

META-ANALYSIS

Comparative efficacy and safety of fimasartan in patients with hypertension: A network meta-analysis of randomized controlled trials

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Abstract

Hypertension is a prevalent risk factor for cardiovascular disease. Angiotensin II receptor blockers are widely prescribed to patients with hypertension, while new drugs are continuously developed. However, data on comparative efficacy and safety of novel agents, such as fimasartan, are scarce. Here, we aimed to collect clinical evidence on different angiotensin II receptor blockers using a network meta-analysis. Randomized controlled trials whose follow-up time is within 12 weeks were identified from eight databases via a systematic literature review. Of the 7909 possibly relevant studies, 61 studies with 14,249 adult patients were included in the analysis. These studies were further subjected to quality appraisal using Cochran's Risk of Bias, and sitting systolic blood pressure was considered the primary endpoint. A Bayesian random effect generalized linear model was used for the network meta-analysis, and the treatment rank probability was determined. Olmesartan (standardized mean difference -0.987 [-1.29, -0.729]) and fimasartan (standardized mean difference -0.966 [-1.21, -0.745]) showed the highest rank probabilities (37% and 35%) in the 4-week group, considering the primary endpoint. Furthermore, the odds ratio of adverse events for all agents did not differ significantly from that of the placebo. The treatment rank of angiotensin II receptor blockers varied depending on the outcome type and follow-up period considerably. Fimasartan rapidly lowered blood pressure in 4 weeks, which was further maintained until 12 weeks, indicating its competent efficacy and tolerability. Our findings may help medical practitioners and patients to select the best angiotensin II receptor blocker against hypertension.

KEYWORDS

angiotensin II receptor blockers, antihypertensive treatment, comparative efficacy, essential hypertension, fimasartan, network meta-analysis

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1 | INTRODUCTION

Hypertension can be controlled using different treatment options, including angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium channel blockers (CCBs), and thiazide/thiazide-type diuretics, which are all guideline-recommended as the first-line therapy for hypertension.¹⁻⁴ Among these primary treatment agents, ARBs have gained immense attention owing to their excellent efficacy and safety profile. Recent studies revealed competitive efficacy and markedly better safety outcomes of ARBs compared to ACEIs and diuretics.^{5,6}

ARBs selectively bind to angiotensin II receptor type 1 (AT1) and inhibit the binding of angiotensin II to the AT1 receptor. This obstructs functions of the renin-angiotensin-aldosterone system (RAAS), such as vasoconstriction and sodium retention, and leads to reduced blood pressure.⁵ ACEIs inhibit the angiotensin II directly, whereas ARBs affect only the AT1 receptor and not the enzyme; hence, adverse events (AEs), such as dry cough, rarely occur in patients taking ARBs.^{7,8}

Even if all ARBs have a similar mechanism of action, their diverse pharmacokinetic and pharmacodynamic profiles caused by distinct chemical structures imply possible differences in their efficacy.⁵ For instance, some new ARBs differ in their chemical structures from existing ones and have better blood pressure control effects in the short term.^{9,10} Prior studies also suggested the possibility that the best ARB option may change depending on the prescription and patients' conditions.¹¹⁻¹⁵ So far, the selection criteria to choose the best ARB for patients based on comprehensive and scientific comparison is not yet clear.

Although, some meta-analysis studies have evaluated existing ARBs via head-to-head trials,¹¹⁻¹³ a network meta-analysis (NMA) comparing all ARBs, including novel agents, is still lacking. Even recent NMA studies of ARBs carried out in Japan¹⁴ and Canada¹⁵ did not include the ninth developed ARB, fimasartan. In addition, since the follow-up period varied by each clinical trial, most previous meta-analyses could not avoid heterogeneity issues caused by integrating efficacy results from different time points.^{11,15-17} Therefore, we conducted an NMA through a systematic literature review (SLR) to provide updated clinical information on the comparative efficacy and safety of all ARBs, including the novel fimasartan, focusing on short-term treatment effects, which are crucial in predicting long-term outcomes.

2 | METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for NMA.¹⁸ The protocol for this SLR and NMA study was developed before the study and it clearly defined the objective and plan of the research: Patients, Intervention, Comparator, Outcome, Time, Setting, Study Design (PICOTS-SD) frame; search strategy; eligibility criteria for study selection; review method; data extraction plan; quality assessment method; and statistical analysis plan for the NMA.

2.1 | Search strategy

Randomized controlled trials (RCTs) of ARB were identified from four global databases (PubMed, EMBASE, Cochran Library, and Ovid-Medline) and four Korean databases (ScienceON, Korean Medical Database; Kmbase, Korea Citation Index; KCI, Korea Education and Research Information Service; RISS). The search terms were carefully selected to reflect the PICOTS-SD frame of this study: essential hypertension (Patient: P), ARBs (Intervention and Comparator; I&C), blood pressure and AE (outcome; O), and RCT (Study design; SD). Time (T) and setting(S) were not restricted. We used various synonyms of the PICOTS-SD keyword and translated the words to suit each database. The full search term and details of search history can be found in Table S1, supplement contents.

