

| Class II                 | 3169 (48.7%)           | 30 (78.9%)    | 16 (80%)          | 14 (78%)          |
| Class III                | 3223 (49.5%)           | 8 (21.1%)     | 4 (20%)           | 4 (22%)           |
| Class IV                 | 111 (1.7%)             | 0             | 0                 | 0                 |

**Medical history**

| Duration HF (years)      | 4.19 ± 5.04            | 3.9 ± 10.79   | 4.62 ± 8.22       | 3.19 ± 5.14       |
| Hypertension, n (%)      | 4314 (66.3%)           | 15 (39.4%)    | 8 (40%)           | 7 (39%)           |
| Diabete                  | 1979 (30.4%)           | 3 (7.9%)      | 2 (10%)           | 1 (5.6%)          |
| Previous stroke, n (%)   | 523 (8%)               | 2 (5.2%)      | 0                 | 2 (11%)           |
| Atrial fibrillation or flutter | 522 (8%)         | 1 (2.6%)      | 0                 | 0                 |
| COPD                     | 730 (11.2%)            | 4 (10.5%)     | 1 (5%)            | 3 (16.7%)         |
| Hypothyroidism           | NR 4 (10.5%)           | 2 (10%)       | 2 (11%)           |                   |
| Depression               | NR 2 (5.2%)            | 1 (5%)        | 1 (5.6%)          |                   |
| Anaemia                  | NR 1 (2.6%)            | 0             | 1 (5.6%)          |                   |
| eGFR (mL/min/1.73 m²)    | 74.6                   | 72 ± 32.5     | 61 ± 23           | 83 ± 42           |

**Treatment at randomization**

| Beta-blocker            | 5820 (89.5%)           | 33 (86.8%)    | 18 (90%)          | 15 (83.3%)        |
| ACE inhibitor           | 5116 (78.6%)           | 25 (65.7%)    | 15 (75%)          | 10 (56%)          |
| Enalapril (mg)          | NR 8 ± 4.95            | 7.3 ± 5       | 8.8 ± 4.9         |                   |
| ARB                     | 927 (14.3%)            | 7 (18.4%)     | 3 (15%)           | 4 (22%)           |
| Losartan (mg)           | NR 44.5 ± 23           | 33 ± 14       | 56 ± 32           |                   |
| Diuretic                | 5414 (83.2%)           | 35 (92%)      | 18 (90%)          | 17 (94%)          |
| ACEI and /or ARB        | NR 32 (84.2%)          | 18 (90%)      | 14 (78%)          |                   |
| Antiloxidosterone agents | 3922 (60.2%)         | 20 (100%)     | 15 (83%)          |                   |
| Spironolactone (mg)     | NR 26.5 ± 4            | 28 ± 8        | 25 ± 0            |                   |
| Cardiac glycosides      | 1416 (21.7%)           | 17 (44.7%)    | 9 (45%)           | 8 (44%)           |
| Devices                 | 279 (4.2%)             | 0             | 0                 | 0                 |
| Amiodarone              | NR 6 (15.7%)           | 2 (10%)       | 4 (22.13%)        |                   |
| Nitrates                | NR 1 (2.6%)            | 0             | 1 (6%)            |                   |
| Antithrombotic agents   | NR 18 (47.3%)          | 9 (45%)       | 9 (50%)           |                   |
| Acetylsalicylic acid    | NR 16 (42.1%)          | 9 (45%)       | 7 (39%)           |                   |
| Clopidogrel             | NR 1 (2.6%)            | 1 (5%)        | 0                 |                   |
| Vitamin K antagonists   | 1082 (16.6%)           | 2 (5.2%)      | 2 (11.2%)         |                   |

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; ChD HF, Chagas disease heart failure; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Iva, ivabradine; LVEF, left ventricular ejection fraction; NR, not reported; Pla, placebo; SBP, systolic blood pressure.

Data are number of patients (%) or means ± 1 standard deviation.

Heart rate effects of ivabradine

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Functional class

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functional class improved over this period in the ivabradine group in 30% of patients, while it remained stable in 60%, and worsened in 10%. In the placebo group, functional class improved in 22%, remained stable in 44%, and worsened in 33% (comparison X on χ² test: P = 0.02).

