Clinical Hypertension

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Real-world efficacy of fimasartan vs. other angiotensin receptor blockers in combination with calcium channel blockers: a nationwide cohort study

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Abstract

Background The antihypertensive efficacy of fimasartan was assessed based on the transition rate from a combination of calcium channel blockers (CCB) and angiotensin receptor blockers (ARB) to three-drug combination therapy, as compared to other ARBs.

Methods This nationwide cohort study used data obtained from the Korean National Health Insurance Service database. Patients who had received national health checkups within 2 years prior to January 1, 2017, and were concurrently prescribed ARBs and CCBs for > 30 days during the 6 months from January 1, 2017, to June 30, 2017 were included in the study. Patients were categorized into the 'fimasartan group' (those prescribed fimasartan) and the 'non-fimasartan group' (those prescribed ARBs other than fimasartan). The index date was set as the last day of a 30-day prescription period for ARBs and CCBs, with a subsequent 2.5-year follow-up to observe the potential addition of a third drug, such as beta-blockers or diuretics.

Results The study included 34,422 patients with a mean age of 60.3 years and 58.3% being male. The fimasartan group constituted 2.7% ($n = 928$) of the total, and the non-fimasartan group, 97.3% ($n = 33,494$). During the follow-up period, 38 patients in the fimasartan group (14.3 per 1,000 person-years) and 3,557 patients in the non-fimasartan group (42.8 per 1,000 person-years) required additional antihypertensive medications. After multivariate adjustment for age, sex, diabetes mellitus, dyslipidemia, cancer, heart failure, systolic blood pressure, and diastolic blood pressure, the fimasartan group showed a significantly lower rate of adding a third medication (hazard ratio 2.68, 95% confidence interval 1.95–3.69) compared to that of the non-fimasartan group.

Conclusions Fimasartan is associated with a lower need for additional antihypertensive drugs compared to other ARBs. This implies its greater effectiveness in hypertension management, potentially enhancing cardiovascular outcomes, and minimizing polypharmacy.

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Keywords Hypertension, Angiotensin II inhibitor, Fimasartan, Calcium channel blocker

Background

Hypertension has a substantial prevalence affecting approximately 1 billion patients worldwide and the prevalence is increasing [1, 2]. More importantly, hypertension is a well-known risk factor for cardiovascular events [3]. Effective treatment of hypertension significantly reduces cardiovascular disease (CVD)-related events, including a decreased risk of stroke (by 35–40%), myocardial infarction (by 15–25%), and congestive heart failure (by as much as 64%) [4–6].

Despite the availability of more than 100 different medications across various pharmacological categories and large financial investments in hypertension treatment, global blood pressure (BP) control rates remain suboptimal, even in developed countries [7]. Among various factors suggested as reasons for unsatisfactory hypertension control, an expanded medication regimen has been reported to be a significant factor associated with non-compliance [8, 9]. This non-compliance could, in turn, lead to poor BP control.

Angiotensin receptor blockers (ARBs) are renowned for their efficacy and excellent tolerability [10]. Based on these qualities, ARBs stand as the preferred initial therapeutic choice for hypertension management [11–13]. Fimasartan, created by substituting the imidazole ring in losartan with a pyrimidine ring, is one of the most recent additions to the global ARB armamentarium. It has several strengths compared with other ARBs. First, it shows superior angiotensin II receptor type 1 (AT_1) -selective binding when compared to other ARBs [14]. Second, it has an antihypertensive effect over 24 h due to its extended half-life, ranging from 10 to 18 h, ranking it among the most prolonged half-lives within the ARB class [15, 16]. A recent report showed that fimasartan has a more pronounced BP-lowering effect relative to other ARBs [17, 18].

In real-world clinical practice, approximately 60% of patients with hypertension are prescribed two or more antihypertensive medications. Among those, about half use combinations of ARBs and calcium channel blockers (CCBs) [19]. Considering the distinct BP-lowering effects of ARBs, it is reasonable to hypothesize that transition rates from two-drug to three-drug combination therapy may vary across ARBs; fimasartan might have a lower transition rate owing to its high potency in controlling BP.

Based on this background, we aimed to explore the efficacy of fimasartan and other ARBs in patients with hypertension who are already undergoing treatment with CCBs and ARBs by analyzing the transition rates to a three-drug combination therapy.

Participants and methods

Study design and study population

This nationwide cohort study used data from the Korean NHIS database. Detailed information regarding this database has been published earlier [20–22]. In essence, the NHIS is a single public insurer that covers the entire Korean population and encourages eligible Korean adults to receive general health checkups on a regular basis. Demographic information, general health checkup results, and medical history coded according to the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) were collected and recorded in the NHIS database.

A flowchart of the study is shown in Fig. 1. Initially, we screened 137,089 patients who were prescribed CCBs for >30 days between January 1, 2017, and June 30, 2017. Among them, 81,722 patients who were prescribed ARBs for >30 days during the same period were identified. Patients who underwent a health checkup within 2 years prior to receiving CCB and ARB prescriptions were included. After excluding patients taking additional antihypertensive drugs, those aged<20 years, and those with missing health data, 34,422 patients remained. Prescription of ARBs were defined as that of Fimasartan, Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, and Valsartan.

Covariates

Patients with hypertension were identified based on one of the following criteria: (1) at least one annual claim for an antihypertensive prescription associated with ICD-10-CM codes I10-I13 and I15, derived from insurance claims data, or (2) a recorded systolic BP of ≥140 mmHg and/or a diastolic BP of ≥90 mmHg alongside the aforementioned ICD-10-CM codes [23–25]. Patients' demographic data, comorbidities, medications, and results from general health checkups were collected and analyzed as covariates. The comorbidity definitions are summarized in Supplemental Table 1 [23].

