





Is the newest angiotensin-receptor blocker azilsartan medoxomil more efficacious in lowering blood pressure than the older ones? A systematic review and network meta-analysis

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Abstract

Angiotensin-receptor blockers are often considered insufficiently efficacious in reducing blood pressure. However, newer angiotensin-receptor blockers may be more effective than the older ones. A network meta-analysis was performed to compare the efficacy of various angiotensin-receptor blockers in reducing office and ambulatory blood pressure in hypertensive patients. Relevant literature was searched from English and Chinese databases for randomized controlled trials involving angiotensin-receptor blockers in hypertension. Efficacy variables included systolic and diastolic blood pressure either in the office or on ambulatory blood pressure monitoring. Absolute blood pressure reductions at 6-12 weeks of treatment and their credible intervals were reported. A total of 34 publications provided adequate data for analysis ($n = 14\,859$). In 28 studies on office systolic blood pressure ($n = 12\,731$), against the common comparator valsartan 80 mg, the differences in systolic blood pressure were in favor of azilsartan medoxomil (20-80 mg), irbesartan (300 mg), olmesartan (20-40 mg), telmisartan (80 mg), and valsartan (160-320 mg), but not candesartan (8-16 mg), losartan (50-100 mg), irbesartan (150 mg), olmesartan (10 mg), and telmisartan (40 mg). The ranking plot shows that azilsartan medoxomil 80 mg had a possibility of 99% being the best in the class. Similar results were observed for office

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diastolic blood pressure and from 13 studies for 24-hour ambulatory systolic and diastolic blood pressure. In conclusion, angiotensin-receptor blockers had different blood pressure lowering efficacy. The newest angiotensin-receptor blocker azilsartan medoxomil at the dose of 80 mg seemed to be most efficacious in reducing both systolic and diastolic blood pressure in the office and on ambulatory measurement.

1 | INTRODUCTION

Angiotensin-receptor blockers are recommended by the current hypertension guidelines as one of the firstline antihypertensive drug classes. Angiotensin-receptor blockers lower blood pressures through inhibiting the actions of angiotensin II and exhibit good tolerability.¹ Until recently, a number of agents in this class are available for the treatment of hypertension.² However, since the first angiotensin-receptor blocker, losartan, became available, this class of drugs has been unsatisfied for their less or low potency in blood pressure lowering. Some newer agents had been seen more efficacious than the older ones, but eventually found that the dosage might not be equivalent. The more potent blood pressure lowering action was with a problem of more side effects.

Recent technological advances have led to the discovery of a structurally and chemically even newer agent, azilsartan medoxomil. In clinical studies, this new angiotensin-receptor blocker showed strong blood pressure lowering efficacy with similar tolerability and side effects. This new drug has been compared with several but not all available older agents. We therefore performed the present network meta-analysis in attempt to have an overview on this class of antihypertensive drugs in patients with hypertension, with the focus on the efficacy of azilsartan medoxomil at various dosages.

2 | METHODS

2.1 | Search strategy and selection of studies

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for network meta-analysis.³ Medline, Cochrane Library, China National Knowledge Infrastructure, and WANFANG databases were searched for randomized controlled trials published over the period from January 1995 to September 2018. We then screened literature according to the following criteria: 1) hypertension; 2) studies included various angiotensin-receptor blockers either as intervention or comparator; and 3) office or ambulatory blood pressure changes as outcome measure. Angiotensin-receptor blockers, such as azilsartan medoxomil, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan, were also included as a term of literature search. Medical Subject Headings were searched on Medline and Cochrane Library. The search strategy included Medical Subject Headings terms and keywords related to "hypertension", "blood pressure", and "angiotensin II type 1 receptor blocker". The details of the

search strategy are listed and described in the online Supplementary Materials (Table S1). We assessed all relevant English and Chinese articles for eligibility.

2.2 | Outcomes

The primary outcome was the absolute change in office systolic and diastolic blood pressures from baseline. If ambulatory blood pressure data were reported, it was considered as a secondary outcome. The network meta-analysis included both primary and secondary outcomes at six and 12 weeks of follow-up. The 8-week blood pressure measurement was used, wherever available. In case that 8-week measurement was not available, the blood pressure measurement closest in time was reported, for example, at 10 weeks of follow-up. The follow-up time had to be at least four weeks of assigned treatment (medication and dosage).

2.3 | Data extraction and quality assessment

Two investigators independently screened the title and abstract in the search engines to identify potentially relevant studies. The extracted data included study characteristics, patient characteristics, interventions, outcomes, and other relevant findings. We also searched the references of the identified articles for possible inclusion. The extracted data were cross-checked by a third investigator. Discrepancies were resolved on the basis of a consensus approach. The quality of the extracted studies was assessed using the GeMTC package of R (version 3.4.4). Quality was defined in four broad categories: high, moderate, low, and very low. The quality of evidence was assessed on the basis of five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The Cochrane Collaboration's risk of bias assessment tool was used to assess the risk of bias at the study level.⁴

2.4 | Data synthesis and statistical analysis

The effects of various angiotensin-receptor blockers on the changes in systolic and diastolic blood pressures were estimated for all individual studies. The network meta-analysis combined both direct and indirect treatment comparisons. Pairwise meta-analyses of all interventions were performed to evaluate the possible statistical heterogeneity of studies within each comparison. Valsartan 80 mg

was chosen as the common comparator, because valsartan was the mostly used angiotensin-receptor blocker in China and many other countries, and 80 mg was the initial dose.