Mortality and hospitalization

For the overall ChD HF patients, Figure 3A (Kaplan–Meier curve) shows 40% probability of survival at 750 day follow-up, and Figure 3B (Kaplan–Meier curve) shows ~30% probability to be free of death or hospitalization due to worsening HF at the same time of follow-up. Table 3 shows the effects of ivabradine in comparison with placebo in components of primary endpoints, and secondary endpoints. The data show a trend towards reduction in any cause of death in the ivabradine group (P < 0.07) (Figure 4A) (Kaplan–Meier curve) during the follow-up. Figure 4B shows the effect of ivabradine vs. placebo on the primary composite endpoint (cardiovascular death or hospitalization for worsening HF) during the study follow-up.

Adverse effects

Table 4 presents the adverse effects reported in the ivabradine group in comparison with placebo. No differences
were observed comparing both groups concerning total clinical events. Ivabradine was not associated with serious bradycardia, atrioventricular block, hypotension, or syncope.

Discussion

This investigation is, to the best of our knowledge, the first to report ivabradine effects in ChD HF patients and confirmed that ChD HF is an advanced form of HF with very poor prognosis. Ivabradine reduced HR, improved NYHA functional class, and was associated with a trend to reduction in mortality. Ivabradine was not associated with an increment in adverse events in comparison with placebo. Also, optimized, guideline-oriented HF treatment was not well tolerated in ChD HF.

The finding of ivabradine-dependent HR reduction with acceptable safety profile suggests that the $I_f$ current in the sinoatrial node is not importantly affected by ChD HF pathogenic mechanisms in patients with HR heart rate $\geq$ 70 b.p.m. Therefore, use of ivabradine may be feasible in ChD HF patients fulfilling the SHIFT inclusion criterion. The reduction of HR at 28 days compared with pre-treatment observed in ChD HF was close to that described in the SHIFT study. Our findings disagree with the potential concern about use of ivabradine in ChD HF. Chronotropic incompetence and sick sinus node syndrome may be found in ChD cardiomyopathy (ChHD), even in the latent phase when the heart may be apparently normal. The inflammatory and fibrotic processes may damage sinus cells, destroy the innervation, and cause significant barriers to sinus node impulse progression. However, autoantibodies reported in ChHD may exert sometimes effects in favour of increment or decrease in heart chronotropism, depending on the type of antibody or patient characteristics.

Beyond the proposed effects of ivabradine in overall aetiologies, some mechanisms should be taken in account to explain the tendency to reduction of mortality and improvement in functional class ChD HF. ChD HF in comparison with other HF aetiologies is characterized by a remodelling process with frequent right and LV dysfunction besides persistent myocarditis associated with inflammatory infiltrate oedema, contraction band necrosis, myocytolysis, focal and diffuse areas of myocellular hypertrophy, fibrosis, damage

Table 3 Number and % of patients with at least one event in ivabradine/placebo groups for primary and secondary endpoints

| Event                                           | Ivabradine group | Placebo group |
|-------------------------------------------------|------------------|---------------|
| Primary endpoint components                      |                  |               |
| Cardiovascular death or HF hospitalization       | 10 (50%)         | 10 (56%)      |
| Cardiovascular death                             | 6 (30%)          | 8 (44%)       |
| Hospital admission for worsening HF              | 8 (40%)          | 8 (44%)       |
| Secondary endpoints                              |                  |               |
| Death of any cause                               | 7 (35%)          | 9 (50%)       |
| Hospitalization for any cause                    | 13 (65%)         | 10 (56%)      |
| Death from heart failure                         | 4 (20%)          | 5 (28%)       |
| Other                                           |                  |               |
| Non-cardiovascular hospitalization               | 6 (30%)          | 2 (11%)       |
| AMI hospitalization or death                     | 0                | 0             |
| Other cardiovascular hospitalization             | 3 (30%)          | 5 (28%)       |
| Other cardiovascular death                       | 0                | 2 (11%)       |
| Non-cardiovascular death                         | 1 (5%)           | 1 (6%)        |
| Sudden cardiac death                             | 2 (10%)          | 1 (6%)        |

