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Ivabradine in heart failure patients with reduced ejection fraction and history of paroxysmal atrial fibrillation

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Abstract

Aims Ivabradine is indicated for heart failure (HF) patients with reduced ejection fraction (HFrEF), but limited data are available with regards to the use of ivabradine in those with a history of paroxysmal atrial fibrillation (AF). To assess the effect of ivabradine in HFrEF patients with paroxysmal AF, we analysed heart failure (HF) hospitalization and mortality from multiple-centre registry database.

Methods and results We conducted a multicentre observational matched cohort study, and this study enrolled patient with symptomatic HFrEF from 1 January 2015 to 31 December 2018 who had a history of paroxysmal AF in Chang Gung Memorial Hospital medical database in Taiwan. A total of 2042 patients were eligible for the study, of whom 887 were prescribed with ivabradine and 1115 were not. The primary outcome, including HF hospitalization and cardiovascular death, and individual outcome during the 12 month observation period were analysed after inverse probability of treatment weighting. The ivabradine group had significantly lower mean heart rate after 12 months follow-up than the non-ivabradine group ($P < 0.05$). The primary outcome was significantly higher in the ivabradine group than the non-ivabradine group after 12 months follow-up (hazard ratio [HR] = 1.58; 95% confidence interval [CI], 1.26–2.00, $P < 0.001$). Moreover, the ivabradine group had a significantly higher event rate of HF hospitalization (HR = 1.56; 95% CI, 1.40–1.75, $P < 0.001$) and HF death (HR = 1.67; 95% CI, 1.14–2.44, $P = 0.009$) than the non-ivabradine group.

Conclusions Ivabradine treatment was associated with an increased risk of HF hospitalization in symptomatic HFrEF patients with a history of paroxysmal AF. Further prospective randomized studies are warranted.

Introduction

Heart failure (HF) is associated with high mortality, and an elevated resting heart rate (HR) is also associated with adverse outcomes. Reducing HR is an important issue in the management of HF, and particularly those with HF reduced ejection fraction (HFrEF). Ivabradine is a specific inhibitor of I_f current in the sinoatrial node.[1] In the Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT) study, the reduc-

tion in HR with ivabradine treatment in symptomatic patients with left ventricular ejection fraction (LVEF) $\leq$ 35% and sinus rhythm with HR $\geq$ 70 beats per minute (b.p.m.) was associated with significant lower rates of cardiovascular (CV) death and hospitalization for worsening HF.[2] Following the SHIFT study, ivabradine was listed as a class II$_a$ indication in the 2016 European Society of Cardiology (ESC) guidelines for symptomatic patients with LVEF $\leq$35% who are in sinus rhythm with a resting HR $\geq$ 70 b.p.m. and who are unable

to tolerate or are contraindicated for an evidence-based dose of beta-blockers. Ivabradine is indicated only for patients mainly in sinus rhythm, and not in those with persistent or chronic atrial fibrillation (AF).[3,4] Hyperpolarization-activated cyclic nucleotide-gated cation channel 4 has been identified in experimental animal models to be the primary gene responsible for I_f current expression throughout the myocardium,[5] and this has raised interest in the possible role of ivabradine in ventricular rate control in AF.[6] Preclinical studies of ivabradine in animal models with induced AF and preliminary human data have suggested that ivabradine can reduce HR without associated hemodynamic complications in patients with AF.[6] According to the 2021 update to the 2017 ACC expert consensus decision pathway for optimization of HF treatment, a history of paroxysmal AF is not a contraindication to ivabradine, and in the SHIFT study, around 8% of the patients had a history of paroxysmal AF.[4] However, the clinical outcomes of ivabradine treatment in symptomatic HFrEF patients with a history of paroxysmal AF remain unknown. Accordingly, we conducted this study using the Chang Gang Memorial Hospital (CGMH) Medical System database to investigate the clinical outcomes of symptomatic HFrEF patients with a history of paroxysmal AF, who were in sinus rhythm and prescribed with ivabradine.

Materials and methods

Database

The data of this study population were acquired from the CGMH Medical System in Taiwan, which consists of four tertiary care medical centres and three major teaching hospitals with approximately 280 000 admissions per year and a total of 10 050 beds.[7] Data on diagnoses, laboratory data, medications, echocardiography, imaging and detailed chart records of each patient were collected from the CGMH medical database, which contained the records from 1 January 2001 to 31 December 2018. Although the identity of the patient (i.e. chart number or national identification number) was encrypted to protect personal information, each patient had a personal identification number (PIN) which made the medical records of each patient in different datasheets across CGMH medical database could be linked to these PINs. The CGMH medical database has been described in detail elsewhere.[8] The study protocol was approved by the Institutional Review Board of CGMH (IRB no. 201900572B0).

