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ORIGINAL ARTICLE
Hypertension and Circulatory Control

Comparative Effectiveness of Angiotensin II Receptor Blockers in Patients With Hypertension in Japan

— Systematic Review and Network Meta-Analysis —

Tadashi Nakajima, MD; Akinori Oh, BSc; Shun Saita, BSc;
Takuo Yoshida, BSc; Mitsuru Ohishi, MD, PhD; Nobuhiro Nishigaki, PhD

Background: Angiotensin II receptor blockers (ARBs) are widely used for the management of hypertension in Japan; however, comparative efficacy data within the ARB drug class remain limited.

Methods and Results: This systematic literature review identified randomized controlled trials (RCT) indexed in PubMed and Ichushi in Japanese patients with hypertension receiving ARB monotherapy (azilsartan, candesartan cilexetil, irbesartan, losartan potassium, olmesartan medoxomil, telmisartan, valsartan) in at least 1 arm. Of 763 RCTs identified, 77 met the eligibility criteria; of which, 37 reported mean change in systolic blood pressure (SBP) and diastolic blood pressure (DBP) from baseline in the office setting and were used to construct the network. A fixed-effects model (FEM) showed the effect of each drug vs. the reference, azilsartan. Using the FEM, the mean (95% credible interval) change from baseline in SBP/DBP for candesartan cilexetil, irbesartan, losartan potassium, olmesartan medoxomil, telmisartan, and valsartan was 3.8 (2.9–4.8)/2.6 (2.0–3.1), 4.8 (2.0–7.5)/3.7 (1.8–5.6), 3.0 (0.8–5.1)/1.9 (0.5–3.3), 3.2 (1.2–5.1)/2.7 (1.3–4.1), 3.2 (0.8–5.6)/2.0 (0.3–3.6), and 3.1 (1.1–5.1)/2.4 (1.1–3.8) mmHg, respectively.

Conclusions: The results of this meta-analysis provide evidence that azilsartan has a more favorable efficacy profile than the other ARBs in reducing SBP and DBP.

Key Words: Angiotensin II receptor blockers; Antihypertensive treatment; Azilsartan; Network meta-analysis

Hypertension is a medical condition that increases the risk of cardiovascular diseases, including stroke and heart failure.[1] An estimated 7.5 million deaths occur from hypertension every year worldwide,[2] of which 1.5 million are in the South-East Asia region.[3] In 2010, approximately 43 million individuals were living with hypertension in Japan,[4] which is expected to increase owing to the aging population.[5] Despite significant advancements in the diagnosis and treatment of hypertension, the control rates of hypertension remain low, particularly in young and middle-aged patients with hypertension and thus, targeting these populations is vital; however, this remains a major challenge in Japan.[6]

Effective approaches for the treatment of hypertension are paramount for reducing the risk of complications. Over the years there is a consensus that patients with persistent blood pressure (BP) readings of 140/90 mmHg or higher should undergo treatment.[7] The Japanese Society of Hypertension (JSH) define hypertension as systolic BP (SBP) >140 mmHg and diastolic BP (DBP) >90 mmHg.[5] According to the JSH, the general target is to reduce SBP/DBP to <140/90 mmHg, with normal BP classified as <120/80 mmHg.[5]

Lifestyle modifications and antihypertensive drug therapy are 2 key approaches for the treatment of hypertension.[5] Lifestyle modifications include dietary changes, such as a reduction in salt intake, weight control, exercise, smoking cessation, and a reduction in alcohol consumption.[5] There are several antihypertensive drug classes that are currently in use, including calcium channel blockers (CCBs), angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, renin inhibitors, diuretics, and β-blockers.[5] The 2019 JSH guidelines recommend ARBs, CCBs, ACE inhibitors, and low-dose diuretics as first-line treatment for hypertension in Japan.[5]

At the time of writing, 7 ARBs were available in Japan: azilsartan, candesartan cilexetil (CAN), irbesartan, losartan potassium (LOS), olmesartan medoxomil (OLM),

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Japan Medical Office, Takeda Pharmaceutical Company Limited, Tokyo (T.N., A.O., S.S., T.Y., N.N.); Department of Cardiovascular Medicine and Hypertension, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima (M.O.), Japan

M.O. is a member of *Circulation Reports*' Editorial Team.

Mailing address: Tadashi Nakajima, MD, Japan Medical Office, Takeda Pharmaceutical Company Limited, 1-1 Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo 103-8668, Japan. E-mail: tadashi.nakajima@takeda.com

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Table 1. Population, Intervention, Comparator, Outcomes and Study Design (PICOS) Eligibility Criteria

PICOS framework	Eligibility criteria
Patient population	Patients with hypertension[A]
Intervention/comparators	ARB monotherapies[B] (in at least 1 arm) vs. other antihypertensive medications (e.g., AZL, CAN, IRB, LOS, OLM, TEL, VAL) and/or PBO
Publication/study design	RCTs[C]
Outcomes	SBP and/or DBP (office, home, or ABPM)
Publication period	January 1, 1995–August 31, 2018
Geography	Japan

[A]The definition of hypertension depended on the patient population of each randomized controlled trial (RCT); hypertension of any grade, with or without complications, was included to avoid reducing the sample size. [B]At approved doses in Japan; the doses of the medications were not fixed throughout the RCTs. [C]RCTs with no PBO run-in period or no prior antihypertensive treatment were excluded from the analysis. ABPM, ambulatory blood pressure monitoring; ARB, angiotensin II receptor blocker; AZL, azilsartan; CAN, candesartan cilexetil; DBP, diastolic blood pressure; IRB, irbesartan; LOS, losartan potassium; OLM, olmesartan medoxomil; PBO, placebo; SBP, systolic blood pressure; TEL, telmisartan; VAL, valsartan.

telmisartan, and valsartan. Real-world evidence indicates that ARBs are one of the most commonly prescribed antihypertensive drug classes in Japan.[8] As such, it is important that Japanese physicians and patients have access to evidence that examines the comparative efficacy of available antihypertensive drugs used as monotherapy within the ARB drug class in order to make more informed treatment decisions. However, much of the efficacy and safety data available to date for ARBs have been reported from clinical trials that compared the efficacy of an individual ARB vs. drugs from other antihypertensive classes (e.g., ACE inhibitors, and CCBs) or vs. placebo. In-class comparison of the efficacy of ARBs as monotherapy is limited. Thus, we performed the present network meta-analysis (NMA) using literature related to placebo-controlled and/or comparative randomized controlled trials (RCTs) to assess the relative efficacy of the approved ARBs in Japan.

