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Cardiomyopathy & Heart Failure

The Characteristics and Outcomes of Patients with Heart Failure and Reduced Ejection Fraction: The Eligibility of Novel Heart Failure Medications

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Background: Renin-angiotensin system inhibitors and beta-blockers are the initial treatment of choice for heart failure with reduced ejection fraction (HFrEF), whereas sacubitril/valsartan (SAC/VAL) and ivabradine are considered to second-line therapies. The eligibility of SAC/VAL and ivabradine according to the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA) labels, Taiwan National Health Insurance (TNHI) reimbursement regulations, and European Society of Cardiology (ESC) heart failure (HF) guidelines are diverse, and they may not fulfill the needs of real-world HFrEF patients.

Methods: Patients hospitalized for HF with left ventricular ejection fraction (LVEF) ≤ 40% were recruited from 21 hospitals in Taiwan between 2013 and 2014. The criteria for SAC/VAL and ivabradine according to the different regulations were applied.

Results: Of 1,474 patients, 86.8%, 29.4%, and 9.5% met the EMA/FDA label criteria, TNHI-regulation, and ESC guidelines for SAC/VAL, compared to 47.1%, 37.2%, and 45.6% for ivabradine, respectively. Ineligible reasons for the TNHI regulations included LVEF > 35% (19.9%, for SAC/VAL and ivabradine) and sinus rate < 75 beats per minute (bpm) (29.9%, for ivabradine). Although not meeting the TNHI regulations, patients with LVEF 35-40% had a similar 1-year mortality rate (15.6% vs. 15.8%, p = 0.876) to those with LVEF ≤ 35%, whereas patients with a sinus rate 70-74 bpm had a similar 1-year mortality rate (15.3% vs. 16.1%, p = 0.805) to those with a sinus rate ≥ 75 bpm.

Conclusions: Approximately 70% and 63% of TSOC-HFrEF registry patients were ineligible for SAC/VAL and ivabradine, respectively, according to current TNHI regulations. Regardless of the eligibility for novel HFrEF medications, the high incidence of adverse events suggests that all patients should be treated cautiously.

Key Words: Guidelines • Heart failure • Ivabradine • Left ventricular ejection fraction • Sacubitril/valsartan • Taiwan

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INTRODUCTION

Heart failure (HF) is associated with high morbidity, mortality, and prolonged and frequent hospitalizations, leading to a major burden on health care systems worldwide.[1] The population is aging globally as a result of longer life expectancy and lower fertility. With the increases in life expectancy, the proportion of elderly people with HF will continue to increase in the near future.[2-6]

The use of neurohumoral antagonists, including angiotensin-converting enzyme inhibitors (ACEis), angiotensin receptor blockers (ARBs), beta-blockers, and min-

eralocorticoid receptor antagonists (MRAs) has been associated with significant improvements in clinical outcomes in several extensive randomized controlled studies for heart failure with reduced ejection fraction (HFrEF).[7-11] Recently, the PARADIGM-HF trial demonstrated the superiority of sacubitril/valsartan (SAC/VAL), the first-in-class angiotensin receptor neprilysin inhibitor, over enalapril for death from any cause, cardiovascular death, and HF hospitalization.[12]

Following the PARADIGM-HF trial results, both the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved SAC/VAL for patients with chronic symptomatic HFrEF.[13,14] Since the inclusion/exclusion criteria of the PARADIGM-HF trial were complex, in the real world, it is not practical to require that HFrEF patients fulfill all of the trial's inclusion criteria before prescribing SAC/VAL. The 2016 European Society of Cardiology (ESC) guidelines for HF recommended SAC/VAL as a replacement for an ACEi in patients with left ventricular ejection fraction (LVEF) $\leq$ 35% who remained symptomatic despite an adequate dose of ACEis/ARBs (at the equivalent of 20 mg enalapril daily dose), receiving optimal medical therapy unless previously documented intolerance and/or contraindications and an elevated plasma natriuretic peptide level.[15]

