Int J Heart Fail. 2019 Oct;1(1):57-68
https://doi.org/10.36628/ijhf.2019.0007
pISSN 2636-154X·eISSN 2636-1558

International Journal of Heart Failure
IJHF

Original Article

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Real-World Eligibility for Sacubitril/Valsartan in Heart Failure with Reduced Ejection Fraction Patients in Korea: Data from the Korean Acute Heart Failure (KorAHF) Registry

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OPEN ACCESS

Received: Sep 16, 2019
Revised: Oct 6, 2019
Accepted: Oct 7, 2019

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ABSTRACT

Background and Objectives: Sacubitril/valsartan (SV, LCZ696), the first in class drug, called as angiotensin receptor-neprilysin inhibitor (ARNI) can reduce heart failure (HF) hospitalization and cardiovascular mortality. However, SV prescription rate remains still low despite current HF guideline recommendations. Considering the complex inclusion criteria of Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, the real-world eligibility for SV remains uncertain in Asian heart failure with reduced ejection fraction (HFrEF) patients. Therefore, we aimed to assess real-world HF population eligibility for SV in a large Korean acute HF registry.
Methods: From March 2011 to February 2014, a total of 5,625 patients who were admitted for HF were enrolled in Korea. After excluding HF patients with left ventricular ejection fraction >40% and in-hospital death, 2,941 patients were analyzed. Criteria for SV based on Korean Food and Drug Administration (KFDA) label and PARADIGM-HF were applied.
Results: Of 2,941 patients, KFDA label criteria excludes the absence of symptoms (New York Heart Association class I, 20%); PARADIGM-HF criteria excludes chronic kidney disease stage IV (9%), hyperkalemia (1%), hypotension (6%), and sub-optimal pharmacotherapy (52%, e.g. lower dose use of angiotensin converting enzyme inhibitor/angiotensin receptor blocker [ACEI/ARB], beta blocker use). When a daily requirement of ACEI/ARB ≥5 mg

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Funding

This work was supported by grants from Research of Korea Centers for Disease Control and Prevention (2010-E63003-00, 2011-E63002-00, 2012-E63005-00, 2013-E63003-00, 2014-E63003-01, 2015-E63003-02, 2016-ER6303-00, and 2017-ER6303-01).

Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Oh J, Choi DJ, Jeon ES, Cho MC, Oh BH, Kang SM; Data curation: Oh J, Lee SE; Formal analysis: Oh J; Funding acquisition: Choi DJ, Jeon ES, Cho MC, Oh BH, Kang SM; Investigation: Lee CJ, Choi DJ, Cho MC, Oh BH, Kang SM; Methodology: Oh J, Kang SM; Project administration: Lee CJ, Park JJ, Lee SE, Kim MS, Cho HJ, Choi JO, Lee HY, Hwang KK, Kim KH, Yoo BS, Choi DJ, Baek SH, Jeon ES, Kim JJ, Cho MC, Chae SC, Oh BH, Kang SM; Resources: Oh J; Writing - original draft: Oh J, Kang SM.

enalapril (instead of ≥10 mg) was used, the percent of eligibility for SV rose from 12% to 30% based on the PARADIGM-HF criteria.

Conclusions: Among the Korean hospitalized HFrEF patients, 80% met KFDA label criteria, while only 12% met the inclusion criteria of PARADIGM-HF trial for SV if requiring ≥10 mg enalapril. Sub-optimal pharmacotherapy could be the main reason for ineligible SV use based on the PARADIGM-HF criteria.