Methods

This analysis consisted of 2 sequential approaches: a systematic literature review and an NMA. Both parts of the analysis complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for NMAs.[9] The primary objective of the study was to compare the relative efficacy of ARBs with respect to changes from baseline in SBP and DBP in the office and home setting, as well as in mean ambulatory BP.

Systematic Literature Review

The Population, Intervention, Comparator, Outcomes and Study Design (PICOS) framework was adopted to conduct the systematic literature search (**Table 1**). The search was conducted on November 14, 2018 for studies indexed in PubMed and Ichushi between January 1, 1995 and August 31, 2018. Search strategies were based on the combination of title words, abstract words, and indexing terms (e.g., Medical Subject Headings [MeSH]) and their relationship using Boolean terms (**Supplementary Table**).

Publications were included that described RCTs of patients in Japan with primary hypertension in which patients in at least 1 arm of the study were receiving treatment with ARB monotherapy. The RCTs were required to include at least 1 treatment arm with single-agent azilsartan, CAN, irbesartan, LOS, OLM, telmisartan, and valsartan. The definition of hypertension depended upon the study.

In order to be selected for inclusion in the evidence network, studies had to report data on at least 1 of 5 endpoints chosen based on previous reports,[10–15] namely BP in the office setting (mean change in SBP and/or DBP from baseline), BP in the home setting (mean change in SBP and/or DBP from baseline), and change from baseline in mean ambulatory BP monitoring (ABPM; SBP and/or DBP). Trials that did not meet these requirements were excluded.

Study Selection and Data Extraction

Two reviewers (T.A. and H.M.) independently screened the titles and abstracts of the identified citations against the aforementioned selection criteria to identify potentially relevant studies. Any conflicting views were resolved by a third reviewer (S.D.). Studies that met the selection criteria were retained and the full-text articles reviewed. Extracted data included the study description, patient demographics, participant disease characteristics, treatment interventions, and study outcomes. Justification was provided for studies that were disregarded during the full-text review (e.g., off-label prescription, lack of prior antihypertensive treatment, or lack of a placebo run-in period).

NMA

The network was created based on studies reporting office BP. Statistical analyses were conducted using the statistical program R version 3.5.1 (https://cran.r-project.org) and Bayesian inference with Gibbs sampling. All baseline and intervention effect parameters were given flat (uninformative) prior distributions corresponding to a normal (0, 1,000) prior distribution and the between-study standard deviation flat uniform distributions with an appropriately large range given the scale of measurement. The methodology used in this study follows guidance from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on indirect treatment comparisons.[16] Statistical heterogeneity was assessed using the I^2 statistic. Age, weight, body mass index, sex, baseline SBP and DBP, and baseline comorbidities were assessed for between-study heterogeneity.

The fixed-effects model (FEM) and random-effects model (REM) weighted average methods were used in this study. The FEM assumed that the studies were measuring a single true effect, whereas the REM assumed multiple true effects. The patient population in this study consisted

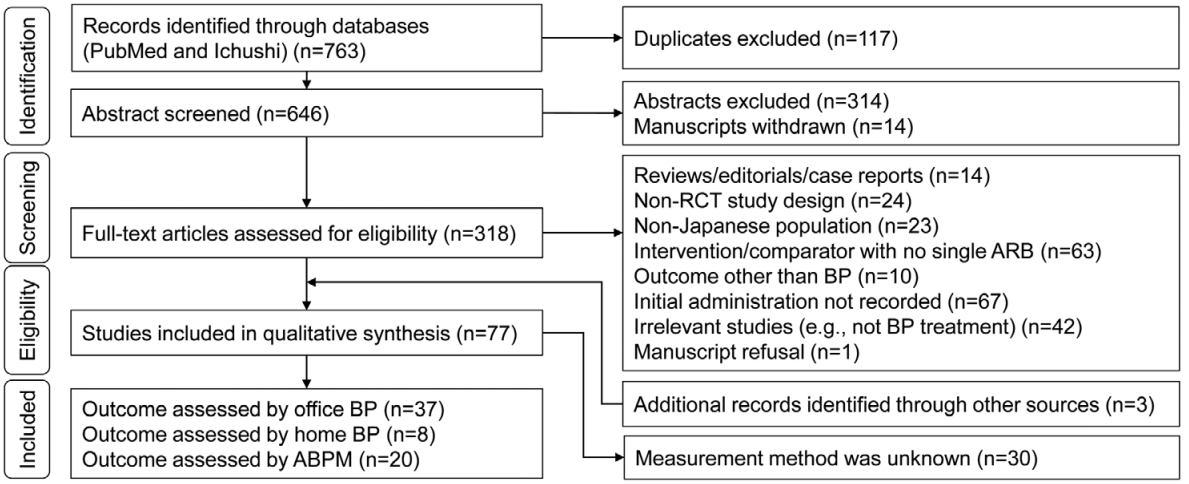

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study selection process. ABPM, ambulatory blood pressure monitoring; ARB, angiotensin II receptor blocker; BP, blood pressure; RCT, randomized controlled trial.