This situation was similar for ivabradine, a novel sinus nodal inhibitor. Following the promising results of the SHIFT trial,[16] the FDA/EMA approved ivabradine,[17,18] and the 2016 ESC guidelines for HF recommended that ivabradine should be considered in symptomatic patients with LVEF $\leq$ 35%, in sinus rhythm, and with a heart rate $\geq$ 70 beats per minute (bpm) despite optimal treatment with a beta-blocker, a renin-angiotensin system inhibitor, and an MRA.[15] Considering the efficacy on clinical outcomes and health insurance budget, the Taiwan National Health Insurance (TNHI) program proposed reimbursement regulations for SAC/VAL. This limited its application to chronic HF patients with LVEF $\leq$ 35% who remained symptomatic New York Heart Association (NYHA) Fc II to IV after treatment with ACEis/ARBs and beta-blockers for 28 days. As for ivabradine, the TNHI regulations limited its application to chronic HF patients with LVEF $\leq$ 35% who remained symptomatic NYHA Fc II to IV after the maximal tolerable dose of beta-blockers and remained in sinus rhythm with a heart rate $\geq$ 75 bpm.

The diversity between label indications, guideline recommendations, and reimbursement regulations may not truly fulfill the needs of real-world HFrEF patients. Therefore, in this study, we aimed to assess the eligibility of these novel HF medications for HFrEF patients in the Taiwan Society of Cardiology-Heart Failure with reduced Ejection Fraction (TSOC-HFrEF) registry according to FDA/EMA labels, TNHI regulations, and ESC guidelines. We also compared the characteristics and outcomes of the HFrEF patients according to LVEF and discharge heart rate.

METHODS

Study designs and patients' characteristics

The TSOC-HFrEF registry is a prospective, multicenter, observational survey of hospitalized patients with either acute new-onset HF or acute decompensation of chronic HFrEF. The institutional review board of each hospital agreed to participate in the registry. The enrollment of patients, the overall characteristics of the patient population, and the management during index hospitalization have been described in detail in a previous manuscript.[19]

There were no specific exclusion criteria, except that all patients should be over 18 years of age, and their LVEF had to be documented as < 40% before enrollment. The data used for the current analysis were collected from baseline characteristics, laboratory tests, and medications in the index hospitalization for HF. The registry enrolled patients from May 2013 to October 2014, and the patients were followed up for 1 year. None of the study patients were treated with SAC/VAL or ivabradine during the entire follow-up period.

Patient eligibility for sacubitril/valsartan and ivabradine based on FDA/EMA labels, TNHI regulations, and 2016 ESC guidelines

According to the FDA label, SAC/VAL is indicated for chronic HF (NYHA class II-IV) and reduced ejection fraction, whereas according to the EMA label, SAC/VAL is indicated for adult patients with symptomatic chronic HFrEF. Although the TSOC-HFrEF registry enrolled patients during HF decompensation, for study purposes, we collected the patients who were safely discharged from their index hospitalization and analyzed their vital signs and

medications at discharge. According to the TNHI reimbursement regulations, patients are considered eligible for SAC/VAL if they have: (1) symptomatic chronic HF with NYHA Fc II to IV, (2) LVEF ≤ 35%, (3) remain symptomatic despite > 28 days of ACEi or ARB and beta-blocker treatment. According to the ESC guidelines, patients are considered eligible for SAC/VAL if they have: (1) symptomatic HF (NYHA Fc II-IV), (2) LVEF ≤ 35%, (3) elevated natriuretic peptide level (BNP ≥ 150 pg/mL or NT-proBNP ≥ 600 pg/mL; alternatively BNP ≥ 100 pg/mL or NT-proBNP ≥ 400 pg/mL if they had been hospitalized for HF within the previous 12 months), (4) daily dose of an ACEi/ARB equal to an enalapril equivalent of ≥ 20 mg, and (5) receiving optimal medical therapy including ACEis/ARBs, beta-blockers, and MRAs unless previously documented intolerance and/or contraindications. Since the TSOC-HFrEF registry was an observational study, only 830 patients (55%) had BNP or NT-proBNP levels available for analysis. Among these patients, only 2.7% did not have elevated natriuretic peptide levels. Therefore, the natriuretic peptide criterion was not used in this study. The reasons for not prescribing ACEis/ARBs, beta-blockers, and MRAs were not recorded, and we could not define whether the patients could not tolerate or were contraindicated for these drugs in this study.