Study design

This retrospective, multicentre, cohort study comprised 35 779 patients who had been admitted for HF from 1 January 2015 to 31 December 2018. Among these patients, 9732

patients who had a diagnosis of paroxysmal AF before the index date were included. The date of prescribing ivabradine was defined as the index date in the ivabradine group. To avoid immortal time bias (survival bias), the index date of the non-ivabradine group was assigned as that of the ivabradine group.[9] According to the ESC guidelines,[3] enrolment criteria of the SHIFT study[2] and selected criteria of SHIFT-type patients in Swedish HF registry,[10] ivabradine should be prescribed to patients who were in sinus rhythm and had reduced LVEF. We first excluded patients without electrocardiography (ECG) data (n = 2893). We then excluded patients whose ECG showed AF within 1 month before or at the index date to ensure that the prescription for ivabradine conformed to the ESC guidelines and the exclusion criteria of the SHIFT study.[2] The other exclusion criteria were (i) those with echocardiography within 3 months before the index date showing a LVEF >40% or without data of LVEF; (ii) those received cardiac resynchronization therapy before the index date; (iii) those who did not have ECG or echocardiography reports within 3 months before the index date and those who did not attend follow-up visits after the index date. Finally, 2042 patients were eligible for the study, of whom 887 were prescribed with ivabradine (ivabradine group) and 1115 patients were not prescribed with ivabradine (non-ivabradine group). The flowchart of the study design was illustrated in *Figure 1*.

The clinical outcomes and definition

Clinical outcomes were assessed during the 12 month follow-up period. The primary endpoint was CV death and HF hospitalization. The other clinical outcomes included all-cause mortality, all-cause hospitalization and CV hospitalization. CV death was defined as death caused by an acute myocardial infarction, sudden cardiac death, or death due to HF, stroke, CV procedures, CV haemorrhage, and other CV causes.[11] HF hospitalization was defined as unscheduled hospitalization with new or worsening symptoms or signs, and diagnostic test results consistent with the diagnosis of HF. In addition, a significant augmentation in oral diuretics, the initiation of intravenous diuretics or vasoactive agents, or receiving mechanical ventilation or mechanical support was also required to define HF hospitalization.[11] Worsening renal function was defined as either a decline in estimated glomerular filtration rate (eGFR) > 50% from baseline or a decline in eGFR >30 mL/min/1.73 m^2 from baseline combined with a follow-up value >60 mL/min/1.73 m^2. Outcomes of worsening renal function were only assessed if eGFR data were available at both baseline and 12 month follow-up or the last follow-up visit.

Left ventricle (LV) and left atrium (LA) were also assessed during the follow-up period. LVEF, LV end diastolic dimension (LVEDD), and LA size were assessed from parasternal or apical

Figure 1 Flow chart of the study population. AF, atrial fibrillation.
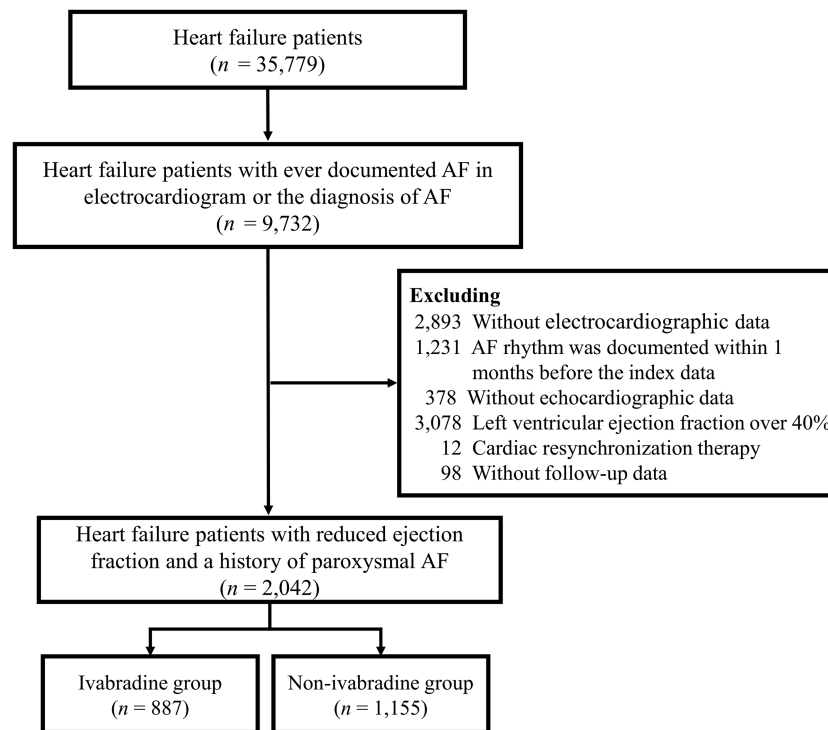
Covariates

The covariates were demographics (age and sex), vital signs (mean arterial pressure and HR), the duration between the initial diagnosis of HF and the index date, annual number of previous HF admissions, comorbidities (including hypertension and diabetes mellitus), previous hospitalization for myocardial infarction or stroke, baseline echocardiography (LVEF, LVEDD, and LA), baseline laboratory data (including haemoglobin and creatinine) and the use of medications (including beta-blockers and digoxin). A complete list of the covariates is shown in *Table 1*. Information of these covariates was extracted from outpatient and inpatient claims data (for diagnosis), laboratory records, echocardiography, pharmacy records, and detailed chart records from the CGMH medical databases.

