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ORIGINAL RESEARCH ARTICLE

The association between ivabradine and adverse cardiovascular events in acute decompensated HFrEF patients

Chia-Te Liao[1,2], Jin-Long Huang[3,4], Huai-Wen Liang[5], Fa-Po Chung[4,6], Ying-Hsiang Lee[7,8], Po-Lin Lin[7,9], Wei-Ru Chiou[7,10], Wen-Yu Lin[11], Chien-Yi Hsu[4,12,13] and Hung-Yu Chang[4,14]*

[1]*Division of Cardiology, Chi-Mei Medical Center, Tainan, Taiwan;* [2]*Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan;* [3]*Cardiovascular Center, Taichung Veterans General Hospital, Taichung, Taiwan;* [4]*Faculty of Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan;* [5]*Division of Cardiology, Department of Internal Medicine, E-Da hospital, I-Shou University, Kaohsiung, Taiwan;* [6]*Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan;* [7]*Department of Medicine, Mackay Medical College, New Taipei, Taiwan;* [8]*Cardiovascular Center, MacKay Memorial Hospital, Taipei, Taiwan;* [9]*Division of Cardiology, Department of Internal Medicine, Hsinchu MacKay Memorial Hospital, Hsinchu, Taiwan;* [10]*Division of Cardiology, Taitung MacKay Memorial Hospital, Taitung, Taiwan;* [11]*Division of Cardiology, Department of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan;* [12]*Division of Cardiology and Cardiovascular Research Center, Department of Internal Medicine, Taipei Medical University Hospital, Taipei, Taiwan;* [13]*Taipei Heart Institute, Division of Cardiology, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; and* [14]*Heart Center, Cheng Hsin General Hospital, No.45 Cheng-Hsin Street, 112 Beitou, Taipei, Taiwan*

Abstract

Aims Ivabradine has been used in patients who have chronic heart failure (HF) with reduced ejection fraction (HFrEF) and concomitant sinus heart rate ≥70 bpm. This administration for acute HFrEF remains a concern. This study used a real-world multicentre database to investigate the effects of ivabradine among patients with acute decompensated HFrEF before discharge.

Methods and results This study retrospectively identified patients with acute decompensated HFrEF who were administered ivabradine at discharge from two multicentre HF databases. Propensity score matching was performed to adjust for confounders. Cardiovascular mortality, all-cause mortality, and recurrent HF rehospitalization risks were then compared between those with and without ivabradine treatment. After 1:2 propensity score matching, 876 patients (age, 60.7 ± 14.6 years; female, 23.2%; left ventricular ejection fraction, 28.2% ± 7.8%; and heart rate at discharge, 84.3 ± 13.8 bpm) were included in the final analysis, including 292 and 584 patients with and without ivabradine treatment at discharge, respectively. No significant differences were observed in baseline characteristics between the two groups. At 1 year follow-up, patients in the ivabradine group had significantly lower heart rates (77.6 ± 14.7 vs. 81.1 ± 16.3 bpm; $P = 0.005$) and lower HF severity symptoms (New York Heart Association Functional class, 2.1 ± 0.7 vs. 2.3 ± 0.9; $P < 0.001$) than those from the non-ivabradine group. Ivabradine users had significantly lower risks of 1 year cardiovascular mortality (5.8 vs. 12.2 per 100-person year; $P = 0.003$), all-cause mortality (7.2 vs. 14.0 per 100-person year; $P = 0.003$), and total HF rehospitalization (42.3 vs. 72.6 per 100-person year; $P < 0.001$) than non-ivabradine users. Following multivariate analysis, the predischarge prescription of ivabradine remained independently associated with lower 1 year all-cause mortality (hazard ratio, 0.45; 95% confidence interval, 0.28–0.74; $P = 0.002$) and cardiovascular mortality (hazard ratio, 0.41; 95% confidence interval, 0.24–0.72; $P = 0.002$).

Conclusions The current study findings suggest that ivabradine treatment is associated with reduced risks of cardiovascular mortality, all-cause mortality, and HF rehospitalization within 1 year among patients with acute decompensated HFrEF in real-world populations.

Keywords Heart failure; Hospitalization; Ivabradine; Mortality; Real-world

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**Correspondence to: Hung-Yu Chang, Heart Center, Cheng Hsin General Hospital, No.45 Cheng-Hsin Street, 112 Beitou, Taipei, Taiwan. Tel: 886-2-28264400; Fax: 886-2-28264406. Email: amadeus0814@yahoo.com.tw*

Introduction

Heart failure (HF) is a global public health concern owing to substantial resource consumption. In addition to inflicting high mortality, HF adversely impacts the quality of life.[1] Repeated hospitalizations for HF that occur shortly after discharge has become a particularly troublesome problem.[2] Despite advances in HF treatment, rehospitalization rates and mortality remain high, resulting in a heavy social and economic burden.[3–5] Recent data demonstrated that the prevalence of HF in Southeast Asia is similar to that in Western countries, with 30-day rehospitalization rates ranging from 3% to 15%.[6] In addition, 1 year all-cause mortality rates after acute decompensated HF hospitalization ranged between 9.2% and 37.5%.[7] In a recently published United States Registry enrolling >10 000 patients, 56% of the patients were rehospitalized within 30 days because of worsening HF events. However, the use of standard-of-care therapies both before and after the onset of worsening HF is low.[8] These findings highlight the importance of adequate patient education, greater optimizations of existing guideline-recommended therapy, and novel pharmacological strategies.

Oral disease-modifying HF therapy, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), beta-blockers, and mineralocorticoid receptor antagonists (MRA), should be continued and/or initiated once achieving haemodynamic stabilization during acute HF hospitalization, based on guideline recommendation.[9] The SHIFT (Systolic Heart failure treatment with I*f* inhibitor ivabradine Trial) trial demonstrated that ivabradine contributes to beneficial effects in patients with sinus rhythm and a heart rate of ≥70 beats per minute (bpm).[10] Nevertheless, the SHIFT study enrolled patients who had been hospitalized for HF within the previous 12 months but not within the preceding 4 weeks. Approximately 73% of patients hospitalized because of HF and reduced ejection fraction (HFrEF) had a heart rate of ≥70 bpm at discharge and significantly higher 1 year all-cause mortality, rehospitalization rate, and corresponding medical costs.[11] Hence, the optimization of heart rate control in the post-acute phase of HFrEF is a crucial issue. Because the SHIFT trial did not include patients who were discharged from hospitalization for acute decompensated HF, the clinical benefits of ivabradine on these patients were less clear. Against this background, two Taiwanese multicentre cohorts of patients with HF were utilized to evaluate the effects of ivabradine prescribed before discharge among patients who were hospitalized for acute decompensated HFrEF.