The network meta-analysis was conducted using a Bayesian random-effects model through a Markov Chain Monte Carlo process using the GeMTC package of R (version 3.4.4).^{5,6} Various angiotensin-receptor blockers were ranked by their effects relative to baseline when the Markov Chain Monte Carlo process was implemented. Hierarchy between various angiotensin-receptor blockers was estimated by the ranking probabilities of the frequency table of iteration results. This was estimated using the surface under the cumulative ranking curves.⁷ The rankings for outcomes were then combined and summarized in a cluster ranking plot. Heterogeneity was assessed using both the Cochrane Q test and the I^2 statistic. The following criteria of the I^2 statistic was used to derive heterogeneity of studies: 25%-50%, 50%-75%, and greater than 75% as low, moderate, and high heterogeneity, respectively. The Cochrane collaboration's risk of bias assessment tool was used to assess risk of bias.⁴ A meta-regression model was used to assess the effect of study-level

duration of treatment and baseline blood pressure on the treatment effect. The analysis was performed using the R statistical software, version 3.4.4. A two-sided P -value ≤ 0.05 was considered statistically significant.

3 | RESULTS

3.1 | Study selection

We identified 1,626 records by searching the databases. The majority of the identified articles were from Cochrane ($n = 681$, 41.9%) and Medline ($n = 603$, 37.1%, Figure 1). A total of 342 (21.0%) Chinese articles were identified from the China National Knowledge Infrastructure and WANFANG database. After removal of 693 (42.6%) duplicates and screening abstracts, 212 (13.0%) articles were assessed for eligibility. From these assessed articles, 178 (82.1%) were removed, because of inappropriate intervention ($n = 75$, 35.4%), outcomes not of interest ($n = 41$, 19.3%), incomplete

