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ORIGINAL RESEARCH

Is There a Role for Ivabradine in the Contemporary Management of Patients with Chronic Heart Failure in Academic and Community Heart Failure Clinics in Canada?

Sherryn Roth · Carlos Fernando · Sadia Azeem · Gordon W. Moe

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ABSTRACT

Introduction: In patients with heart failure (HF) and reduced ejection fraction, increased heart rate (HR) is an independent risk factor for adverse outcomes. In systolic HF treatment with the *If* inhibitor ivabradine trial (SHIFT), Ivabradine improved survival when added to conventional treatment including β-blockers. However, the extent of benefit in the real world is unclear. We examined the characteristics of patients on guideline-directed therapy and determined who had SHIFT-like characteristics.
Methods: A total of 1096 patients with chronic HF were reviewed from June 2014 to April 2015 in two HF clinics in Toronto: an academic institution (AI), and a community hospital (CH) clinic. SHIFT-like characteristics [left ventricular ejection fraction (LVEF) ≤35%; sinus rhythm; and HR ≥ 70 bpm] were described.
Results: For all patients, mean age was 75 ± 13 years, overall LVEF was 44 ± 15%, AI less than CH (41.9 ± 14.0% vs. 45.7 ± 15.0%; $p < 0.0001$). More than two-thirds of patients in both groups were on β-blockers; with less than one-third at target dose. The proportion of patients with SHIFT-like characteristics was 8.4% AI and 11.7% CH, respectively ($p = 0.0658$).
Conclusion: In HF clinics from both academic and community hospitals in Toronto, up-titration in the dose of β-blockers and other guideline therapy can be improved on. A small proportion of patients with HF and SHIFT-like characteristics may potentially benefit from the addition of Ivabradine, just approved in Canada; this number will be further reduced if target dosage for β-blockers is achieved.
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Keywords: Chronic heart failure; Heart failure guidelines; *If* inhibitor; Ivabradine; Slow heart rate

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S. Roth · S. Azeem
The Scarborough Hospital, General Division, Scarborough, ON, Canada

S. Roth · G. W. Moe (✉)
Faculty of Medicine, Institute of Medical Science, University of Toronto, Toronto, ON, Canada
e-mail: moeg@smh.ca

S. Roth
Sunnybrook Health Sciences Centre, Toronto, ON, Canada

C. Fernando · G. W. Moe
Department of Medicine, Division of Cardiology, St Michael's Hospital, Toronto, ON, Canada

INTRODUCTION

Increased resting heart rate (HR) has been proven as an independent risk factor for cardiovascular outcomes and mortality [1, 2]. HR of

70 beats per minute (bpm) or higher was associated with 34% increased risk of cardiovascular death and 53% increase in admission to hospital for heart failure compared with HR lower than 70 bpm in patients with coronary artery disease and left ventricular (LV) dysfunction [3]. Treatment of patients with chronic heart failure with β-blockers leads to an improvement of symptoms and LV function and prolonged survival [4–6].

Ivabradine is a drug that specifically blocks the I_f channel in the sinoatrial node, resulting in a slower HR [7, 8] but without negative inotropic effect or worsening respiratory symptoms. The SHIFT (systolic heart failure treatment with the *If* inhibitor Ivabradine trial) study has demonstrated that Ivabradine exerts a benefit in addition to standard guideline-based treatment including β-blockers in patients with heart failure in sinus rhythm, with reduced left ventricular ejection function (LVEF) $\leq$35% and HR $\geq$ 70 bpm [7].