According to the FDA and EMA labels, ivabradine is indicated for chronic HF, NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy including beta-blockers or when beta-blockers are contraindicated or not tolerated. According to the TNHI reimbursement regulations, patients are considered eligible for ivabradine if they have: (1) symptomatic chronic HF with NYHA Fc II to IV, (2) LVEF ≤ 35%, (3) sinus rhythm and heart rate ≥ 75 bpm, in combination with a maximal tolerable dose of beta-blockers, or if beta-blockers are not tolerated. According to the 2016 ESC HF guidelines, patients are considered eligible for ivabradine if they are symptomatic with LVEF ≤ 35%, in sinus rhythm and a resting heart rate ≥ 70 bpm despite treatment with an evidence-based dose of beta-blockers, and if beta-blockers, ACEis (or ARBs), and MRAs are contraindicated or not tolerated.

Outcomes

Data on death from any cause, HF-related death (including HF death and sudden cardiac death), and HF rehospitalization were retrieved from medical records. The follow-up period was 1 year following the index HF hospitalization. Clinical status was ascertained via telephone interview for the patients who did not attend outpatient clinic visits.

Statistical analysis

The quantitative data were expressed as the mean value ± standard deviation, and categorical variables were reported as percentages. Descriptive summaries were presented for all patients and subgroups of patients. Student's *t*-test or the Mann-Whitney U-test was used to compare continuous data, and the chi-square test was used for comparisons between categorical data. Kaplan-Meier survival analysis was used to present survival curves. A p-value of < 0.05 was considered to be statistically significant. All tests were two-sided. All statistical analyses were performed using SPSS Statistics 17.0 software (Chicago, IL, USA).

RESULTS

Clinical presentations at hospital entry and discharge

From May 2013 to October 2014, 1,509 hospitalized patients (age 63.9 ± 16.1 years, 72.4% male) from 21 hospitals were included in the TSOC-HFrEF registry. Thirty-five patients (2.4%) died during hospitalization. At hospital entry, 11.8%, 50.3%, and 37.8% of the patients were in NYHA Fc II, III, and IV, respectively. At discharge, 13.2% of the patients had recovered to NYHA Fc I, whereas 59.4%, 22.9%, and 4.4% remained symptomatic with NYHA Fc II, III, and IV, respectively.

Of 1,474 patients discharged from the index hospitalization, 213 (14.5%) and 138 (9.4%) had chronic kidney disease stage IV and stage V at discharge, respectively. A total of 81 (5.5%) patients had a baseline serum potassium level > 5.0 mmol/L.

TSOC-HFrEF registry patient eligibility for SAC/VAL based on EMA/FDA labels, TNHI reimbursement regulations, and 2016 ESC guideline criteria

Of the 1,474 HFrEF patients discharged from the index hospitalization, 86.8%, 29.4%, and 9.5% met EMA/FDA label, TNHI reimbursement regulation, and ESC guide-

line criteria for SAC/VAL, respectively. The summary of eligibility for SAC/VAL is shown in Table 1.

A total of 294 patients had baseline LVEF > 35% (19.9%) and, therefore, were ineligible for SAC/VAL according to both TNHI regulations and ESC guidelines. A total of 194 patients (13.2%) were asymptomatic (NYHA Fc I) and were therefore ineligible for SAC/VAL according to EMA/FDA labels, TNHI regulations, and ESC guidelines. Renin-angiotensin system blockers were prescribed in 62.1% of the patients at discharge. The prescribing rates of beta-blockers and MRAs at discharge were 59.6% and 49.0%, respectively. According to the TNHI regulations, patients needed to be treated with ACEis or ARBs and beta-blockers before the initiation of SAC/VAL, and a total of 893 patients (60.6%) did not meet this criterion. The ESC guidelines suggest that patients should receive adequate ACEi/ARB therapy at the equivalent of 20 mg enalapril daily dose before the initiation of SAC/VAL. This was the most difficult criterion to meet in the TSOC-HFrEF registry since only 223 patients (15.1%) received a renin-angiotensin system blocker at such an equivalent dose or higher.

TSOC-HFrEF registry patient eligibility for ivabradine based on EMA/FDA label, TNHI reimbursement regulation, and 2016 ESC guideline criteria

Of the 1,474 HFrEF patients discharged from the index hospitalization, 47.1%, 37.2%, and 45.6% met the EMA/FDA labels, TNHI reimbursement regulations, and ESC guidelines for ivabradine, respectively. The summary of eligibility for ivabradine is shown in Table 1.