2.2 | Study selection

The inclusion criteria for study selection were: (1) appropriate medical results for the clinical efficacy of ARBs in adult patients with essential hypertension were reported, (2) medical interventions in which ARB or placebo was administered to the control group and another ARB was administered to the experimental group, and (3) RCTs which could be accessed as an open article, or clinical study reports for RCTs that were provided by pharmaceutical companies. We applied more detailed exclusion criteria to select relevant studies: (1) indication of the investigational product did not reveal essential hypertension or the subjects were not adults (e.g., pediatric patients); (2) interventions in the study excluded at least one ARB monotherapy among the mainly prescribed ARBs (losartan, valsartan, irbesartan, candesartan, telmisartan, olmesartan, fimasartan, and azilsartan), and the comparator presented combination therapy or agents from other drug classes; (3) a study, in which it was impossible to extract the efficacy data described in the protocol; (4) a study excluding the short-term outcomes within 12 weeks; (5) study type: no RCT studies of humans or impossible to access the full text of the research (e.g., abstract-only paper, poster, thesis, opinion, and gray literature.); (6) written in any other language except English or Korean; and (7) in the case of overlapping data, the largest data were selected. Two independent reviewers (S.S.M. and I.S.H.) screened the literature according to the criteria, and all disagreements were resolved after careful review and discussion at each level of screening.

2.3 | Data extraction and quality assessment

The primary efficacy endpoint of this analysis was sitting SBP based on clinical trial guidelines for hypertension. The sitting DBP and ambulatory blood pressure monitoring (ABPM) of SBP and DBP (24 h, daytime, and nighttime), as well as the response rate (RR) and control rate (CR), were considered as secondary efficacy outcomes. In most study, CR means the ratio of patients whose BP was controlled with

SBP < 140 mmHg and DBP < 90 mmHg after completion of treatment, and RR refers to the proportion of patients with SBP decreased by 20 mmHg or more and DBP decreased by 10 mmHg or more after end of treatment. The outcomes wherein RR and CR coexisted were extracted as RR, a more comprehensive concept. AEs, serious AEs (SAEs), and adverse drug reactions (ADRs) were recorded. All the outcomes mentioned so far were extracted from the included studies. Furthermore, we collected basic information, such as publication year, country, authors, follow-up period, patient baseline characteristics (race, sex, age, body mass index), treatment regimens, eligibility criteria for subjects, and trial design. In addition, the adjusted mean change and mean difference (MD) were not used to avoid the heterogeneity problem.¹⁹ The data from each study were obtained using a pre-specified format by one author first and reviewed by the second author. During this process, all discordances were resolved, and the quality of extracted data was controlled. Quality assessment was performed by S.S.M. and I.S.H. independently, the method and result of quality appraisal are detailed in supplement content S2 and Figure S2-1.

2.4 | Data synthesis

The continuous endpoints were sitting SBP, sitting DBP, and ABPM of SBP and DBP (24 h, daytime, nighttime). Differences between the two treatment groups were measured based on the differences in mean change from baseline. The categorical endpoints were safety event (AE, ADR, SAE) rate, RR, and CR. Odds ratio (OR) was used to compare categorical variables between the two treatment groups. To further guarantee clinical homogeneity, the analysis with 12 weeks of the follow-up period was divided into two sub-periods; the first period was ≤ 4 weeks, where short-term effects were identified, whereas the other was > 4 weeks and ≤ 12 weeks. In the case of multiple periods in the same group within one study, the data of the longest period were preferred for analysis. In the case of more than one dose of the same treatment in one study, data from the most prescribed regimen were chosen for analysis. Considering continuous variables, if one study did not present a standard deviation of the mean change, the standard deviation was derived using a correlation from another study with a similar study design. In addition, if only the difference between two groups and p -value were specified in the study, standardized mean difference (SMD) and standard error of SMD were obtained using these values.

2.5 | Statistical analysis

The population was comprised of patients with essential hypertension treated with ARB monotherapy. The target population group exhibited different characteristics and was not homogeneous (e.g., race, region, age). Therefore, we selected a random-effects model (REM) because it is more reliable in meta-analysis and allows diverse studies to draw one conclusion. By combining both direct and indirect

treatment comparisons, this analysis summarizes the RCTs of different treatments and offers point estimates (and 95% confidence intervals [CI]) of associations for specific endpoints.¹³ NMA was performed using a Bayesian randomized effect generalized linear model with a consistency assumption for direct and indirect treatment effects.

The *gemtc* package of R version 4.0.2 was used to implement the NMA. *gemtc* is an interface for the Just Another Gibbs Sampler (JAGS) algorithm that executes the Bayesian estimation of the model parameters through a Markov chain Monte Carlo (MCMC) process. Default priors for treatment effectiveness and heterogeneity parameters were used in all analyses. In the case of continuous variables, we set an adaption phase of 50000 samples, a burn-in phase of 5000 samples, and a thinning interval of 1, resulting in 50000 samples being used for inference in the MCMC process. In the case of binary variables, the simulation model was identical except for a thinning interval of 10, which resulted in 5000 samples. Eventually, a ranking analysis was conducted, which estimated the probability of each treatment to the best, second best, and so on among comparators in the analysis. In each NMA, the geometry of the network, consistency assumption test results, forest plot, summary of each point estimate of different ARBs, and the treatment ranking probability were assessed for each outcome.