Methods

Study designs and patient characteristics

The present study extracted and analysed data from two multicentre HF cohorts in Taiwan: (1) the TSOC-HFrEF registry initiated by the Taiwan Society of Cardiology, which contains data on a prospective, multicentre, and observational survey of 1,509 patients with HFrEF recently admitted in 21 hospitals in Taiwan for HF from 2013 to 2014,[12] and (2) a principal investigator-initiated multicentre and retrospective HF study, which comprised 1845 patients with HFrEF from 10 hospitals between 2016 and 2018.[13] The definition of acute decompensated HF refers to the rapid onset or worsening of symptoms and/or signs of HF (e.g. fluid retention and/or reduced cardiac output with peripheral hypoperfusion).[9] The inclusion criteria for the current study were (i) >20-year-old male or female patients with symptomatic HFrEF, (ii) patients discharged from hospitalization for acute decompensated HF, and (iii) patients having a sinus rhythm with a resting heart rate of ≥70 bpm at discharge. The exclusion criteria included patients who refused medical advice or were lost to follow-up and had a non-sinus rhythm (atrial pacing, atrial fibrillation, or atrial flutter) or a sinus rhythm with a resting heart rate of <70 bpm. The eligible patients were further divided into two groups according to ivabradine prescription at discharge (ivabradine and non-ivabradine groups). The flowchart of the current study is shown in *Figure 1*.

The protocols of the two HF cohorts were similar, and 50 variables per patient in both cohorts were obtained during index HF hospitalization, including age, gender, body mass index, HF aetiologies, systolic blood pressure, heart rate, New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF), estimated glomerular filtration rate (eGFR), comorbidities, drug therapy, laboratory data, and cardiac device use. This study complied with the ethical principles of the Declaration of Helsinki and was approved by the institutional ethics committee of each hospital.

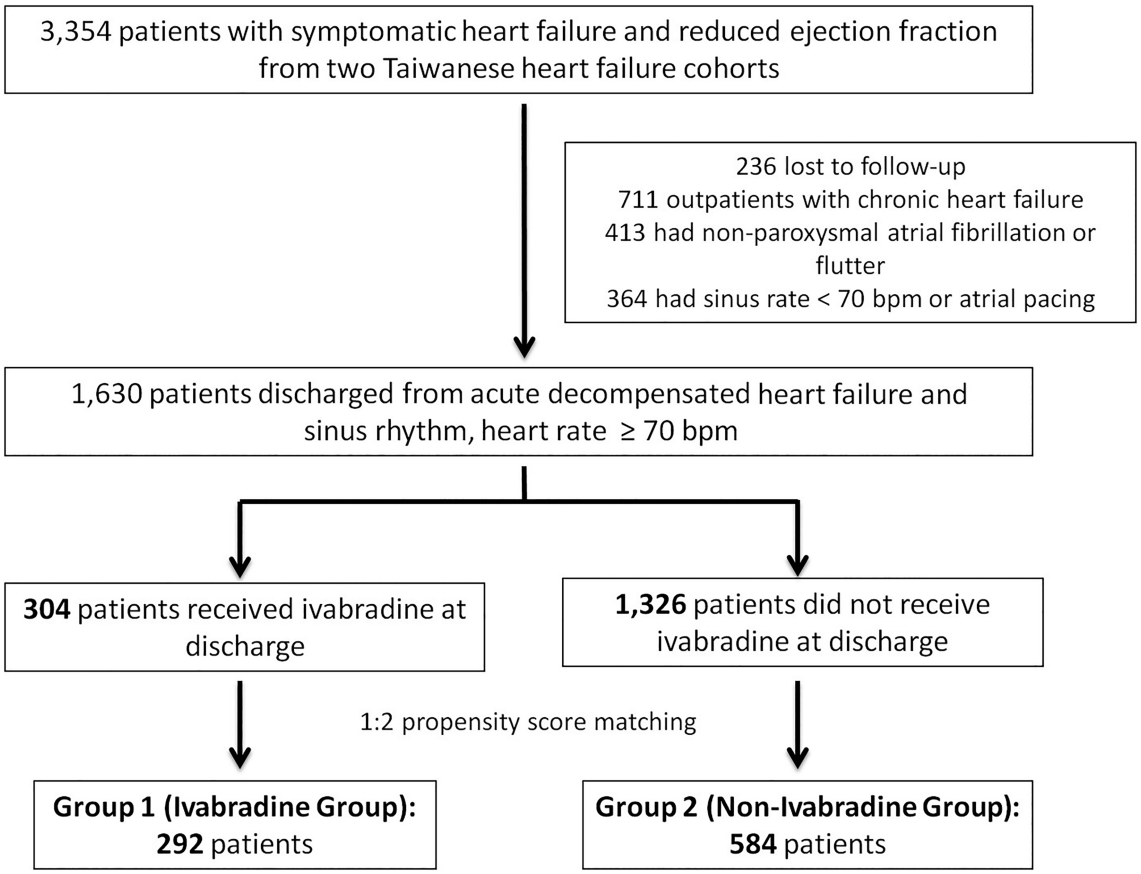
Study outcomes

Three clinical outcomes were identified in the study during 1 year follow-up as follows: mortality from cardiovascular causes, all-cause mortality, and hospital rehospitalization owing to HF. Data on hospital rehospitalization for HF were collected within 6 months and between 6 and 12 months after discharge. The frequencies of HF rehospitalization were categorized into 0, 1, 2, and ≥3 times.

Statistical analyses

Continuous and categorical variables are expressed as the mean values ± standard deviations and percentages, respectively. Propensity score matching was performed to adjust for confounders. Propensity was estimated using a logistic regression model with the following covariates: age, gender, body mass index, systolic blood pressure, heart rate, and NYHA functional class at discharge, LVEF, eGFR, HF aetiology,

Figure 1 The flowchart of current study.



and 13 comorbidities (hypertension, diabetes mellitus, dyslipidaemia, peripheral arterial disease, atrial fibrillation, chronic obstructive pulmonary disease (COPD) or asthma, chronic kidney disease, sleep apnoea, history of stroke, thyroid disorder, prior history of myocardial infarction, malignancy, and depression). Because more patients did not receive ivabradine, each patient in the ivabradine group was matched with two patients in the non-ivabradine group (1:2 matching). In the matching process, the greedy, nearest-neighbour method without replacement and with a calliper of 0.01 of the propensity score was used.