A total of 294 patients had baseline LVEF > 35%

Table 1. Eligibility for novel heart failure medications based on different regulations and the 2016 European Society of Cardiology guidelines

	EMA approval	TNHI regulation	2016 ESC guidelines
Sacubitril/valsartan			
Eligibility criteria	• HFrEF (LVEF ≤ 40%) • NYHA Fc II-IV	• HFrEF (LVEF ≤ 35%) • NYHA Fc II-IV • Receiving ≥ 28 days of ACEi/ARB & BB	• HFrEF (LVEF ≤ 35%) • NYHA Fc II-IV • ACEi/ARB equivalent to 20 mg of enalapril daily • Receiving optimal medical therapy unless previously documented intolerance and/or contraindication
Eligible proportion	1280 (86.8%)	434 (29.4%)	140 (9.5%)
Ineligible reason	NYHA Fc I, 194 (13.2%)	NYHA Fc I, 194 (13.2%) LVEF > 35%, 294 (19.9%) Not using ACEi or ARB or BB, 893 (60.6%)	NYHA Fc I, 194 (13.2%) LVEF > 35%, 294 (19.9%) Inadequate dosage of ACEi/ARB, 1251 (84.9%)
Ivabradine			
Eligibility criteria	• HFrEF (LVEF ≤ 40%) • NYHA Fc II-IV • Sinus rate ≥ 75 bpm	• HFrEF (LVEF ≤ 35%) • NYHA Fc II-IV • Sinus rate ≥ 75 bpm	• HFrEF (LVEF ≤ 35%) • NYHA Fc II-IV • Sinus rate ≥ 70 bpm • A HF hospital admission within the previous year
Eligible proportion	694 (47.1%)	549 (37.2%)	672 (45.6%)
Ineligible reason	NYHA Fc I, 194 (13.2%) Non sinus rhythm, 210 (14.2%) Sinus rhythm, rate < 75 bpm, 440 (29.9%)	NYHA Fc I, 194 (13.2%) LVEF > 35%, 294 (19.9%) Non sinus rhythm, 210 (14.2%) Sinus rhythm, rate < 75 bpm, 440 (29.9%)	NYHA Fc I, 194 (13.2%) LVEF > 35%, 294 (19.9%) Non sinus rhythm, 210 (14.2%) Sinus rhythm, rate < 70 bpm, 277 (18.8%)

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; BNP, B-type natriuretic peptide; EMA, European Medicines Agency; ESC, European Society of Cardiology; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA Fc, New York Heart Association Functional class; TNHI, Taiwan National Health Insurance.

(19.9%) and were therefore ineligible for ivabradine according to both TNHI regulations and ESC guidelines. A total of 194 patients (13.2%) were asymptomatic (NYHA Fc I), and a total of 210 patients (14.2%) were not in sinus rhythm, and were therefore ineligible for ivabradine according to EMA/FDA labels, TNHI regulations, and ESC guidelines. The distribution of discharge heart rate in the patients in sinus rhythm is shown in Figure 1. A total of 440 patients (29.9%) were in sinus rhythm but had a heart rate < 75 bpm, and were therefore ineligible for ivabradine according to EMA/FDA labels and TNHI regulations. A total of 277 (18.8%) were in sinus rhythm but had a heart rate < 70 bpm, and were therefore ineligible for ivabradine according to the ESC HF guidelines.

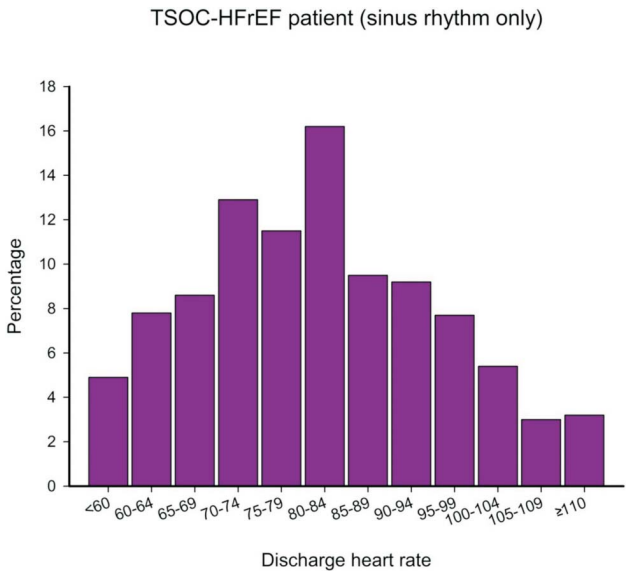

Figure 1. *The distribution of discharge heart rate (patients with sinus rhythm).*

Characteristics and outcomes according to LVEF

Both TNHI reimbursement regulation and ESC guideline criteria consider that patients are eligible for SAC/VAL and ivabradine if they have LVEF ≤ 35%, whereas the EMA/FDA labels state that SAC/VAL and ivabradine are indicated for symptomatic HFrEF (LVEF < 40%) patients. Therefore, we divided the patients into two groups according to LVEF. The baseline characteristics of the study patients with LVEF ≤ 35% and LVEF 35% to 40% are shown in Table 2.