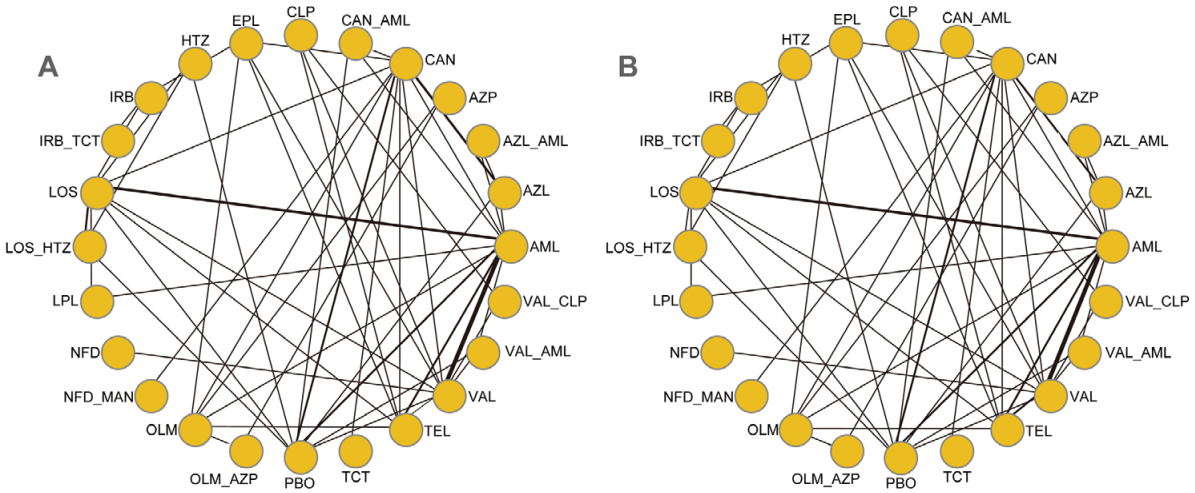

Figure 2. Network of treatment comparisons among 37 clinical trials (**Table 2**), where blood pressure (BP) was measured in the office setting. (**A**) Systolic blood pressure; (**B**) diastolic blood pressure. Each node (orange circles) represents the individual treatments from the randomized controlled trials. Comparisons are linked with a line, the thickness of which corresponds to the number of trials that assessed the comparison. AML, amlodipine besilate; AZL, azilsartan; AZP, azelnidipine; CAN, candesartan cilexetil; CLP, cilnidipine; EPL, enalapril maleate; HTZ, hydrochlorothiazide; IRB, irbesartan; LOS, losartan potassium; LPL, lisinopril hydrate; NFD, nifedipine; OLM, olmesartan medoxomil; PBO, placebo; TCT, trichlormethiazide; TEL, telmisartan; VAL, valsartan.

of hypertensive Japanese patients who were receiving interventions that included ARB monotherapy. For this reason, the relevant effect modifiers that assessed for heterogeneity were predicted to be similar among studies, and thus, the FEM was adopted based on the assumption that the studies were measuring a single true effect. To improve the robustness of the results, the REM was also used.

The robustness of the base model was examined. Publication bias was assessed using funnel plots. A sensitivity analysis was performed to assess the effect of study quality, to control for differences in baseline characteristics, or to test the robustness of assumptions used in the NMA.

Assessment of Convergence

Convergence was assessed using the Brooks-Gelman-Rubin diagnostic. The first 20,000 simulations were discarded to avoid the burn-in period. Results were presented based on a further sample of at least 50,000 simulations, or until convergence. Finally, the Monte Carlo standard error reflected both the number of simulations and the degree of