Differences in baseline characteristics and clinical parameters were tested using the χ^2 test for categorical variables, and continuous data were compared using Student's *t* test or the Mann–Whitney *U* test. The risks of cardiovascular mortality and all-cause mortality were analysed using survival analysis with the Kaplan–Meier method and log-rank test. Because the baseline HF treatment between the two groups was significantly different, subgroup and multivariate Cox regression analyses were performed to assess the consistency of the treatment effects of ivabradine and evaluate the influence of each treatment on clinical outcomes. A *P* value of <0.05 was considered statistically significant, and statistical analyses were performed using IBM SPSS Statistics 24.0 software (IBM SPSS, IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

This study included 1,630 patients with HFrEF discharged from hospitalization for acute decompensated HF with a sinus rate of ≥70 bpm. Among these patients, 304 received ivabradine at discharge (ivabradine group), whereas 1,326 patients did not receive ivabradine at discharge (non-ivabradine group). Patients in the non-ivabradine group were significantly older, had a higher measurement of heart rate at discharge, and were prone to have an associated history of paroxysmal atrial fibrillation before propensity score matching. By contrast, patients in the ivabradine group were more likely to have a history of myocardial infarction and dyslipidaemia. After 1:2 propensity score matching, 876 patients were included in the final analysis. The mean age of

the study subjects and the mean LVEF were 60.7 years and 28.2%, respectively. Overall, the two matched cohorts were well balanced. *Table 1* shows the detailed baseline characteristics of both cohorts before and after propensity score matching.

Heart failure medications and device therapies at discharge

The prescription rates of beta-blockers (70.2% vs. 68.2%, $P = 0.536$), loop diuretics (68.8% vs. 73.1%, $P = 0.185$), and anticoagulants (15.4% vs. 15.2%, $P = 0.947$) were similar between the two groups at discharge. Patients in the matched ivabradine group were more likely to receive ACEi, ARB, or sacubitril/valsartan (80.5% vs. 71.1%, $P = 0.003$); sacubitril/valsartan (38.0% vs. 18.0%, $P < 0.001$); or MRA (71.6% vs. 51.9%, $P < 0.001$), whereas patients in the non-ivabradine group were more likely to receive ACEi/ARB (53.1% vs. 42.5%, $P = 0.003$), digoxin (24.0% vs. 16.1%, $P = 0.007$), and amiodarone (14.2% vs. 8.9%, $P = 0.025$). Compared with patients in the non-ivabradine group, patients in the ivabradine group were more likely to receive cardiac device implantation, including cardiac resynchronization therapy (7.2% vs. 2.4%, $P = 0.001$) and implantable cardioverter defibrillator (11.0% vs. 4.1%, $P < 0.001$). Despite discrepancies in heart rate-lowering regimens at discharge, patients in both groups had comparable heart rate measurements at discharge (83.5 ± 15.0 vs. 84.7 ± 13.1 bpm, $P = 0.248$).

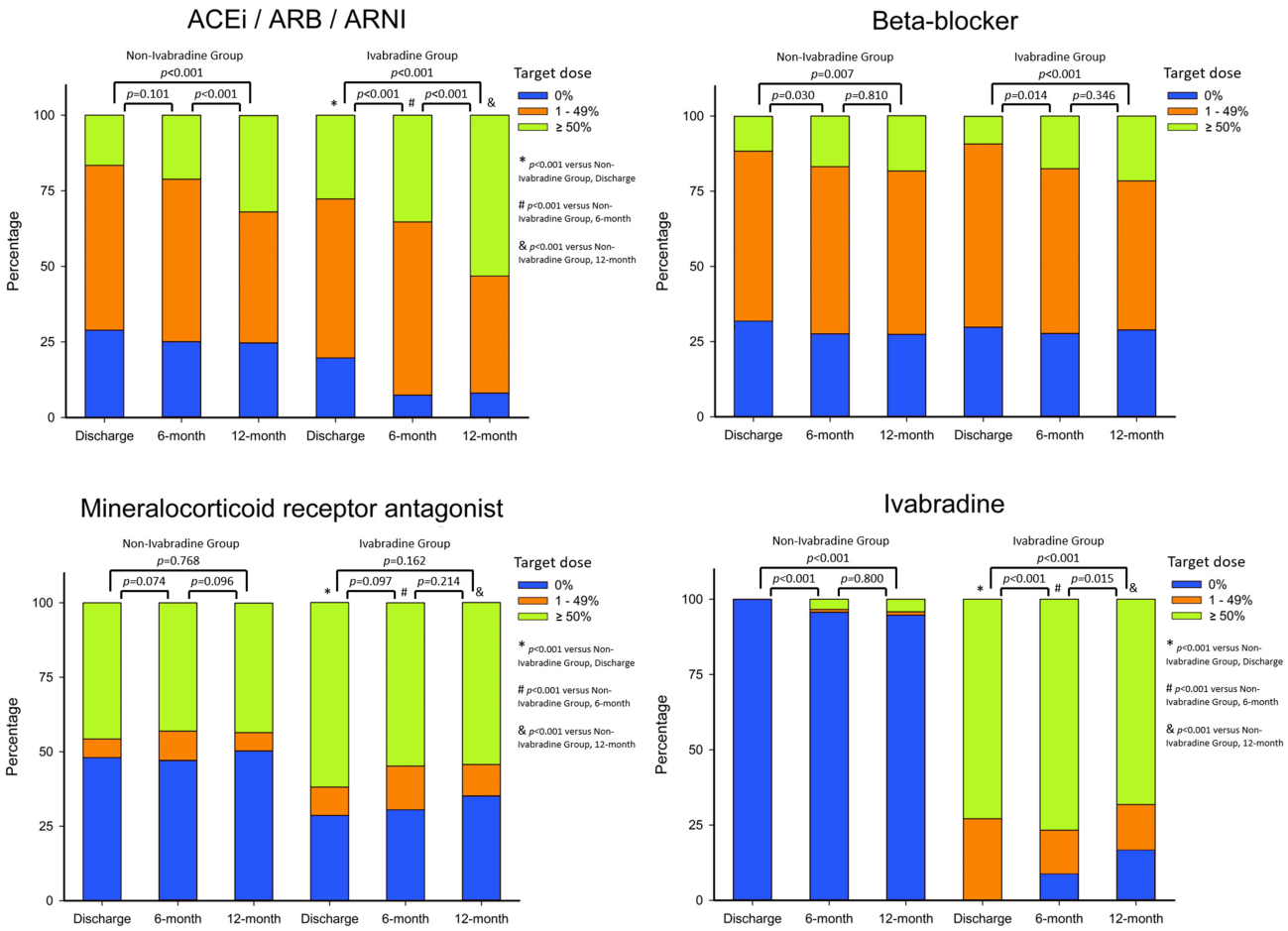
The prescription rates and dosages of renin–angiotensin system inhibitors, beta-blockers, MRAs, and ivabradine at discharge, 6 months, and 12 months after index hospitalization are shown in *Figure 2*. Renin–angiotensin system inhibitor