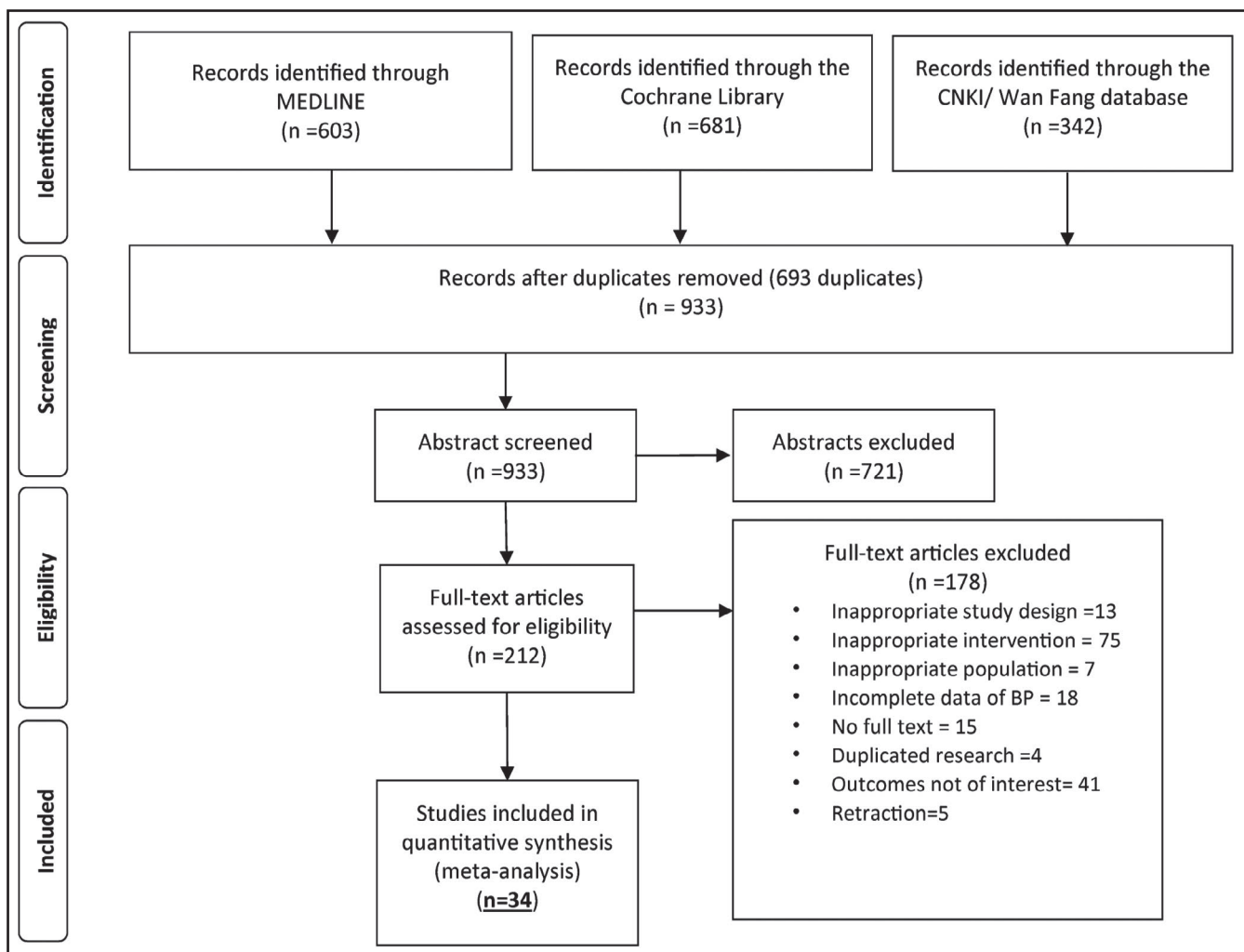


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of the systematic review search strategy

TABLE 1 Characteristics of the included studies

Author, year of publication	Country	Sample size	Trial design	Treatment	Study duration	Efficacy variable ^c
Kalikar et al, 2017 ^[40]	India	60	O	Olmesartan 20 mg Telmisartan 40 mg Losartan 50 mg	8 weeks	Mean change in SBP and DBP from baseline
Perez et al, 2017 ^[41]	US, Mexico, Argentina & Peru	449	DB	AM 5 mg; 10 mg; 20 mg; 40 mg; 80 mg Olmesartan 20 mg Placebo	8 weeks	Mean change in SBP and DBP from baseline ABPM as primary end point
Flack et al, 2012 ^[38]	US	941	PD	Olmesartan 20-40 mg Losartan 50-100 mg	8 weeks	Mean change in SBP and DBP from baseline
Punzi et al, 2012 ^[39]	US	945	PD	Olmesartan 20 mg Losartan 50 mg	8 weeks	Mean change in SBP and DBP from baseline
Bakris et al, 2011 ^[35]	US, Peru, Argentina, & Mexico	1275	DB	AM 20 mg; 40 mg; 80 mg Olmesartan 40 mg	6 weeks	Mean change in SBP and DBP from baseline
Weir et al, 2011 ^[36]	US	941	PD	Olmesartan 20 mg Losartan 50 mg	8 weeks	Mean change in SBP and DBP from baseline
White et al, 2011 ^[37]	US, Guatemala, Mexico Peru, & Puerto Rico	1291	DB	AM 20 mg; 40 mg Valsartan 160 mg Olmesartan 20 mg	6 weeks	Mean change in SBP and DBP from baseline
Chrysant et al, 2008 ^[33]	US	1940	DB	Olmesartan 10 mg; 20 mg; 40 mg Amlodipine 5 mg; 10 mg Olmesartan/amlodipine 10/5 mg; 20/5 mg; 40/5 mg; 10/10 mg; 20/10 mg; 40/10 mg Placebo	8 weeks	Mean change in SBP and DBP from baseline
Fogari et al, 2008 ^[34]	Italy	126	PO	Olmesartan 20 mg Telmisartan 80 mg	8 weeks	Mean change in SBP and DBP from baseline
Bahadir et al, 2007 ^[30]	Turkey	42	RCT	Losartan 50 mg Telmisartan 80 mg	8 weeks	Mean change in SBP and DBP from baseline
Giles et al, 2007 ^[31]	US	723	DB, titration	Olmesartan 20 mg Losartan 50 mg Valsartan 80 mg	8 weeks	Mean change in SBP and DBP from baseline
Phillip et al, 2007 ^[32]	Study1: 6 countries Study2: 10 countries/ regions	1911	DB	Amlodipine 2.5 mg; 5 mg Valsartan 40 mg; 80 mg; 160 mg; 320 mg Amlodipine 10 mg Valsartan 160 mg; 320 mg	8 weeks	Mean change in SBP and DBP from baseline
Baguet et al, 2006 ^[28]	France	256	DB	Candesartan 8 mg Losartan 50 mg Placebo	6 weeks	Mean change in SBP and DBP from baseline ABPM as primary end point
Zhu et al, 2006 ^[29]	China	287	DB, active	Olmesartan 20 mg Losartan 50 mg	8 weeks	Mean change in SBP and DBP from baseline

(Continues)

TABLE 1 (Continued)