Statistics

We created an inverse probability of treatment weighting (IPTW)-adjusted cohort based on propensity score to achieve comparability between the study groups (ivabradine vs. non-ivabradine) when comparing outcomes. Compared to propensity score matching (PSM), the main advantage of IPTW is without loss of sample size and therefore, yields a greater statistical power. The propensity score was calculated using multivariable logistic regression where the study group was regressed on all of the covariates (listed in *Table 1*, except for follow-up month which was replaced by the index date). We used a stabilized weight to mitigate the impact of extreme propensity scores.[12] The balance of covariate distribution between groups was checked using the absolute value of the standardized difference (STD) before and after weighting, where a value of <0.2 was considered to be a small difference.

In addition, due to the existence of missing echocardiographic data of LVEDD and LA diameter and laboratory data, the missing values were first imputed using the single expectation–maximization (EM) imputation method, and IPTW was conducted using the imputed data. An EM algorithm is an iterative method to find maximum likelihood of the parameter estimates in statistical models, where the model depends on unobserved latent variables. Compared the conventional methods to impute missing data (i.e. mean imputation, regression-based methods, etc.), the methods based on EM algorithm provide more precise imputed values and are more robust to the assumptions.[13] The risks of time to event outcomes between groups were compared using a

views using the standard M-mode or 2D Simpson method in transthoracic echocardiography. Data of HR at the 1st, 3rd, 6th, and 12th month follow-ups were also recorded.

Table 1 Baseline characteristics of the study patients before and after EM imputation and IPTW adjustment