Study outcome and follow-up

The index date was defined as the last day of the 30-day ARBs and CCBs prescription period. Patients were followed up for a period of 2.5 years from the index date. The transition to three-drug combination therapy was defined as the addition of beta-blockers or diuretics during the follow-up period. Transition rates were analyzed between patients receiving fimasartan and those receiving all other ARBs (non-fimasartan), as well as between those receiving fimasartan and each individual ARB.

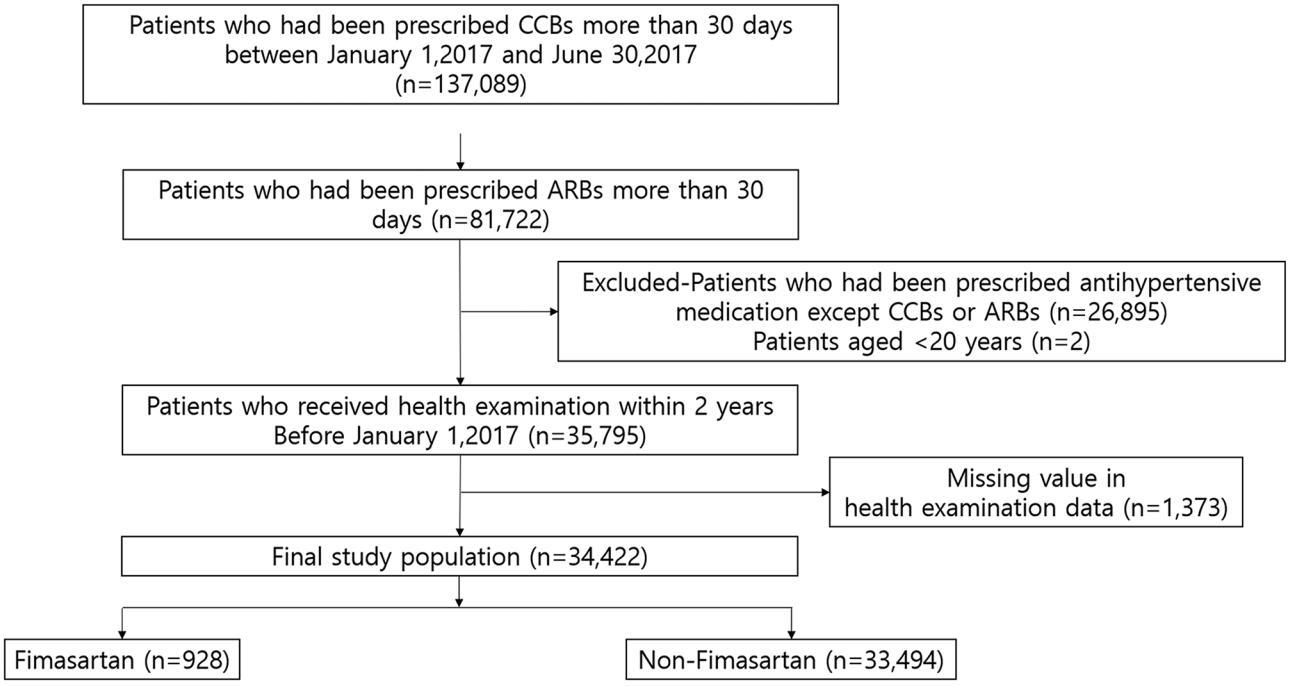

Fig. 1 Flow chart detailing the study enrollment process. Abbreviations: CCB - calcium channel blocker; ARB - angiotensin receptor blocker

Statistical analysis

Data were presented as the mean±standard deviation for continuous variables and as counts and percentages for categorical variables. Chi-squared or Fisher's exact tests were used for categorical variables, as appropriate. Continuous variables were analyzed using unpaired Student's t-test, and one-way analysis of variance was used for comparisons between more than two groups. The annualized incidence rate (IR) of transitioning to three-drug combination therapy was calculated by dividing the number of new cases by the total follow-up period, and was expressed as a rate per 1,000 person-years. For the category 'transition to three-drug combination therapy,' we established two definitions: Definition 1 required prescriptions of CCBs, ARBs, and either beta-blockers or diuretics, within the timeframe of July 1, 2017, to December 31, 2020. Definition 2 mirrored these criteria but additionally necessitated the consistent use of the initially prescribed ARB, which was sustained until the issuance of a third antihypertensive prescription (either a beta-blocker or diuretic). Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated using Cox proportional hazard regression models. The multivariate models were adjusted for a variety of covariates, including age, sex, systolic and diastolic BP, and comorbidities such as diabetes mellitus, dyslipidemia, atrial fibrillation, and cancer. The HRs were reported using the fimasartan group as a reference. Considering the time required to initiate antihypertensive medication, assess its efficacy, and introduce additional medications, we conducted a sensitivity analysis incorporating a 6-month lag period. To exclude biases from other cardiovascular events, we further analyzed the differences in the incidence of myocardial infarction (MI), heart failure (HF), and atrial fibrillation (AF) during follow-up between the fimasartan group and the non-fimasartan group. Additionally, we analyzed the transition rate to three-drug combination therapy in patients without a prior medical history of AF, MI, HF, and chronic kidney disease (CKD) as sensitivity analyses. Statistical significance was defined as a two-sided P-value <0.05. All the statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics

We analyzed 34,422 patients with a mean age of 60.3±11.5 years, and 20,071 patients (58.3%) were men. Among the total study population, 928 patients (2.7%) were classified into the fimasartan group and 33,494 patients (97.3%) were classified into the non-fimasartan group. The non-fimasartan group comprised patients who were prescribed candesartan, esprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan (n=1,541, 92, 590, 7,390, 5,293, 7,319, and 11,269, respectively). Baseline characteristics according to ARBs use are presented in Table 1. There were no significant differences in age, sex, or body mass index between the fimasartan and non-fimasartan groups. Regarding comorbid conditions, the fimasartan group showed unfavorable

Table 1 Baseline characteristics

	Total (*n* = 34,422)	Fimasartan group (*n* = 928)	Non-Fimasartan group (*n* = 33,494)	*P*-value	Candesartan (*n* = 1,541)	Eporsartan (*n* = 92)	Irbesartan (*n* = 590)	Losartan (*n* = 7,390)	Olmesartan (*n* = 5,293)	Telmesartan (*n* = 7,319)	Valsartan (*n* = 11,269)	*P*-value
Age (years)	60.33 ± 11.5	59.7 ± 11.8	60.4 ± 11.5	0.080	60.6 ± 11.5	64.9 ± 10.4	63.2 ± 11.0	62.4 ± 11.2	59.8 ± 11.5	59.1 ± 11.3	59.9 ± 11.6	< 0.001
Sex, male	20,071 (58.3)	534 (57.5)	19,537 (58.3)	0.632	887 (57.6)	46 (50.0)	330 (55.9)	4019 (54.4)	3172 (59.9)	4486 (61.3)	6597 (58.5)	< 0.001
Comorbidities												
Diabetes mellitus	8203 (23.8)	213 (23.0)	7990 (23.9)	0.525	400 (26.0)	23 (25.0)	178 (30.2)	1662 (22.5)	1295 (24.5)	1645 (22.5)	2787 (24.7)	< 0.001
Dyslipidemia	15,692 (45.6)	465 (50.1)	15,227 (45.5)	0.005	744 (48.3)	60 (65.2)	283 (48.0)	3040 (41.1)	2515 (47.5)	3341 (45.7)	5244 (46.5)	< 0.001
Atrial fibrillation	276 (0.8)	15 (1.6)	261 (0.8)	0.005	17 (1.1)	4 (4.4)	8 (1.4)	58 (0.8)	41 (0.8)	52 (0.7)	81 (0.7)	< 0.001
Heart failure	239 (0.7)	15 (1.6)	224 (0.7)	0.001	28 (1.8)	0 (0)	5 (0.9)	45 (0.6)	35 (0.7)	36 (0.5)	75 (0.7)	< 0.001
Prior MI	94 (0.3)	3 (0.3)	91 (0.3)	0.766	7 (0.5)	0 (0)	4 (0.7)	20 (0.3)	11 (0.2)	21 (0.3)	28 (0.3)	0.442
PAD	5652 (16.4)	140 (15.1)	5512 (16.5)	0.266	262 (17.0)	13 (14.1)	91 (15.4)	1311 (17.7)	823 (15.6)	1063 (14.5)	1949 (17.3)	< 0.001
Stroke	1541 (4.5)	62 (6.7)	1479 (4.4)	0.001	71 (4.6)	14 (15.2)	49 (8.3)	299 (4.1)	332 (6.3)	287 (3.9)	427 (3.8)	< 0.001
Cancer	1074 (3.1)	43 (4.6)	1031 (3.1)	0.007	54 (3.5)	2 (2.2)	17 (2.9)	270 (3.7)	155 (2.9)	196 (2.7)	337 (3.0)	0.004
Health exam parameters												
BMI (kg/m2)	25.6 ± 3.4	25.6 ± 3.5	25.6 ± 3.4	0.563	25.6 ± 3.5	25.3 ± 3.7	25.3 ± 3.2	25.3 ± 3.39	25.8 ± 3.4	25.7 ± 3.4	25.7 ± 3.4	< 0.001
Waist circumference (cm)	86.3 ± 8.8	86.2 ± 8.9	86.3 ± 8.8	0.882	86.2 ± 9.1	85.3 ± 8.8	86.1 ± 8.8	85.7 ± 8.7	86.6 ± 8.7	86.5 ± 8.8	86.3 ± 8.8	< 0.001
Systolic BP (mmHg)	132.6 ± 15.5	133.8 ± 16.2	132.6 ± 15.5	0.016	133.7 ± 15.6	131.9 ± 16.4	132.3 ± 14.2	132.1 ± 15.1	131.9 ± 15.8	132.4 ± 15.9	133.1 ± 15.5	< 0.001
Diastolic BP (mmHg)	81.0 ± 10.7	82.0 ± 11.5	81.0 ± 10.7	0.004	81.7 ± 11.2	79.5 ± 10.1	80.5 ± 10.1	80.3 ± 10.2	80.6 ± 10.9	81.1 ± 10.9	81.4 ± 10.6	< 0.001
Fasting glucose (mg/dL)	110.0 ± 31.0	109.4 ± 34.3	110.1 ± 30.9	0.485	109.9 ± 31.7	108.0 ± 26.6	111.1 ± 28.7	108.8 ± 29.1	110.7 ± 30.9	109.8 ± 30.8	110.7 ± 32.2	0.004
Total cholesterol (mg/dL)	190.8 ± 39.6	192.2 ± 41.7	190.8 ± 39.6	0.285	190.3 ± 39.4	180.5 ± 36.7	186.6 ± 38.4	191.1 ± 38.4	190.5 ± 39.9	191.6 ± 39.9	190.5 ± 40.0	0.007
HDL-C (mg/dL)	53.1 ± 14.0	53.3 ± 15.1	53.1 ± 13.9	0.592	52.7 ± 13.3	54.9 ± 15.1	51.9 ± 13.2	53.3 ± 14.5	53.0 ± 13.8	52.9 ± 13.8	53.1 ± 13.8	0.157
LDL-C (mg/dL)	108.8 ± 37.1	109.4 ± 37.7	108.8 ± 37.1	0.618	108.4 ± 35.8	98.7 ± 29.7	105.6 ± 34.6	109.5 ± 36.4	108.1 ± 36.5	110.0 ± 38.3	108.1 ± 37.4	< 0.001
eGFR (ml/min/1.73m^2)	89.0 ± 50.8	87.9 ± 44.0	89.1 ± 50.9	0.511	88.3 ± 57.4	86.1 ± 21.5	82.6 ± 27.6	86.4 ± 36.2	89.4 ± 59.5	90.6 ± 52.3	90.1 ± 54.0	< 0.001