Keywords: Sacubitril-valsartan; Heart failure; Drung therapy; Patient care

INTRODUCTION

Sacubitril/valsartan (SV, LCZ696) is the first in class drug, called as angiotensin receptor-neprilysin inhibitor (ARNI).[1)2)] In the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, SV reduced heart failure (HF) hospitalization and cardiovascular mortality compared to angiotensin converting enzyme inhibitor (ACEI), enalapril.[3)] Based on these results, the current United States, European and Korean guidelines recommend SV use for the patients with heart failure with reduced ejection fraction (HFrEF),[4-6)] and both the Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved SV for symptomatic HFrEF patients. In Korea, SV was approved by Korean Food and Drug Administration (KFDA) in April 2016 then we can use SV under insurance coverage from October 2017.[2)] However, the inclusion criteria of PARADIGM-HF trial were complex, requiring symptomatic HF (New York Heart Association [NYHA] class II–IV), left ventricular ejection fraction (LVEF) ≤40% (later amended to ≤35%), elevated natriuretic peptides (NPs) levels, a dose of ACEI or angiotensin receptor blocker (ARB) equivalent to ≥10 mg of enalapril daily dose for the run-in and ≥20 mg of enalapril daily dose for randomization, and beta-blocker (BB) therapy as tolerated according to current HF guidelines.[3)] So, HFrEF patients not meeting the enrollment criteria of PARADIGM-HF could be also eligible for SV use on the basis of current FDA/EMA and KFDA approval.[7)] It could be the reason why SV prescription rate remains still low despite current HF guideline recommendations.[8)] So many researchers have paid more attention to the difference in HF patients from between real-world or registry vs. clinical trial.

There has been known differences in clinical characteristics between Western and Asian HF patients.[9-14)] Although the PARADIGM-HF trial also enrolled Asian HFrEF patients, the real-world eligibility for SV remains uncertain in Asian HFrEF patients especially for large sample-sized population. Therefore, we aimed to assess in a large, Korean real-world HF population eligibility for SV according to the inclusion criteria of PARADIGM-HF and the current HF guideline/label criteria. For this analysis, we enrolled HF patients after discharge from acute decompensated heart failure (ADHF) from the Korean Acute Heart Failure (KorAHF) registry considering inborn limitation of study population.

METHODS

Study design and population

The KorAHF registry is a multicenter prospective cohort study in Korea.[11)] Briefly, patients were consecutively enrolled on initial admission for ADHF and followed-up at outpatient clinic. Patients who have signs or symptoms of HF and one of the following criteria are

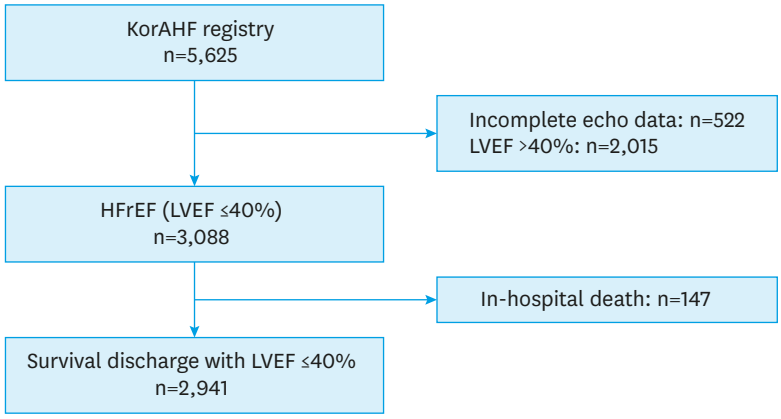

Figure 1. Study population.
HFrEF = heart failure with reduced ejection fraction; KorAHF = Korean Acute Heart Failure; LVEF = left ventricular ejection fraction.

acceptable for the study: 1) pulmonary congestion or 2) objective findings of left ventricular systolic dysfunction or structural heart disease. The study protocol was approved by the ethics committee at each hospital (4-2011-0075). More detailed information on the study design and results of the KorAHF registry were described previously.[11][12] From March 2011 to February 2014, a total of 5,625 patients who were admitted for ADHF were enrolled consecutively in 10 tertiary university hospitals in Korea. Among them, we selected patients with HFrEF, which was defined as LVEF ≤40% using echocardiography. After excluding 522 patients without quantitative LVEF data and 2,015 patients with LVEF >40% and 147 patients with in-hospital death or heart transplantation, 2,941 patients were analyzed (**Figure 1**). Estimated glomerular filtration rate (eGFR) was calculated by Modification of Diet in Renal Disease (MDRD) equation.[15]

On-treatment angiotensin converting enzyme inhibitor/angiotensin receptor blocker/enalapril equivalent dose