Variables	Valid N	Before EM imputation and IPTW			After EM imputation and IPTW		
		Ivabradine (n = 887)	Non-ivabradine (n = 1155)	STD	Ivabradine	Non-ivabradine	STD
Age, years	2042	62.3 ± 16.0	63.2 ± 14.0	−0.06	61.8 ± 15.2	63.2 ± 14.2	−0.09
Male sex	2042	650 (73.3)	897 (77.7)	−0.10	77.9%	76.2%	0.04
MAP, mmHg	1753	89.1 ± 16.9	92.1 ± 16.9	−0.18	91.4 ± 17.0	90.3 ± 14.4	91.4 ± 17.0
Heart rate, b.p.m.	1749	93.2 ± 16.6	83.6 ± 16.3	0.59	87.2 ± 17.0	88.8 ± 16.4	87.2 ± 17.0
The duration of HF*, months	2042						
≤3 months		536 (60.4)	804 (69.6)	−0.19	67.1%	65.9%	0.02
4–6 months		39 (4.4)	93 (8.1)	−0.15	7.0%	5.9%	0.04
7–12 months		52 (5.9)	84 (7.3)	−0.06	5.9%	6.0%	0.00
> 12 months		260 (29.3)	174 (15.1)	0.35	20.0%	22.1%	−0.05
Annual number of HF Admissions before the index date	2042						
<1		151 (17.0)	134 (11.6)	0.16	12.7%	13.0%	−0.01
1–6		189 (21.3)	247 (21.4)	0.00	20.9%	22.4%	−0.04
7–12		71 (8.0)	116 (10.0)	−0.07	8.3%	8.6%	−0.01
>12		476 (53.7)	658 (57.0)	−0.07	58.1%	55.9%	0.05
Co-morbidities							
Hypertension	2042	596 (67.2)	848 (73.4)	−0.14	69.7%	69.4%	0.00
Diabetes mellitus	2042	422 (47.6)	627 (54.3)	−0.13	54.9%	51.2%	0.07
Ischaemic heart disease	2042	528 (59.5)	661 (57.2)	0.05	55.1%	58.9%	−0.08
Dyslipidaemia	2042	411 (46.3)	579 (50.1)	−0.08	46.9%	46.5%	0.01
Gout	2042	168 (18.9)	204 (17.7)	0.03	16.8%	19.2%	−0.06
COPD	2042	194 (21.9)	180 (15.6)	0.16	19.0%	19.1%	0.00
Peripheral arterial disease	2042	104 (11.7)	140 (12.1)	−0.01	10.9%	11.5%	−0.02
Chronic kidney disease	2042	427 (48.1)	584 (50.6)	−0.05	47.4%	48.4%	−0.02
Dialysis	2042	99 (11.2)	177 (15.3)	−0.12	13.3%	13.2%	0.00
History of events							
Myocardial infarction	2042	301 (33.9)	344 (29.8)	0.09	29.0%	32.9%	−0.08
Stroke	2042	101 (11.4)	149 (12.9)	−0.05	10.6%	11.3%	−0.02
Echocardiography							
LVEF, %	2042	26.8 ± 7.5	31.3 ± 6.9	−0.62	29.6 ± 7.2	29.4 ± 7.6	0.03
LVEDD, mm	2013	61.0 ± 9.2	59.5 ± 8.6	0.17	60.5 ± 8.6	60.2 ± 8.8	0.03
LA, mm	2002	44.0 ± 8.0	43.2 ± 7.4	0.10	43.3 ± 8.0	43.4 ± 7.7	0.00
Baseline lab data							
Haemoglobin, g/dL	1842	12.3 ± 2.5	12.2 ± 2.6	0.03	12.4 ± 2.4	12.2 ± 2.5	0.10
Creatinine, mg/dL	1958	2.1 ± 2.4	2.5 ± 3.1	−0.13	2.3 ± 2.8	2.3 ± 2.8	0.00
eGFR, mL/min/1.73 m^2	1958	59.3 ± 46.1	58.0 ± 37.2	0.03	59.4 ± 50.5	58.3 ± 35.6	0.03
BUN, mg/dL	1787	34.6 ± 24.9	34.0 ± 27.0	0.02	32.8 ± 23.3	34.1 ± 26.3	−0.06
ALT, U/L	1839	27.0 [17.0, 49.0]	23.0 [15.0, 37.0]	NA	25.0 [17.0, 46.0]	27.0 [17.0, 51.0]	NA
BNP, pg/mL	1290	1500.0 [649.1, 2948.0]	1172.0 [441.0, 2441.0]	NA	1340.0 [718.0, 2359.6]	1538.4 [923.0, 2227.7]	NA
Potassium (K), mEq/L	1885	4.0 ± 0.6	4.1 ± 0.6	−0.15	4.1 ± 0.6	4.1 ± 0.6	0.00
Albumin, mg/dL	1304	3.5 ± 0.6	3.5 ± 0.6	−0.03	3.6 ± 0.5	3.6 ± 0.5	0.02
HDL, mg/dL	1498	36.9 ± 12.5	38.8 ± 12.4	−0.15	37.5 ± 10.9	38.0 ± 10.1	−0.05
LDL, mg/dL	1582	97.2 ± 44.6	99.9 ± 48.9	−0.06	101.5 ± 47.8	100.1 ± 44.8	0.03
Total cholesterol, mg/dL	1577	157.6 ± 52.8	164.8 ± 51.0	−0.14	163.1 ± 53.4	162.4 ± 43.2	0.01
Medications							
Sacubitril/Valsartan	2042	101 (11.4)	73 (6.3)	0.18	9.4%	8.5%	0.03
ACEi/ARB	2042	747 (84.2)	875 (75.8)	0.21	78.6%	80.6%	−0.05

(Continues)

Table 1 (continued)

Variables	Valid N	Before EM imputation and IPTW			After EM imputation and IPTW		
		Ivabradine (n = 887)	Non-ivabradine (n = 1155)	STD	Ivabradine	Non-ivabradine	STD
Beta-blocker	2042	719 (81.1)	945 (81.8)	−0.02	84.2%	82.1%	0.06
Dihydropyridine CCB	2042	177 (20.0)	362 (31.3)	−0.26	25.4%	26.8%	−0.03
Digoxin	2042	182 (20.5)	117 (10.1)	0.29	13.9%	14.6%	−0.02
Diuretics	2042	781 (88.0)	848 (73.4)	0.38	78.0%	80.8%	−0.07
Spironolactone	2042	475 (53.6)	421 (36.5)	0.35	43.6%	44.0%	−0.01
Statins	2042	467 (52.6)	651 (56.4)	−0.07	55.4%	56.0%	−0.01
Metformin	2042	190 (21.4)	316 (27.4)	−0.14	27.4%	24.7%	0.06
DPP4i	2042	179 (20.2)	244 (21.1)	−0.02	19.6%	20.4%	−0.02
Sulfonylurea	2042	125 (14.1)	214 (18.5)	−0.12	16.1%	15.6%	0.01
Thiazolidinedione	2042	15 (1.7)	21 (1.8)	−0.01	1.8%	1.9%	−0.01
Insulin	2042	312 (35.2)	381 (33.0)	0.05	31.1%	34.1%	−0.06
Propensity score	2042	0.597 ± 0.233	0.309 ± 0.214	1.28	0.421 ± 0.272	0.447 ± 0.276	−0.09
Follow-up months	2042	7.4 ± 4.4	7.4 ± 4.2	−0.01	7.7 ± 4.2	7.4 ± 4.2	0.05

EM, expectation maximization; IPTW, inverse probability of treatment weighting; STD, standardized difference; MAP, mean arterial pressure; HF, heart failure; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LA, left atrium; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; ALT, alanine aminotransferase; NA, not available; BNP, B-type natriuretic peptide; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; ARNI, angiotensin receptor-neprilysin inhibitor; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DPP4i, dipeptidyl peptidase 4 inhibitor.