3 | RESULTS

In total, 7909 studies were found from eight databases as presumably relevant. Among these, more than 50% were identified as duplicates and excluded. Then 3,642 studies were screened by reviewing their title and abstract, and 170 studies were screened again via full-article review. After level 2 screening, 109 studies were excluded owing to irrelevant population ($n = 3$), intervention ($n = 14$), outcomes ($n = 71$), follow-up period ($n = 6$), study type ($n = 3$), or because they were not full articles ($n = 2$), not written in English or Korean ($n = 6$), or were overlapping publications ($n = 4$). Finally, 61 studies with 14,249 patients were included in this analysis (Figure 1).

Table 1 summarizes the characteristics of the selected studies, indicating the interventions included in the clinical trials conducted in Asia, Europe, America, and Africa. Eleven studies (18%) were implemented as multinational trials. The sample size, which can be interpreted as the power of trial, also varied from 16²⁰ to 930²¹ subjects. Lee et al.²² reported the results of two independent clinical trials, and we considered them as different studies.

The network diagram, forest plot, and treatment ranking probability histogram of primary outcome analysis are illustrated in Figure 2, and the results of the secondary outcome analysis are presented in Figure S3, supplement contents. To analyze the sitting SBP, 22 studies were included in the 4-week group. Studies on irbesartan were not included, as no relevant studies were available in 4 weeks. All comparisons satisfied the consistency assumption, except for telmisartan and olmesartan ($p = 0.02938$). Thus, the hypothesis of consistency in this model was not rejected in general, but the comparison between telmisartan and olmesartan required careful interpretation. The forest plot shows the synthesis results of all data, which indicated a significant