Abbreviation: MI, myocardial infarction; PAD, peripheral artery disease; BMI, body mass index; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate

baseline characteristics, including dyslipidemia, atrial fibrillation, stroke, cancer, and heart failure, compared to the non-fimasartan group. Additionally, significant differences were observed in the systolic BP and diastolic BP between the two groups.

Different transition rates to three-drug combination therapy

During a median follow-up of 2.1 years (interquartile range 2.05–2.35 years), 3,595 patients (10.5%) transitioned to three-drug combination therapy. Significant differences in the transition to three-drug combination therapy were observed between the fimasartan and non-fimasartan groups ($P<0.001$), as well as across ARBs ($P<0.001$) (Table 2). Notably, the patients taking fimasartan exhibited a remarkably lower rate of adding other antihypertensive medications; only 38 patients (4.1%) taking fimasartan required additional medication. In contrast, eprosartan (29.4%) and irbesartan (29.8%) exhibited the highest transition rates in three-drug combination therapy, followed by candesartan (21.5%) and losartan (20.4%). Olmesartan (5.8%), telmisartan (6.3%), and valsartan (6.6%) showed comparatively lower rates.

The time taken to use additional antihypertensive medications was also significantly different across ARBs (Table 2). Indeed, patients taking fimasartan showed a longer duration of two-drug combination therapy before additional medication was required, with a median time of 213.5 days (interquartile range, 184–278 days), indicating a longer interval than that for most other ARBs. Irbesartan demonstrated the shortest duration (median: 193 days; interquartile range, 183–211 days).

The annualized IRs of each ARB were quite different. The fimasartan group showed an IRs of 14.26 per 1,000 PY, whereas the non-fimasartan group showed an IRs of 42.76 per 1,000 PY. As shown in the Kaplan-Meier curves (Fig. 2), the probability of taking additional antihypertensive medications was significantly lower in the fimasartan group than in the non-fimasartan group (log-rank $P<0.001$). After multivariable adjustment, the non-fimasartan group consistently showed significantly higher transition rates to three-drug combination therapy (HR 2.68, 95% CI 1.95–3.69) compared to the fimasartan group (Fig. 3). These results highlight the potential clinical efficacy of fimasartan in minimizing the need for additional antihypertensive agents. When comparing the rate of transition in the three-drug combinations involving fimasartan and telmisartan (Supplemental Fig. 1A, $p=0.047$) and fimasartan and olmesartan (Supplemental Fig. 1B, $p=0.027$), the rate of transition in the three-drug combination was statistically significantly lower for fimasartan than for both telmisartan and olmesartan. The results of sensitivity analysis with the 6-month landmark analysis were consistent with the main results (Supplemental Fig. 2).

We further compared the transition rate to three-drug combination therapy for each ARB, with patients taking fimasartan as the reference group. Supplemental Fig. 3 illustrates the trend of adding antihypertensive medications to each ARB. In multivariate analysis, all other ARBs showed significantly higher risks of additional antihypertensive medications than that of fimasartan. Specifically, candesartan (HR 5.78, 95% CI 4.13–8.09), eprosartan (HR 7.68, 95% CI 4.69–12.58), and irbesartan (HR 8.33, 95% CI 5.86–11.82) demonstrated remarkably higher transition rates to three-drug combination therapy compared to fimasartan. Regarding olmesartan, telmisartan, and valsartan, the relative magnitude of increased risks for adding additional antihypertensive medications was comparatively small compared to that

Table 2 Time to addition of third antihypertensive medication: comparison among angiotensin II receptor blockers

	Fimasartan (*n* = 928)	Candesartan (*n* = 1,541)	Eprosartan (*n* = 92)	Irbesartan (*n* = 590)	Losartan (*n* = 7,390)	Olmesartan (*n* = 5,293)	Telmisartan (*n* = 7,319)	Valsartan (*n* = 11,269)	*P*-value
Third medication addition rate, *n* **(%)**									
definition 1	58 (6.25)	372 (24.14)	29 (31.52)	186 (31.53)	1609 (21.77)	441 (8.33)	589 (8.05)	1049 (9.31)	< 0.001
definition 2	38 (4.09)	332 (21.54)	27 (29.35)	176 (29.83)	1507 (20.39)	308 (5.82)	462 (6.31)	745 (6.61)	< 0.001
Time to third medication addition, days									
definition 1 (Median [IQR1 - IQR3])	243 (194, 547)	203 (187, 239.5)	210 (188, 280)	194 (184, 218)	201 (186, 241)	225 (188, 552)	238 (193, 538)	238 (192, 548)	< 0.001
definition 2 (Median [IQR1 - IQR3])	213.5 (184, 278)	198 (186, 218)	203 (187, 240)	193 (183, 211)	198 (186, 231)	198 (185, 242.5)	213 (190, 357)	204 (188, 267)	< 0.001

Definition 1: A claim exists for the prescription of CCBs, ARBs, and beta-blockers or diuretics between July 1, 2017, and December 31, 2020