In the KorAHF registry, patients administered with various types of ACEI/ARB so we have to adjust these ACEI/ARB dose to enalapril equivalent dose according to the pre-specified criteria used in Safety and Tolerability of Initiating LCZ696 in Heart Failure Patients (TITRATION) trial as follows (**Table 1**).[16] 'High-dose' received a total daily dose >160 mg of valsartan or >10 mg of enalapril, or equivalent doses of other ARBs or ACEIs, respectively; 'low-dose' received a total daily dose ≤160 mg of valsartan or ≤10 mg of enalapril, or equivalent. Drug administration doses were collected at discharge, and during follow-up (30 days, 3 months, 6 months, and 1 years) and average on-treatment ACEI/ARB dose was calculated from enalapril equivalent dose at discharge and at each follow-up before the occurrence of an event. With the same method, we can calculate on-treatment blood pressure (BP) using BP at discharge and at each follow-up before the occurrence of an event.[17]

Statistical analysis

All data were analyzed using the SPSS 25.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as number (percentages) and continuous variables as means±standard deviation (SD). Normally distributed continuous variables were compared using one-way analysis of variance, and categorical variables were compared using χ^2 tests. The p value of <0.05 was considered statistically significant.

https://doi.org/10.36628/ijhf.2019.0007

Table 1. Definition of low-dose and high-dose ACEI/ARB inhibition strata based on pre-study ACEI/ARB total daily dose at screening

Medication	Low-dose RAAS inhibitor stratum	High-dose RAAS inhibitor stratum
ACEIs		
Enalapril	≤10	>10
Captopril	≤100	>100
Cilazapril	≤2.5	>2.5
Imidapril	≤10	>10
Lisinopril	≤10	>10
Perindopril	≤4	>4
Ramipril	≤5	>5
ARBs		
Candesartan	≤16	>16
Eprosartan	≤400	>400
Fimasartan	≤60	>60
Irbesartan	≤150	>150
Losartan	≤50	>50
Olmesartan	≤10	>10
Telmisartan	≤40	>40
Valsartan	≤160	>160

All dose units are based on mg.
ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; RAAS = Renin-Angiotensin-Aldosterone System.

RESULTS

Baseline clinical characteristics

The baseline characteristics of 2,941 HFrEF outpatients of the KorAHF registry are shown in **Table 2**. Mean age was 66±15 years old and more than half had a history of hypertension and approximately one third had diabetes. Patients in our registry were similar with those in European Society of Cardiology-EURObservational Research Programme-Heart Failure Association Heart Failure Long-Term (ESC-EORP-HFA HF-LT) registry regarding age, prevalence of ischemic origin HF & hypertension and to those in PARADIGM-HF regarding age, LVEF and eGFR.[18] The patients enrolled in the KorAHF registry were more female, diabetes and had lower body mass index (BMI), systolic blood pressure (SBP) and higher natriuretic peptide levels compared those with ESC-EORP-HFA HF-LT registry and PARADIGM-HF trial. Regarding HF guideline-directed medical therapy (GDMT) in the KorAHF HFrEF patients vs. ESC-EORP-HFA HF-LT or PARADIGM-HF, patients were less likely to use BB and mineralocorticoid receptor antagonist (MRA) and had implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT).

On-treatment angiotensin converting enzyme inhibitor/angiotensin receptor blocker/enalapril equivalent daily dose

Table 3 showed the representative data for ACEI/ARB daily dose and switched enalapril equivalent daily dose at discharge. In the KorAHF registry, more ARBs (40.1%) were used for HFrEF patients than ACEIs (36.5%). The most commonly prescribed ACEI was perindopril (37.2%), followed by ramipril (35.6%) & captopril (18.3%) and the most commonly prescribed ARB was candesartan (35.6%), followed by losartan (30.1%) & valsartan (20.1%). The prescription rates of current American College of Cardiology/American Heart Association (ACC/AHA; captopril, enalapril, lisinopril, perindopril, ramipril) and ESC (captopril, enalapril, lisinopril, ramipril) HF guideline recommended ACEI use was 99.3% and 62.1%, respectively. Those for ARB were 85.8% for both ACC/AHA and ESC HF guideline

https://doi.org/10.36628/ijhf.2019.0007

Table 2. Baseline characteristics in Korean AHF Registry and ESC-EORP-HFA HF-LT Registry and in PARADIGM-HF patients