Table 2. Studies Comprising the Network

Network	Number of studies	Study code	Reference	SBP	DBP
AZL vs. AML	1	L086_1	*Clin Ther* 2014; **36:** 711–721	✓	✓
AZL_AML vs. AML	1	L086_1	*Clin Ther* 2014; **36:** 711–721	✓	✓
CAN vs. AML	1	L154_1	*Clin Ther* 2012; **34:** 838–848	✓	✓
CAN_AML vs. AML	1	L154_1	*Clin Ther* 2012; **34:** 838–848	✓	✓
LOS vs. AML	4	L179_1	*J Am Soc Hypertens* 2012; **6:** 73–82	✓	
		L379_1	*Diabetes Care* 2005; **28:** 1862–1868	✓	✓
		L412_1	*Heart Vessels* 2004; **19:** 13–18	✓	✓
		L419_1	*Clin Exp Nephrol* 2003; **7:** 221–230	✓	✓
LPL vs. AML	1	L412_1	*Heart Vessels* 2004; **19:** 13–18	✓	✓
OLM vs. AML	1	L711_1	*J Blood Press (Ketsuatsu)* 2006; **13:** 563–567 [in Japanese]	✓	✓
PBO vs. AML	2	L154_1	*Clin Ther* 2012; **34:** 838–848	✓	✓
		L589_1	*J Blood Press (Ketsuatsu)* 2006; **17:** 314–328 [in Japanese]	✓	✓
TEL vs. AML	2	L155_1	*Clin Exp Nephrol* 2003; **7:** 221–230	✓	✓
		L602_1	*Ther Res* 2009; **30:** 1597–1604 [in Japanese]	✓	✓
VAL vs. AML	6	L078_1	*Clin Neuropharmacol* 2014; **37:** 129–132	✓	✓
		L200_1	*J Hum Hypertens* 2011; **25:** 334–339	✓	✓
		L403_1	*J Am Coll Cardiol* 2004; **43:** 2116–2123	✓	✓
		L409_1	*Am J Hypertens* 2004; **17:** 112–117	✓	✓
		L589_1	*J Blood Press (Ketsuatsu)* 2010; **17:** 314–328 [in Japanese]	✓	✓
		L733_1	*Ther Res* 2004; **25:** 1585–1589 [in Japanese]	✓	✓
VAL_AML vs. AML	1	L589_1	*J Blood Press (Ketsuatsu)* 2010; **17:** 314–328 [in Japanese]	✓	✓
AZL_AML vs. AZL	1	L086_1	*Clin Ther* 2014; **36:** 711–721	✓	✓
CAN vs. AZL	3	L153_1	*Hypertens Res* 2012; **35:** 552–558	✓	✓
		TAK-536/CCT-01_1 (ClinicalTrials.gov ID: NCT01289132)	NDA review report [in Japanese]	✓	✓
		TAK-536/CCT-005_1 (JAPIC CTI ID: JapicCTI-090762)	NDA review report [in Japanese]	✓	✓
PBO vs. AZL	1	TAK-536/CCT-001_1 (ClinicalTrial.gov ID: NCT01289132)	NDA review report [in Japanese]	✓	✓
OLM vs. AZP	1	L255_1	*Hypertens Res* 2009; **32:** 1148–1154	✓	✓
OLM_AZP vs. AZP	1	L255_1	*Hypertens Res* 2009; **32:** 1148–1154	✓	✓
CAN_AML vs. CAN	1	L154_1	*Clin Ther* 2012; **34:** 838–848	✓	✓
EPL vs. CAN	1	L761_1	*J Clin Ther Med (Rinshoiyaku)* 1998; **14:** 871–918 [in Japanese]	✓	✓
LOS vs. CAN	1	L316_1	*Mol Med Rep* 2008; **1:** 391–393	✓	✓
NFD_MAN vs. CAN	1	L445_1	*Circulation* 2001; **104:** 281–285	✓	✓
OLM vs. CAN	1	L560_1	*Hypertens Res* 2010; **33:** 790–795	✓	✓
PBO vs. CAN	2	L154_1	*Clin Ther* 2012; **34:** 838–848	✓	✓
		TAK-536/CCT-001_1 (ClinicalTrial.gov ID: NCT01289132)	NDA review report [in Japanese]	✓	✓
TCT vs. CAN	1	L640_1	*J Blood Press (Ketsuatsu)* 2008; **15:** 896–897 [in Japanese]	✓	✓
TEL vs. CAN	1	L316_1	*Mol Med Rep* 2008; **1:** 391–393	✓	✓
VAL vs. CAN	1	L316_1	*Mol Med Rep* 2008; **1:** 391–393	✓	✓
PBO vs. CAN_AML	1	L154_1	*Clin Ther* 2012; **34:** 838–848	✓	✓
TEL vs. CLP	1	L625_1	*Prog Med* 2009; **29:** 1393–1397 [in Japanese]	✓	✓
VAL vs. CLP	1	L491_1	*J Clin Ther Med (Rinshoiyaku)* 2015; **31:** 97–114 [in Japanese]	✓	✓
VAL_CLP vs. CLP	1	L491_1	*J Clin Ther Med (Rinshoiyaku)* 2015; **31:** 97–114 [in Japanese]	✓	✓
IRB vs. EPL	1	L648_1	*J Clin Ther Med (Rinshoiyaku)* 2008; **24:** 507–542 [in Japanese]	✓	✓
OLM vs. EPL	1	L738_1	*J Clin Ther Med* 2004; **20:** 115–159	✓	✓

(**Table 2** continued the next page.)

Network	Number of studies	Study code	Reference	SBP	DBP
TEL vs. EPL	1	L750_1	*Jpn Pharmacol Ther (Yakuritochiryo)* 2002; **30:** 639–660 [in Japanese]	✓	✓
VAL vs. EPL	1	L760_1	*J Clin Ther Med (Rinshoiyaku)* 1998; **14:** 2355–2404 [in Japanese]	✓	✓
LOS vs. HTZ	1	L336_1	*Hypertens Res* 2007; **30:** 729–739	✓	✓
LOS_HTZ vs. HTZ	1	L336_1	*Hypertens Res* 2007; **30:** 729–739	✓	✓
PBO vs. HTZ	1	L336_1	*Hypertens Res* 2007; **30:** 729–739	✓	✓
IRB_TCT vs. IRB	1	L522_1	*J Blood Press (Ketsuatsu)* 2013; **20:** 598–611 [in Japanese]	✓	✓
LOS vs. IRB	1	L647_1	*J Clin Ther Med (Rinshoiyaku)* 2008; **24:** 543–573 [in Japanese]	✓	✓
LOS_HTZ vs. LOS	2	L336_1	*Hypertens Res* 2007; **30:** 729–739	✓	✓
		L720_1	*Prog Med* 2005; **25:** 2385–2389	✓	
LPL vs. LOS	1	L412_1	*Heart Vessels* 2004; **19:** 13–18	✓	✓
PBO vs. LOS	1	L336_1	*Hypertens Res* 2007; **30:** 729–739	✓	✓
TEL vs. LOS	1	L316_1	*Mol Med Rep* 2008; **1:** 391–393	✓	✓
VAL vs. LOS	1	L316_1	*Mol Med Rep* 2008; **1:** 391–393	✓	✓
PBO vs. LOS_HTZ	1	L336_1	*Hypertens Res* 2007; **30:** 729–739	✓	✓
VAL vs. NFD	1	L397_1	*Am J Hypertens* 2004; **17:** 1050–1055	✓	✓
OLM_AZP vs. OLM	1	L255_1	*Hypertens Res* 2009; **32:** 1148–1154	✓	✓
TEL vs. OLM	1	L548_1	*Ther Res* 2012; **33:** 229–237	✓	✓
VAL vs. PBO	1	L589_1	*J Blood Press (Ketsuatsu)* 2010; **17:** 314–328 [in Japanese]	✓	✓
VAL_AML vs. PBO	1	L589_1	*J Blood Press (Ketsuatsu)* 2010; **17:** 314–328 [in Japanese]	✓	✓
VAL vs. TEL	2	L316_1	*Mol Med Rep.* 2008; **1:** 391–393	✓	✓
		L572_1	*J Rural Med [Japanese]* 2010; **5:** 165–174	✓	✓
VAL_AML vs. VAL	1	L589_1	*J Blood Press (Ketsuatsu)* 2010; **17:** 314–328 [in Japanese]	✓	✓
VAL_CLP vs. VAL	1	L491_1	*J Clin Ther Med (Rinshoiyaku)* 2015; **31:** 97–114 [in Japanese]	✓	✓