Author, year of publication	Country	Sample size	Trial design	Treatment	Study duration	Efficacy variable ^c
Destro et al, 2005 ^[25]	Italy	114	PO	Olmesartan 20 mg Valsartan 160 mg	8 weeks	Mean change in SBP and DBP from baseline ABPM as primary end point
Liau et al, 2005 ^[26]	Taiwan & China	126	DB, active	Olmesartan 20 mg Losartan 50 mg	12 weeks	Mean change in SBP and DBP from baseline
Smith et al, 2005 ^[27]	US	588	DB, active	Olmesartan 20 mg Losartan 50 mg Valsartan 80 mg Irbesartan 150 mg	8 weeks	Mean change SBP and DBP from baseline ABPM as primary end point
Calvo et al, 2004 ^[20]	Spain	70	PO	Telmisartan 80 mg Valsartan 160 mg	12 weeks	Mean change in SBP and DBP from baseline
Ding et al, 2004 ^[21]	Taiwan & China	61	DB	Telmisartan 40 mg Losartan 50 mg	6 weeks	Mean change in SBP and DBP from baseline
Lee et al, 2004 ^[22]	Taiwan & China	180	DB	Telmisartan 40 mg Losartan 50 mg	8 weeks	Mean change in SBP and DBP from baseline
White et al, 2004 ^[23]	US & Canada	490	DB, forced titration	Telmisartan 40 mg Valsartan 80 mg	8 weeks	Mean change SBP and DBP from baseline ABPM as primary end point
Bai et al, 2002 ^[19,24]	China	330	DB	Telmisartan 40 mg Losartan 50 mg	12 weeks	Mean change in SBP and DBP from baseline
Bakris et al, 2002 ^[18]	US	426	PO	Telmisartan 80 mg Valsartan 80 mg	8 weeks	Mean change in SBP and DBP from baseline
Bakris et al, 2001 ^[15]	US	654	DB, forced titration	Candesartan 16 mg Losartan 50 mg	8 weeks	Mean change in SBP and DBP from baseline
Elliot et al, 2001 ^[16]	US	495	DB	Losartan 50 mg Valsartan 80 mg	12 weeks	Mean change in SBP and DBP from baseline
Vidt et al, 2001 ^[17]	US	611	DB, forced titration	Candesartan 16 mg Losartan 50 mg	8 weeks	Mean change in SBP and DBP from baseline
Monterroso et al, 2000 ^[14]	9 countries in Africa, Europe, & Latin America	187	DB	Losartan 50 mg Valsartan 80 mg	6 weeks	Mean change in SBP and DBP from baseline
Gradman et al, 1999 ^[10]	US	332	DB	Candesartan 16 mg Losartan 50 mg	8 weeks	Mean change in SBP and DBP from baseline
Hedner et al, 1999 ^[11]	Sweden	1369	DB	Valsartan 80 mg Losartan 50 mg	8 weeks	Mean change in SBP and DBP from baseline
Lacourcière et al, 1999 ^[12]	France	231	DB	Candesartan 8 mg Losartan 50 mg	8 weeks	Mean change in SBP and DBP from baseline ABPM as primary end point

(Continues)

TABLE 1 (Continued)

Author, year of publication	Country	Sample size	Trial design	Treatment	Study duration	Efficacy variable ^c
Mallion et al, 1999 ^[13]	France	223	DB	Placebo Losartan 50 mg Telmisartan 40 mg; 80 mg	6 weeks	Mean change in SBP and DBP from baseline
Andersson et al, 1998 ^[8]	Sweden & Denmark	337	DB	Candesartan 8 mg; 16 mg Losartan 50 mg Placebo	8 weeks	Mean change in SBP and DBP from baseline
Kassler-Taub et al, 1998 ^[9]	US, Canada, Mexico, Argentina & Brazil	567	DB	Placebo Losartan 100 mg Irbesartan 150 mg; 300 mg	8 weeks	Mean change in SBP and DBP from baseline

Abbreviations: ABPM, ambulatory blood pressure monitoring; AM, azilsartan medoxomil; DB, double-blinded placebo/actively controlled, O, open-label; DBP, diastolic blood pressure; PD, prospective double-blinded; PO, prospective open-label blinded end point; RCT, randomized controlled trial; SBP, systolic blood pressure.

The studies are listed in the descending order of the publication year.

^aBelgium, Canada, France, Germany, Mexico, and the United States.

^bEgypt, France, Germany, Korea, Malaysia, Norway, Peru, Portugal, Spain, and Taiwan.

^cClinic blood pressure in the sitting position, unless indicated otherwise.

data (n = 18, 8.5%), and so on (n = 40, 18.9%). Finally, a total of 34 studies were included in the present analysis.⁸⁻⁴¹

3.2 | Characteristics of the selected studies

Table 1 summarizes the characteristics of the included studies. The majority of the studies had a double-blind design (n = 28, 82.4%), and included two (n = 22, 64.7%) to three or more treatment arms (n = 12, 35.3%). Losartan was the most commonly studied treatment (n = 24, 70.6%), followed by olmesartan (n = 14, 41.2%), telmisartan (n = 11, 32.4%), valsartan (n = 11, 32.4%), and candesartan (n = 6, 17.6%). Azilsartan medoxomil and irbesartan represented the remaining study treatments (n = 5, 14.7%). The study duration ranged from six weeks to one year. Our analysis only included data between six and 12 weeks from baseline.

Heterogeneity was observed between studies in patient population, age, gender, and body mass index ($P \leq .05$). The 14,859 patients from 34 studies had a mean age of 45.7 to 60.1 years (Table 2), and included more men than women except for the study of Bahadir et al.³⁰ Mean (\pm SD) values of systolic blood pressure at baseline ranged from 140.0 mm Hg (\pm 12.7) to 170.5 mm Hg (\pm 12.6) and diastolic blood pressure from 86.0 mm Hg (\pm 10.1) to 104 mm Hg (\pm 5.0).