Definition 2: A claim exists for the prescription of CCBs, ARBs, and beta-blockers or diuretics between July 1, 2017, and December 31, 2020, with a consistent ARB since index time, maintained until the third drug claim

Abbreviation: SD, standard deviation; IQR, interquartile

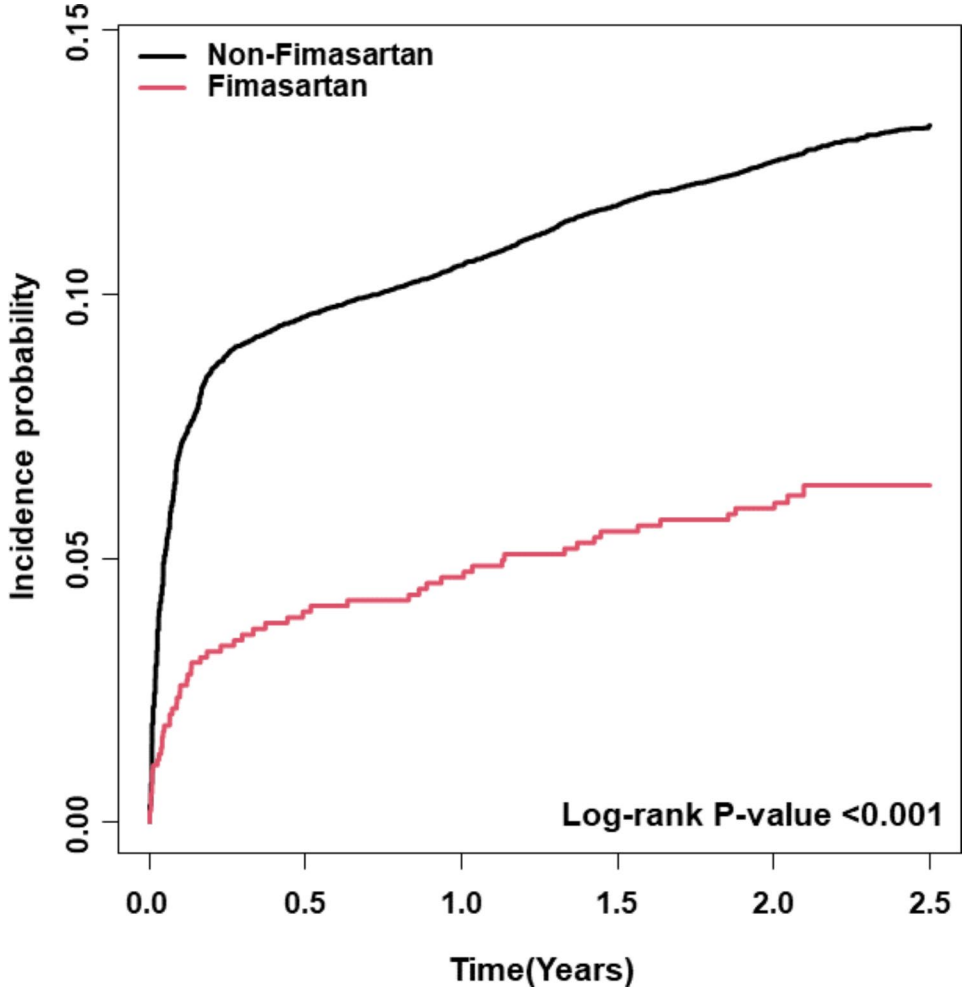

Fig. 2 Survival analysis contrasting the transition rate to a three-drug combination therapy regimen between the fimasartan and non-fimasartan cohorts

	Definition 1					Definition 2			
Group	Number	Events	IR	Model 4 HR (95% CI)		Events	IR	Model 4 HR (95% CI)	
Fimasartan	928	58	22.0	1 (Reference)		38	14.3	1 (Reference)	
non-Fimasartan	33494	4275	52.1	2.13 (1.65-2.77)		3557	42.8	2.68 (1.95-3.69)	
Fimasartan	928	58	22.0	1 (Reference)		38	14.3	1 (Reference)	
Candesartan	1541	372	95.3	4.30 (3.26-5.67)		332	83.7	5.78 (4.13-8.09)	
Eprosartan	92	29	125.9	5.60 (3.59-8.75)		27	114.6	7.68 (4.69-12.58)	
Irbesartan	590	186	107.8	5.87 (4.37-7.89)		176	100.4	8.33 (5.86-11.82)	
Losartan	7390	1609	84.0	3.82 (2.94-4.97)		1507	77.8	5.40 (3.91-7.45)	
Olmesartan	5293	441	33.4	1.37 (1.04-1.80)		308	23.0	1.45 (1.03-2.03)	
Telmisartan	7319	589	32.9	1.33 (1.01-1.74)		462	25.6	1.58 (1.14-2.20)	
Valsartan	11269	1049	40.4	1.52 (1.17-1.99)		745	28.2	1.64 (1.19-2.27)	

Fig. 3 Multivariate Cox-proportional hazard regression analysis assessing the transition rate to three-drug combination therapy across fimasartan and non-fimasartan groups, and the aggregate of all angiotensin receptor blockers. The fimasartan group is utilized as a reference. Incidence rate is expressed per 1,000 person-years. Abbreviations: CI = confidence interval; HR = hazard ratio; IR = incidence rate

of candesartan, eprosartan and irbesartan, but these also showed significantly higher risks compared to fimasartan (HR 1.45, 95 CI 1.03–2.03; HR 1.58, 95% CI 1.14–2.20; and HR 1.64, 95% CI 1.19–2.27, respectively) (Fig. 3). This result was consistently observed in the sensitivity analysis with a 6-month lag period. (Supplemental Fig. 3) and in the analysis excluding patients with a past medical history of MI, HF, AF, and CKD (Supplemental Tables 2 and Supplemental Fig. 4).

