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Comparison Between Fimasartan Versus Other Angiotensin Receptor Blockers in Patients With Heart Failure After Acute Myocardial Infarction

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ABSTRACT

Backgrounds: Fimasartan is the most recently developed, potent, and long-acting angiotensin II receptor blocker (ARB). However, data are limited regarding treatment effects of fimasartan in patients with heart failure.
Methods: Between 2010 and 2016, patients who underwent coronary revascularization for myocardial infarction (MI) with heart failure and prescription of ARB at hospital discharge were enrolled from the Korean nationwide medical insurance data. Clinical outcomes were compared between patients receiving fimasartan and those receiving other ARBs (candesartan, valsartan, losartan, telmisartan, olmesartan, and irbesartan). The primary outcome was a composite of all-cause death, recurrent MI, hospitalization for heart failure, and stroke.
Results: Of 2,802 eligible patients, fimasartan was prescribed to 124 patients (4.4%). During a median follow-up of 2.2 years (interquartile range, 1.0–3.9), 613 events of the primary outcome occurred. There was no significant difference in the primary outcome between patients receiving fimasartan and those receiving other ARBs (adjusted hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.46–1.45). Compared with patients receiving other ARBs, those receiving fimasartan had comparable incidence of all-cause death (adjusted HR, 0.70; 95% CI, 0.30–1.63), recurrent MI (adjusted HR, 1.28; 95% CI, 0.49–3.34), hospitalization for heart failure (adjusted HR, 0.70; 95% CI, 0.27–1.84), and stroke (adjusted HR, 0.59; 95% CI, 0.18–1.96).
Conclusion: In this nationwide cohort, fimasartan, compared with other ARBs, had comparable treatment effects for a composite of all-cause death, recurrent MI, hospitalization for heart failure, and stroke in patients with heart failure after MI.

Keywords: Angiotensin Receptor Blocker; Myocardial Infarction; Heart Failure

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Disclosure

The authors have no potential conflicts of interest to disclose.

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INTRODUCTION

In patients with myocardial infarction (MI) and heart failure or left ventricular systolic dysfunction, current guidelines recommend angiotensin II receptor blocker (ARB) therapy during and after hospitalization for those who do not tolerate an angiotensin-converting enzyme inhibitor (ACEI).[1-3] However, due to high rate of adverse symptoms and consequent discontinuation of ACEIs,[4-7] ARBs are often prescribed as a first-line drug in these populations. In the nationwide registry of acute MI between 2005 and 2016, the prescription rate of ARBs at hospital discharge was 26%.[8] Although valsartan is preferably recommended by the guideline for management of acute MI,[1] various ARBs are used in real world practice.[9]

Fimasartan is the ninth ARB that is a derivative of losartan, but is more potent and longer-acting than losartan.[10] Fimasartan demonstrated an effective blood pressure lowering effect in patients with hypertension and excellent safety profile in a large population observational study.[11] In animal studies, fimasartan ameliorates heart failure[12] and is cardioprotective after acute MI.[13] However, so far, no data are available for treatment effects of fimasartan in patients with heart failure after acute MI. Therefore, in the present study, we sought to compare fimasartan with other ARBs in patients with heart failure after MI using the nationwide medical insurance data of Korean population.

METHODS

Study population

Korea has a single-payer national health system, and the National Health Insurance Service (NHIS) maintains national records of all covered inpatient and outpatient visits, procedures, and prescriptions. This is a population–based retrospective cohort study which was built using the NHIS data.[14-16] NHIS provides 50% of the random sample of the national data if the study includes information about specific drugs.

Among all Korean men and women over 18-years-old between January 1, 2010 and November 31, 2016, we selected patients who underwent revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery) due to MI (n = 64,934). Because our objective was to compare clinical outcomes according to different types of ARBs after hospital discharge in patients with heart failure, we excluded patients who did not have heart failure at hospital discharge regardless of previous diagnosis (n = 52,765). We also excluded patients who had history of MI (I21–I23, I252) (n = 3,984), stroke (I60–I63) (n = 5,315), and renal disease (N18, N19) (n = 2,359). Then we excluded patients without any prescription of ARB or ACEI (n = 3,252), or those with prescription of ACEI (n = 3,799) or both ARB and ACEI (n = 97) at discharge. Patients who received eprosartan (n = 8) were excluded due to low prescription rate. In addition, we excluded patients who had death, recurrent MI, heart failure, or stroke within 30 days after index MI (n = 1,904) or those without any medical record available after discharge (n = 172). Finally, 2,802 patients were included in this study (**Fig. 1**).