3.3 | Network geometry

Figure 2 shows the network of treatment comparisons between various angiotensin-receptor blockers for systolic and diastolic blood pressure. For systolic blood pressure, 19 angiotensin-receptor blockers and dosages were studied with 34 out of 171 potential pairwise direct comparisons. For diastolic blood pressure, 18 were studied with 31 out of 153 pairwise comparisons. These studied angiotensin-receptor blockers and dosages were azilsartan medoxomil (20 mg, 40 mg and 80 mg), candesartan (8 mg, 16 mg and 32 mg), irbesartan (150 mg and 300 mg), losartan (50 mg and 100 mg), olmesartan (10 mg, 20 mg and 40 mg), telmisartan (40 mg and 80 mg), and valsartan (40 mg, 80 mg, 160 mg, and 320 mg).

3.4 | Risk of bias assessment

Table S2 shows the risk of bias assessment for the included studies. All 34 studies were either of uncertain or low risk of selection bias. The risk of bias was unclear for random sequence generation in 20 (58.8%) studies and unclear for allocation concealment in 24 (70.6%) studies (Figure S1). The risk of bias was low with blinding of outcome assessment in 31 (91.2%) studies; it was low with incomplete outcome data, selective reporting and other sources in all 34 studies. The risk of bias was high with blinding of participants in five (14.7%) studies, and with blinding of outcome assessment in two (5.9%) studies.

TABLE 2 Baseline characteristics of the study participants

Author, year	Sample analyzed	Treatment	Demographics				Baseline Office Blood Pressure, mmHg			
			Mean age, years	Male, %	BMI	Diabetes mellitus	Definition of hypertension ^a	SBP (SD)	DBP (SD)	
Kalikar et al, 2017	57	Olmesartan 20 mg	46.2	65	—	—	SBP 140-159 or DBP 90-99	148.3 (6.07)	95.05 (2.15)	
		Telmisartan 40 mg	48.26	63.2	—	—	SBP 140-159 or DBP 90-99	148.8 (6.02)	94.53 (2.65)	
		Losartan 50 mg	49.94	66.7	—	—	SBP 140-159 or DBP 90-99	149.9 (3.84)	93.44 (2.45)	
Perez et al, 2017	183	AM 20 mg	54.6	53	31.2	—	DBP 95-114	140.3 (12.7)	86.6 (11.4)	
		AM 40 mg	55.3	47	31.5	—	DBP 95-114	141 (12.6)	86 (10.1)	
		AM 80 mg	53.5	56	31.4	—	DBP 95-114	141 (16.5)	86.5 (9.6)	
		Olmesartan 20 mg	53.4	46	29.3	—	DBP 95-114	141.3 (13.8)	88.4 (10.5)	
Flack et al, 2012	922	Olmesartan 20-40 mg (Stage 1-2 hypertension)	50.1	47.5	33.2	12.8%	SBP 140-159 or DBP 90-99 & SBP ≥ 160 or DBP ≥ 100	149.5 (6.7)	97.9 (1.3)	
		Losartan 50-100 mg (Stage 1-2 hypertension)	51.4	55.2	31.5	11.2%	SBP 140-159 or DBP 90-99 & SBP ≥ 160 or DBP ≥ 100	162 (9.4)	102.5 (4.0)	
		Losartan 50-100 mg (Stage 1-2 hypertension)	52.4	54.9	32.6	12.5%	SBP 140-159 or DBP 90-99 & SBP ≥ 160 or DBP ≥ 100	149.7 (7.1)	97.6 (1.3)	
Punzi et al, 2012	934	Olmesartan 20 mg (Naive, non-naïve)	48.6	64.2	32.8	2.1%	DBP 95-114 or SBP < 180	157.4 (10.89)	101.8 (4.26)	
		Losartan 50 mg (Naïve, non-naïve)	52.5	51.1	32.4	11.9% (Metabolic syndrome 37.9% vs 41.1%)	DBP 95-114 or SBP < 180	158.4 (10.22)	100.9 (3.96)	
		Losartan 50 mg (Naïve, non-naïve)	49.3	56	31.8	3.3%	DBP 95-114 or SBP < 180	156.3 (10.75)	101.1 (3.94)	
Bakris et al, 2011	1109	AM 20 mg	57.1	47	30.4	—	SBP 150-179 & 24-h SBP 130-169	—	—	
		AM 40 mg	57.4	50.2	30.6	—	SBP 150-179 & 24-h SBP 130-169	—	—	
		AM 80 mg	58.1	52.3	30	—	SBP 150-179 & 24-h SBP 130-169	—	—	
Weir et al, 2011	934	Olmesartan 40 mg	51.7	53.8	32.5	9.9%, 12.2%	DBP 95-114 & SBP < 180	158.2 (10.4)	101.1 (4.0)	
		Losartan 100 mg	52.1	55	32.3	—	DBP 95-114 & SBP < 180	158.3 (10.2)	101.3 (4.1)	
		AM 40 mg	57	53	31.7	—	SBP 150-179 & 24-h SBP 130-169	157 (13)	93 (11)	
White et al, 2011	1093	AM 80 mg	56	53	30.7	—	SBP 150-179 & 24-h SBP 130-169	158 (12)	92 (11)	
		Valsartan 320 mg	55	54	31.1	—	SBP 150-179 & 24-h SBP 130-169	157 (13)	93 (10)	
		Olmesartan 40 mg	56	55	31.1	—	SBP 150-179 & 24-h SBP 130-169	158 (13)	92 (9)	
Chrysant et al, 2008	484	Olmesartan 10 mg	53.8	54	33.5	—	Not specified	162.9 (16.7)	101.8 (5.9)	
		Olmesartan 20 mg	53.6	55.9	32.9	—	Not specified	164.1 (16.5)	101.5 (4.6)	
		Olmesartan 40 mg	53.9	50.6	33.6	—	Not specified	162.8 (15.7)	101.2 (5.1)	
Fogari et al, 2008	126	Olmesartan 20 mg	60.1	54	25.6	—	DBP ≥ 90	170.5 (12.6)	104.1 (7.5)	
		Telmisartan 80 mg	59.9	55.6	25.4	—	DBP ≥ 90	170.1 (12.1)	103.7 (7.1)	
Bahadiret al, 2007	42	Losartan 50 mg	47.7	33.3	32.8	—	SBP 140-169 or DBP 90-109	144.3 (6)	94.8 (5.1)	
		Telmisartan 80 mg	52.3	28.6	31.5	—	SBP 140-169 or DBP 90-109	149.1 (7.7)	94.8 (7.5)	
Giles et al, 2007	596	Olmesartan 40 mg	52.2	62.8	—	—	DBP 100-114	155.4 (11.2)	103.5 (3.1)	
		Losartan 100 mg	51.3	60.5	—	—	DBP 100-114	155 (11.5)	103.6 (2.8)	
		Valsartan 160 mg	52.2	66	—	—	DBP 100-114	154.3 (10.6)	163.9 (11)	