AML, amlodipine besilate; AZP, azelnidipine; CLP, cilnidipine; EPL, enalapril maleate; HTZ, hydrochlorothiazide; JAPIC CTI, Japan Pharmaceutical Information Center Clinical Trial Information; LPL, lisinopril hydrate; MAN, manidipine; NDA, new drug application; NFD, nifedipine; TCT, trichlormethiazide. Other abbreviations as in Table 1.

autocorrelation. The analyses conducted were considered as continuous outcomes. The results corresponding to continuous outcomes are presented as the standard mean standard difference.

Results

Systematic Literature Review

Figure 1 presents the PRISMA flow diagram that illustrates the study selection process. A total of 763 abstracts for potential inclusion were retrieved, from which 117 abstracts were removed because they appeared in both PubMed and Ichushi. Upon review of the titles and abstracts, 318 abstracts were retained and the full-text publications evaluated. Of these, 244 citations were excluded because they did not meet the predefined selection criteria. Three additional articles were included, resulting in a total of 77 RCTs that met the PICOS-defined eligibility criteria.

NMA

Figure 2 shows the results produced by the NMA. The results are based on 37 studies listed in **Table 2** that reported mean change in SBP (**Figure 2A**) and DBP (**Figure 2B**) from baseline in the office setting. In **Figure 2**, each circle represents a treatment; the lines between circles represents a comparison of the 2 interventions, with the width of the lines representing the total number of trials for each comparison (i.e., the thicker the line, the more RCTs assessed the comparison). Networks based on clinical studies reporting BP in the home setting and ABPM were not possible. The results of heterogeneity and robustness studies are summarized in **Table 3**, **Figure 3**, and **Supplementary Figure 1**. Most studies had I^2 values <50%, with the exception of some studies that are listed in **Table 3**. Funnel plots suggested the presence of bias from 2 publications, namely studies L522[17] and L153[18] (**Figure 3**). Removing study L522[17] in the leave-1-out sensitivity analysis did not have a noticeable effect on the result (**Supplementary Figure 1**). Study L153 was necessary for building the network and therefore the leave-1-out sensitivity analysis could not be performed.[18]

Population Characteristics

Across the 77 publications, the mean age of patients ranged from 35.7 to 81 years. The mean weight of all patients varied from 55.5 to 85.5 kg. Across the 37 studies used to build the network (**Table 2**), 13,945 patients with hypertension measured in the office setting were included. Of these 13,945 patients with hypertension, 2,598 (18.63%) were treated with azilsartan, 3,400 (24.38%) were treated with CAN, 932 (6.68%) were treated with irbesartan, 1,821 (13.06%) were treated with LOS, 1,564 (11.22%) were

Table 3. Studies Demonstrating Heterogeneity With I^2 >50%

Study	SBP		DBP	
	I^2 (%)	Mean difference (95% CrI)	I^2 (%)	Mean difference (95% CrI)
AZL vs. AML				
L086_1		4.9 (1.0, 8.8)		1.6 (−1.3, 4.5)
Pooled (pair-wise)		4.9 (1.0, 8.8)		1.6 (−1.3, 4.5)
Indirect (back calculated)		−0.91 (−2.8, 0.98)		−0.82 (−2.1, 0.47)
Pooled (network)	85.6	0.20 (−1.5, 1.9)	56.1	−0.41 (−1.6, 0.76)
P value		0.144475		0.208775
LOS vs. AML				
L179		9.0 (2.2, 16.0)		
L379		1.1 (−39.0, 41.0)		
L412		−0.71 (−4.4, 3.0)		
L419		4.1 (−1.7, 9.9)		
Pooled (pair-wise)	55.3	2.2 (−0.64, 5.0)	69.4	
Indirect (back calculated)		3.8 (1.6, 6.0)		
Pooled (network)	47.1	3.2 (1.4, 4.9)	70.2	
P value		0.90465		0.55555
VAL vs. AML				
L078		−0.0053 (−9.3, 9.3)		−7.5 (−15.0, −0.26)
L200		2.0 (−7.2, 11.0)		2.0 (−4.8, 8.8)
L403		−0.99 (−3.7, 1.7)		0.99 (−1.1, 3.1)
L409		13.0 (6.8, 19.0)		3.0 (−2.3, 8.3)
L589		6.9 (3.3, 10.0)		4.3 (2.0, 6.6)
L733		−1.7 (−4.8, 1.5)		−0.89 (−3.1, 1.4)
Pooled (pair-wise)	82.9	1.6 (−0.015, 3.3)		1.3 (0.044, 2.5)
Indirect (back calculated)		6.6 (4.3, 8.9)		3.2 (1.7, 4.7)
Pooled (network)	85.3	3.3 (2.0, 4.6)		2.0 (1.1, 3.0)
P value		0.60055		0.56815
CAN vs. AZL				
L153		4.3 (3.1, 5.5)		
TAK-356/CCT-001		2.6 (−3.7, 8.9)		
TAK-356/CCT-005		4.6 (2.4, 6.8)		
Pooled (pair-wise)	0.0	4.3 (3.3, 5.3)		
Indirect (back calculated)		−0.78 (−4.0, 2.4)		
Pooled (network)	67.9	3.8 (2.9, 4.8)		
P value		0.197475		0.328725
OLM vs. CAN				
L560		1.0 (−1.1, 3.1)		
Pooled (pair-wise)		1.0 (−1.1, 3.1)		
Indirect (back calculated)		−3.9 (−6.9, −0.91)		
Pooled (network)	85.5	−0.64 (−2.4, 1.1)		
P value		0.567225		
TEL vs. CAN				
L316		5.5 (−0.75, 12.0)		
Pooled (pair-wise)		5.5 (−0.78, 12.0)		
Indirect (back calculated)		−1.5 (−3.9, 0.97)		
Pooled (network)	75.7	−0.56 (−2.8, 1.7)		
P value		0.052925		
IRB vs. EPL				
L648		1.8 (−1.2, 4.9)		0.70 (−1.1, 2.5)
Pooled (pair-wise)		1.8 (−1.2, 4.9)		0.70 (−1.1, 2.5)
Indirect (back calculated)		−2.1 (−5.9, 1.7)		−2.9 (−6.3, 0.39)
Pooled (network)	59.5	0.30 (−2.1, 2.7)	71.6	−0.14 (−1.7, 1.5)
P value		0.6681		0.26375