AMI; acute myocardial infarction; HF, heart failure.
to the parasympathetic system causing sympathetic overactivity, and microvascular abnormalities.\(^{16,17}\) The reported improvement in right ventricular function with ivabradine might be clinically significant in ChD HF because right ventricular dysfunction is a challenge in the management of ChD HF.\(^{18}\) Concerning the myocarditis, beneficial pleiotropic effects of ivabradine beyond HR were reported in experimental coxsackievirus B3 myocarditis partially mediated by the inhibition of both the production of proinflammatory cytokines and the synthesis of NO by iNOS.\(^ {19,20}\) Also, ivabradine in chronic viral myocarditis in mice significantly increased the survival rate; attenuated the myocardial lesions and fibrosis; improved the impairment of the LV function; diminished the heart dimension; decreased the production of collagen I and collagen III; reduced the expression of the proinflammatory cytokines tumour necrosis factor alpha and interleukins 1\(\beta\) and 6; and lowered the production of phospho-p38 MAPK.\(^ {21}\) In HF patients, ivabradine increased LV ejection fraction and led to a significant reduction of tumour necrosis factor alpha serum levels and a reconstitution of circulating dendritic cells.\(^ {22}\) Furthermore, ivabradine reduced microvascular derangements in experimental sepsis and improved endothelial function in patients undergoing percutaneous coronary intervention.\(^ {23,24}\)

The mortality observed in our study (60%) in ChD HF is much higher in comparison with that of the SHIFT overall population (~17.5%) and of the recent PARADIGM-HF trial (~15%) at 750 day follow-up.\(^ {11,25}\) This finding is in agreement with previous publication.\(^ {9,26}\) Multiple mechanisms can contribute such as the remodelling process in ChD HF, the low dosage of medications for HF observed in our results, and the lower systemic blood pressure of patients in this post hoc analysis in comparison with that of the overall SHIFT population.

**Limitation of the study**

The present study is based on a post hoc analysis of a prospective randomized controlled trial in chronic stable HF patients (SHIFT trial), and this trial was not designed to investigate the effect of ivabradine treatment in ChD HF.
patients. Thus, the data have to be interpreted with caution given the rather small sample size, the low statistical power, and the retrospective analysis. However, a high percentage of primary and secondary endpoints were observed. Some differences between the groups ChD HF ivabradine and ChD HF placebo were observed concerning baseline frequency and dose of medication under use for HF. However, the impact of these differences on outcome is controversial because there are no prospective trials proving that these medications improve outcome in ChD HF. Despite the safety of ivabradine use in ChD HF reported in this study, the risk of bradycardia should be carefully assessed in ChD HF because patients were selected to be enrolled based on HR ≥ 70 b.p.m.

Clinical implications

There are doubts if the beneficial effects of standard HF treatment reported in other aetiologies can be translatable to ChD HF. In addition, medication tolerance in ChD HF may differ from other aetiologies. Sometimes, the heart transplantation is the unique alternative. The challenge in clinical practice is when to consider new drugs, such as ivabradine, in the scenario of neglected disease such as ChD. The finding of favourable benefit–risk profile of ivabradine in ChD HF patients can improve the decision-making process in the treatment of ChD HF.

Conclusions

Our analysis demonstrates that the overall outcome in ChD HF patients included in SHIFT was poor. ChD HF seems to be an advanced form of HF. The need for new medications in the treatment of ChD HF is clear. Although our results are based on a very limited sample and should be interpreted with caution, they suggest that ivabradine may have a favourable benefit–risk profile in CH HF patients. These findings encourage for further investigations of HR as a potential treatment target in ChD HF and provide the rationale for a randomized controlled trial to evaluate the benefit of ivabradine treatment in patients with ChD HF.

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Conflict of interest

Edimar Alcides Bocchi reports fees for board membership for AstraZeneca and Novartis; consultancy fees from Servier; speaker’s bureau for Novartis; and grants and personal fees from Merck Sharp & Dohme, Janssen Research & Development—Bayer, and Servier while conducting studies according to contract of the companies with the Heart Institute (InCor). Salvador Rassi reports fees for board membership for Novartis; speaker’s bureau for Novartis; and fees from Servier while conducting studies according to contract of the companies with the Heart Institute (InCor). Guilherme Guimarães does not have anything to disclose.

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