Multidisciplinary strategies for the management of patients with HF including management in a HF clinic reduce HF hospitalizations and mortality [9]. The clinical characteristics from centers of university-affiliated academic institutions versus those of community clinics in Canada have not been well characterized. The goal of this study was therefore to examine two cohorts of patients with chronic HF in two centers in Toronto, Canada, one from an academic institution and another from a community hospital, both of which have large well-established HF specialty clinics attended by cardiologists. In addition, we looked at the proportion of patients who have reduced ejection fractions and whose patients were felt to be on appropriate or near-appropriate guideline therapy but still have HR > 70 bpm, i.e. the cohort of patients who might benefit from Ivabradine. Accordingly, this study sought to provide insight regarding practice in the two centers, specifically on the use evidence-based medicines as described in the Canadian Cardiovascular Society Heart Failure guidelines and to see where Ivabradine might fit in with the management of these patients [10].

METHODS

Patient population

This study was approved by the St. Michael's Hospital Research Ethics Board and the Scarborough Hospital Research and Ethics Committee. Data were collected from 491 consecutive patients attending the academic institution's (AI) Heart Failure Clinic at St. Michael's Hospital and from 605 patients attending the community hospital's (CH) Heart Function Clinic at The Scarborough Hospital, General Division, between June 2014 and April 2015. Patients were followed by two cardiologists with nurse practitioners and resident staff at the AI and eight cardiologists and three Clinical Nurse Specialists at the CH. All patients had been referred to the clinics after at least one hospital admission or emergency room visit for heart failure. Each patient had at least one recent electrocardiogram documented and had undergone a recent echocardiogram.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013.

Data Collection

A total of 1096 medical records were reviewed from June 2014 to April 2015. Demographics, medical history, HF etiology, HR, blood pressure, and medications including dosage that the patients were prescribed for treatment of their HF were recorded. Medications specifically included diuretics, digitalis, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), β-blockers, mineralocorticoids receptor antagonists (MRAs), and calcium channel blockers. The dosages were reviewed to see if titration to target was achieved. Electrocardiography data were reviewed to assess the heart rhythm (sinus vs. atrial fibrillation), and the most recent echocardiographic data were reviewed.

Patients who were deemed according to SHIFT study criteria to be appropriate for Ivabradine therapy were patients who had left ventricular ejection fraction (LVEF) ≤35%, sinus rhythm and HR ≥ 70 bpm. Ivabradine is approved for use in Europe and the United States (US), and most recently in Canada. The guidelines in the US advise the use of Ivabradine for HR greater than 70 bpm [11], and the European Medicine Agency advises for HR greater than 75 bpm [12–14]. Health Canada also requires the use of the agent in patients with HR greater than 77 bpm [15].

Statistical Analysis

Data were presented as the percentage of patients wherever indicated. Rates were analyzed by the Chi-squared test for comparison between AI versus CH. Continuous data were analyzed using the independent samples *t* test. We used the statistical software SAS Enterprise Guide 6.1 for Windows (SAS Institute, Cary, NC, USA). *p* values of ≤0.05 were accepted as statistically significant.

RESULTS

Demographics

The demographic data of patients from these two clinics are shown in Table 1. Combining both centers, the average age was 75 ± 13 years, predominantly male (61%). The mean weight was 75.7 ± 21.8 kg, mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 118 ± 19 and 65 ± 21 mmHg, respectively. The mean HR was 71 ± 15 bpm. Mean LVEF was 44 ± 15%. Comparing the two clinics, AI patients were slightly younger, both clinics have predominantly male patients, and there was no significant difference in SBP in both groups; however, DBP at CH was lower than AI.

In patients with heart failure with reduced ejection fraction (HFrEF), combining the two centers, the average age was 71 ± 14 years, mean weight was 75.7 ± 19.7 kg, SBP and DBP were 113 ± 18 and 63 ± 12 mmHg, respectively, mean HR was 72 ± 15 bpm and LVEF was 27.2 ± 6.4%.

Medical History, Risk Factors and Co-morbid Conditions

A total of 14% (101/710) patients were classified as New York Heart Association (NYHA) class I; more patients at the CH were in NYHA Class I than at the AI. There were no significant differences between the two centers in NYHA Class II patients, reaching 52% (368/710) altogether. A total of 29% (209/710) were classified as NYHA class III; more patients at the AI than CH were in Class III, while there was more Class IV at the CH comprising 4.5% (32/710) of the total subjects.