Characteristics	KorAHF (n=2,941)	ESC-EORP-HFA HF-LT (n=5,443)	PARADIGM-HF (n=8,339)
Male	60%	78%	78%
Age (years)	66±15	64±13	64±11
BMI (kg/m^2)	23.2±3.8	27.8±4.9	28.2±5.5
Ischemic origin	44.8%	47%	60%
Diabetes	41.2%	15%	13%
Hypertension	58.5%	56%	71%
COPD	10.4%	15%	13%
SBP (mmHg)	113±17	121±20	121±15
NYHA functional classification			
I	17%	16%	5%
II	72%	55%	70%
III	7%	26%	24%
IV	4%	2%	1%
LVEF (%)	27.1±7.6	-	29.5±6.2
≤15%	7.3%	5%	-
15–20%	14.2%	13%	-
21–25%	20.5%	18%	-
26–30%	20.8%	28%	-
31–35%	20.9%	24%	-
36–40%	16.3%	12%	-
eGFR (mL/min/1.73m^2)	72.2±36.8	-	70.0±20.0
≥60	63.1%	56%	-
45–59	15.5%	23%	-
30–44	10.4%	15%	-
<30	10.9%	7%	-
Potassium (mmol/L)	4.2±0.5	4.5±0.5	4.5±0.5
Hemoglobin (g/dL)	12.4±2.2	13.5±1.8	-
BNP (pg/mL)	847 [428–1,721]	348 [128–862]	-
NT-proBNP (pg/mL)	5,068 [2,386–12,526]	1,608 [646–3,939]	1,631 [885–3,154] for LCZ696 1,594 [886–3,305] for enalapril
HF treatments			
ACEI	36.5%	69%	78%
ARB	40.1%	21%	23%
BB	57.3%	90%	93%
MRA	53.1%	63%	56%
Loop diuretics	78%	96%	80%
ICD	4%	23%	23%
CRT	2%	18%	7%

Continuous data presented as mean±standard deviation or median [interquartile range], as appropriate. Categorical data presented as proportions. Data adapted from reference 23.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; BMI = body mass index; BNP = B-type natriuretic peptide; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; EORP = EURObservational Research Programme; ESC = European Society of Cardiology; HF = heart failure; HFA = Heart Failure Association; HF-LT = Heart Failure Long-Term; ICD = implantable cardioverter defibrillator; KorAHF = Korean Acute Heart Failure registry; LCZ696 = sacubitril/valsartan; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PARADIGM-HF = Prospective Comparison of ARNi with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure.

(candesartan, valsartan, losartan). Based on the pre-specified criteria used in TITRATION trial (**Table 1**), we switched each ACEI/ARB dose to enalapril equivalent dose. This equivalent daily dose was similar in ACEI and ARB group in the KorAHF registry. More potent blood pressure-lowering ARBs (e.g. telmisartan, olmesartan) were used in higher enalapril equivalent daily dose.

https://doi.org/10.36628/ijhf.2019.0007

Table 3. ACEI/ARB daily dose and enalapril equivalent daily dose at discharge

Medication	Prevalence	ACEI/ARB daily dose (mg)	Enalapril equivalent daily dose (mg)
ACEIs			
Enalapril	5.4	7.3±3.9	7.3±3.9
Captopril	18.3	42.4±49.4	4.2±4.9
Cilazapril	0.1	2.5±0.0	7.3±3.9
Imidapril	0.6	8.3±4.9	8.3±4.9
Lisinopril	2.8	8.5±3.7	8.5±3.7
Perindopril	37.2	3.7±1.9	9.3±4.7
Ramipril	35.6	3.8±2.5	7.7±5.1
ARBs			
Candesartan	35.6	9.5±6.9	5.9±4.3
Eprosartan	0.8	510.0±144.59	12.8±3.6
Fimasartan	3.1	56.7±26.6	9.4±4.4
Irbesartan	1.9	218.2±86.3	14.5±5.8
Losartan	30.1	46.5±24.2	9.3±4.8
Olmesartan	1.0	25.8±19.8	25.8±19.8
Telmisartan	7.4	52.2±27.3	13.0±6.8
Valsartan	20.1	88.9±61.4	5.6±3.8

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker.