Outcomes and definitions

NHIS claims for inpatient and outpatient visits, procedures, and prescriptions were coded using the International Classification of Diseases, 10th Revision.[17] As the NHIS routinely audits the claims, such data are considered reliable and used in numerous peer-reviewed publications.[14,15] In regard to diagnosis of MI, the validation study in 2013 showed the value of 93%.[18]

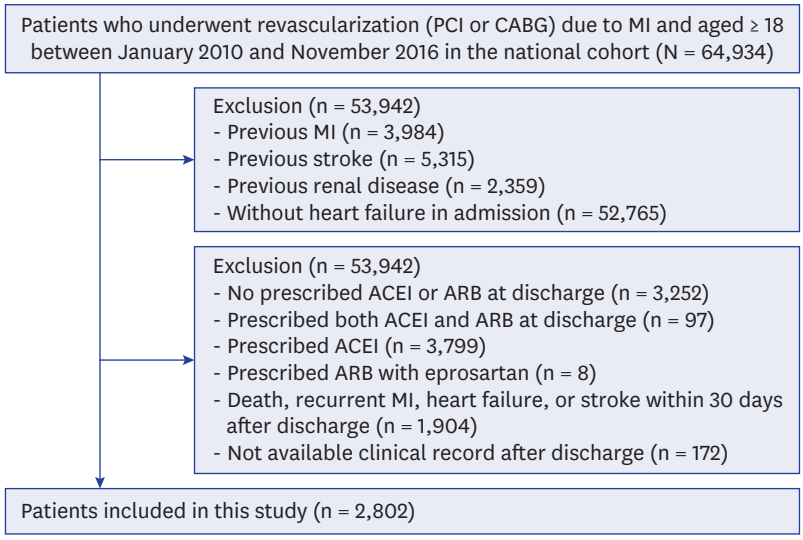

Fig. 1. Flow chart of subjected patients.
ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, CABG = coronary artery bypass grafting, MI = myocardial infarction, PCI = percutaneous coronary intervention.

The primary outcome was a composite of all-cause death, recurrent MI, hospitalization for heart failure, and stroke. Vital status and cause of death were obtained from death certification collected by Statistics Korea at the Ministry of Strategy and Finance of South Korea.[14] The secondary outcomes were individual components of the primary outcome.

Study exposure was an initial type of ARB used at hospital discharge. The initial use of study drugs was defined as prescription for at least 7 days among the admission claim or as prescription at first outpatient clinic. Previous ARB therapy was defined as presence of prescription during 6 months prior to index MI. Comorbidities were summarized using Charlson index. In addition, we included diabetes mellitus (E11–E14), hypertension (I10–I13, I15), atrial fibrillation or flutter (I48), chronic obstructive pulmonary disease (J43–J46), and peripheral artery disease (I73, I701, I702, I708, I709, I771, I792, K551, K558, K559). Comorbidities were defined as presence of code in claims within a year before index MI. We identified medications including calcium channel blocker, statin, aspirin, clopidogrel, ticagrelor or prasugrel, anticoagulant, beta-blocker, and spironolactone at discharge. Medications were identified with using the Korean Drug and Anatomical Therapeutic Chemical Codes (**Supplementary Table 1**).

Statistical analysis

Patients were followed-up until the development of study outcomes, or the end of the study period (December 31, 2016). Clinical outcomes of fimasartan were compared with other ARBs or valsartan. Cumulative incidence of outcome was estimated by the Kaplan-Meier method and log rank tests were applied to evaluate differences between the groups. We calculated hazard ratios (HRs) with 95% confidence intervals (CIs) for incidence of clinical outcome using a mixed-effects Cox regression model including an admitted hospital as a random intercept to adjust hospital effect. Furthermore, to account for potential confounding factors, we adjusted for age, sex, previous revascularization, previous ARB or ACEI therapy, diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation of flutter, chronic obstructive pulmonary disease, peripheral artery disease, malignancy, admission at tertiary hospital, and discharge medication including calcium channel blocker, statin, aspirin, clopidogrel, ticagrelor or

prasugrel, anticoagulant, beta-blocker, or spironolactone. We examined the proportional hazards assumption using plots of the log-log survival function and Schoenfeld residuals.

Additionally, clinical outcomes of each ARB were compared with other ARBs in the same way as fimasartan. All P values were 2-sided, and a *P* value of less than 0.05 was considered as significant. Analyses were performed with the use of SAS® Visual Analytics (SAS Institute Inc., Cary, NC, USA).

Ethics statement

The Institutional Review Board of Samsung Medical Center approved this study and informed consent was waived as we used de-identified administrative data.