Ischaemic heart disease comprises 52% (571/1096) of all patients, similar in both groups, while 24% (265/1096) patients were identified with non-ischaemic heart disease which did show a significant difference between the two groups (Table 1). Hypertension was identified in 48% (530/1096), atrial fibrillation 41% (451/1096), diabetes mellitus 41% (449/1096), dyslipidemia 34% (376/1096), chronic obstructive pulmonary disease (COPD) 12% (132/1096), bronchial asthma 5% (53/1096), and chronic kidney disease (CKD) 23% (251/1096). Just 5% (53/1096) used alcohol and 12% (135/1096) were actively smoking. There were, however, significant difference in hypertension, COPD, bronchial asthma, CKD (defined as estimated glomerular filtration rate of less than 60 ml/min/1.73 m^2), dyslipidemia, ethanol use, smoking, and obesity between the two groups.

In the HFrEF patient group, 59% (211/356) were due to ischaemic heart disease and 36% (129/356) were identified non-ischemic in etiology. Hypertension was identified in 40% (143/356), atrial fibrillation 34% (122/356), diabetes mellitus 40% (142/356), dyslipidemia 36% (127/356), COPD 13% (46/356), bronchial asthma 3% (10/356), CKD 19% (68/356). 6% (22/356) alcohol abuse and 17% (60/356) were smokers, with few differences between the AI and CH groups except for hypertension.

Table 1 Demographic and clinical characteristics of all patients and those patients stratified with heart failure with reduced ejection fraction all patients patients with reduced ejection fraction

	All patients			Patients with reduced ejection fraction		
	AI $n = 491$	CH $n = 605$	p value AH/CH	AI $n = 172$	CH $n = 184$	p value AH/CH
Age, mean (years) ±SD	72 ± 13	77 ± 13	<0.0001*	70 ± 13	73 ± 15	0.0663
Male, *n* (%)	338 (69)	333 (55)	<0.0001*	138 (80)	114 (62)	0.0002*
Systolic BP, mm Hg	119 ± 19	118 ± 20	0.4780	114 ± 19	113 ± 18	0.3783
Diastolic BP, mm Hg	67 ± 29	63 ± 10	0.0005*	66 ± 13	61 ± 10	0.0005*
HR, mean (per min) ± SD	70 ± 14	73 ± 15	0.0004*	69 ± 15	74 ± 15	0.0019*
Weight (kg) ± SD	76.7 ± 21.0	75.3 ± 22.0	0.3494	77.8 ± 18.7	74.0 ± 19.9	0.1013
LVEF, mean (years) ± SD	41.9 ± 14.0	45.7 ± 15.0	<0.0001*	26.7 ± 6.3	27.6 ± 6.5	0.2030
Medical history, *n* (%)						
IHD	260 (53.0)	311 (52.4)	0.9137	112 (65.12)	99 (53.80)	0.0300*
Non-IHD	142 (28.9)	123 (20.8)	0.0019*	71 (41.28)	58 (31.52)	0.0556
Hypertension	307 (62.5)	223 (36.9)	<0.0001*	95 (55.23)	48 (26.09)	<0.0001*
Atrial fibrillation	212 (43.0)	239 (40.0)	0.2191	70 (40.70)	52 (28.26)	0.0135*
Diabetes mellitus	204 (41.5)	245 (40.5)	0.6743	82 (47.67)	60 (32.61)	0.0037*
Dyslipidemia	251 (51.1)	125 (20.7)	<0.0001*	95 (55.23)	32 (17.39)	<0.0001*
COPD	72 (14.7)	60 (9.8)	0.0172*	24 (13.95)	22 (11.96)	0.5746
Bronchial asthma	33 (6.7)	20 (3.3)	0.0088*	7 (4.07)	3 (1.63)	0.1639
Chronic kidney disease	127 (25.9)	124 (20.5)	0.0354*	46 (26.74)	22 (11.96)	0.0004*
Ethanol use	37 (7.5)	16 (2.6)	0.0002*	16 (9.30)	6 (3.26)	0.0180*
Smoking	87 (17.7)	48 (7.9)	<0.0001*	44 (25.58)	16 (8.70)	<0.0001*
Obesity	134 (28.0)	44 (7.3)	<0.0001*	46 (26.74)	12 (6.52)	<0.0001*
NYHA class, *n*	**$n = 327$**	**$n = 383$**	**p value**	**$n = 124$**	**$n = 107$**	**p value**
Class I	12/327 (3.7)	89/383 (23.2)	<0.0001*	4/124 (3.2)	25/107 (23.4)	<0.0001*
Class II	180/327 (55.0)	188/383 (49.1)	0.1132	64/124 (51.6)	45/107 (42.0)	0.1468
Class III	124/327 (37.9)	85/383 (22.2)	<0.0001*	52/124 (41.9)	22/107 (20.6)	0.0005*
Class IV	11/327 (3.4)	21/383 (5.5)	0.1749	4/124 (3.2)	15/107 (14.0)	0.0029*