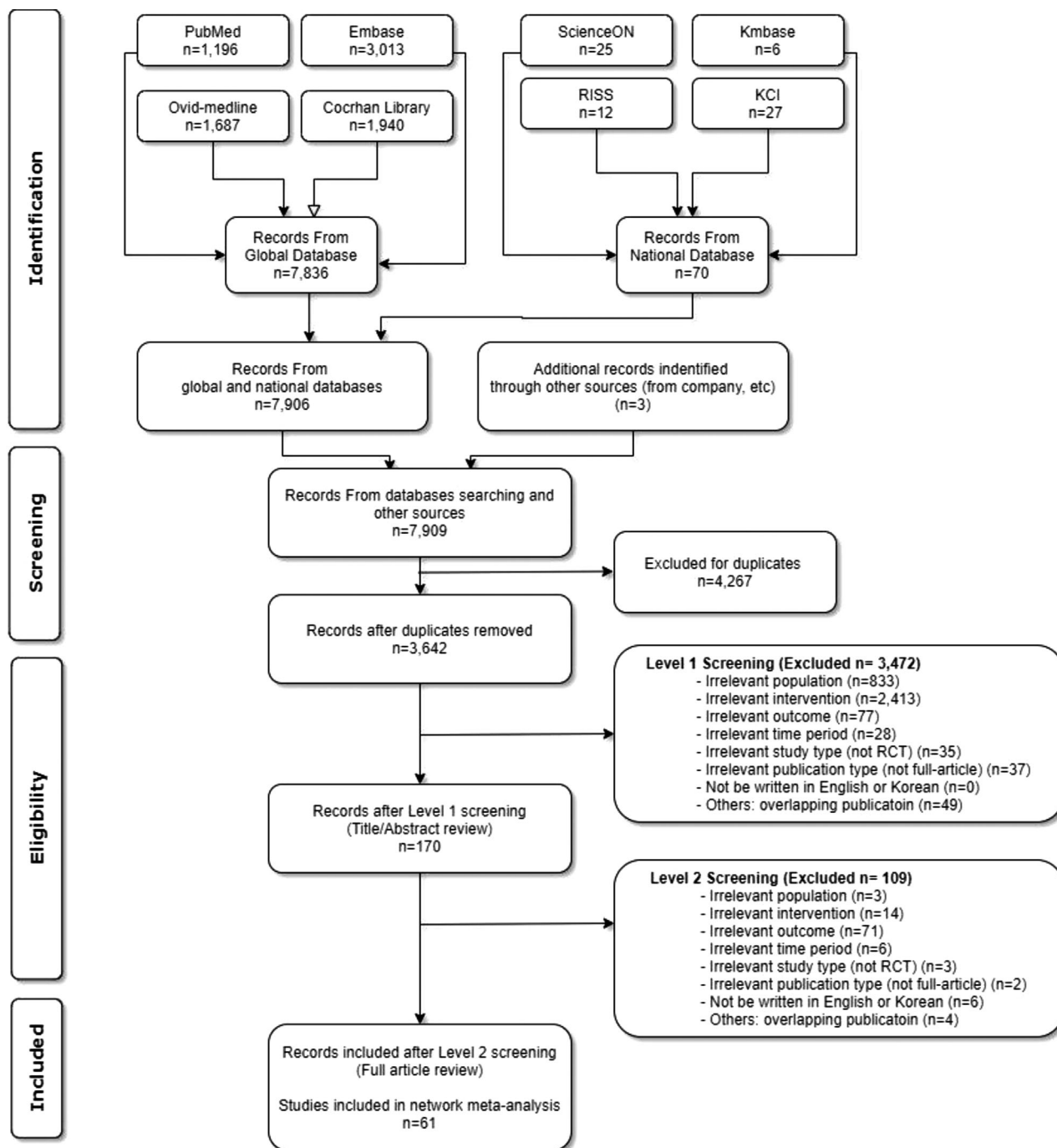


FIGURE 1 PRISMA Flow chart of study selection

reduction in the sitting SBP by all ARBs, except for azilsartan which exhibited a 95% CI of SMD including 0. Table 2 summarizes the ranking probability in the 4-week group, showing that olmesartan had the highest rank probability (SMD: -0.987 [-1.29, -0.729]; 0.371980; ranking 1), followed by fimasartan (SMD: -0.966 [-1.21, -0.745]; 0.356435; ranking 2) and telmisartan (SMD: -0.922 [-1.37, -0.472]; 0.228645; ranking 3). SMD value is considered to be small if 0.2–0.5, medium if 0.5–0.8, large if > 0.8 for effect sizes.²³ The average mean SBP change of olmesartan, which had the highest rank probability, was estimated to be -14.1 ± 10.8 mmHg at 4 weeks.

During NMA of 12-week group for sitting SBP, 42 studies were considered. All comparisons satisfied the consistency assumption, and the forest plot revealed that all agents caused a significant decrease in the sitting SBP (95% CI of SMD compared with placebo was <0 for all agents). Table 3 suggests that telmisartan had the highest rank probability (SMD: -1.22 [-1.77, -0.671]; 0.489065; ranking 1) followed by azilsartan (SMD: -1.10 [-2.14, -0.0389]; 0.226455; ranking 2) and fimasartan (SMD: -0.871 [-1.39, -0.346]; 0.288030; ranking 3). The average mean SBP change in telmisartan, which had the highest rank probability, was estimated to be -16.2 ± 4.0 mmHg at 12 weeks.

TABLE 1 Study characteristics of included RCTs in the SLR and NMA

First author	year	Country	Number of patients	Age(range or mean)	Interventions	Follow-up time (week)
M. Garg [1]	2020	India	700	18–70	AZL, TEL	2,4,12
W. B. Chung [2]	2020	Korea	365	19–70	FIM, VAL, OLM	2,6
H. Y. Lee [3]	2017	Korea	67	20–70	FIM, VAL	4,8
M. Kalikar [4]	2017	India	57	18–	OLM, TEL	2,4,8,12
Y. Kakio [5]	2017	Japan	84	20–85	OLM, AZL	16
J. H. Lee [6]	2016	South Korea	274	19–75	FIM, CAN	4,8,12
K. Ushijima [7]	2015	Japan	77	about 60	VAL, OLM	16
J. C. Youn [8]	2014	South Korea	283	19–75	FIM, VAL, PBO	4,8
R. Fida [9]	2014	Pakistan	80	about 50	VAL, PBO	8
S. Kinoshita [10]	2014	Japan	219	about 60	TEL, CAN	12
H. Lee [11]	2013	South Korea	92	18–70	FIM, VAL	4,8
J. Morii [12]	2012	Japan	54	about 70	OLM, IBR	12
H. Lee	2012	South Korea	61	18–65	FIM, PBO	4
H. Lee	2012	South Korea	195	18–70	FIM, PBO	2,4,8
H. Rakugi [13]	2012	Japan	622	20–	AZL, CAN	16
S. E. Lee [14]	2012	South Korea	485	18–70	FIM, LOS	4,8,12
S. Y. Lim [15]	2011	South Korea	60	about 48	TEL, VAL	12
D. A. De Luis [16]	2010	Spain	34	about 58	OLM, IBR	12
D. A. de Luis [17]	2010	Spain	65	about 58	TEL, OLM	12
S. I. Masuda [18]	2009	Japan	30	18–	LOS, TEL	12
Y. Kawano [19]	2008	Japan	76	25–79	IBR, PBO	6
S. Nakayama [20]	2008	Japan	20	about 63	VAL, OLM, TEL	8
Y. Yano Shimada [21]	2007	Japan	51	about 65	VAL, TEL	12
T. D. Giles [22]	2007	USA	696	18–	OLM, LOS, VAL	2,4,8,12
O. Bahadir [23]	2007	Turkey	42	about 50	LOS, TEL	8
A. Andrés [24]	2006	multinational	106	18–75	VAL, PBO	4,8
H. R. Brunner [25]	2006	Germany, Poland, and the Czech Republic	645	18–	OLM, CAN	1,2,8
J. P. Baguet [26]	2006	France	256	18–75	CAN, LOS, PBO	6
A. Dang [27]	2006	China	325	18–	LOS, IBR	8
C. S. Liau [28]	2005	Taiwan	106	20–75	OLM, LOS	4,8,12
M. Destro [29]	2005	Italy	107	35–75	OLM, VAL	2,8
P. Y. A. Ding [30]	2004	Taiwan	61	18–	TEL, LOS	6
J. R. Zhu [31]	2004	China	330	18–75	TEL, LOS	6
W. B. White [32]	2004	USA and Canada	490	about 55	TEL, VAL	4
T. Skurk [33]	2004	Germany	74	about 46	CAN, PBO	1
H. R. Brunner [34]	2003	Germany, Poland, and the Czech Republic	635	18–	OLM, CAN	8
S. S. Samra [35]	2003	India	45	18–65	TEL, LOS	2,4,6,8
G. Bakris [36]	2002	USA	426	about 53	TEL, VAL	8
G. Mancina [37]	2002	Italy, UK, Netherlands	426	18–75	VAL, IBR	8
R. Fogari [38]	2002	Italy	30	40–60	PBO, LOS VAL, TEL	2,4