(**Table 3** continued the next page.)

Study	SBP		DBP	
	I^2 (%)	Mean difference (95% CrI)	I^2 (%)	Mean difference (95% CrI)
OLM vs. EPL				
L738		−4.0 (−6.5, −1.5)		−2.5 (−4.1, −0.87)
Pooled (pair-wise)		−4.0 (−6.5, −1.5)		−2.5 (−4.1, −0.87)
Indirect (back calculated)		2.7 (−0.31, 5.6)		1.1 (−1.0, 3.1)
Pooled (network)	91.3	−1.3 (−3.2, 0.61)	85.8	−1.1 (−2.4, 0.13)
P value		0.197025		0.097775
VAL vs. EPL				
L760_1		2.0 (−1.7, 5.7)		
Pooled (pair-wise)		2.0 (−1.7, 5.6)		
Indirect (back calculated)		−2.9 (−5.4, −0.43)		
Pooled (network)	78.8	−1.4 (−3.4, 0.70)		
P value		0.4124		
LOS vs. IRB				
L647_1		−0.55 (−3.3, 2.2)		0.15 (−2.6, 2.9)
Pooled (pair-wise)		−0.54 (−3.3, 2.2)		0.16 (−2.6, 2.9)
Indirect (back calculated)		−4.6 (−8.6, −0.53)		−3.3 (−5.8, −0.86)
Pooled (network)	61.5	−1.8 (−4.1, 0.47)	70.7	−1.8 (−3.6, 0.082)
P value		0.670375		0.275075
PBO vs. LOS				
L336				2.8 (0.21, 5.4)
Pooled (pair-wise)				2.8 (0.21, 5.4)
Indirect (back calculated)				5.4 (4.0, 6.7)
Pooled (network)			66.6	4.8 (3.6, 6.0)
P value				0.0669
TEL vs. LOS				
L316_1		5.4 (−0.23, 11.0)		4.3 (−0.55, 9.1)
Pooled (pair-wise)		5.4 (−0.23, 11.0)		4.3 (−0.55, 9.2)
Indirect (back calculated)		−0.89 (−3.6, 1.8)		−0.53 (−2.3, 1.3)
Pooled (network)	74.4	0.28 (−2.1, 2.7)	70.2	0.043 (−1.6, 1.7)
P value		0.069		0.02895
TEL vs. OLM				
L548		−5.7 (−13.0, 1.3)		−6.2 (−13.0, 0.59)
Pooled (pair-wise)		−5.7 (−13.0, 1.3)		−6.2 (−13.0, 0.59)
Indirect (back calculated)		0.89 (−1.7, 3.5)		−0.33 (−2.2, 1.5)
Pooled (network)	66.7	0.083 (−2.4, 2.5)	62.7	−0.72 (−2.5, 1.0)
P value		0.183275		0.167475
VAL vs. PBO				
L589		−4.0 (−7.7, −0.28)		
Pooled (pair-wise)		−4.0 (−7.7, −0.27)		
Indirect (back calculated)		−7.6 (−9.7, −5.5)		
Pooled (network)	62.8	−6.7 (−8.5, −4.9)		
P value		0.28465		

CrI, credible interval. Other abbreviations as in Tables 1,2.

treated with OLM, 672 (4.82%) were treated with telmisartan, and 2,958 (21.21%) were treated with valsartan.

Antihypertensive Effects of ARBs

Figure 4 shows the relative antihypertensive effect of the 6 approved ARBs vs. azilsartan with regard to SBP and DBP. The effect of azilsartan was more favorable in terms of lowering SBP and DBP compared with that of the other ARBs, as illustrated in the forest plots of the network results using FEM (**Figure 4**). With regard to the efficacy of ARBs in lowering SBP, analyzed using FEM, the drugs with the smallest to largest mean difference compared with azilsartan were LOS, valsartan, OLM, telmisartan, CAN, and irbesartan (**Figure 4A**). Using REM, the drugs with the smallest to largest mean difference in lowering SBP compared with azilsartan were telmisartan, OLM, LOS, valsartan, CAN, and irbesartan (**Supplementary Figure 2A**). With regard to the efficacy of the 6 ARBs vs. azilsartan in lowering DBP, both FEM and REM indicated similar patterns of outcome (**Figure 4B**; **Supplementary Figure 2B**). Using FEM and REM, the drugs with the smallest to largest mean difference in DBP compared with azilsartan were LOS, telmisartan, valsartan, CAN, OLM, and irbesartan (**Figure 4B**; **Supplementary Figure 2B**).