Table 1 Baseline characteristics among patients with different groups

	Before propensity score matching			After propensity score matching		
	IVA group ($n = 304$)	Non-IVA group ($n = 1326$)	*P* value	IVA group ($n = 292$)	Non-IVA group ($n = 584$)	*P* value
Age (year)	60.1 ± 14.9	62.4 ± 15.3	0.018	60.5 ± 14.9	60.8 ± 14.4	0.764
Male gender, *n* (%)	226 (76.9)	967 (72.9)	0.165	224 (76.7)	449 (76.9)	0.955
BMI (kg/m^2)	25.4 ± 5.6	25.3 ± 4.9	0.659	25.4 ± 5.6	25.1 ± 5.1	0.433
Length of stay (day)	13.6 ± 24.4	12.7 ± 13.1	0.437	13.6 ± 24.6	12.4 ± 11.9	0.342
Admission SBP (mmHg)	129.1 ± 21.2	130.6 ± 25.2	0.286	129.2 ± 21.2	129.9 ± 25.5	0.675
Admission HR (bpm)	92.9 ± 16.1	94.7 ± 19.9	0.092	92.8 ± 16.1	93.4 ± 20.0	0.622
Discharge SBP (mmHg)	119.5 ± 20.7	120.4 ± 19.0	0.487	119.6 ± 20.7	119.7 ± 20.2	0.967
Discharge HR (bpm)	83.7 ± 14.7	86.0 ± 12.2	0.010	83.5 ± 15.0	84.7 ± 13.1	0.248
Discharge NYHA Fc	2.6 ± 0.7	2.6 ± 0.7	0.101	2.6 ± 0.7	2.6 ± 0.7	0.225
LVEF (%)	28.2 ± 7.2	28.5 ± 8.1	0.488	28.2 ± 7.3	28.2 ± 8.1	0.930
eGFR (ml/min/1.73m^2)	65.7 ± 47.4	61.4 ± 35.1	0.073	65.5 ± 48.0	63.9 ± 32.6	0.573
ICMP, *n* (%)	152 (50.0)	628 (47.4)	0.406	140 (47.9)	280 (47.9)	1.000
Comorbidities, *n* (%)						
Diabetes mellitus	156 (51.3)	611 (46.1)	0.099	150 (51.4)	301 (51.5)	0.962
Hypertension	166 (54.6)	719 (54.3)	0.904	160 (54.8)	312 (53.4)	0.701
Prior myocardial infarction	103 (33.9)	364 (27.5)	0.025	97 (33.2)	173 (29.6)	0.277
PAD	24 (7.9)	99 (7.5)	0.799	24 (8.2)	45 (7.7)	0.790
Prior stroke	27 (8.9)	128 (9.7)	0.679	27 (9.2)	51 (8.7)	0.801
Paroxysmal atrial fibrillation	40 (13.2)	249 (18.8)	0.019	40 (13.7)	89 (15.2)	0.544
Dyslipidaemia	141 (46.4)	519 (39.2)	0.020	129 (44.2)	269 (46.1)	0.598
COPD	36 (11.8)	157 (11.8)	0.999	36 (12.3)	84 (14.4)	0.404
Chronic kidney disease	113 (37.2)	456 (34.4)	0.359	107 (36.6)	219 (37.5)	0.805
History of thyroid disease	21 (6.9)	69 (5.2)	0.241	21 (7.2)	42 (7.2)	1.000
Sleep apnoea	10 (3.3)	36 (2.7)	0.585	10 (3.4)	17 (2.9)	0.678
History of malignancy	21 (6.9)	62 (4.7)	0.110	19 (6.5)	40 (6.8)	0.849
Depression	9 (3.0)	28 (2.1)	0.370	9 (3.1)	10 (1.7)	0.189
Heart failure treatment, n (%)						
RASi	241 (79.3)	943 (71.1)	0.004	235 (80.5)	415 (71.1)	0.003
ACEi/ARB	125 (41.1)	713 (53.8)	<0.001	124 (42.5)	310 (53.1)	0.003
Sacubitril/valsartan	116 (38.2)	230 (17.3)	<0.001	111 (38.0)	105 (18.0)	<0.001
Beta blocker	209 (68.8)	856 (64.6)	0.124	205 (70.2)	398 (68.2)	0.536
MRA	215 (70.7)	689 (52.0)	<0.001	209 (71.6)	303 (51.9)	<0.001
Digoxin	47 (15.5)	310 (23.4)	0.003	47 (16.1)	140 (24.0)	0.007
CRT	21 (6.9)	33 (2.5)	<0.001	21 (7.2)	14 (2.4)	0.001
ICD	32 (10.5)	48 (3.6)	<0.001	32 (11.0)	24 (4.1)	<0.001

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary diseases; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HR, heart rate; ICD, *I*mplantable cardioverter defibrillator; ICMP, ischaemic cardiomyopathy; IVA, ivabradine; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA Fc, New York Heart Association Functional class; PAD, peripheral artery diseases; RASi, renin–angiotensin system inhibitor; SBP, systolic blood pressure.

Figure 2 Types and dosages of disease-modifying medications for heart failure among study patients over time. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor.



and beta-blocker uptitrations were significant in both groups at 1 year follow-up (all *P* values <0.01). There was no significant change in the prescription patterns of MRA at 1 year follow-up in both groups. Ivabradine was initiated in 5.3% of the patients in the non-ivabradine group and discontinued in 16.8% of the patients in the ivabradine group at 1-year follow-up.