Eligibility for the inclusion criteria of PARADIGM-HF trial

Table 4 showed the eligibility for the inclusion criteria of PARADIGM-HF trial. Among the 2,491 patients with HFrEF, there were 80% symptomatic patients (NYHA class II–IV) at discharge. In overall, 11% patients had advanced chronic kidney disease (CKD, eGFR < 30 mL/min/1.73m^2) and 9% patients had lower SBP (<95 mmHg) and only 1 patient had hyperkalemia (Serum K^+ >5.4 mmol/L). However, about 60% patients did not take BB nor MRA and more than 65% patients were administered lower dose of ACEI/ARB (enalapril equivalent dose <10

Table 4. Eligibility for the inclusion criteria of PARADIGM-HF trial

PARADIGM-HF criteria	Prevalence
Single criteria	
a. Age ≥18 years	100%
b. LVEF ≤40%	100%
c. NYHA class II–IV	80%
d. eGFR ≥30 mL/min/1.73m^2	89%
e. Serum K+ ≤5.4 mmol/L	99%
f. SBP, mmHg ≥95 mmHg	91%
g. Equivalent more than enalapril 10 mg/day	34%
h. BB treatment	57%
i. MRA treatment	53%
Combination criteria	
a + b + c + d	71%
a + b + c + d + e	70%
a + b + c + d + e + f	64%
a + b + c + d + e + f + g	18%
a + b + c + d + e + f + g′	39%
a + b + c + d + e + f + g + h	12%
a + b + c + d + e + f + g′ + h	30%
a + b + c + d + e + f + g + h + i	7%
a + b + c + d + e + f + g′ + h + i	15%
a + b + c + d + e + f + h + i	23%
a + b + c + d + e + g′	43%

Means equivalent more than enalapril 5 mg/day.
BB = beta-blocker; eGFR = estimated glomerular filtration rate; g′ = equivalent more than enalapril 5 mg/day; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; PARADIGM-HF = Prospective Comparison of ARNi with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure; SBP = systolic blood pressure.

https://doi.org/10.36628/ijhf.2019.0007

mg/day). When combining these criteria, 9% were excluded from advanced CKD, 1% from hyperkalemia, 6% from lower SBP and 46% were excluded from lower dose of ACEI/ARB use. In addition, 6% and 5% were excluded from BB and MRA non-users, respectively. So, we changed the ACEI/ARB criteria from enalapril 10 to 5 mg/day and reanalyzed. Then, we could find the increase of eligible patients from 7% to 15% (with both BB and MRA use), from 12% to 30% (with only BB use), from 18% to 39% (without neither BB nor MRA use).

Among the PARADIGM-HF inclusion criteria, we found that lower dose use for ACEI/ARB and lower SBP were clinical barriers to be ineligible so further analysed regarding these 2 factors. Firstly, we compared clinical characteristics between low-dose and high-dose ACEI/ARB inhibition strata based on current definition (**Table 5**). To be enrolled in the PARADIGM-HF trial, patients should be tolerated to, at least, enalapril 10 mg/day. So, we divided into 2 groups based on this daily dose of enalapril. Low-dose ACEI/ARB inhibition group showed higher age, eGFR and lower BMI, SBP, and LVEF compared with high-dose group. The prevalence of diabetes & hypertension was lower and the prescription rate of MRA and loop diuretics at discharge was higher in low-dose ACEI/ARB inhibition strata. Then we analyzed regarding on-treatment SBP during outpatient clinic (**Table 6**). Only when the patients' SBP was higher than 95 mmHg, they could be screened in the PARADIGM-HF trial. That is why we defined the SBP cut-off value as 95 mmHg. Lower SBP group showed higher eGFR and lower age, BMI, SBP, and LVEF compared to higher SBP group. The prevalence of diabetes