The patients with LVEF > 35% were older (68.0 ± 14.6 y/o vs. 62.8 ± 15.9 y/o, p < 0.001) and more likely to be female (37.4% vs. 25.3%, p < 0.001) compared to those with LVEF ≤ 35%. Regarding the etiology of HF, patients with an LVEF 35% to 40% more frequently presented with ischemic cardiomyopathy (62.5% vs. 42.6%, p < 0.001). With regards to past medical history, the patients with LVEF 35% to 40% more frequently presented with a history of myocardial infarction (29.9% vs. 23.5%, p = 0.022), diabetes mellitus (49.3% vs. 42.2%, p = 0.028), and chronic kidney disease (37.4% vs. 29.2%, p = 0.006), but were less likely to have a history of HF hospitalization (32.0% vs. 42.6%, p = 0.001) and implantable cardioverter-defibrillator and/or cardiac resynchronization therapy (1.0% vs. 3.8%, p = 0.016) than those with LVEF ≤ 35%.

Generally, the mortality rate did not differ significantly between the patients with LVEF 35% to 40% and LVEF ≤ 35%. At 12 months of post-hospital discharge, the all-cause mortality rates were 15.6% and 15.8% (p = 0.876) and HF-related mortality rates were 8.9% and 10.8% (p = 0.335) in the patients with LVEF 35% to 40% and LVEF ≤ 35%, respectively. Kaplan-Meier survival curves are shown in Figure 2.

Among all patients in the TSOC-HFrEF registry, the re-hospitalization rates for worsening HF were 31.9% and 38.5% at 6 and 12 months after the index hospitalization, respectively. The 1-year readmission rates for HF in both groups were similar (33.7% in LVEF 35% to 40% patients and 39.8% in LVEF ≤ 35% patients, p = 0.061, Figure 3). The number of HF re-hospitalization was comparable in both groups (1.0 ± 0.1 times in LVEF 35% to 40% patients vs. 1.2 ± 0.0 times in LVEF ≤ 35% patients, p = 0.065).

Outcomes according to discharge heart rate

Both TNHI reimbursement regulations and EMA/FDA labels consider patients eligible for ivabradine if the sinus rate ≥ is 75 bpm, whereas the ESC guidelines state that ivabradine is indicated for patients with a sinus rate ≥ 70 bpm. Kaplan-Meier survival curves for patients with sinus rhythm stratified by discharge heart rate are shown in Figure 4. The all-cause mortality rates were 16.1%, 15.3%, and 13.6% in the patients with sinus rhythm and discharge heart rate ≥ 75 bpm, 70-74 bpm, and < 70 bpm, respectively (p = 0.454).