Clinical outcomes

The overall incidence of cardiovascular mortality was 10.0 per 100-person year at 1 year follow-up. The incidences of cardiovascular mortality were 5.8 and 12.2 per 100-person year for the matched ivabradine and non-ivabradine groups, respectively [hazard ratio (HR), 0.45; 95% confidence interval (CI), 0.26–0.76; *P* = 0.003; *Figure 3A*]. The incidences of mortality from any causes in patients in the matched ivabradine and non-ivabradine groups were 7.2 and 14.0 per 100-person year, respectively (HR, 0.48; 95% CI, 0.30–0.77; *P* = 0.003; *Figure 3B*).

During the first 6 months after index HF hospitalization, 319 rehospitalizations for HF occurred in 221 patients. Moreover, 20.3% and 27.7% of the patients in the matched ivabradine and non-ivabradine groups experienced rehospitalization for HF at least once within 6 months after index hospitalization, respectively (*P* = 0.004). Between 6 and 12 months after index HF hospitalization, 187 rehospitalizations for HF occurred in 132 patients. Furthermore, 12.2% and 19.5% of the patients in the matched ivabradine and non-ivabradine groups, respectively, experienced rehospitalization for HF at least once between 6 and 12 months following index hospitalization (*P* = 0.007). *Figure 4A* shows the significantly lower incidence of first and repeated HF rehospitalizations in patients in the matched ivabradine group than that in patients in the non-ivabradine group (the odds ratio for the first unplanned HF rehospitalization within 1 year was 0.65; 95% CI, 0.48–0.89; *P* = 0.006).

Figure 3 Kaplan–Meier curves of death from cardiovascular causes (A), and death from any causes (B) within 1 year in study patients.CI, confidence interval; HR, hazard ratio.

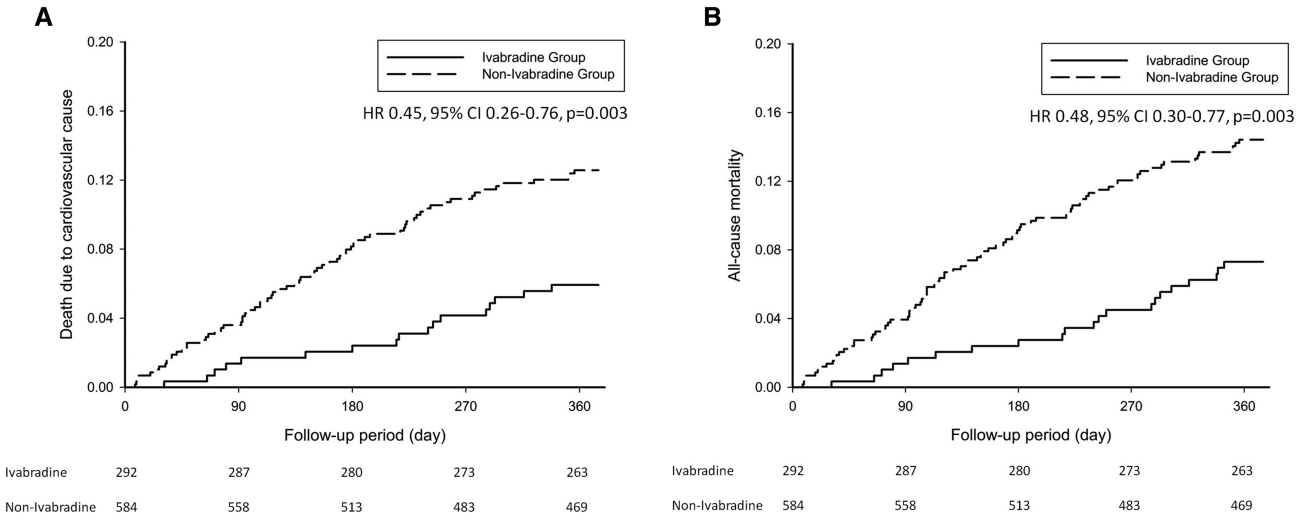
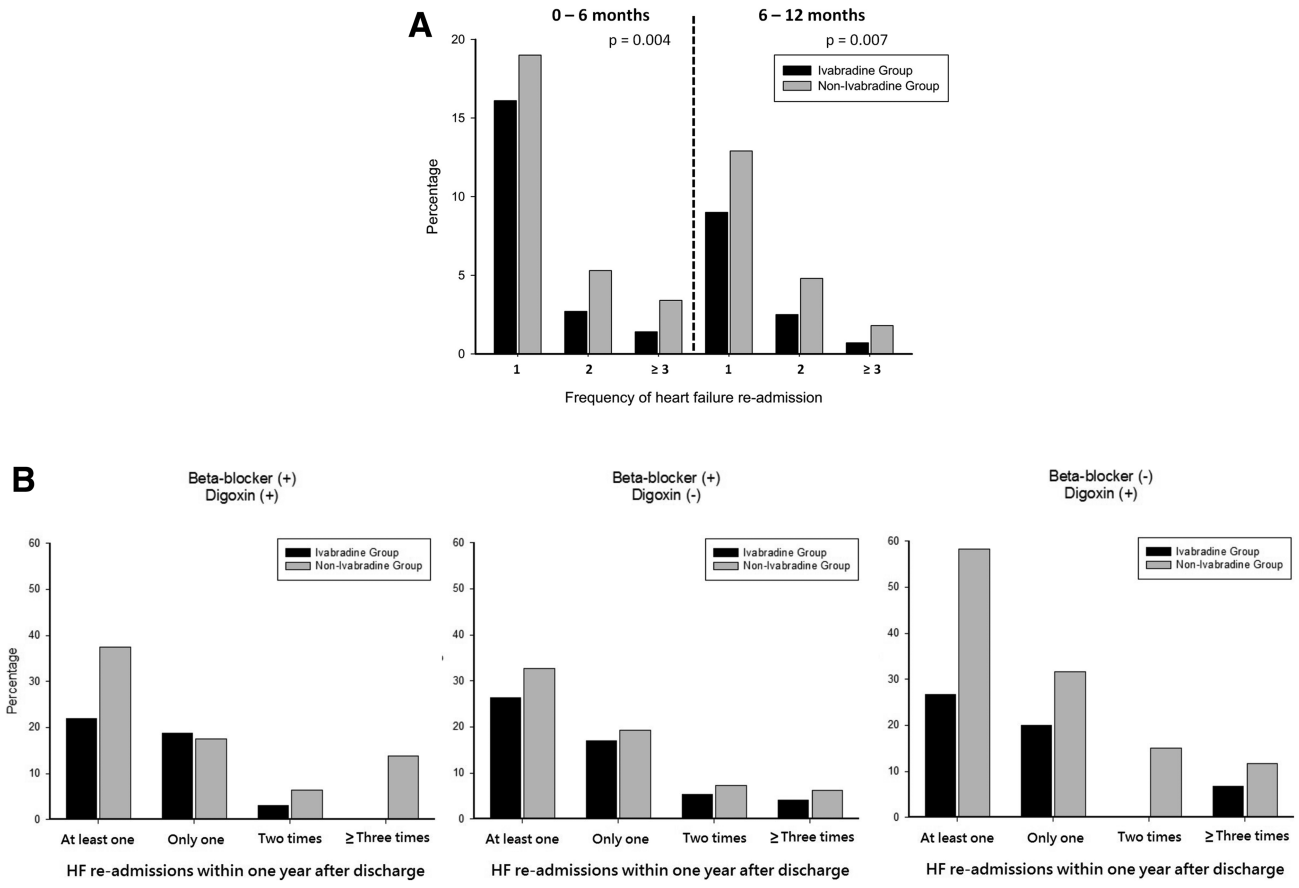