RESULTS

Clinical characteristics

The mean age of 2,802 study patients was 65.2 years, 68.7% were male, and 42.7% had a history of ARB or ACEI prescription before the index MI. At hospital discharge, the most frequently prescribed ARB was candesartan (30.2%), followed by valsartan (26.5%), losartan (21.3%), telmisartan (7.6%), Olmesartan (6.0%), fimasartan (4.4%), and irbesartan (4.0%).

Compared with other ARBs, patients receiving fimasartan were less likely to be treated in tertiary hospital and to receive clopidogrel and spironolactone (**Table 1**). There were no significant differences in age, sex, previous history of ACEI or ARB prescription and comorbidities between patients receiving fimasartan and those receiving other ARBs. Baseline characteristics according to each type of ARBs are summarized in **Supplementary Table 2**.

Table 1. Characteristics of study participants between valsartan and other ARBs

Characteristics	Overall (N = 2,802)	Fimasartan (n = 124)	Other ARBs (n = 2,678)	*P* value
Age, yr	65.2 ± 13.4	64.1 ± 12.7	65.3 ± 13.4	0.329
Sex, male	1,924 (68.7)	79 (63.7)	1,845 (68.9)	0.224
Previous revascularization	158 (5.6)	4 (3.2)	154 (5.8)	0.233
Previous ACEI/ARB	1,196 (42.7)	55 (44.4)	1,141 (42.6)	0.700
Charlson Comorbidity Index	0.8 ± 1.1	0.8 ± 1.1	0.8 ± 1.1	> 0.999
Comorbidity				
Diabetes mellitus	626 (22.3)	30 (24.2)	596 (22.3)	0.612
Hypertension	1,159 (41.4)	53 (42.7)	1,106 (41.3)	0.750
Hyperlipidemia	125 (4.5)	4 (3.2)	121 (4.5)	0.496
Atrial fibrillation of flutter	44 (1.6)	1 (0.8)	43 (1.6)	0.484
COPD	229 (8.2)	8 (6.5)	221 (8.3)	0.474
Peripheral artery disease	54 (1.9)	3 (2.4)	51 (1.9)	0.683
Tertiary hospital	794 (28.3)	17 (13.7)	777 (29.0)	< 0.001***
Medications at discharge				
Calcium channel blocker	884 (31.5)	36 (29.0)	848 (31.7)	0.537
Statin	2,605 (93.0)	117 (94.4)	2,488 (92.9)	0.537
Aspirin	2,761 (98.5)	124 (100.0)	2,637 (98.5)	0.165
Clopidogrel	2,187 (78.1)	73 (58.9)	2,114 (78.9)	< 0.001***
Ticagrelor or prasugrel	794 (28.3)	50 (40.3)	744 (27.8)	0.002**
Anticoagulant	92 (3.3)	3 (2.4)	89 (3.3)	0.581
Beta-blocker	2,540 (90.6)	111 (89.5)	2,429 (90.7)	0.657
Spironolactone	837 (29.9)	25 (20.2)	812 (30.3)	0.016*

Values were presented number (%), mean ± standard deviation or median (interquartile range).
ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, COPD = chronic obstructive pulmonary disease.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

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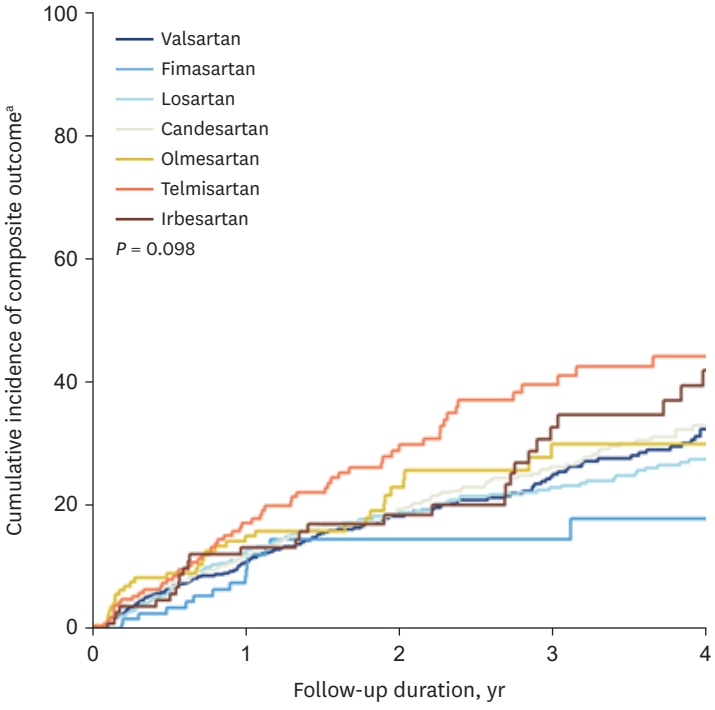
Clinical outcomes of fimasartan