(Continues)

TABLE 1 (Continued)

First author	year	Country	Number of patients	Age(range or mean)	Interventions	Follow-up time (week)
M. Hanefeld [39]	2001	Germany	123	35–78	VAL, PBO	12
G. Bakris [40]	2001	USA	654	18–80	CAN, LOS	8
R. Fogari [41]	2001	Italy	156	51–60	PBO, LOS, VAL IBR, CAN	6,12
E. Malacco [42]	2000	Italy	40	31–60	IBR, VAL	4
V. H. Monterroso [43]	2000	9 countries across Europe, Latin America, and Africa	187	about 54	LOS, VAL	6
C. A. Zuschke [44]	1999	USA	92	18–80	CAN, PBO	8
P. Trenkwalder [45]	1998	Germany, Norway, Finland, and the Netherlands	161	30–75	CAN, PBO	12
R. Guthrie [46]	1998	USA and Canada	319	18–	IBR, PBO	6,12
O. K. Andersson [47]	1998	Sweden and Denmark	334	20–80	CAN, LOS, PBO	8
J. Neutel [48]	1997	United States	216	about 55	VAL, PBO	8
G. Paolisso	1997	Italy	16	about 46	LOS, PBO	4
L. S. Ikeda [49]	1997	USA	366	21–75	LOS, PBO	6,12
R. Fogari [50]	1997	Italy	215	18–	IBR, PBO	8
R. L. Byyny [51]	1996	USA	122	21–	LOS, PBO	4
A. H. Van Den Meiracker [52]	1995	The Netherlands	86	18–70	IBR, PBO	1
R. L. Byyny [53]	1995	USA	122	21–	LOS, PBO	4
S. Sinha [54]	2021	India	303	18–	AZL, TEL	2,6
J. M. Neutel [55]	2000	USA	146	65–	VAL, PBO	8
A. Zanchetti [56]	1997	Italy	201	about 55	IBR, PBO	8
Y. Lacourcière	2004	USA, Canada, Europe, South Africa	930	18–	TEL, VAL	6,8
Y. Lacourcière [57]	1999	Canada and France	268	20–80	CAN, LOS, PBO	4,8
CSR ^a	2020	South Korea	341	19–70	FIM, LOS	4,8,12

Abbreviations: AZL, azilsartan; C, candesartan cilexetil; CSR, clinical study report; FIM, fimasartan; IBR, irbesartan; LOS, losartan; NMA, network meta-analysis; OLM, olmesartan; PBO, placebo; RCT, randomized controlled trial; SLR, systematic literature review; TEL, telmisartan; USA, United States of America; VAL, valsartan.

^aCSR is provided from Boryung Co., Ltd. (not published).

The results of sitting DBP and SBP were similar in the 4-week group but were different in the 12-week group; for the sitting DBP in the 12-week group, azilsartan (SMD: -1.38 [-2.34, -0.428]; 0.542080) had the highest rank probability with a first ranking, followed by telmisartan (SMD: -1.34 [-1.83, -0.850]; 0.402295; ranking 2). For ABPM—SBP and DBP (24 h, daytime, nighttime), NMA for the 4-week group was not possible due to limited data and thus inability to build a network. Therefore, the analysis results were obtained only for data between 5 and 12 weeks in ABPM. Table 4 summarizes the number of studies included in each outcome analysis, results of the consistency assumption test, significance of treatments that could be identified using forest plot, and agents with the highest probability from first to third ranking; all figures and rank probability are available in Figures S3–S7,

supplemental contents. Analysis results for CR could not be obtained owing to insufficient data, whereas RR was analyzed to show similar results with that of sitting SBP and DBP, but slightly different in specific ranking probability (see Table 3 and Figure S7, supplemental contents).

Safety outcomes, such as AEs, ADRs, and SAEs were then analyzed to show all networks have passed the consistency assumption test (see Figure S8, supplemental contents). The ORs of all ARBs did not differ statistically significantly from the placebo for AE and ADR, which indicated that all ARBs were as safe as placebos. Therefore, Table 3 does not contain a treatment rank probability of safety outcomes. In the SAE analysis considered with statistical significance, the estimates of OR in azilsartan, candesartan, fimasartan, and losartan did not differ from that of the placebo, while the estimates of telmisartan and olmesartan