Figure 4 Frequencies of heart failure (HF) re-admission following index hospitalization within 1 year (A), and stratified by baseline prescription of beta-blocker and digoxin (B).



Clinical outcomes in different background HF therapies

Among patients with concomitant background beta-blocker treatment, patients who received ivabradine treatment had a significantly lower risk of cardiovascular mortality than those who did not receive ivabradine (3.9 vs. 9.5 per 100-person year; HR, 0.39; 95% CI, 0.18–0.83; *P* = 0.011). The favourable outcomes of ivabradine in cardiovascular mortality were consistent across the variable examined subgroups of different background HF medications and implantable devices (*Figure 5*). The incidences of cardiovascular mortality were similar among patients not on ivabradine treatment between the 2013–2014 and 2016–2018 cohorts (*P* = 0.540).

Table 2 demonstrates the univariate and multivariate Cox regression analyses for baseline HF treatments associated with 1-year outcomes. The prescription of ivabradine at discharge was independently associated with a lower risk of 1-year all-cause mortality (HR, 0.45; 95% CI, 0.28–0.74; *P* = 0.002). Beta-blocker and renin–angiotensin system inhibitor use at discharge were also independently associated with better survival (HR, 0.59; 95% CI, 0.40–0.88; *P* = 0.009 for beta-blockers and HR, 0.58; 95% CI, 0.38–0.86; *P* = 0.008 for renin–angiotensin system inhibitors). Furthermore, the prescriptions of ivabradine, renin–angiotensin system inhibitors,

Figure 5 Hazard ratio of cardiovascular death according to heart failure treatment subgroups in two cohorts. ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor.

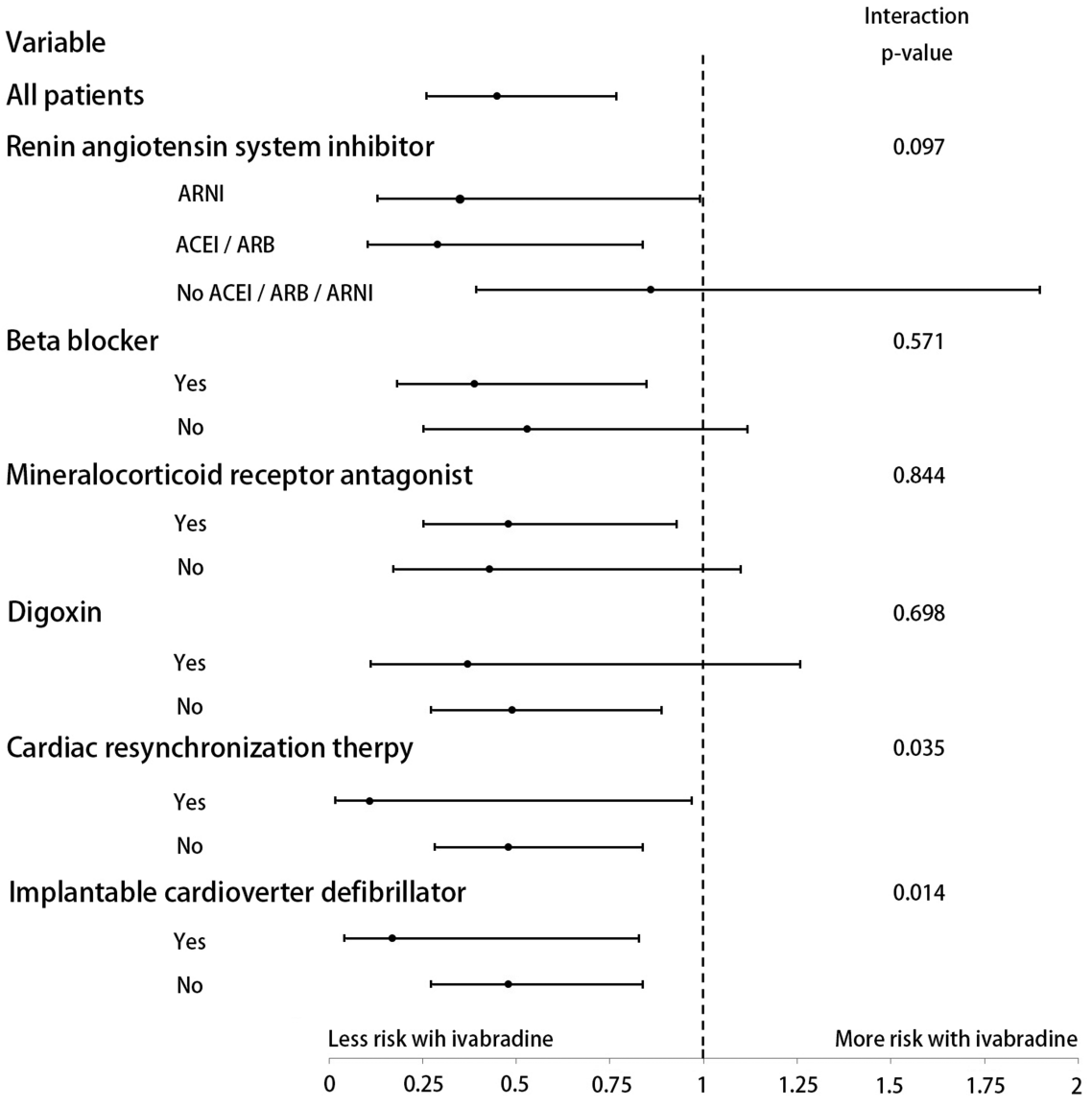


Table 2 Multivariate analysis for heart failure treatments associated with one-year outcomes following index heart failure hospitalization