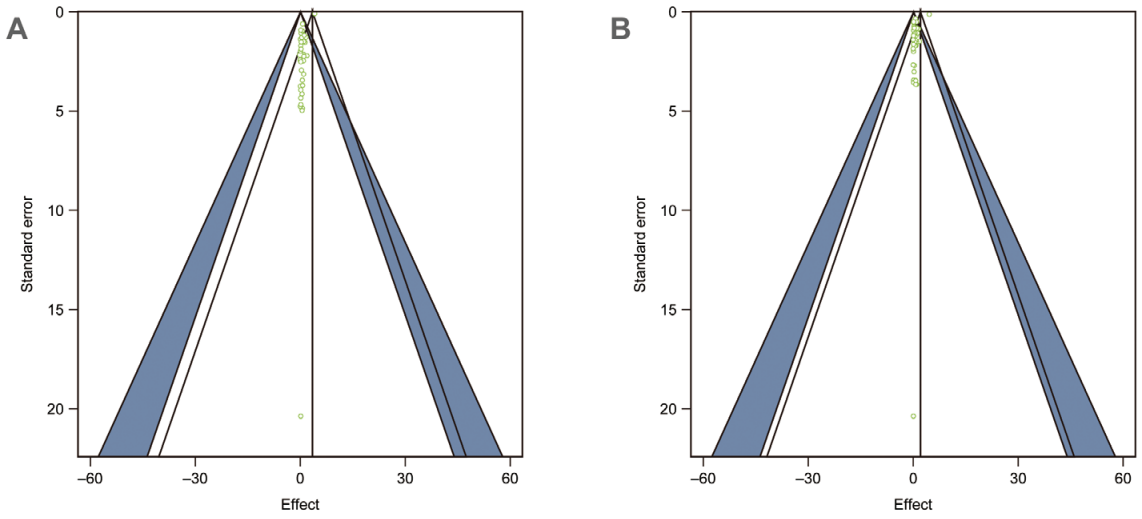

Figure 3. Funnel plots showing the presence of publication bias in studies investigating; (**A**) systolic blood pressure and (**B**) diastolic blood pressure.

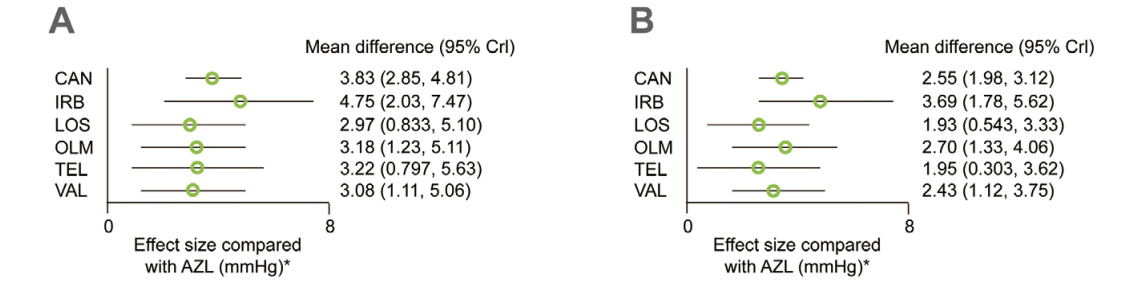

Figure 4. Forest plots for the comparison of angiotensin II receptor blockers (ARBs) vs. azilsartan (AZL) as the comparator in studies investigating; (**A**) systolic blood pressure and (**B**) diastolic blood pressure (fixed-effects model). *The mean difference was calculated by subtracting the effect size (mean change in blood pressure from baseline) of the indicated ARB from the effect size of AZL. CAN, candesartan cilexetil; CrI, credible interval; IRB, irbesartan; LOS, losartan potassium; OLM, olmesartan medoxomil; TEL, telmisartan; VAL, valsartan.

Discussion

The present study is the first meta-analysis to compare the degree of reduction in SBP and DBP in the office setting between individual ARBs in Japan. In this meta-analysis, it was possible to conduct indirect comparisons between drugs within the ARB drug class in the absence of direct head-to-head comparisons; for example, to the best of our knowledge, OLM has not been previously compared with LOS in Japanese patients with hypertension. Corresponding data from 37 studies (**Table 2**) that investigated the reduction in BP with ARB monotherapy, at approved doses, in patients with hypertension in Japan were calculated from the literature and used to assess the comparative efficacy of the antihypertensive drugs with respect to lowering SBP and DBP.

There has been a rapid increase in the use of NMA methods in the past decade,[19,20] which has allowed the simultaneous comparison of multiple interventions in a single analysis by combining both direct and indirect evidence within a network of RCTs.[21] The results of an NMA can provide valuable insights for clinicians in terms of the comparative efficacy of different treatments used in clinical practice,[21] which can be particularly useful when head-to-head comparisons of treatments are not available or have not been conducted.[22]

While network meta-analyses are becoming increasingly influential in informing clinicians and decision makers,[23] they are not without their challenges, largely due to the multitude of comparisons involved (heterogeneity, consistency, precision), which may generate inconsistency or incoherence in the model. In light of these issues, a consensus-based questionnaire has been developed to help decision makers assess the relevance and credibility of indirect treatment comparisons and NMAs to help inform decision making.[24] Moreover, it is important to exercise caution in generalizing the results of an NMA due to the variability in the quality of each RCT, and the similarities and con-

cordance of each clinical trial. When conducting an indirect treatment comparison, it is important to maintain the internal validity by preserving the randomization within each trial (i.e., it is critical to ensure that randomization is not disrupted).[25–27]

Combined evidence from both direct and indirect comparisons may provide robust evidence and more accurate estimates of treatment effect through an expansion of the network than direct comparisons alone.[22,28] Therefore, we believe that the current NMA, which consists of direct and indirect comparisons, provides reliable estimates of treatment effect.