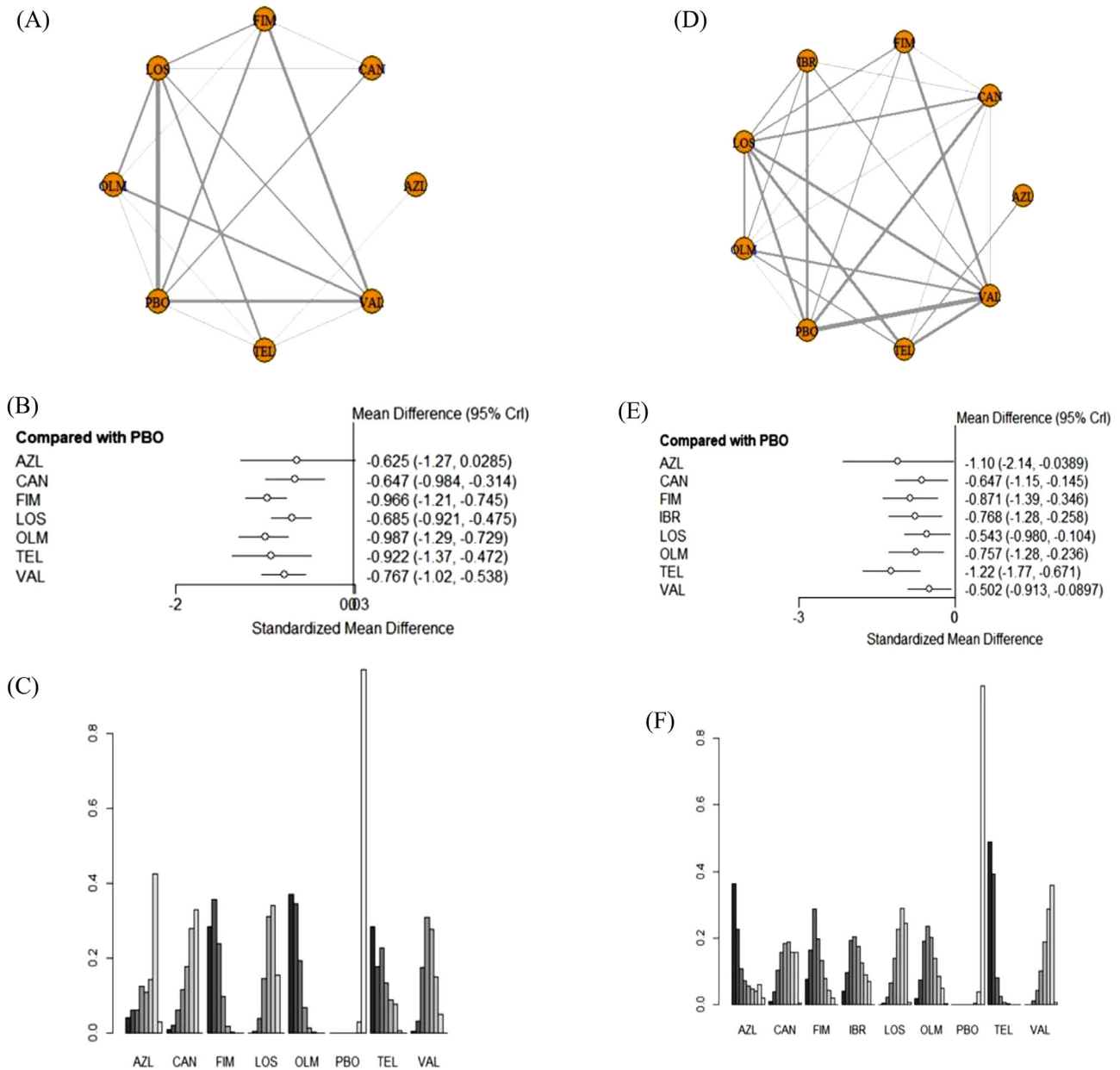


FIGURE 2 NMA result of primary endpoint: sitting SBP. (A) Network diagram in 4-week group. (B) Forest plot in 4-week group. (C) Rank probabilities histogram in 4-week group. (D) Network diagram in 12-week group. (E) Forest plot in 12-week group. (F) Rank probabilities histogram in 12-week group. The thickness of edge of A represents the number of studies underlying each comparison. (C, F) Histograms provide rank probability for each treatment (from left to right) to be the best, the second best, the third second etc. AZL, azilsartan; CAN, candesartan cilexetil; FIM, fimasartan; IBR, irbesartan; LOS, losartan; OLM, omlsartan; PBO, placebo; TEL, telmisartan; and VAL, valsartan

were higher than those of the placebo, and the estimates of irbesartan and valsartan were lower.

4 | DISCUSSION

This is a comprehensive study that compared the effectiveness and safety of all ARBs. We synthesized all possible relevant RCTs of ARBs and compared their efficacy using sitting SBP as a primary outcome because it is regarded as an important surrogate endpoint for cardiovascular disease. In a short period of 4 weeks, olmesartan,

fimasartan, and telmisartan exhibited better performance than the others, and azilsartan, telmisartan, and fimasartan worked better than other ARBs in a moderately short period of 12 weeks.