To exclude the biases from the newly developed cardiovascular events except hypertension, we further analyzed the differences in the incidence of MI, HF, and AF during follow-up between the two groups. Supplemental Fig. 5 illustrates the multivariate analysis of these four outcomes, showing similar risks in the non-fimasartan group for MI (HR: 0.79, 95 CI: 0.35–1.79), HF (HR: 0.74, 95 CI: 0.44–1.24), AF (HR: 0.87, 95 CI: 0.48–1.59), and the composite outcome (HR: 0.77, 95 CI: 0.53–1.13).

Discussion

We evaluated the efficacy of ARBs by examining the rate at which patients transitioned from a combination of CCBs and ARBs to a triple-drug regimen. The key findings are as follows: First, fimasartan was associated with a lower frequency of introducing a third antihypertensive agent compared to other ARBs. Second, patients on fimasartan had a longer median duration (778 days) before the addition of a third antihypertensive agent than those on other ARBs (median 764 days). This trend persisted even after adjusting for covariates, with fimasartan showing a decreased likelihood of requiring a third antihypertensive medication. It is important to note that despite unfavorable baseline characteristics in the fimasartan group, there was less need for an additional antihypertensive agent. These results suggest that fimasartan may offer superior antihypertensive efficacy, as evidenced by both a lower incidence of, and delayed requirement for, additional antihypertensive medication.

Because of the unacceptably high global disease burden of hypertension, numerous efforts have been made to improve clinical outcomes, demanding lifelong compliance with treatment [26, 27]. However, most patients with hypertension remain asymptomatic despite the increased risk of cardiovascular events. Consequently, adherence to antihypertensive medications, which may not provide immediate benefits, is crucial for these patients. The documented correlation between complex medication schedules, involving multiple drugs and daily doses, and reduced compliance underscores the challenge [28–30]. This complexity is further compounded when considering comorbidities, leading to intricate drug regimens involving multiple medications and doses [31]. In consideration of this, it is essential for physicians to simplify the antihypertensive medication regimen while preserving equivalent medical and antihypertensive benefits to enhance outcomes.

ARBs have a shared molecular structure that contributes to their class effect [32], yet variations exist, leading to different clinical benefits. The number of hydrogen bonds, which affect binding affinity, varies among ARBs and influences their antihypertensive effects [33]. Fimasartan is distinct in the replacement of losartan's imidazole ring with a pyrimidine ring, resulting in enhanced AT_1-selective binding compared to other ARBs [14]. It also has an extended half-life and potent BP-lowering effect [15, 16, 18]. Considering that fimasartan belongs to the later generation of ARBs, comparisons are made with with earlier ARBs to establish its antihypertensive efficacy. The antihypertensive efficacy of fimasartan has been investigated compared to losartan [34], valsartan [16, 35, 36], and candesartan [37] and it is clear that fimasartan has comparable or superior BP-lowering effects. A previous head-to-head study clearly demonstrated that fimasartan has superior efficacy in BP reduction compared with valsartan [38]. As expected from its novel molecular characterization, fimasartan has consistently demonstrated a more pronounced BP-lowering effect than other ARBs in clinical studies [15, 16, 18].

The use of the conversion rate to the three-drug combination therapy as a surrogate measure in our study offers a novel approach for evaluating the effectiveness of antihypertensive medications, bypassing the traditional method of direct BP measurement. Additionally, the potential of this conversion rate as an indicator of patient compliance with antihypertensive medications is noteworthy. Our cohort of >30,000 participants is a strength, although the implications and broader applications of these findings warrant further exploration.

Our study had several limitations. First, as this was an observational study, unmeasured confounders may have influenced our results. Second, the study, which was based on the NHIS database, encountered limitations in accessing data on the degree of BP change from the index date to the prescription of a third antihypertensive medication. However, it is important to note that our findings align with a previous study that reported the effectiveness of fimasartan in lowering BP compared to other ARBs. Additionally, this study was conducted only in South Korea, and thus, generalizing the findings to global populations with diverse genetic and environmental backgrounds should be approached with caution. Another limitation is the absence of data regarding the discontinuation of ARB prescriptions. While we included individuals who were prescribed ARBs for 30 days or more within the inclusion period, we were unable to ascertain the subsequent discontinuation status of these prescriptions. In the future, research on more specific topics, such as cost-effectiveness, will be necessary.

Conclusions

The use of fimasartan is associated with a significantly lower transition rate to three-drug combination therapy and extends the time to the incorporation of a third drug into the treatment regimen. The antihypertensive efficacy of fimasartan in the management of hypertension minimizes the need for additional medications.

Abbreviations

CVD	Cardiovascular disease
BP	Blood pressure
ARBs	Angiotensin receptor blockers
AT1	Angiotensin II receptor type 1
CCBs	Calcium channel blockers
NHIS	National Health Insurance Service
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IR	Incidence rate
HRs	Hazard ratios
CIs	Confidence intervals

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40885-024-00287-4.

Supplementary Material 1

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Author contributions
Conception: Hyung-Kwan Kim, Kyung-Do Han; Design: Hyung-Kwan Kim, Kyung-Do Han; Supervision: Yong-Jin Kim, Hyung-Kwan Kim, Kyung-Do Han; Fundings: Hyung-Kwan Kim; Materials: Tae-Min Rhee, Heesun Lee; Data collection and processing: Bongseong Kim, Kyung-Do Han; Analysis and interpretation: Bongseong Kim, Kyung-Do Han, Huijin Lee, Chan Soon Park. Hyung-Kwan Kim; Writer: Huijin Lee, Chan Soon Park. Critical review: Chan Soon Park. Hyung-Kwan Kim.