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% confidence interval	*P* value	Hazard ratio	95% confidence interval	*P* value
All-cause mortality						
Ivabradine	0.48	0.30–0.77	0.003	0.45	0.28–0.74	0.002
RASi	0.51	0.35–0.76	0.001	0.58	0.38–0.86	0.008
Beta-blocker	0.45	0.31–0.66	<0.001	0.59	0.40–0.88	0.009
MRA	0.66	0.45–0.97	0.034	NS	NS	NS
Digoxin	1.33	0.86–2.06	0.206	NS	NS	NS
CRT	1.49	0.65–3.39	0.345	NS	NS	NS
ICD	1.50	0.76–2.97	0.246	NS	NS	NS
Cardiovascular death						
Ivabradine	0.45	0.26–0.76	0.003	0.41	0.24–0.72	0.002
RASi	0.49	0.32–0.76	0.001	0.54	0.35–0.84	0.006
Beta-blocker	0.48	0.32–0.73	0.001	0.65	0.42–0.99	0.047
MRA	0.77	0.51–1.17	0.225	NS	NS	NS
Digoxin	1.48	0.93–2.35	0.097	NS	NS	NS
CRT	1.76	0.77–4.02	0.183	NS	NS	NS
ICD	1.78	0.90–3.56	0.100	NS	NS	NS

Multivariate analysis was adjusted for age, gender, heart failure aetiology, body mass index, length of stay, left ventricular ejection fraction, systolic blood pressure, heart rate, estimated glomerular filtration rate, New York Heart Association functional class at discharge, history of heart failure hospitalization, atrial fibrillation, hypertension, diabetes, chronic obstructive pulmonary disease, peripheral arterial disease, prior stroke, history of thyroid disease, sleep apnoea, history of malignancy, depression, device therapies, and prescriptions of heart failure medications at discharge.
Abbreviations: CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; MRA, mineralocorticoid receptor antagonist; NS, not significant; RASi, renin–angiotensin system inhibitor.

and beta-blockers at discharge were independently associated with a lower risk of 1 year cardiovascular mortality (*Table 2*).

Figure 4B shows the percentages of total HF rehospitalizations 1 year after discharge, stratified by different heart rate-lowering regimens. Irrespective of the different combinations of beta-blockers and digoxin at discharge, add-on ivabradine showed reduced risks of first and/or repeated HF rehospitalization within 1 year after discharge from index hospitalization.

Alternations of blood pressure, heart rate, and left ventricular ejection fraction

Table 3 shows the alternations of vital signs and clinical outcomes within 1 year. At 1 year follow-up, patients in the ivabradine group had significantly lower heart rates (77.6 ± 14.7 vs. 81.1 ± 16.3 bpm; $P = 0.005$) and lower severity of HF symptoms (NYHA functional class, 2.1 ± 0.7 vs. 2.3 ± 0.9; $P < 0.001$) than those from the non-ivabradine group. Moreover, patients in the ivabradine group had numerically higher LVEF measurements than those from the non-ivabradine group, although not statistically significant (39.2% ± 14.0% vs. 37.3% ± 15.2%; $P = 0.104$).

Discussion

Adverse events frequently occurred following discharge from hospitalization for acute decompensated HF. In the current study, one-fourth of the patients suffered from HF rehospitalization within 6 months and one-tenth died because of cardiovascular causes within 1 year after index HF hospitalization, suggesting that timely and appropriate treatment should be provided to these high-risk patients.

Patients admitted for acute HF are often fragile owing to more comorbidities, for example, renal impairment and COPD, haemodynamic instability, and need for vasopressors and inotrope treatment. These conditions usually limit the initiation and titration of guideline-recommended therapies, that is, MRA, renin–angiotensin system inhibitors, and beta-blockers.[14] Nevertheless, different from the above medications, ivabradine highly and specifically works at the I*f* current in the sinoatrial node and does not adversely affect renal and bronchial systems. The subgroup analysis of the SHIFT trial produced promising evidence in terms of consistent cardiovascular benefits and safety in patients with HF and renal dysfunction or COPD.[14,15] Regarding treating patients with HF and hypotension or haemodynamic instability, using ivabradine (compared with beta-blockers) may be more appropriate in these situations because of its distinguishing feature in heart rate reduction without inducing negative inotropy or hypotension.[16–18] A case series presented the safety and effectiveness of ivabradine in five patients with cardiogenic shock.[18] Another study enrolling 10 patients with advanced HF with pulmonary capillary wedge pressure ≥15 mmHg and sinus tachycardia demonstrated that intravenous ivabradine significantly reduced heart rate and increased stroke volume and LV systolic work.[16] Likewise, 52 patients with decompensated HF on dobutamine treatment were found to have lower heart rates and better stroke

Table 3 Patient characteristics at discharge and in those who survived to 12 months after discharge

	IVA group (n = 292)	Non-IVA group (n = 584)	P value
Baseline			
Systolic blood pressure (mmHg)	129.2 ± 21.2	129.9 ± 25.5	0.675
Heart rate (bpm)	83.5 ± 15.0	84.7 ± 13.1	0.248
LVEF (%)	28.2 ± 7.3	28.2 ± 8.1	0.930
NYHA Fc	2.6 ± 0.7	2.6 ± 0.7	0.225
At 12 months[a]			
Systolic blood pressure (mmHg)	120.4 ± 19.4	121.5 ± 21.5	0.489
Heart rate (bpm)	77.6 ± 14.7	81.1 ± 16.3	0.005
LVEF (%)	39.2 ± 14.0	37.3 ± 15.2	0.104
NYHA Fc	2.1 ± 0.7	2.3 ± 0.9	<0.001
Cardiovascular death, n (%)	17 (5.8%)	71 (12.2%)	0.002
All-cause mortality, n (%)	21 (7.2%)	82 (14.0%)	0.002
At least 1 HF re-admission, n (%)	79 (27.1%)	212 (36.3%)	<0.001