Because ARBs are widely used, not only in Japan, but also world-wide, meta-analyses examining the efficacy among ARBs have been conducted.[29–34] We searched PubMed (on November 22, 2019) using the search terms "meta-analysis azilsartan", which identified 2 meta-analyses focusing on the antihypertensive effects of azilsartan.[35,36] The results from the present analysis are consistent with both published meta-analyses. Takagi et al reported a greater reduction in BP with azilsartan therapy than with control therapies including some ARBs in patients with hypertension.[35] Similarly, Zhao et al reported that the reduction in office SBP in patients with essential hypertension was greater after azilsartan than OLM treatment.[36] It should be noted that both these meta-analyses included data pertaining to azilsartan medoxomil 80 mg/day, approved in the US, Europe, and other countries.[35,36] It is important to mention that the absolute bioavailability and milligram : milligram dose of the azilsartan tablet formulation is approximately equivalent to half that of the commercial azilsartan medoxomil tablet; thus, azilsartan medoxomil 80 mg is equivalent to azilsartan 40 mg approved in Japan.

The results of the present study are further supported by the findings of Tsoi et al,[37] who reported no significant differences in the comparative efficacy between ARBs (including eprosartan, irbesartan, LOS, OLM, telmisartan, and valsartan, except for azilsartan) with regard to BP control in an NMA of RCTs. The robustness of the present NMA was confirmed by the results of the funnel plot and sensitivity analyse. In addition, heterogeneity was evaluated. Study L153 was a randomized, double-blind clinical trial that compared the efficacy and safety of azilsartan with that of CAN in Japanese patients with hypertension.[18] The bias observed from the inclusion of study L153 may have been due to the differences in BP at baseline vs. the other studies in the NMA. Of note, homogeneity across the studies would have resulted in similar results for the FEM and REM, whereas heterogeneity widens the confidence interval for the REM. Moreover, I^2 values >50% indicate the presence of heterogeneity. In the present analysis, the target population was that of hypertensive Japanese patients who were treated with ARB monotherapy in at least 1 arm; however, patient demographics, and in particular BP levels at baseline, varied between studies. Azilsartan demonstrated a favorable antihypertensive effect in both the REM and FEM.

Other factors may explain why the antihypertensive effect of azilsartan was favorable in reducing BP in the present meta-analysis, such as its relatively shorter time on the market compared with the other ARBs. Salt intake, which is a known risk factor for hypertension, has been shown to be decreasing over time in the Japanese population.[38] In addition, the prescription rate of diuretics has remained unchanged between 2005 and 2011,[39] and remains limited in Japan.[40] Under conditions of lower salt intake and limited use of diuretics, the BP-lowering effect of ARBs is likely to increase.[41,42] Therefore, it may have been easier to detect a favorable effect of azilsartan because it is the latest drug to have been launched in Japan.

Target BP differs depending on the individual patient and the presence of comorbidities.[6] For example, recommended target BP is <130/80 mmHg in patients with diabetes or ischemic heart disease, but <140/90 mmHg in patients aged ≥75 years.[6] Because stroke and heart failure are associated with high BP, lowering the BP goal to <130/80 mmHg would be suitable for Japanese hypertensive patients. However, a reduction of BP below 140/90 mmHg should be individualized in patients aged ≥75 years because older patients may have many different conditions.[6] For these reasons, differences in BP-lowering effects among antihypertensive drugs should be taken into consideration by the prescribing physician when selecting treatment. When initiating ARB treatment it is important to assess the clinical effects of each agent and their indications in light of patient comorbidities.[43] Moreover, individualized antihypertensive treatment is key, in particular for patients with an increased risk of end organ damage.[43] The 2019 JSH guidelines advocate the selection of antihypertensive drugs by considering individual background factors, adverse effects, health expenditure, and prescribing practices of the physician.[5] Of note, BP should not be overly reduced.[5,44] A gradual reduction in BP to the target level is generally recommended in hypertensive patients.[5] An excessive reduction in BP should be avoided because it may expose patients to added risk instead of benefit.[45] It is therefore necessary for physicians to be well informed of in-class differences in drug efficacy. Thus, the findings from the present analysis will support physicians in prescribing an antihypertensive ARB that will result in the appropriate hypotensive effect for the patient. However, a drug must be prescribed by taking into consideration its safety, effectiveness, and any patient comorbidities. In the future, NMAs evaluating the safety of ARBs are warranted.

The present meta-analysis has several limitations. First, the network could not be built using studies that reported on ABPM and home BP due to the lack of cases and measurement methods, and so this study was limited to studies that reported office BP. Second, only data from RCTs were used, and thus patients enrolled in randomized trials may not be representative of patients observed in clinical practice. However, randomized trials balance known and unknown confounders across treatment groups, and therefore the study design is least vulnerable to bias. Third, the results of this meta-analysis may not be representative of populations outside Japan. Fourth, the data were extracted only from literature published in English or Japanese; literature published in other languages, such as Korean or Chinese, was not included in the meta-analysis. A meta-analysis that includes pertinent studies published in other languages is warranted and may help build robust evidence. With the limited available evidence at the time of analysis, the results from the present meta-analysis should be interpreted with caution. Nevertheless, the findings provide notable insights that warrant further research to confirm our conclusions.

Conclusions

In conclusion, the results of this meta-analysis have shown

the relative BP-lowering effects of ARBs vs. azilsartan among Japanese patients with hypertension. Azilsartan demonstrated a more favorable efficacy profile than the other ARBs investigated with respect to lowering SBP and DBP in the patient population studied.

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IRB Information

Ethics approval was not obtained for this study because human participants were not involved and no individual person's data were collected or included in this manuscript. The anonymized data used in this study were derived from publicly available data reported in previous publications, and so ethics approval was not applicable.

Data Availability

The data used in this analysis were extracted from a collection of published articles (see **Table 2**); thus, the data are accessible in each of the articles.

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Supplementary Files

Please find supplementary file(s);
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