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Data availability
All raw data were accessible from designated terminals approved by the National Health Insurance Service (NHIS). On reasonable request from the corresponding author, the data will be available under approval and oversight by the NHIS.

Declarations

Ethics approval and consent to participate
This study adhered to the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital (E-2103-004-120), which waived the need for informed consent due to the use of de-identified data.

Consent for publication
Not applicable.

Competing interests
Hyung-Kwan Kim has received research grants from HK Inno. N, Johnson and Johnson, GSK, Samjin Pharm, ChongKunDang Pharm, Boryung Pharm, and JW Pharm. The authors declare no conflict of interest.

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References

1. Worldwide trends in. Hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet. 2021;398:957–80.
2. Zhou B, Perel P, Mensah GA, Ezzati M. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. Nat Rev Cardiol. 2021;18:785–802.
3. Fuchs FD, Whelton PK. High blood pressure and Cardiovascular Disease. Hypertension. 2020;75:285–92.
4. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr., Jones DW, Materson BJ, Oparil S, Wright JT Jr., Roccella EJ, Joint National Committee on Prevention DE, Treatment of High Blood Pressure, National Heart L. Blood I and National High Blood Pressure Education Program Coordinating C. Seventh report of the Joint National Committee on Prevention, detection, evaluation, and treatment of high blood pressure. Hypertension. 2003;42:1206–52.
5. Neal B, MacMahon S, Chapman N, Blood Pressure Lowering Treatment Trialists C. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood pressure lowering treatment trialists' collaboration. Lancet. 2000;356:1955–64.
6. Psaty BM, Smith NL, Siscovick DS, Koepsell TD, Weiss NS, Heckbert SR, Lemaitre RN, Wagner EH, Furberg CD. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. JAMA. 1997;277:739–45.
7. Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, Bahonar A, Chifamba J, Dagenais G, Diaz R, Kazmi K, Lanas F, Wei L, Lopez-Jaramillo P, Fanghong L, Ismail NH, Puoane T, Rosengren A, Szuba A, Temizhan A, Wielgosz A, Yusuf R, Yusufali A, McKee M, Liu L, Mony P, Yusuf S. and investigators PS. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA. 2013;310:959 – 68.
8. Neutel JM, Smith DH. Improving patient compliance: a major goal in the management of hypertension. J Clin Hypertens (Greenwich). 2003;5:127–32.
9. Castellano JM, Sanz G, Penalvo JL, Bansilal S, Fernandez-Ortiz A, Alvarez L, Guzman L, Linares JC, Garcia F, D'Aniello F, Arnaiz JA, Varea S, Martinez F, Lorenzatti A, Imaz I, Sanchez-Gomez LM, Roncaglioni MC, Baviera M, Smith SC Jr., Taubert K, Pocock S, Brotons C. Farkouh ME and Fuster V. A polypill strategy to improve adherence: results from the FOCUS project. J Am Coll Cardiol. 2014;64:2071–82.
10. Abraham HM, White CM, White WB. The comparative efficacy and safety of the angiotensin receptor blockers in the management of hypertension and other cardiovascular diseases. Drug Saf. 2015;38:33–54.
11. Whelton PK, Carey RM, Aronow WS, Casey DE Jr., Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr., Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Sr., Williamson JD, Wright JT Jr, 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice guidelines. Circulation. 2018;138:e484–594.
12. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis

C, Aboyans V, Desormais I, Group ESCSD. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–104.
13. Lee HY, Shin J, Kim GH, Park S, Ihm SH, Kim HC, Kim KI, Kim JH, Lee JH, Park JM, Pyun WB, Chae SC. 2018 Korean Society of Hypertension Guidelines for the management of hypertension: part II-diagnosis and treatment of hypertension. Clin Hypertens. 2019;25:20.
14. Kim TW, Yoo BW, Lee JK, Kim JH, Lee KT, Chi YH, Lee JY. Synthesis and antihypertensive activity of pyrimidin-4(3H)-one derivatives as losartan analogue for new angiotensin II receptor type 1 (AT1) antagonists. Bioorg Med Chem Lett. 2012;22:1649–54.
15. Chi YH, Lee H, Paik SH, Lee JH, Yoo BW, Kim JH, Tan HK, Kim SL. Safety, tolerability, pharmacokinetics, and pharmacodynamics of fimasartan following single and repeated oral administration in the fasted and fed states in healthy subjects. Am J Cardiovasc Drugs. 2011;11:335–46.
16. Lee H, Kim KS, Chae SC, Jeong MH, Kim DS, Oh BH. Ambulatory blood pressure response to once-daily fimasartan: an 8-week, multicenter, randomized, double-blind, active-comparator, parallel-group study in Korean patients with mild to moderate essential hypertension. Clin Ther. 2013;35:1337–49.
17. Oh H, Kim KY, Yoo DW, Yoon IM. Blood pressure-lowering effect of Fimasartan Versus comparators: a cross-inference with a systematic review and Meta-analysis through a quality-management system. Clin Ther. 2023;45:437–55.
18. Lee HY, Oh BH. Fimasartan: a new angiotensin receptor blocker. Drugs. 2016;76:1015–22.
19. Kim HC, Lee H, Lee HH, Lee G, Kim E, Song M, Moon J, Seo Y, Korean Society of Hypertension -Hypertension Epidemiology Research Working G. Korea hypertension fact sheet 2022: analysis of nationwide population-based data with a special focus on hypertension in the elderly. Clin Hypertens. 2023;29:22.
20. Choi YJ, Kim B, Rhee TM, Lee HJ, Lee H, Park JB, Lee SP, Han KD, Kim YJ, Kim HK. Augmented risk of ischemic stroke in hypertrophic cardiomyopathy patients without documented atrial fibrillation. Sci Rep. 2022;12:15785.
21. Park CS, Choi YJ, Rhee TM, Lee HJ, Lee HS, Park JB, Kim YJ, Han KD, Kim HK. U-Shaped associations between Body Weight Changes and Major Cardiovascular events in type 2 diabetes Mellitus: a Longitudinal follow-up study of a Nationwide Cohort of Over 1.5 million. Diabetes Care. 2022;45:1239–46.
22. Park JB, Kim DH, Lee H, Hwang IC, Yoon YE, Park HE, Choi SY, Kim YJ, Cho GY, Han K, Ommen SR, Kim HK. Obesity and metabolic health status are determinants for the clinical expression of hypertrophic cardiomyopathy. Eur J Prev Cardiol. 2020;27:1849–57.
23. Choi E-K. Cardiovascular Research using the Korean National Health Information Database. Korean Circ J. 2020;50:754–72.
24. Lee SR, Park CS, Choi EK, Ahn HJ, Han KD, Oh S, Lip GYH. Hypertension Burden and the risk of New-Onset Atrial Fibrillation: a Nationwide Population-based study. Hypertension. 2021;77:919–28.
25. Park CS, Kim B, Rhee TM, Lee HJ, Lee HS, Park JB, Kim YJ, Han KD, Kim HK. Association between renin-angiotensin-aldosterone system blockade and clinical outcomes in patients with hypertension: real-world observation from a nationwide hypertension cohort. Clin Res Cardiol. 2023;112:1577–86.
26. Ferdinand KC, Senatore FF, Clayton-Jeter H, Cryer DR, Lewin JC, Nasser SA, Fiuzat M, Califf RM. Improving Medication Adherence in Cardiometabolic Disease: practical and Regulatory implications. J Am Coll Cardiol. 2017;69:437–51.
27. Sabaté E. Adherence to long-term therapies: evidence for action. World Health Organization; 2003.
28. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353:487–97.
29. Hill MN, Miller NH, Degeest S, American Society of Hypertension, Writing G, Materson BJ, Black HR, Izzo JL Jr., Oparil S, Weber MA. Adherence and persistence with taking medication to control high blood pressure. J Am Soc Hypertens. 2011;5:56–63.
30. Burnier M. Drug adherence in hypertension. Pharmacol Res. 2017;125:142–9.
31. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017;17:230.
32. Miura S, Karnik SS, Saku K. Review: angiotensin II type 1 receptor blockers: class effects versus molecular effects. J Renin Angiotensin Aldosterone Syst. 2011;12:1–7.
33. Zhang H, Unal H, Gati C, Han GW, Liu W, Zatsepin NA, James D, Wang D, Nelson G, Weierstall U, Sawaya MR, Xu Q, Messerschmidt M, Williams GJ, Boutet S, Yefanov OM, White TA, Wang C, Ishchenko A, Tirupula KC, Desnoyer R, Coe J, Conrad CE, Fromme P, Stevens RC, Katritch V. Karnik SS and Cherezov V. Structure of the angiotensin receptor revealed by serial femtosecond crystallography. Cell. 2015;161:833–44.
34. Lee SE, Kim YJ, Lee HY, Yang HM, Park CG, Kim JJ, Kim SK, Rhee MY, Oh BH, Investigators. Efficacy and tolerability of fimasartan, a new angiotensin receptor blocker, compared with losartan (50/100 mg): a 12-week, phase III, multicenter, prospective, randomized, double-blind, parallel-group, dose escalation clinical trial with an optional 12-week extension phase in adult Korean patients with mild-to-moderate hypertension. Clin Ther. 2012;34:552–68. 568 e1-9.
35. Youn JC, Ihm SH, Bae JH, Park SM, Jeon DW, Jung BC, Park TH, Lee NH, Song JM, Yoon YW, Shin ES, Sung KC, Jung IH, Pyun WB, Joo SJ, Park WJ, Shin JH, Kang SM. Efficacy and safety of 30-mg fimasartan for the treatment of patients with mild to moderate hypertension: an 8-week, multicenter, randomized, double-blind, phase III clinical study. Clin Ther. 2014;36:1412–21.
36. Lee HY, Kim CH, Song JK, Chae SC, Jeong MH, Kim DS, Oh BH. 24-Hour blood pressure response to lower dose (30 mg) fimasartan in Korean patients with mild to moderate essential hypertension. Korean J Intern Med. 2017;32:1025–36.
37. Lee JH, Yang DH, Hwang JY, Hur SH, Cha TJ, Kim KS, Kim MH, Chun KJ, Cha GS, Hong GR, Lee SG, Kim DS, Kim DI, Chae SCA, Randomized. Double-blind, Candesartan-controlled, parallel Group Comparison Clinical Trial to evaluate the antihypertensive efficacy and safety of Fimasartan in patients with mild to moderate essential hypertension. Clin Ther. 2016;38:1485–97.
38. Chung WB, Ihm SH, Jang SW, Her SH, Park CS, Lee JM, Chang K, Jeon DS, Yoo KD, Seung KB. Effect of Fimasartan versus Valsartan and Olmesartan on Office and ambulatory blood pressure in Korean patients with mild-to-moderate essential hypertension: a Randomized, Double-Blind, active control, Three-Parallel Group, forced Titration, Multicenter, Phase IV Study (Fimasartan Achieving Systolic blood pressure target (FAST) study). Drug Des Devel Ther. 2020;14:347–60.

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