When focusing on the novel agent, the efficacy of fimasartan in rapidly lowering blood pressure lasted for 12 weeks, which was also supported by another endpoint, RR, where fimasartan ranked second in both the 4-week and 12-week groups. All significant NMAs showed that fimasartan maintained a high rank, and its efficacy was evident in ABPM–DBP nighttime where the probability of it being preferred as a first-rank was the highest. Moreover, azilsartan which was the most recently developed, exhibited its efficacy in the 12-week group and its

TABLE 2 Treatment ranking probability of sitting SBP in the 4-week group

Rank probability of sitting SBP in the 4-week group								
Ranking	1	2	3	4	5	6	7	8
AZL	0.042285	0.062735	0.061485	0.125965	0.109965	0.142855	0.425180	0.029530
CAN	0.009570	0.021910	0.063120	0.117540	0.176970	0.280850	0.329630	0.000410
FIM	0.285060	0.356435	0.239755	0.097280	0.017885	0.003225	0.000360	0
LOS	0.000380	0.004400	0.039035	0.146920	0.312685	0.341225	0.155355	0
OLM	0.371980	0.345795	0.193470	0.069270	0.015035	0.003800	0.000650	0
TEL	0.285195	0.176900	0.228645	0.133865	0.090145	0.076850	0.008355	0.000045
VAL	0.005530	0.031825	0.174490	0.309160	0.277315	0.151045	0.050635	0
PBO	0	0	0	0	0	0.000150	0.029835	0.970015

Preferred direction = -1, AZL, azilsartan; C, candesartan cilexetil; FIM, fimasartan; IBR, irbesartan; LOS, losartan; OLM, olmesartan; PBO, placebo; TEL, telmisartan; and VAL, valsartan. Ranking nearer 1 suggest greater efficacy and each value means the probability that interventions are selected as corresponding ranking.

Bold values indicate the highest rank probabilities in each week group.

TABLE 3 Treatment ranking probability of sitting SBP in the 12-week group

Rank probability of sitting SBP in the 12-week group									
Ranking	1	2	3	4	5	6	7	8	9
AZL	0.362780	0.226455	0.108435	0.072845	0.047505	0.047505	0.041880	0.061740	0.020780
CAN	0.009890	0.038945	0.102570	0.156230	0.184460	0.188610	0.156995	0.156905	0.005395
FIM	0.076415	0.163330	0.288030	0.197060	0.133295	0.078960	0.042235	0.020060	0.000615
IBR	0.041930	0.097690	0.193975	0.203735	0.174860	0.126600	0.089695	0.069890	0.001625
LOS	0.000280	0.004115	0.022330	0.066245	0.138480	0.227075	0.289925	0.245150	0.006400
OLM	0.019345	0.075300	0.191445	0.235380	0.202205	0.138600	0.086815	0.048960	0.001950
TEL	0.489065	0.392545	0.081600	0.025630	0.008210	0.002360	0.000515	0.000070	0.000005
VAL	0.000095	0.001620	0.011610	0.042840	0.100930	0.189490	0.287730	0.357950	0.007735
PBO	0	0	0.000005	0.000035	0.000180	0.0008	0.004210	0.039275	0.955495

Preferred direction = -1, AZL, azilsartan; C, candesartan cilexetil; FIM, fimasartan; IBR, irbesartan; LOS, losartan; OLM, olmesartan; PBO, placebo; TEL, telmisartan; and VAL, valsartan. Ranking nearer 1 suggest greater efficacy and each value means the probability that interventions are selected as corresponding ranking.

Bold values indicate the highest rank probabilities in each week group.

RR was more effective in DBP. It presented the highest rank probability at the first rank for sitting DBP, ABPM-24H SBP, and RR in the 12-week group. This result was supported by the findings of Nakajima et al.¹⁴ who concluded that azilsartan was more effective than other ARBs for lowering SBP and DBP in Japanese patients.

As the nighttime SBP and the 24 h DBP were difficult to control using all ARBs, further exploration is required with other drug classes and combination therapies to supplement the limitation of ARB monotherapy. The efficacy of olmesartan was better than that of losartan and valsartan in most cases, such as sitting SBP, sitting DBP, ABPM-24H, ABPM-Daytime, and RR. This result was consistent with previous studies conducted to compare olmesartan with other ARBs.¹¹ However, our study, by analyzing ABPM data, showed that losartan has better effectiveness than olmesartan for nighttime DBP, and it may be preferred for controlling DBP at night.

Although, the overall safety of all ARBs concerning AEs and ADRs was comparable to that of the placebo as previous

studies revealed,^{11,15,24} some significant results and differences were detected within ARBs in SAEs. Telmisartan and olmesartan, whose efficacies were considerably excellent, had significantly higher ORs than the placebo in SAEs, whereas the ORs of irbesartan and valsartan were significantly lower than those of the placebo. The ORs of the other agents in SAEs did not differ significantly from those in the placebo group. This result implied that novel ones, such as azilsartan and fimasartan, exhibited competitive safety profile compared to their performance in efficacy. However, since SAEs do not directly reflect AEs caused by the investigational product, the conclusion on safety issues should not be drawn based solely on SAEs. When a more precise safety indicator, ADR, was considered, it was clear that ARBs did not have safety issues overall, as none of them differed significantly from the placebo.