AH Academic hospital, *BP* blood pressure, CH community hospital, *COPD* chronic obstructive pulmonary disease, *HFrEF* heart failure with reduced ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *IHD* ischemic heart disease, *Hg* mercury, *Kg* kilograms, *mm* millimeters *NYHA* New York Heart Association, *%* percentage, *SD* standard deviation

* Significant *p* value

Table 2 SHIFT study-like characteristics potential Ivabradine patients

Characteristic, *n* (%)	AI *n* = 491	CH *n* = 605	*p* value AH/CH
LVEF ≤ 35%	172/491 (35.0)	184/605 (30.4)	0.1045
Sinus rhythm	279/491 (56.8)	366/605 (60.5)	0.2191
HR ≥ 70 bpm	205/491 (41.8)	317/605 (52.4)	0.0004*
"SHIFT study-like" characteristics	41 (8.4)	71 (11.7)	0.0658

AH Academic hospital, *CH* community hospital, *HR* heart rate, *LVEF* left ventricular ejection fraction, *%* percentage
* Significant *p* value

SHIFT Study-like Characteristics

A total of 32.5% (356/1096) of those at both centers had LVEF of equal to or less than 35% (Table 2). There were more patients identified having HR ≥ 70 bpm at the CH than AI (52.4% vs. 41.8%, $p = 0.0004$), while 60.0% of patients at the CH were in sinus rhythm versus 57.0% at the AI ($p = 0.2191$). However, in the overall tabulation following the SHIFT-like characteristics, 11% of the total patients at both centers fit the criteria (8.4% AI vs 11.7% CH, $p = 0.0658$) (Table 2).

Medications

Differences between the two centers were noted in the use of evidence-based guideline-directed heart failure medications. β-blockers were prescribed in 80.3% overall and 91.6% of the HFrEF cohort, more in AI patients than in CH patients. Bisoprolol is the most predominant β-blocker used at both centers, 45% (397/880), followed by Carvedilol, 31% (276/880), and third was Metoprolol, 23% (198/880). Only 13% (146/1096) of patients taking β-blockers were on the evidence-based target dose (Bisoprolol 10 mg target dose, Carvedilol 50 mg target dose, Metoprolol 200 mg target dose [16, 17]). Of those patients with HFrEF, 50% or more were not on target doses of β-blockers. An average of 22% of patients used calcium channel blockers (CCB) at both centers. This indicates that both centers have equal numbers of patients that use CCB in treating hypertension and/or angina. A total of 59% of patients at the AI and 42% at the CH use ACE inhibitors. Nearly 20% of all patients use ARBs. MRA's were used more at the CH (37.2%) versus AI (25.7%) (Table 3). In addition, 24.9% (122/491; 77 single chamber and 45 dual chamber) of patients at the AI had received a pacemaker versus 18.2% (110/605; 63 single chamber and 47 dual chamber) of patients at the CH ($p = 0.0072$). A total of 11.8% (58/491) received ICD at the AI and 4.8% (29/605) at the CH ($p < 0.0001$), while 3.5% (17/491) received ICD + CRT at the AI and 7.9% (48/605) at the CH ($p = 0.0018$).