During follow-up (median 2.2 years, interquartile range 1.0–3.9), 613 events of the primary outcome occurred. There was no significant difference in the primary outcome among 7 different ARBs (P = 0.098; **Fig. 2**). Compared with patients receiving other ARBs, those receiving fimasartan had the numerically lowest incidence of the primary outcome (63.6 per 1,000 person-years) but it was not statistically significant (adjusted HR, 0.82; 95% CI, 0.46–1.45; P = 0.489 vs. other ARBs) (**Tables 2** and **3**).

Patients receiving fimasartan had no significant differences in the incidence of all-cause death (adjusted HR, 0.70; 95% CI, 0.30–1.63; P = 0.412), recurrent MI (adjusted HR, 1.28; 95% CI, 0.49–3.34; P = 0.614), hospitalization for heart failure (adjusted HR, 0.70; 95% CI, 0.27–1.84; P = 0.471), or stroke (adjusted HR, 0.59; 95% CI, 0.18–1.96; P = 0.393) compared with those receiving other ARBs.

When compared with patients receiving valsartan, there were no significant differences in the incidence of primary and secondary outcomes in those receiving fimasartan (**Table 3**).



No. at risk					
Valsartan	743	544	362	250	171
Fimasartan	124	91	57	36	10
Losartan	597	450	356	273	202
Candesartan	845	593	427	265	148
Olmesartan	168	123	76	44	34
Telmisartan	214	147	105	72	51
Irbesartan	111	87	67	50	39

Fig. 2. Clinical outcomes according to different types of angiotensin II receptor blockers.
[a]A composite of all-cause death, recurrent myocardial infarction, hospitalization for heart failure, and stroke.

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Table 2. Incidence of a composite of all-cause death, recurrent myocardial infarction, hospitalization for heart failure, and stroke according to types of angiotensin II receptor blockers

Variables	Fimasartan	Candesartan	Valsartan	Losartan	Telmisartan	Olmesartan	Irbesartan
Number of patients	124	845	743	597	214	168	111
Number of cases	16	179	156	130	63	37	32
Incidence rate (per 1,000 person-years)	63.6	92.8	85.5	74.5	119.3	96.7	95.6

Table 3. HRs (95% CIs) of fimasartan for clinical outcomes compared to other ARBs or valsartan

Clinical outcomes of fimasartan	Number of cases	Incidence rate (per 1,000 person-years)	Unadjusted		Adjusted	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
A composite outcome[a]	16	63.6				
Versus other ARBs			0.68 (0.37–1.24)	0.21	0.82 (0.46–1.45)	0.489
Versus valsartan			0.74 (0.37–1.45)	0.36	0.84 (0.45–1.57)	0.593
All-cause death	6	22.4				
Versus other ARBs			0.50 (0.22–1.12)	0.09	0.70 (0.30–1.63)	0.412
Versus valsartan			0.61 (0.25–1.49)	0.28	0.86 (0.32–2.28)	0.764
Recurrent myocardial infarction	5	19.4				
Versus other ARBs			1.30 (0.50–3.35)	0.59	1.28 (0.49–3.34)	0.614
Versus valsartan			1.18 (0.44–3.19)	0.75	1.24 (0.43–3.61)	0.690
Hospitalization for heart failure	5	18.9				
Versus other ARBs			0.62 (0.21–1.79)	0.37	0.70 (0.27–1.84)	0.471
Versus valsartan			0.58 (0.18–1.88)	0.36	0.61 (0.20–1.82)	0.373
Stroke	2	7.5				
Versus other ARBs			0.47 (0.13–1.61)	0.23	0.59 (0.18–1.96)	0.393
Versus valsartan			0.46 (0.13–1.64)	0.23	0.49 (0.13–1.81)	0.278

HRs were adjusted for age, sex, previous revascularization, previous ARB or angiotensin-converting enzyme inhibitor therapy, diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation of flutter, chronic obstructive pulmonary disease, peripheral artery disease, malignancy, admission at tertiary hospital, and discharge medications.

ARB = angiotensin II receptor blocker, CI = confidence interval, HR = hazard ratio.

[a]A composite of all-cause death, recurrent myocardial infarction, hospitalization for heart failure, and stroke.

Clinical outcomes of other ARBs

Each ARB (candesartan, valsartan, losartan, telmisartan, olmesartan, or irbesartan) had no significant differences in the incidence of the primary outcome compared with other ARBs (**Supplementary Table 3**). The secondary outcomes are presented in **Supplementary Table 4**.