(Continues)

TABLE 2 (Continued)

Author, year	Sample analyzed	Treatment	Demographics				Baseline Office Blood Pressure, mmHg		
			Mean age, years	Male, %	BMI	Diabetes mellitus	Definition of hypertension ^a	SBP (SD)	DBP (SD)
Phillip et al, 2007	922	Study 1:	56.8	52.3	-	-	DBP 90-109 at week -4 to -2 & DBP 95-109 at randomization	154.6 (11.41)	99.3 (3.59)
		Valsartan 320 mg							
		Valsartan 160 mg							
		Valsartan 80 mg							
Zhu et al, 2006	253	Study 2:	53.29	64.3	-	DBP 95-109 or SBP < 180	153.2 (11.63)	99.2 (3.55)	
		Valsartan 40 mg							
		Valsartan 80 mg							
		Valsartan 160 mg							
Destro et al, 2005	107	Study 1:	56.7	51.9	-	-	157.5 (11.5)	99.1 (3.6)	
		Valsartan 320 mg							
		Valsartan 160 mg							
		Valsartan 80 mg							
Baguet et al, 2006	176	Study 2:	56.8	44.4	-	-	155.6 (11.3)	98.9 (3.3)	
		Valsartan 320 mg							
		Valsartan 160 mg							
		Valsartan 80 mg							
Liu et al, 2005	106	Study 1:	54	60.9	-	-	140 (14)	91 (10)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Smith et al, 2005	534	Study 2:	54.78	65.7	-	-	149.43 (12.56)	99.21 (3.28)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Calvo et al, 2004	70	Study 3:	45.7	55.9	26.8	-	146 (5.7)	90.8 (4.3)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Ding et al, 2004	78	Study 4:	49.2	36.1	28	-	146.4 (5.3)	90.7 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Lee et al, 2004	176	Study 5:	52.1	65.4	-	-	148.4 (11.6)	102.4 (4.3)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
White et al, 2004	490	Study 6:	54.3	68.9	26.2	-	149.3 (12.4)	103.2 (4.3)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bai et al, 2002	330	Study 7:	50.5	54.8	-	-	152.1	94.3	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2002	426	Study 8:	52.7	66.7	-	-	152.3	95.2	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 9:	52.1	54.6	25.8	-	152.2	94.7	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 10:	54.3	68.9	26.2	-	151.6	94.8	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 11:	54.2	57.8	-	-	151.5 (16.4)	89.3 (12.1)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 12:	54.1	58.4	-	-	156.5 (14.9)	91.9 (10.5)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 13:	50.8	73.8	-	-	153.6 (11.5)	101.1 (5.5)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 14:	50.8	74.5	-	-	154.5 (12.2)	99.1 (4.8)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 15:	53.6	68.2	-	-	153.5 (11.8)	100.5 (4.8)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 16:	53.1	67.9	-	-	155.1 (11.8)	101.8 (5.1)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 17:	54.2	57.8	-	-	150 (12)	94 (6)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 18:	54.1	58.4	-	-	149 (12)	93 (6)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 19:	50.8	73.8	-	-	148.9 (12.8)	99.3 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 20:	50.8	74.5	-	-	150.6 (12.4)	100.2 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 21:	53.6	68.2	-	-	157 (12.9)	100.3 (4.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 22:	53.1	67.9	-	-	157.1 (12.4)	101.2 (5.1)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 23:	54.2	57.8	-	-	152.6 (12.3)	100.1 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 24:	54.1	58.4	-	-	152 (12.6)	99.9 (4.2)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 25:	53.6	68.2	-	-	150.6 (12.4)	100.2 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 26:	53.1	67.9	-	-	157.1 (12.4)	101.2 (5.1)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 27:	54.2	57.8	-	-	152.6 (12.3)	100.1 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 28:	54.1	58.4	-	-	152 (12.6)	99.9 (4.2)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 29:	53.6	68.2	-	-	150.6 (12.4)	100.2 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 30:	53.1	67.9	-	-	157.1 (12.4)	101.2 (5.1)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 31:	54.2	57.8	-	-	152.6 (12.3)	100.1 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 32:	54.1	58.4	-	-	152 (12.6)	99.9 (4.2)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 33:	53.6	68.2	-	-	150.6 (12.4)	100.2 