This is the first NMA study to include all new ARBs, such as fimasartan and azilsartan. Additionally, we analyzed the ABPM data, which could not be explored in preliminary studies due to insufficient data, as

TABLE 4 Treatment ranking probability of sitting SBP in the 12-week group

Outcome (week)	Number of included studies	Number of comparisons not satisfying consistency assumption test	Forest plot (Statistical significance of meta-analysis)	Highest probability of treatment rank at top 3 rankings
siSBP (w4)	22	1 (TEL vs. OLM)	All estimates were significant except for one agent (AZL)	- Ranking 1: OLM (0.37) - Ranking 2: FIM (0.36) - Ranking 3: TEL (0.23)
siSBP (w12)	42	0	All estimates were significant	- Ranking 1: TEL (.49) - Ranking 2: AZL (0.23) - Ranking 3: FIM (0.29)
siDBP (w4)	22	1 (TEL vs. OLM)	All estimates were significant except for one agent (AZL)	- Ranking 1: OLM (0.37) - Ranking 2: FIM (0.35) - Ranking 3: TEL (0.22)
siDBP (w12)	43	0	All estimates were significant	- Ranking 1: AZL (0.52) - Ranking 2: TEL (0.51) - Ranking 3: FIM (0.36)
ABPM-24H-SBP (w12)	21	0	All estimates were significant	- Ranking 1: AZL (0.51) - Ranking 2: TEL (0.50) - Ranking 3: FIM (0.25)
ABPM-24H-DBP (w12)	21	0	All estimates were not significant except for one agent (TEL)	- Ranking 1: TEL (0.47) ^a
ABPM-Daytime-SBP (w12)	14	0	All estimates were significant	- Ranking 1: CAN (0.65) - Ranking 2: FIM (0.28) - Ranking 3: IBR (0.23)
ABPM-Daytime-DBP (w12)	13	0	All estimates were significant except for one agent (TEL)	- Ranking 1: CAN (0.72) - Ranking 2: FIM (0.33) - Ranking 3: IBR (0.25)
ABPM-Nighttime-SBP (w12)	12	2 (TEL vs. OLM/VAL vs. TEL)	All estimates were not significant	The efficacy of all agents was not statistically significant
ABPM-Nighttime-DBP (w12)	11	0	All estimates were significant except for one agent (TEL)	- Ranking 1: FIM (0.43) - Ranking 2: CAN (0.26) - Ranking 3: LOS (0.22)
RR (W4)	7	0	All estimates were significant except for one agent (CAN)	- Ranking 1: OLM (0.53) - Ranking 2: FIM (0.51) - Ranking 3: VAL (0.39)
RR (W12)	19	1 (PBO vs. LOS)	All estimates were significant	- Ranking 1: AZL (0.84) - Ranking 2: FIM (0.29) - Ranking 3: TEL (0.30)
AE	36	0	All estimates were not significantly different with PBO (95% CI included 0)	
ADR	16	0	All estimates were not significantly different with PBO (95% CI included 0)	
SAE	16	0	4(AZL, CAN, FIM, LOS) estimates were not significantly different with PBO (95% CI included 0), 2(TEL, OLM) estimates were significantly higher than PBO(95% CI > 0), 2(IBR,VAL) estimates were significantly lower than PBO(95% CI < 0)	

Abbreviations: ADR, adverse drug reaction; AE, adverse event; AZL, azilsartan; CAN, candesartan cilexetil; CI, confidence interval; FIM, fimasartan; IBR, irbesartan; LOS, losartan; NMA, network meta-analysis; OLM, omlesartan; PBO, placebo; RR, response rate; SAE, serious adverse event; siSBP, sitting systolic blood pressure; TEL, telmisartan; VAL, valsartan.

^aThe efficacy of other agents was not statistically significant.

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shown in Wang et al.¹¹ and Nakajima et al.¹⁴ We clarified that the best ARB depends on the outcome measure desired by the practitioner and the patient. Each ARB produced different efficacy results based on the follow-up period and measurements in different situations (daytime, nighttime, sitting SBP, and sitting DBP). This study presented

comparative effectiveness of short-term effects in ARBs, including periods as short as 4 weeks, which were not comprehensively elaborated in previous studies.

This study had several limitations. First, we could not explore the outcomes that reflect the duration of controlling blood pressure in

each ARB, such as the trough and peak ratio and smoothness index, as it was difficult to synthesize them and to interpret the meaning of the integrated value. Nevertheless, we could derive blood pressure-lowering persistency of ARBs using the results of ABPM analysis. Second, it was impossible to further analyze CR and include every dosage of ARBs in the RCTs due to the lack of data. In case of several dosages of one intervention in a single study, we selected the most prescribed dose. Third, we only used data on blood pressure change as the crude mean instead of the adjusted data. Although, the adjusted mean using regression was more precise, it would present a risk of heterogeneity during integration because the exact method or all considered variables in the adjusting process were not clear. Using crude data was also recommended for synthesizing RCT results since most of the important confounding variables were already controlled by the study design. Finally, this NMA focused on only the short-term effects; hence, follow-up analysis is required to obtain information on the long-term comparative efficacy and safety of ARBs.

In conclusion, through a comprehensive NMA including all commercially accessible ARBs, this research demonstrated that the efficacy of ARBs varied depending on the outcome type and follow-up duration. Although, a careful review on the result of this study will be required to choose the best ARB for patients' conditions, it is obvious that novel agents showed excellent efficacy and safety profile overall. Specifically, fimasartan, exerted a powerful and rapid BP-lowering effect in 4 weeks, which lasted 12 weeks, and exhibited competitive efficacy and safety compared to all other ARBs. Follow-up research on long-term effects may be required, and the detailed finding of each agent can be a useful reference for medical practitioners and patients to select the best ARB.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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