Table 5. Clinical characteristics regarding on-treatment enalapril equivalent daily dose 10 mg (low-dose vs. high-dose ACEI/ARB inhibition strata)

Characteristics	Enalapril ≤10 mg (n=1,575)	Enalapril >10 mg (n=820)	p value
Male	60.5%	60.6%	0.965
Age (years)	66±14	65±15	0.014
BMI (kg/m^2)	23.1±3.6	24.0±4.1	<0.001
Ischemic origin	40.7%	41.0%	0.896
Diabetes	38.7%	44.0%	0.012
Hypertension	53.5%	70.5%	<0.001
COPD	10.5%	10.7%	0.889
SBP (mmHg)	112±14	121±15	<0.001
<95	11.5%	4.6%	<0.001
NYHA class II/III	71.9%/5.6%	70.7%/7.8%	-
LVEF (%)	26.8±7.5	27.8±7.6	0.002
31–35%	85.4%	82.1%	0.038
36–40%	14.6%	17.9%	-
eGFR (mL/min/1.73m^2)	75.1±35.1	71.0±38.4	0.009
<30	7.1%	13.4%	<0.001
Potassium (mmol/L)	4.2±0.5	4.2±0.5	0.787
>5.4	1.1%	0.9%	0.672
Hemoglobin (g/dL)	12.5±2.1	12.5±2.3	0.628
BNP (pg/mL)	859 [438–1,663]	730 [402–1,712]	0.557
NT-proBNP (pg/mL)	4,549 [2,081–10,532]	4,839 [2,041–12,696]	0.384
ACEI	45.4%	43.8%	0.462
ARB	47.9%	51.6%	0.093
BB	59.7%	63.7%	0.064
MRA	58.2%	50.6%	<0.001
Loop diuretics	81.4%	76.1%	0.009

Continuous data presented as mean±standard deviation or median [interquartile range], as appropriate. Categorical data presented as proportions.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; BMI = body mass index; BNP = B-type natriuretic peptide; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure.

https://doi.org/10.36628/ijhf.2019.0007

Table 6. Clinical characteristics regarding on-treatment SBP

Characteristics	SBP <95 mmHg (n=262)	SBP ≥95 mmHg (n=2,675)	p value
Male	59.5%	60.2%	0.843
Age (years)	64±15	66±15	0.011
BMI (kg/m^2)	22.1±3.6	23.3±3.8	<0.001
Ischemic origin	40.8%	41.7%	0.793
Diabetes	30.5%	42.3%	<0.001
Hypertension	33.2%	61.0%	<0.001
COPD	9.2%	10.5%	0.595
SBP (mmHg)	89±4	117±13	<0.001
<95	11.5%	4.6%	<0.001
NYHA class II/III	66.7%/5.9%	72.8%/6.5%	-
LVEF (%)	23.9±7.6	27.4±7.5	<0.001
31–35%	90.8%	83.1%	0.001
36–40%	9.2%	16.9%	-
eGFR (mL/min/1.73m^2)	80.0±34.0	71.5±37.0	<0.001
<30	5.3%	11.5%	0.002
Potassium (mmol/L)	4.2±0.5	4.5±0.5	0.239
>5.4	0.8%	1.0%	>0.999
Hemoglobin (g/dL)	12.2±2.0	12.4±2.2	0.201
BNP (pg/mL)	814 [438–1,964]	851 [425–1,720]	0.889
NT-proBNP (pg/mL)	5,627 [2,469–12,502]	4,977 [2,374–12,538]	0.343
ACEI	32.8%	36.9%	0.202
ARB	46.6%	39.4%	0.029
BB	46.9%	58.3%	<0.001
MRA	69.5%	51.5%	<0.001
Loop diuretics	84.0%	77.5%	0.045

Continuous data presented as mean±standard deviation or median [interquartile range], as appropriate. Categorical data presented as proportions.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; BMI = body mass index; BNP = B-type natriuretic peptide; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SBP = systolic blood pressure.

and hypertension was lower and the prescription rate of MRA and loop diuretics at discharge was higher in low SBP group, but BB administration rate was lower in low SBP group.