DISCUSSION

Table 1 shows the differences between the two centers: patients with heart failure at the AI tends to be younger, predominantly male, having higher diastolic pressure but lower HR, and lower LVEF, more NYHA class III but less class I. In medical history, AI patients have more co-morbidities than CH patients, although CH patients have more atrial fibrillation and diabetes mellitus than AI patients. The exact reasons why these two centers differ is currently unknown.

Multiple studies have shown improvement in mortality and morbidity with the use of β-blockers [5, 18, 19]. Part of that positive effect may be due to reducing the HR. Hence, it is considered one of the mainstays in the management of patients with heart failure; however, their use may be limited by the perceived or real concern for the non-cardiac adverse effects limiting their widespread use or prescribing lower than recommended dosage [20]. In our review, 8.4% (41) at the AI and 11.7% (71) at the CH were identified to have SHIFT-like characteristics. Although we found that 87.5% [98/112 (40/98 AI, 58/98 CH)] were on β-blockers, only 28.6% (28/98) of these patients were noted to be on target dose: Carvedilol 8.2% [8/98 (2 at the

Table 3 Medications used by all patients and those patients stratified with heart failure with reduced ejection fraction

	All patients			Patients stratified with heart failure with reduced ejection fraction		
	AI $n = 491$	CH $n = 605$	p value AH/CH	AI $n = 172$	CH $n = 184$	p value AH/CH
β-blockers, *n* (%)	406/491 (82.7)	474/605 (78.3)	0.0724	165/172 (95.9)	161/184 (87.5)	<0.0042*
Bisoprolol	217/406 (53.4)	180/474 (38.0)	<0.0001*	85/165 (51.5)	51/161 (31.7)	<0.0001*
Carvedilol	117/406 (28.8)	159/474 (33.5)	0.3524	71/165 (43.0)	86/161 (53.4)	0.2998
Metoprolol	63/406 (15.5)	135/474 (28.5)	<0.0001*	9/165 (5.5)	24/161 (14.9)	<0.0111*
Others	9 (2.2)	0 (0)	n/a	0	0	n/a
Mean (SD) daily dosage of β-blocker in mg						
Bisoprolol	7.0 (12.1)	4.96 (5.8)	0.0434	5.9 (3.1)	4.0 (1.9)	0.0002*
Carvedilol	27.4 (18.1)	20.4 (14.0)	0.0004*	26.9 (17.5)	19.4 (14.4)	0.0039*
Metoprolol	82.1 (56.2)	87.0 (61.8)	0.5581	52.8 (23.2)	75.5 (47.6)	0.1821
Patients on β-blockers target doses	100 (20.3)	46 (7.6)	<0.0001*	13 (7.5)	36 (19.6)	0.0010*
Other evidence-based medications, mean (SD)						
Calcium channel blockers	102 (20.8)	144 (23.8)	0.2322	22 (12.8)	22 (12.0)	0.8111
ACE inhibitors	288 (58.7)	252 (41.7)	<0.0001*	126 (73.3)	90 (48.9)	<0.0001*
ARB	92 (18.7)	111 (18.4)	0.8687	30 (17.4)	22 (12.0)	0.1431
Digitalis	54 (11.0)	82 (13.6)	0.2019	25 (14.5)	28 (15.2)	0.8565
MRA	126 (25.7)	225 (37.2)	<0.0001*	66 (38.4)	92 (50)	0.0273*

AH Academic hospital, *CH* community hospital, *%* percentage, *mg* milligrams, *ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *MRA* mineralocorticoid receptor antagonist, *SD* standard deviation

* Significant *p* value

AI, 6 at the CH)], Bisoprolol 10.2% [10/98 (2 at the AI, 8 at the CH)], and Metoprolol 10.2% [10/98 (3 at the AI, 7 at the CH)]. It is unlikely that reluctance to titrate such a large percentage of patients is due to adverse effects alone.