Data are presented as number (%), mean ± standard deviation or median [25th, 75th percentile].
*The duration of HF was defined as the interval from the first diagnosis of HF to the index date, and the history could be traced to 1 January 2001.

Cox proportional hazard model. To come closer to randomization, the aforementioned Cox model was also conducted using the cohort after PSM. Each patient in the ivabradine group was matched to one patient in the non-ivabradine group. The PSM was processed using a greedy, nearest-neighbour algorithm, with a calliper of 0.2-times the standard deviation of the logit of the propensity score, with random matching order and without replacement. The data of echocardiography (LVEF, LVEDD, and LA) at the 12th month and HR at follow-up visits between groups were compared using a linear regression model. A two-sided P value of <0.05 was considered to be statistically significant. All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Among the 2042 HFrEF patients who had a history of paroxysmal AF enrolled in this study, there were 887 patients (mean age: 62.3 ± 16.0 years) in the ivabradine group and 1115 patients (mean age: 63.2 ± 14.0 years) in the non-ivabradine group (STD = −0.06). *Table 1* shows the baseline characteristics of the ivabradine and non-ivabradine groups. Before IPTW, there were no significant differences in age and gender between the two groups. The ivabradine group had a mean HR of 93.2 ± 16.6 b.p.m., which was significantly higher than that in the non-ivabradine group (83.6 ± 16.3 b.p.m.; STD = 0.59). The ivabradine group had slightly lower prevalence rates of hypertension, diabetes mellitus and dialysis, and worse LV function (mean LVEF: 26.8 ± 7.5% vs. 31.3 ± 6.9%; STD = −0.62)) than the non-ivabradine group. In addition, a higher proportion of the patients in the ivabradine group had a longer interval (>12 months) from the diagnosis of HF to the index date, whereas a higher proportion of the patients in the non-ivabradine group had a shorter interval (≤6 months) from the diagnosis of HF to

the index date. In terms of baseline medications, the ivabradine group had higher prescription rates of angiotensin converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs), digoxin, diuretics and spironolactone, but a comparable prescription rate of beta-blockers compared to the non-ivabradine group. After IPTW adjustments, all covariates listed in *Table 1* were well-balanced between the two groups (Supporting Information, *Figure S1*). In addition, the data before and after EM imputation and missing rate of each covariate were provided in the supplement (Supporting Information, *Table S1*).

Heart rate during the follow-up period

The mean follow-up durations were 7.7 ± 4.2 and 7.4 ± 4.2 months in the ivabradine and non-ivabradine groups after IPTW adjustment, respectively (STD = 0.05). HR data at the 1st, 3rd, 6th, and 12th month follow-ups in both study groups are summarized in Supporting Information, *Table S2* and *Figure 2*. There was a trend of reduction in HR during the follow-up period in both groups. In the ivabradine group, the HR was lower at 1, 3, 6 and 12 month follow-ups (78.3 ± 17.4, 77.9 ± 16.3, 77.9 ± 15.3 and 76.4 ± 16.9 b.p.m., respectively) compared with baseline HR (87.2 ± 17.2 b.p.m.). In the non-ivabradine group, the HR values at 1, 3, 6 and 12 month follow-ups were lower (81.9 ± 15.4, 81.3 ± 15.3, 80.3 ± 16.1 and 80.1 ± 15.9 b.p.m., respectively) compared with baseline HR (89.1 ± 18.6 b.p.m.). Of note, the ivabradine group, with a mean daily dose of 7.6 ± 2.5 mg/day (Supporting Information, *Table S3*), had a significantly lower mean HR at each follow-up visit than the non-ivabradine group (Supporting Information, *Table S2* and *Figure 3*).