DISCUSSION

Among the Korean acute HFrEF patients, 80% met KFDA label criteria, while only 12% met the inclusion criteria of PARADIGM-HF trial for SV if requiring ≥10 mg enalapril. Then we found that sub-optimal pharmacotherapy was the main reason for ineligible SV use based on the PARADIGM-HF criteria in Korea HF population.

SV is the first in class drug, called ARNI,[1)2)] and the PARADIGM-HF trial clearly demonstrated that SV reduced HF hospitalization and cardiovascular mortality compared to current ACEI/ARB.[3)] Following this study, up-to date both ACC/AHA and ESC HF guidelines strongly recommend SV use for HFrEF patients. However, the limited clinical application of SV even after current HF guidelines' recommendation has been documented in the Western population. The report from United States using data from Change the Management of Patients With Heart Failure (CHAMP-HF) registry showed that only 15% patients were administered SV (ACEI/ARB for 59%).[8)] They found that patients prescribed SV were younger, had lower LVEF, less likely to have CKD and more likely to have cardiac resynchronization therapy (CRT). Currently on-going prospective registry, Study of real-world treatment patterns and patients reported outcomes in

https://doi.org/10.36628/ijhf.2019.0007

heart failure patients in Korea (SPARK), can reveal the Korean real-world trend for SV use soon or later. It could inform useful clinical data for Asian HF population.

In general, the gap between randomized controlled trial (RCT) and real-world data is inevitable considering limited medical and economic resources for RCT. So many researchers have paid attention to real-world evidences following RCT evidences. Regarding SV eligibility, there have been many publications in Western population but there have been no reports in Asian population as far as we know.[18-23] Recently-published large, European registry data showed that sub-optimal pharmacotherapy was the main reason for SV ineligibility for PARADIGM-HF criteria[18] and it was consistent with our findings (only 12% met the PARADIGM-HF criteria and sub-optimal pharmacotherapy accounted for 52% ineligibility). In our study, only one third patients tolerated to enalapril 10 mg daily dose and very few patients could use target dose of ACEI/ARB (e.g. enalapril 40 mg daily in ESC HF guideline). In addition, previous studies also reported that GDMT for HF was related to improved clinical outcomes in both chronic and acute HFrEF patients in Korea.[24-26] Therefore, our findings highlight that the need for better strategies to integrate GDMT in a real-world, especially for target medication dose in Korean population.

There has been known differences in clinical characteristics between Western and Asian HF patients. Our data (**Table 2**) showed comparable findings with previous studies, which found Asian HF patients had lower BMI, SBP, ischemic origin HF and higher use of ARB (rather than ACEI) than Western population.[9][11][27][28] That could be why Asian HF patients are usually prone to lower dose of GDMT use like as finding from our study. In another point of view, HF patients with low SBP or low tolerated ACEI/ARB dose may be high risk patients. Current guidelines defined advanced heart failure as low SBP (< 100 mmHg), low dose of GDMT or cannot tolerated GDMT considering severe pump failure status. So, the patients who could not be enrolled in the PARADIGM-HF trial may be advanced HF patients. It suggests that we do not have enough clinical evidence for SV administration for advanced HF patients. However, recent report from the CHAMP-HF registry showed that the number of advanced practice providers was related with SV use after multivariate adjusting.[8] It seems that physicians prescribe SV more for advanced HF although lack of clinical evidence. However, a recently-published Taiwan study demonstrated that in patients with baseline SBP lower than 100 mmHg, there were no significant differences in clinical outcomes between SV and ACEI/ARB groups.[29] Therefore, the ongoing trial (EntrestoTM (LCZ696) In Advanced Heart Failure; LIFE, NCT02816736) which evaluate the clinical role of SV in advanced HF patients will uncover these unmet needs and further prospective study should be warranted to support the clinical evidence of SV use beyond inclusion criteria of the PARADIGM-HF trial.