DISCUSSION

This study used data from the largest real-world HF

Table 2. Baseline characteristics

	LVEF ≤ 35% (n = 1,180)	LVEF 35-40% (n = 294)	p value
Age	62.8 ± 15.9	68.0 ± 14.6	< 0.001
Female	299 (25.3%)	110 (37.4%)	< 0.001
Ischemic cardiomyopathy	483 (42.6%)	175 (62.5%)	< 0.001
Left ventricular ejection fraction	25.4 ± 6.7	38.1 ± 1.4	< 0.001
Admission heart rate	93.1 ± 22.6	91.1 ± 20.6	0.164
Admission systolic blood pressure	130.1 ± 27.2	135.5 ± 27.7	0.002
Admission BMI	25.4 ± 5.1	24.6 ± 4.8	0.023
ICU admission	352 (29.8%)	120 (40.8%)	< 0.001
Discharge heart rate	80.9 ± 15.0	78.6 ± 13.5	0.011
Discharge systolic blood pressure	118.5 ± 18.4	124.0 ± 18.1	< 0.001
Discharge NYHA Fc			0.030
I	168 (14.2%)	26 (8.8%)	
II	686 (58.1%)	189 (64.3%)	
III	266 (22.5%)	70 (23.8%)	
IV	60 (5.1%)	9 (3.1%)	
Discharge GFR	60.0 ± 40.9	56.4 ± 35.6	0.148
Past medical history			
Old myocardial infarction	277 (23.5%)	88 (29.9%)	0.022
Previous HF hospitalization	503 (42.6%)	94 (32.0%)	0.001
Valvular surgery	57 (4.8%)	10 (3.4%)	0.293
Stroke/TIA	102 (8.6%)	32 (10.9%)	0.232
Peripheral arterial disease	74 (6.3%)	22 (7.5%)	0.451
Atrial fibrillation	307 (26.0%)	73 (24.8%)	0.677
CRT/ICD	45 (3.8%)	3 (1.0%)	0.016
Hypertension	406 (34.4%)	101 (34.4%)	0.986
Hypercholesterolemia	254 (21.5%)	78 (26.5%)	0.066
Diabetes mellitus	498 (42.2%)	145 (49.3%)	0.028
Chronic kidney disease	344 (29.2%)	110 (37.4%)	0.006
COPD/asthma	127 (10.8%)	32 (10.9%)	0.952
Hyperthyroidism	29 (2.5%)	8 (2.7%)	0.796
Hypothyroidism	25 (2.1%)	5 (1.7%)	0.650
Cancer with chemotherapy	32 (2.7%)	8 (2.7%)	0.993

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA Fc, New York Heart Association Functional class; TIA, transient ischemic attack.

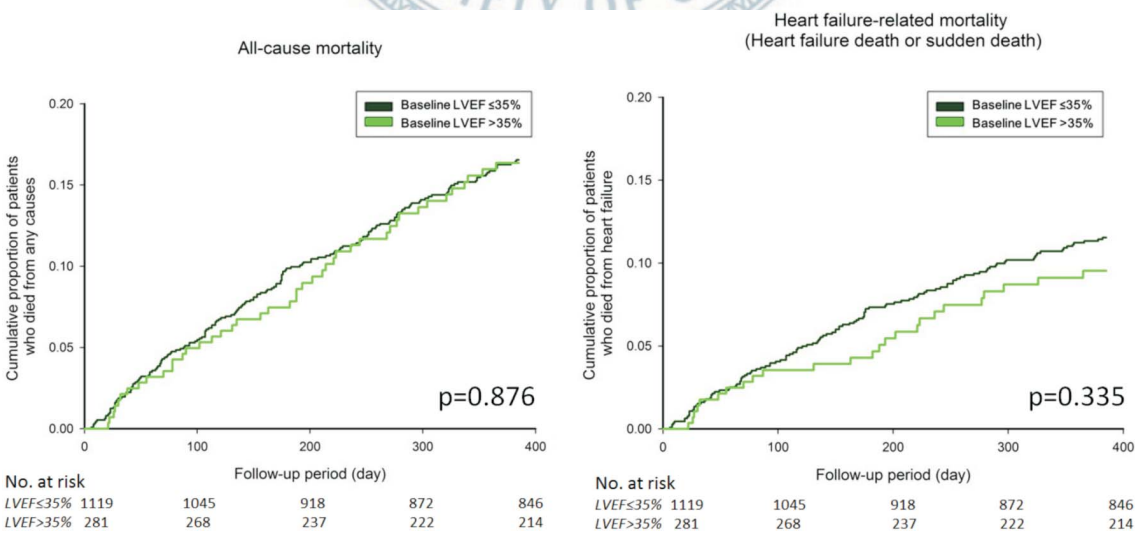

Figure 2. *Kaplan-Meier survival curves of all-cause mortality and HF-related mortality. HF, heart failure; LVEF, left ventricular ejection fraction.*

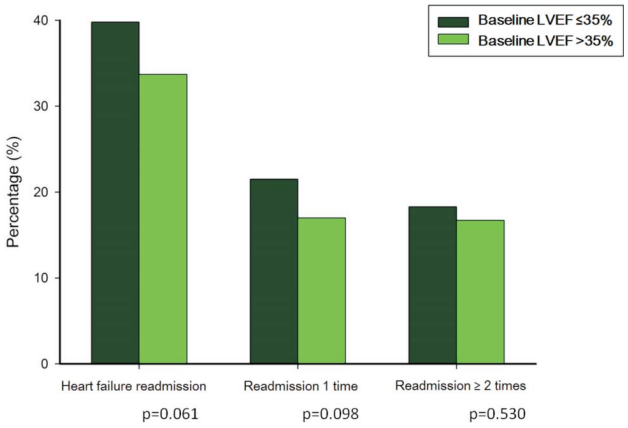

Figure 3. *The one-year readmission rates for HF in patients with baseline LVEF ≤ 35% and LVEF > 35%. HF, heart failure; LVEF, left ventricular ejection fraction.*