A more rigorous protocol for drug titration to target should be implemented in HF Clinics in order to achieve best outcomes, including reducing HR to less than 70 bpm. Once HF clinics routinely use a set protocol to titrate β-blockers and other HF medications, it will enable knowledge translation to other health providers who routinely care for HF patients and slow HR as well as improve outcomes.

The benefit of Ivabradine increases with increased HR as shown in the SHIFT trial, in which the hazard ratio was 0.75 (95% CI 0.67–0.85) for patients with HR of more than

77 bpm versus 0.93 (95% CI 0.80–1.08) in patients with HR of less than 77 bpm ($p = 0.029$) [7]. SHIFT demonstrated the importance of HR in the pathophysiology of HF and further confirms that HR reduction is beneficial to patients with HF. This agent has just received approval in Canada for clinical use for patients suffering from chronic HF. It should only be introduced to patients who have first been optimized regarding β-blockers (and/or calcium channel blockers or other guideline agents for HF which also slow HR) therapy. It may be useful in a very select population.

Up-titration of β-blockers was not fully optimized in these two centers, as revealed by the number of patients on evidence-based target daily dose (20.6% AI vs. 7.4% CH, $p < 0.0001$). However, in practice, clinicians always aim at the target dose. Although in the SHIFT study it was assumed that patients were up-titrated as much as possible to evidence-based target dose, it appears that thyis may not have been the case. Enrolled patients were also identified to be in different dose ranges [7]. Comparing our findings with the SHIFT trial, AI was found to be similar, with the SHIFT population achieving the target dose of β-blockers (20.6% vs. 23.2%, $p = 0.1732$), but lower at the CH (7.4% vs. 23.2%, $p < 0.0001$). The reasons are unclear; certain co-morbidities such as COPD and bronchial asthma might limit its use [21]. These patients would, therefore, potentially benefit from Ivabradine use as the sole agent for slowing HR. Additionally, it has been shown that the effects of Ivabradine on cardiovascular death or HF hospitalization were not significantly impacted by the dose of β-blocker therapy [21].

The 11% of patients who might benefit from Ivabradine in this cohort is similar to other studies, but lower than that found by Elder et al. in Scotland [22], who determined that 19% met the indication for Ivabradine. Of these Ivabradine-suitable patients, less than 15% achieved the target dose of β-blockers. Another study by Dierckx et al. found 12% were appropriate [23], but Cullington et al. [24] initially determined 43% in the study population to be eligible but this later dropped to 12% after guideline-directed therapy was initiated.

Study Limitations

Our study has limitations that merit further discussion. Ivabradine was approved in Canada on February 10, 2017, indicated for patients with HR greater than 77 bpm. Stratification capturing of patients with HR greater than 77 bpm was not done. Patient compliance is an important factor, difficult to quantify. The rigor with which guideline-based dose optimization of conventional medications is applied is not known. Visit frequency and evidence for attempt to titrate were not recorded and often not available. Similarly, many patients were new to the clinic and had not been fully optimized at the recorded visit, while others had had the benefit of several visits to up-titrate medication which might change their NYHA class, LVEF, and HR, as noted in previous studies [24].

CONCLUSION

We found that most AI (80%) and CH (92%) HF clinic patients were not optimized on medications that are well documented in HF management guidelines. Although there is a role for Ivabradine, it is likely appropriate for a relatively small segment of the HF population. In HF patients, their treatment should be optimized first using conventional medications specifically including β-blockers, and then, if the HR is still above 70–77 bpm and the patient is in sinus rhythm and has reduced EF, Ivabradine might be of further benefit.

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version to be published. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Compliance with Ethics Standards. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013.

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Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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