[a]Systolic blood pressure, heart rate and left ventricular ejection fraction were collected from those who survived to 12 months after discharge (IVA group n = 271, non-IVA group n = 502).
Abbreviations: HF, heart failure; IVA, ivabradine; LVEF, left ventricular ejection fraction; NYHA Fc, New York Heart Association functional class.

volume after ivabradine treatment.[17] Apart from these advantages, ivabradine has another specific effect on improving coronary blood flow and contractile function without affecting adrenoceptors.[19] A *post hoc* analysis of the SHIFT study showed that patients in ivabradine and non-ivabradine groups experienced an increase in blood pressure by 12 and 11 mmHg after 24 months, respectively, and the baseline blood pressure did not affect the impact of heart rate reduction on clinical outcomes.[20] Our results echoed the aforementioned study and showed no differences in systolic blood pressure at 1 year follow-up between the two groups. These advantages and specific pharmacological properties of ivabradine may support its utilization in patients with acute HF with high comorbidity burden and haemodynamic instability and even enable an early initiation or uptitration of beta-blocker dose in real-world practice.[21]

A rise in heart rate increases myocardial oxygen consumption, exacerbates myocardial injury, and results in negative ventricular remodelling.[19] Moreover, in contrast to the increased contraction force accompanied with an increased frequency of muscle depolarization in a normal heart, a negative force–frequency relationship was noted in the failing myocardium caused by decreased coronary blood flow, defective calcium transient and sarcoplasmic reticulum activity, and increased oxidative stress.[19,22,23] Therefore, when managing patients with acute decompensated HF, the occurrence of tachycardia is regarded as a red flag because elevated heart rate is associated with unfavourable cardiovascular outcomes at different stages during HF hospitalization.[11,24–26] Of note, although our data showed that the absolute difference in heart rates between the two groups was smaller than that observed in the SHIFT study (3.5 vs. 8 bpm),[10] the additional ivabradine treatment was still associated with a significantly lower 1-year cardiovascular mortality and fewer recurrent hospitalizations for HF. This phenomenon may imply other cardioprotective effects from ivabradine beyond that induced by reducing heart rates. First, when beta-blockade-associated heart rate reduction is prevented by pacing, the alpha-adrenergic coronary vasoconstriction is unmasked, which may deteriorate coronary flow and heart function.[27] Different from beta-blockades, ivabradine can simultaneously reduce heart rates and improve coronary flow and cardiac function by the preservation of the endothelium-mediated vasodilation and lack of unmasked alpha-adrenergic coronary vasoconstriction or negative inotropic action.[28,29] This would permit a better performance in heart function during daily life activity or exercise.[30] Second, the benefits of ivabradine against myocardial infarction are beyond heart rate reduction.[31] Studies revealed that ivabradine may decrease cardiac infarction size and preserve more cardiomyocyte viability after ischaemia or reperfusion by reducing mitochondrial reactive oxygen species formation and increasing adenosine triphosphate production and calcium retention capacity.[31,32] In addition, ivabradine was observed to attenuate adverse cardiac remodelling and improve angiogenesis after myocardial infarction.[33] These pleiotropically cardioprotective effects may provide plausible explanations why the patients treated with ivabradine had a significant improvement in clinical outcomes even with the small heart rate reduction.

Thus far, the rate of ivabradine utilization is still low in real-world practice, although the ESC-HF long-term registry reported that the ivabradine prescription rate increased from 1.2% to 3.2% before HF hospitalization and at discharge.[34] In theory, it is suggested that ivabradine be used as an add-on heart rate-lowering regimen following a beta-blocker. However, although relevant studies suggested that beta-blocker therapy should be continued in patients with acute decompensated HF if their clinical condition permits,[35] the negative inotropic effect of beta-blockers on cardiovascular haemodynamics causes reluctance among some physicians when prescribing them, particularly during the acute

decompensated period. In the real-world setting, the use of beta-blockers significantly decreased from 89.9% to 69.1% at 6 months after the worsening of HF event.[8] Hence, it is unrealistic to assume that all hospitalized patients with HFrEF can receive and tolerate beta-blocker therapy first and gradually be introduced to ivabradine over subsequent months because many patients are still at a high risk of rehospitalization during the vulnerable phase. This obstacle may limit the timely administration of ivabradine. A *post hoc* analysis from the SHIFT study showed that continuous ivabradine therapy was associated with fewer all-cause hospitalizations at 1, 2, and 3 months.[36] Moreover, the ETHIC-AHF trial demonstrated that patients treated with ivabradine and beta-blockers at discharge had significantly lower heart rates and better LVEF at 4 months than patients treated with beta-blockers alone.[37] Likewise, a study from the post-Soviet states showed that add-on ivabradine to beta-blocker therapy for patients with acute HF during hospitalization contributed to a reduction in all-cause mortality and HF rehospitalization within 1 year compared with using beta-blockers alone.[38] In accordance, owing to the beneficial effects of the ivabradine and beta-blocker combination in patients with acute decompensated HF, some clinicians started to advocate the non-stepped approach rather than introducing each class in a stepwise manner.[39] This real-world study supports this approach and provides favourable results that ivabradine could be effectively used in any clinical circumstances as long as the HF patients have been discharged with a sinus rhythm and heart rate of ≥70 bpm.

Several limitations inherent in the retrospective design of this study should be mentioned. First, treatment decisions were based on real-world practice by the participating cardiologists. This type of retrospective study might have potential unmeasured biases. However, this study aimed to include a broad range of patients reflecting the current reality of post-acute practice for ivabradine and not to enrol the narrowly defined HF population included in clinical trials. Second, the number of patients was relatively small. An ongoing randomized, placebo-controlled trial evaluating the efficacy and safety of ivabradine in 674 patients with acute HF may ascertain the role of early heart rate reduction by ivabradine among these patients.[40]

In conclusion, among real-world Asian populations with acute decompensated HF and reduced LVEF, treatment with ivabradine was associated with a reduced risk of cardiovascular mortality, all-cause mortality, and HF rehospitalization within 1 year. These benefits of ivabradine were consistent across various background HF medications. Additional large-scale clinical trials are needed to confirm the benefits of ivabradine among patients with acute decompensated HFrEF.

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Conflict of interest

None declared.

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