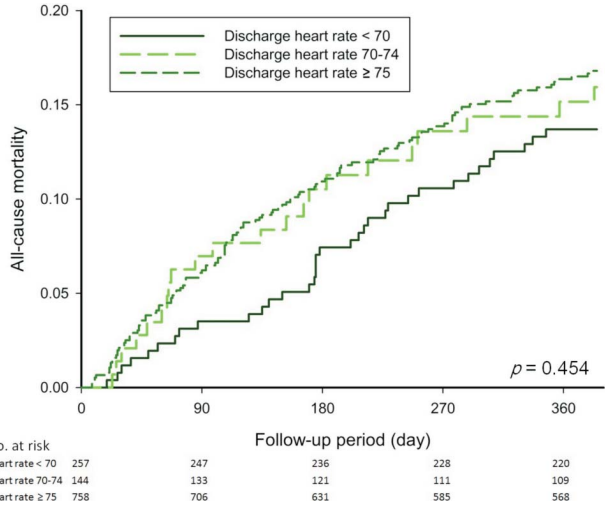

Figure 4. *Kaplan-Meier curves of death from any causes stratified according to discharge sinus rate.*

cohort in Taiwan, and showed that 86.8% of the patients met the EMA/FDA label criteria for SAC/VAL treatment, compared to only 29.4% for the TNHI reimbursement regulations and 9.5% for the ESC guideline criteria. This wide range of eligibility depended on the background dose of ACEis/ARBs and different LVEF cut-off values. Although not contraindicated, a total of 23.9% of the TSOC-HFrEF patients had a baseline glomerular filtration rate < 30 ml/min, and this may have hindered physicians from prescribing ACEis/ARBs. Patients in the TSOC-HFrEF registry did receive a suboptimal dose of ACEis/ARBs,[20] but since only 9.5% of the patients met the relatively strict ESC guidelines for up-titration to an optimal dose of ACEis/ARBs, 20 mg daily equivalent dose of enalapril may not be a suitable threshold for Taiwanese patients. A similar situation was observed in the ESC-EORP-HFA Long-Term HF Registry between March 2011 and November 2013. In this European HF registry, only 12% of the patients met the ESC guideline eligibility criteria for SAC/VAL treatment, but when a daily requirement of ACEis/ARBs decreased to 10 mg enalapril (instead of 20 mg), eligibility rose from 12% to 28%.[21]

On the other hand, the regulatory labels for SAC/VAL in both the EMA and USA FDA are more flexible. Neither of them require any specific dose of ACEis or ARBs.[13,14] The TNHI reimbursement regulations also do not require any specific ACEi or ARB dose but do require concurrent ACEi or ARB and beta-blocker treatment. Consequently, patients who could not tolerate beta-blocker for any reason were ineligible for SAC/VAL treatment according to the TNHI regulations. In the ESC guidelines, optimal medical therapy including beta-blockers and MRAs are recommended before SAC/VAL treatment, but the ESC guidelines are relatively liberal and allow exceptions such as drug intolerance or contraindications.

The cut-off value of LVEF 35% was another major factor for the diverse eligibility. The use of LVEF in characterizing patients in clinical practice and research in HF is important. The PARADIGM-HF trial enrolled patients with HF symptoms and LVEF ≤ 40%, and 11.4% of the patients had baseline LVEF > 35%. The p-value for the interaction of the primary endpoint (death from cardiovascular causes or hospitalization for HF) between the patients whose baseline LVEF was ≤ 35% and > 35% was 0.36.[12] This result demonstrated that the effect of SAC/VAL was consistent across these two patient subgroups. In another analysis of the PARADIGM-HF trial, the 5-year estimated number needed-to-treat for the primary outcome of cardiovascular death or HF hospitalization was 18, compared to 23 for all-cause mortality with SAC/VAL in addition to ACEis for patients with LVEF 35-40%.[22] In a pre-specified pooled analysis of 13,195 patients with HF enrolled in the PARADIGM-HF (LVEF ≤ 40%; n = 8,399) and PARAGON-HF (LVEF ≥ 45%; n = 4,796) trials, all randomized patients were divided according to the following LVEF categories: ≤ 22.5%, > 22.5% to 32.5%, > 32.5% to 42.5%, > 42.5% to 52.5%, > 52.5% to 62.5%, and > 62.5%.[23] They evaluated the time to first cardiovascular death and HF hospitalization, all HF hospitalizations, all-cause mortality, and non-cardiovascular mortality. All