DISCUSSION

In the present study, we investigated clinical outcomes of fimasartan compared with other ARBs in patients with MI with heart failure. The main findings were as follows. First, there was no significant difference in the incidence of a composite of all-cause death, recurrent MI, hospitalization for heart failure, or stroke in patients receiving fimasartan compared with those receiving other ARBs. Second, the clinical outcomes with fimasartan were comparable with valsartan, the recommended ARB by practice guideline.

Current guidelines for management of MI recommend ACEI as a first-line drug over ARB in patients with heart failure. ACEIs, however, have frequent side effects. For example, the rate of cough is reported up to 44% in Asian population taking ACEI.[19] Therefore, as an alternative to ACEI, ARBs are often prescribed in real-world practice.[20] The prescription rate of ARBs has been increased over time,[9] and the reported rate at hospital discharge was up to 26%.[8] Although there are various ARBs commercially available, current practice guidelines for heart failure management[21,22] recommended the candesartan, losartan, and valsartan as evidence-based drugs. In guidelines for MI,[1,3] the preferred ARB is valsartan based on the VALsartan in Acute myocardial iNfarcTion (VALIANT) trial that showed non-

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inferiority of valsartan compared to captopril.[5] In real world practice, however, various ARBs are prescribed in patients with MI with heart failure. In observational studies, ARBs other than valsartan was prescribed in more than 70% of all patients.[9,23] Because of different pharmacokinetic-pharmacodynamic profiles between ARBs available on market,[24,25] treatment effect on reducing cardiovascular events could be also different between ARBs.[26,27] However, data are very limited on this issue in patients with MI and heart failure.

Fimasartan is one of the latest ARBs developed in 2010's. Fimasartan, a pyrimidin-4(3H)-one derivative of losartan with the imidazole ring replaced, which enables higher potency and longer duration than losartan. With a strong binding affinity to AT_1 receptor, fimasartan had the highest association rate compared to other ARBs[28] and better efficacy on blood pressure lowering.[29-31] In addition, fimasartan has the cardioprotective effects against myocardial ischemia and reperfusion injury,[32] or heart failure progression[12] in preclinical studies. Hence, the favorable data so far suggest the clinical benefit of fimasartan in high-risk population, such as those with MI with heart failure. In this nationwide study, incidence of a composite of all-cause death, recurrent MI, hospitalization for heart failure, or stroke was not significantly different between patients receiving fimasartan and those receiving other ARBs. In addition, clinical outcomes in patients receiving fimasartan was not significantly different compared with those receiving valsartan, the preferable ARB by current guidelines for management of MI.[1,3] Taken together with previous preclinical and clinical evidence, our findings suggest the clinical efficacy of fimasartan in patients with MI with heart failure.

Our study has several limitations. First, this was an observational study. The choice of drug was at the physician's discretion. Although we conducted an intraclass comparison among different ARBs in patients with MI with heart failure, there is a potential selection bias induced by unrecorded confounders. Second, we did not consider the changes of medication during follow up. The current results should be interpreted considering that each ARB was a prescription at the time of discharge. Third, patients who were event-free at 1 month after discharge were included in the final analysis. The adverse events immediately after discharge might be affected by the severity of disease or patients' sickness than the beneficial effect of ARBs, especially in high-risk patients such as those with MI complicated by HF. Therefore, we conducted a 1-month landmark analysis to compare outcomes according to the different ARBs. Fourth, although this was a nationwide study using health insurance data, the sample size of each type of ARBs could be inadequate to conclude statistical significance to compare clinical outcomes among different drugs. Last, because the diagnosis of heart failure was based on claims, not the specific criteria such as left ventricular ejection fraction, care should be taken in the interpretation of this study. Despite these limitations, our study has strengths to present clinical outcomes of fimasartan, the latest ARB, in patients with MI with heart failure. In addition, we compared clinical outcomes among various ARBs currently available in real world practice. A large-scale randomized study is needed to determine the current findings, including patients with heart failure unrelated to MI.

In this nationwide cohort study of patients with MI with heart failure, there was no significant difference in incidence of a composite of all-cause death, recurrent MI, hospitalization for heart failure, and stroke in patients receiving fimasartan compared with those receiving other ARBs.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

List of medication codes

Click here to view

Supplementary Table 2

Characteristics of study patients according to types of ARBs

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Supplementary Table 3

The incidence rate of a composite of all-cause death, recurrent MI, hospitalization for heart failure, and stroke among different types of ARBs

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Supplementary Table 4

Clinical outcomes among patients with different types of ARBs

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