The clinical evidence for GDMT for HF in CKD population was limited especially in patients with advanced CKD (stage 4 & 5, eGFR <30 mL/min/m^2) and end stage of renal disease (ESRD). However, many patients have administered GDMT (e.g. ACEI or ARB) like as non-CKD HF patients in real world. In our study, 9% HF patients were ineligible for PARADIGM-HF criteria based on advanced CKD/ESRD (**Table 4**). Regarding the clinical evidence of SV in these population, the PARADIGM-HF trial could not answer these issues. So, the efficacy and safety of SV in these population remains uncertain. A recently published retrospective study demonstrated that in patients with advanced CKD (eGFR <30 mL/min/m^2), SV treatment lowered cardiovascular death or HF hospitalizations by 28%.[29] Therefore, further prospective study should be warranted to examine the effect and safety of SV in HFrEF patients with advanced CKD and ESRD.

Regarding LVEF, the ESC guideline recommends SV use in patients with LVEF ≤35%, but the PARADIGM-HF trial enrolled patients with LVEF ≤40%. In Korea, the label criteria for LVEF was 35% following the ESC guideline at the start of approval. Since September 2019, the Korean government widened the SV use criteria under insurance coverage, LVEF from 35% to 40%. In our study, there were 16% patients in LVEF group from 35% to 40% so these group can get benefit from SV treatments nowadays.

Our study does not go without limitations. Firstly, the patients in this study were not enrolled in outpatient clinic settings although enrolled prospectively and followed-up well. In addition, some laboratory parameters (e.g. eGFR, serum potassium) at discharge after HF hospitalization were used for this analysis. It can over or underestimate HF severity and risk factors because we can assume that patients in our study may be less stabilized than chronic stable HF patients. However, the recently published Comparison of Sacubitril/Valsartan Versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode (PIONEER-HF) study showed the clinical effectiveness and safety of SV in destabilized HFrEF patients following ADHF.[30] So, our study population also have some clinical implication for widening the eligibility of SV in addition to chronic stable HFrEF patients like PIONEER-HF trial. And just 1–3 months after discharge from HF hospitalization, the patients have been known more fragile, so prone to decompensation and following rehospitalization.[25] So, we have to consider this period as vulnerable phase of HF and pay more attention to GDMT. Therefore, our study can support the SV eligibility for this vulnerable period, too. Secondly, we could not adopt the inclusion criteria of PARADIGM-HF using natriuretic peptides in our analysis. As you can see in **Table 2**, the natriuretic peptide levels were relatively higher in the KorAHF registry compared to other registry because we had natriuretic peptide levels only at discharge after hospitalization (not at outpatient clinic at stabilized status). Thirdly, clinical evidences for optimal GDMT usually come from the trials of chronic stable HF patients, not from those of ADHF. So, there may be concerns for our conclusion that sub-optimal pharmacotherapy was the main reason for ineligible SV use based on the PARADIGM-HF criteria in Korean HF population. However, there has been no large data about the dosing of HF GDMT in chronic stable HF patients in Korea as far as we know. Therefore, this study has enough novelty for real-world evidences of HF in Korea even though inborn limitation of this study population. On-going SPARK study could be helpful to answer this question further. Fourthly, the KFDA criteria for SV has one more criterion as at least four weeks of stable prescription for ACEI/ARB and other standard HF medications. We could not have detailed prescription data for preadmission period so we could not adopt this criterion for our analysis. Fifthly, our study population was limited to Korean population. However, this is the first and largest study to show the SV eligibility in Asian HFrEF patients considering many studies have been published in Western population (e.g. Western Europe, Norther American). Larger prospective, long term follow-up study including RCT should be warranted in Asian population. Lastly, the patients were recruited only from tertiary hospital centers. So, our study is not free from selection bias that higher risk patients were included in this analysis.

In conclusion, among the Korean hospitalized HFrEF patients, 80% met the KFDA label criteria, while only 12% met the inclusion criteria of PARADIGM-HF trial for SV when we used the ACEI/ARB dose criteria as ≥10 mg enalapril equivalent daily dose. In addition, we found that sub-optimal pharmacotherapy could be the main reason for ineligible SV use based on the PARADIGM-HF criteria in Asian population for the first time. Therefore, our findings highlight that the need for better strategies to integrate GDMT in a real-world, especially for target medication dose in Asian population.

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