Clinical outcomes

Comparisons of the clinical outcomes between the two study groups after IPTW are summarized in *Table 2* and *Figure 4*. After 12 months follow-up, the primary outcome of HF hospi-

Figure 2 The mean and standard error of heart rate at the follow-up visits in the ivabradine and non-ivabradine groups in the IPTW-adjusted cohort. b.p.m., beats per minute; IPTW, inverse probability of treatment weighting.
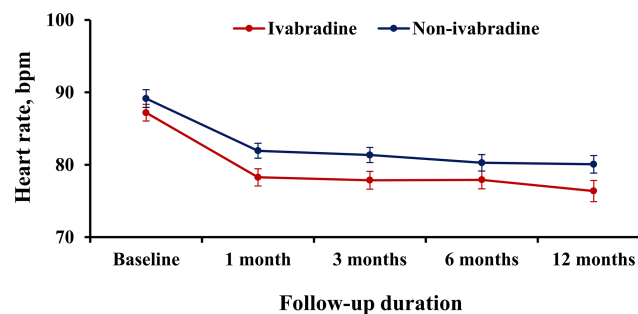
Figure 3 Differences in heart rate at the follow-up visits between the ivabradine and non-ivabradine groups in the IPTW-adjusted cohort. CI, confidence interval; IPTW, inverse probability of treatment weighting.
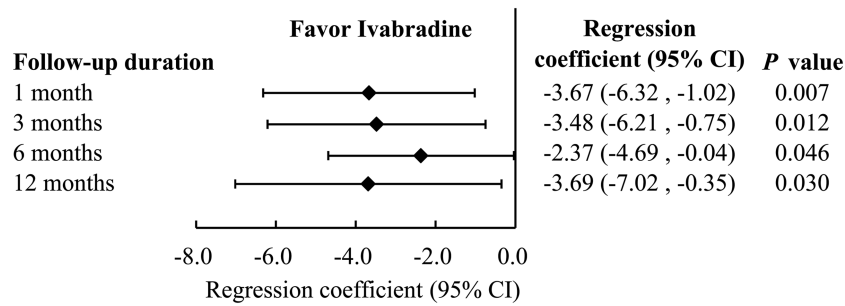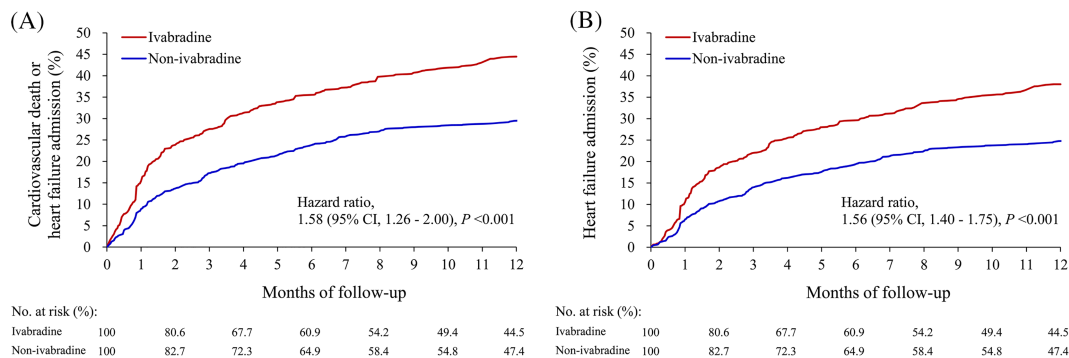
Follow-up duration	Favor Ivabradine	Regression coefficient (95% CI)	*P* value
1 month		-3.67 (-6.32 , -1.02)	0.007
3 months		-3.48 (-6.21 , -0.75)	0.012
6 months		-2.37 (-4.69 , -0.04)	0.046
12 months		-3.69 (-7.02 , -0.35)	0.030

Regression coefficient (95% CI)
-8.0   -6.0   -4.0   -2.0   0.0

Table 2 Clinical outcomes and echocardiographic parameters between the two groups after 12 months follow-up

	Valid N	Before IPTW adjustment		After IPTW adjustment		After IPTW adjustment	
		Ivabradine (*n* = 887)	Non-ivabradine (*n* = 1155)	Ivabradine	Non-ivabradine	Ivabradine vs. Non-ivabradine	
Survival outcomes						HR (95% CI)	*P* value
Primary outcome							
CV death or HF hospitalization	2042	404 (45.5)	340 (29.4)	44.5%	29.5%	1.58 (1.26–2.00)	<0.001
Mortality outcome							
All-cause mortality	2042	142 (16.0)	102 (8.8)	12.9%	8.5%	1.48 (1.06–2.07)	0.022
CV death	2042	124 (14.0)	91 (7.9)	11.2%	7.8%	1.42 (0.99–2.03)	0.057
Heart failure death	2042	109 (12.3)	72 (6.2)	10.1%	6.0%	1.67 (1.14–2.44)	0.009
Other outcome							
All-cause hospitalization	2042	382 (43.1)	401 (34.7)	43.8%	33.4%	1.33 (1.20–1.46)	<0.001
CV hospitalization	2042	357 (40.2)	379 (32.8)	40.9%	31.9%	1.27 (1.15–1.41)	<0.001
HF hospitalization	2042	327 (36.9)	286 (24.8)	38.0%	24.8%	1.56 (1.40–1.75)	<0.001
Worsening renal function*	1789	39 (4.8)	30 (3.1)	4.1%	3.3%	1.28 (0.78–2.10)	0.332
Results from echocardiography						*B* (95% CI)	*P* value
LVEF, %	1200	38.8 ± 16.1	41.4 ± 15.1	41.6 ± 15.7	39.8 ± 14.9	1.80 (−0.54, 4.14)	0.132
LVEDD, mm	1181	59.4 ± 10.6	57.3 ± 9.3	59.0 ± 10.2	58.2 ± 9.4	0.80 (−0.73, 2.32)	0.306
LA, mm	1169	42.1 ± 7.6	42.0 ± 7.4	42.3 ± 7.6	42.4 ± 8.0	−0.09 (−1.50, 1.31)	0.897

IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval; CV, cardiovascular; HFH, heart failure hospitalization; B, regression coefficient; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LA, left atrium.
*A decline in eGFR >30 mL/min/1.73 m^2 from baseline for patients whose baseline eGFR was <60 mL/min/1.73 m^2 or a decline in eGFR >50% from baseline for patients whose baseline eGFR was ≥60 mL/min/1.73 m^2.

Figure 4 The cumulative event rate of the primary outcome of cardiovascular death and heart failure hospitalization (A), and heart failure hospitalization (B) between the ivabradine and non-ivabradine groups in the IPTW-adjusted cohort. CI, confidence interval.

(A)

Cardiovascular death or heart failure admission (%)

Hazard ratio, 1.58 (95% CI, 1.26 - 2.00), *P* <0.001

Months of follow-up

No. at risk (%):
| Ivabradine | 100 | 80.6 | 67.7 | 60.9 | 54.2 | 49.4 | 44.5 |
| Non-ivabradine | 100 | 82.7 | 72.3 | 64.9 | 58.4 | 54.8 | 47.4 |

(B)

Heart failure admission (%)

Hazard ratio, 1.56 (95% CI, 1.40 - 1.75), *P* <0.001

Months of follow-up

No. at risk (%):
| Ivabradine | 100 | 80.6 | 67.7 | 60.9 | 54.2 | 49.4 | 44.5 |
| Non-ivabradine | 100 | 82.7 | 72.3 | 64.9 | 58.4 | 54.8 | 47.4 |

talization and CV death was significantly higher in the ivabradine group than the non-ivabradine group (44.5% vs. 29.5% at 12 month follow-up; hazard ratio [HR] = 1.58; 95% confidence interval [CI], 1.26–2.00, *P* < 0.001) (*Table 2* and *Figure 4A*). The difference in the primary outcome was mainly driven by HF hospitalization. The ivabradine group had a significantly higher event rate of HF hospitalization than the non-ivabradine group (38.0% vs. 24.8% at 12 month follow-up; HR = 1.56; 95% CI, 1.40–1.75, *P* < 0.001) (*Table 2* and *Figure 4B*). After 12 months follow-up, the ivabradine group had a significantly higher event rate of all-cause mortality (12.9% vs. 8.5%; HR = 1.48; 95% CI, 1.06–2.07, *P* = 0.022) and HF death (10.1% vs. 6.0%; HR = 1.67; 95% CI, 1.14–2.44, *P* = 0.009) than the non-ivabradine group. Furthermore, after 12 months follow-up, the ivabradine group had a significantly higher event rate of all-cause hospitalization (43.8% vs. 33.4%; HR = 1.33; 95% CI, 1.20–1.46, *P* < 0.001) and CV hospitalization (40.9% vs. 31.9%; HR = 1.27; 95% CI, 1.15–1.41, *P* < 0.001) than the non-ivabradine group (*Table 2*).

Echocardiographic parameters and renal outcomes

After 12 months follow-up, there were no significant differences in LVEF, LVEDD, and LA size between the ivabradine and non-ivabradine groups (*Table 2*). After 12 months follow-up, there was no significant difference in the rate of worsening renal function between the ivabradine and non-ivabradine group (*Table 2*).

Subgroup analysis of patients with left ventricular ejection fraction ≤35% that were consistent with the participants in SHIFT study

There were 786 (88.6%) patients in the ivabradine group and 772 (66.8%) in the non-ivabradine group, whose LVEF were ≤35%. The HR was still significantly lower in the ivabradine group than in the non-ivabradine group at different follow-up time. The comparisons of the clinical outcomes and LV function between the ivabradine group and non-ivabradine group with LVEF ≤35% after IPTW are summarized in Supporting Information, *Table S4*. After 12 months follow-up, the primary outcome of HF hospitalization and CV death was significantly higher in the ivabradine group than in the non-ivabradine group (43.4% vs. 30.9%; HR = 1.47; 95% CI, 1.15–1.87, *P* = 0.002). Similarly, CV death, HF hospitalization and all-cause hospitalization were significantly higher in the ivabradine group than in the non-ivabradine group (Supporting Information, *Table S4*). There were no differences in the LVEF, LVEDD, and LA size between the ivabradine group and non-ivabradine group with LVEF ≤35%.