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 34:	53.1	67.9	-	-	157.1 (12.4)	101.2 (5.1)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 35:	54.2	57.8	-	-	152.6 (12.3)	100.1 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 36:	54.1	58.4	-	-	152 (12.6)	99.9 (4.2)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 37:	53.6	68.2	-	-	150.6 (12.4)	100.2 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 38:	53.1	67.9	-	-	157.1 (12.4)	101.2 (5.1)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 39:	54.2	57.8	-	-	152.6 (12.3)	100.1 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 40:	54.1	58.4	-	-	152 (12.6)	99.9 (4.2)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 41:	53.6	68.2	-	-	150.6 (12.4)	100.2 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 42:	53.1	67.9	-	-	157.1 (12.4)	101.2 (5.1)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 43:	54.2	57.8	-	-	152.6 (12.3)	100.1 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 44:	54.1	58.4	-	-	152 (12.6)	99.9 (4.2)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 45:	53.6	68.2	-	-	150.6 (12.4)	100.2 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 46:	53.1	67.9	-	-	157.1 (12.4)	101.2 (5.1)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 47:	54.2	57.8	-	-	152.6 (12.3)	100.1 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 48:	54.1	58.4	-	-	152 (12.6)	99.9 (4.2)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 49:	53.6	68.2	-	-	150.6 (12.4)	100.2 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 50:	53.1	67.9	-	-	157.1 (12.4)	101.2 (5.1)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 51:	54.2	57.8	-	-	152.6 (12.3)	100.1 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 52:	54.1	58.4	-	-	152 (12.6)	99.9 (4.2)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 53:	53.6	68.2	-	-	150.6 (12.4)	100.2 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 54:	53.1	67.9	-	-	157.1 (12.4)	101.2 (5.1)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 55:	54.2	57.8	-	-	152.6 (12.3)	100.1 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 56:	54.1	58.4	-	-	152 (12.6)	99.9 (4.2)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 57:	53.6	68.2	-	-	150.6 (12.4)	100.2 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 58:	53.1	67.9	-	-	157.1 (12.4)	101.2 (5.1)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Bakris et al, 2001	654	Study 59:	54.2	57.8	-	-	152.6 (12.3)	100.1 (3.9)	
		Valsartan 80 mg							
		Valsartan 40 mg							
		Valsartan 20 mg							
Elliot et al, 2001	486	Study 60:	54.1	58.4	-	-	152 (12.6)	99.9 (4.2)	
		Valsartan 80 mg							
		Valsartan 40 mg							

TABLE 2 (Continued)

Author, year	Sample analyzed	Treatment	Demographics				Baseline Office Blood Pressure, mmHg		
			Mean age, years	Male, %	BMI	Diabetes mellitus	Definition of hypertension ^a	SBP (SD)	DBP (SD)
Vidt et al, 2001	611	Candesartan 32 mg Losartan 100 mg	55.5 55.1	58.3 58.9	—	—	DBP 95-114	153.6 (11.7) 151.5 (11.7)	100.4 (4.3) 97.8 (6.1)
Monterroso et al, 2000	187	Losartan 50 mg Valsartan 80 mg	54.6 54.1	58.1 48.9	—	—	DBP 95-114	—	100.8 (5.6) 100.8 (6.6)
Gradman et al, 1999	322	Candesartan 32 mg Losartan 100 mg	54 57	57 58	—	—	DBP 95-114	152.9 154.1	100.3 100.5
Hedher et al, 1999	1096	Valsartan 160 mg Losartan 100 mg	55.7 54.9	56.8 56.7	—	—	DBP 95-114	157 (16.3) 157.4 (15.9)	101.4 (4.6) 101.6 (5.1)
Lacourciere et al, 1999	215	Candesartan 16 mg Losartan 100 mg	55 55	62.1 62.6	—	—	DBP 95-114 or SBP < 200 & 24-h DBP ≥ 85	155.1 153	101.8 100.2
Mallion et al, 1999	167	Losartan 50 mg Telmisartan 40 mg Telmisartan 80 mg	56 58 57	58 67 65	29.1 28.5 29.3	—	DBP 95-114 or SBP 140-199 & 24-h DBP > 85	162.4 (16.3) 161.9 (14.7) 164.2 (15.3)	100.7 (4.5) 100.8 (4.2) 101.8 (4.9)
Andersson et al, 1998	249	Candesartan 8 mg Candesartan 16 mg Losartan 50 mg	60 59 59	57 67 57	—	—	DBP 95-114	169 (14) 168 (15) 168 (16)	102 (5) 103 (5) 104 (5)
Kassler-Taub et al, 1998	394	Losartan 100 mg Irbesartan 150 mg Irbesartan 300 mg	55 53.1 55.6	50 54 57	—	—	DBP 95-109	153.3 (15.5) 155.3 (16.2) 155.4 (16)	100.6 (4.4) 101.1 (4.6) 100.4 (4.5)