outcomes of the three subgroups in which LVEF ≤ 42.5% appeared to benefit from SAC/VAL treatment compared with renin angiotensin system inhibitors. Moreover, the clinical impact of SAC/VAL treatment in patients with LVEF > 32.5% to 42.5% was not inferior to the other two subgroups with lower LVEF. These data support the recommendations for SAC/VAL therapy for patients with LVEF 35-40%.

In our study, the patients with baseline LVEF 35% to 40% had similar 1-year all-cause mortality rates and HF-related mortality rates compared to those with baseline LVEF ≤ 35%. The patients with baseline LVEF ≤ 35% had a numerically higher 1-year HF readmission rate than those with LVEF 35% to 40%, but the difference was not statistically significant. In particular, the 1-year re-hospitalization rates for HF were more than 30% regarding baseline LVEF, emphasizing that timely and effective therapy should be initiated in these patients. In the PARADIGM-HF trial, SAC/VAL was superior to enalapril in reducing HF hospitalization by 21%, and this effect was observed from the first 30 days after randomization. The PIONEER-HF trial also showed that SAC/VAL reduced NT-proBNP to a greater degree compared with enalapril among eligible patients who were admitted with acute decompensated HF [-46.7% vs. -25.3%, hazard ratio 0.71, 95% confidence interval 0.63-0.81, $p < 0.001$].[24,25] In addition, re-hospitalization for HF was 44% lower than in the enalapril group, and this substantial reduction occurred as early as 1 week after initiating treatment. Hence, the early initiation of SAC/VAL treatment is reasonable and should be considered in stabilized acute decompensated HF patients.

Overall, 47.1% of the TSOC-HFrEF patients met the EMA/FDA label criteria, 45.6% met the ESC guideline criteria, while only 37.2% met the TNHI reimbursement regulation criteria for ivabradine. This diversity in eligibility was related to different LVEF cut-off values and was associated with different heart rate cut-off values. As mentioned above, the patients with LVEF 35% to 40% were at a similar risk to those with LVEF ≤ 35%. Further, Kaplan-Meier survival curves showed that the patients with discharge sinus rate < 70 bpm had numerically better outcomes, whereas the mortality rates were similar in the patients with a sinus rate of 70 to 74 bpm and those with a sinus rate ≥ 75 bpm at discharge. The ASCEND-HF trial enrolled 2,906 patients, and demonstrated that those with a sinus rate ≥ of 70 bpm at discharge had a significantly lower survival rate than those with a sinus rate < 70 bpm.[26] The initiation of ivabradine before discharge has been shown to reduce the risk of re-hospitalization following hospitalization for HF, and this strategy was recommended by the 2019 focused update of the TSOC HF guidelines.[27,28]

The current study has several limitations. First, considering health insurance budget limitations, it may not be relevant to compare the insurance reimbursement system with clinical guidelines directly. However, the findings of this study emphasized that the risks were high among all HF patients regardless of LVEF and sinus rate, so treatment should be personalized but not merely follow the regulations. Second, the TSOC-HFrEF registry did not record the reason for not prescribing ACEis/ARBs, beta-blockers, and MRAs. Patients not using these drugs may have chronic kidney disease, hypotension, or other comorbidities, which may have contributed to selection bias.

CONCLUSIONS

According to the TSOC-HFrEF registry, 70.6% of the patients were ineligible for SAC/VAL, and 61.8% of the patients were ineligible for ivabradine according to the TNHI reimbursement regulations. However, the patients had equally high rates of 1-year mortality and HF re-hospitalization regardless of the cut-off values of 35% (by LVEF) or 75 bpm (by heart rate in sinus rhythm). The high incidence of adverse events in this registry indicated no “mild” HF patients, and timely escalation therapy with SAC/VAL and/or ivabradine should be considered once clinically indicated.

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CONFLICT OF INTEREST

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