Sensitivity analysis by propensity-score matching

The clinical outcomes, echocardiographic results and HR were analysed after PSM and these were summarized in Supporting Information, *Table S5*. Briefly, HR was lower in ivabradine group than non-ivabradine group in the 12 month follow-up period. After 12 months follow-up, the primary outcome of HF hospitalization and CV death was significantly higher in the ivabradine group than in the non-ivabradine group (43.6% vs. 31.4%; HR = 1.47; 95% CI, 1.20–1.78, *P* < 0.001). Similarly, HF hospitalization was significantly higher in the ivabradine group than in the non-ivabradine group (35.4% vs. 26.2%; HR = 1.37; 95% CI, 1.10–1.70, *P* = 0.006) (Supporting Information, *Table S5*). There were also no differences in the LVEF, LVEDD, and LA size between the ivabradine group and non-ivabradine group after PSM.

Discussion

In this study, we found that symptomatic HFrEF patients with a history of paroxysmal AF prescribed with ivabradine had a significantly lower mean HR than those not prescribed with ivabradine. However, the incidence rates of CV death and HF hospitalization were significantly higher in the ivabradine group than in the non-ivabradine group, even though there were no differences in the rates of worsening renal function and LVEF after 12 months follow-up between the two groups.

Pre-existing AF was an exclusion criterion in the SHIFT study, in which ivabradine treatment reduced HR by 8.1 b.p. m. and resulted in a 5% reduction in hospitalization for worsening HF. However, patients in the ivabradine group were more likely to develop new-onset AF (ivabradine 9% vs. placebo 8%; *P* = 0.012).[2] Moreover, ivabradine treatment was associated with a relative risk of AF of 1.15 (95% CI 1.07 to 1.24, *P* = 0.0027) among 21 571 patients in a previous meta-analysis.[14] Although several case reports and one small-volume randomized controlled study reported that ivabradine significantly decreased the ventricular rate in patients with non-paroxysmal AF compared to placebo,[15–18] the clinical outcomes of ivabradine treatment in symptomatic HFrEF patients with a history of paroxysmal AF remain unknown. In this study, we showed that symptomatic HFrEF patients with a history of paroxysmal AF prescribed with ivabradine had significantly higher incidence rates of CV death and HF hospitalization than those without ivabradine, despite a significantly lower HR in the ivabradine group. Our results suggest that ivabradine may not be suitable for symptomatic HFrEF patients with a history of paroxysmal AF. Several potential mechanisms may explain our observations. Ivabradine may contribute to new-onset AF as shown in SHIFT study and previous meta-analysis.[14] Prior study with heart failure rabbit model showed that ivabradine treatment

increased pulmonary vein arrhythmogenesis and contributed to the development of AF, particularly in HF rabbits.[19] Therefore, we hypothesized that ivabradine might increase AF burden in symptomatic HFrEF patients with a history of paroxysmal AF and AF burden has been reported to be associated with mortality and hospitalization for HF in patients with HFrEF.[20] The increased AF burden potentially induced by ivabradine could contribute to our results that ivabradine group had higher incidence rates of CV death and HF hospitalization than non-ivabradine group despite that ivabradine group had a lower mean HR.

There were several limitations to this study. First, it is a retrospective cohort study, and we could not rule out bias in our study. Although some baseline characteristics, such as duration of HF and prescription rates of medications, were relatively different between the two groups, we conducted IPTW to match all important baseline characteristics between the two groups in order to minimize the effect of baseline characteristics on clinical outcomes. However, some baseline characteristics, such as physical activity, fragile status and functional class, could not be adjusted. Second, HR is an important parameter in ivabradine studies. However, we could not completely exclude daily variations in HR during follow-up. Lastly, we hypothesized that ivabradine may contribute to increased AF burden in HFrEF patients, and AF burden was associated with mortality and hospitalization for HF in HFrEF patients.[20] However, we did not specifically examine AF burden during follow-up in this retrospective cohort study.

Conclusion

Ivabradine treatment was associated with an increased risk of HF hospitalization and CV death in symptomatic HFrEF patients, including those with LVEF ≤ 35%, with a history of paroxysmal AF. Further large prospective randomized studies are warranted to validate our findings.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of the study patients before and after EM imputation.
Table S2. Heart rate in the ivabradine and non-ivabradine groups during the 12-month follow-up.
Table S3. The dose of ivabradine in the ivabradine group.
Table S4. Clinical outcomes and echocardiographic parameters between the two subgroups with LVEF ≤ 35% after 12 months follow-up.
Table S5. Clinical outcomes and echocardiographic parameters after 12 months follow-up between the two subgroups after propensity-score matching.
Figure S1. The distribution of absolute standardized differences before and after imputation and inverse probability of treatment weighting.

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