Abbreviations: AM, azilsartan medoxomil; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.

The studies are listed in the descending order of the publication year.

^aClinic blood pressure in the sitting position, unless indicated otherwise.

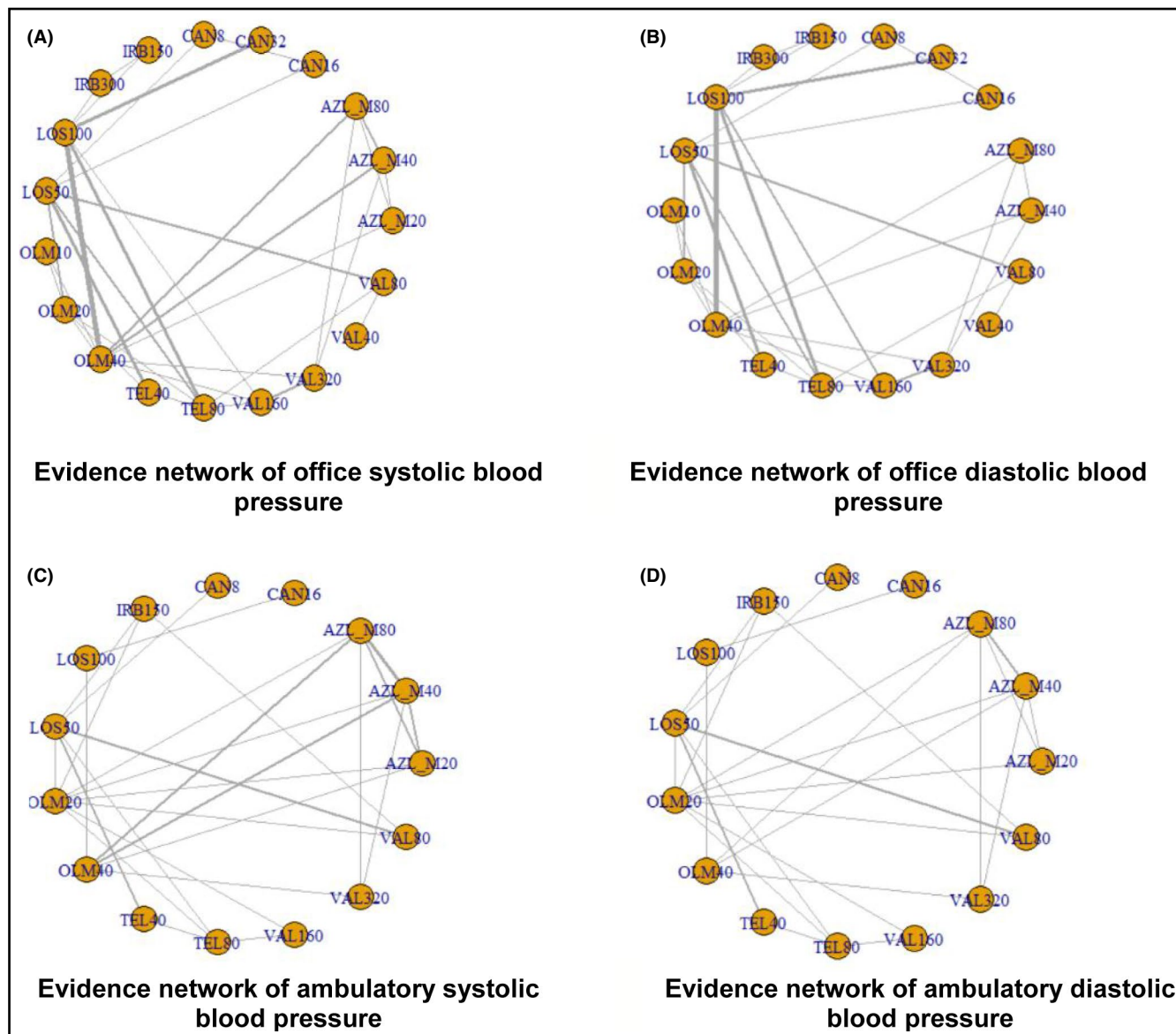


FIGURE 2 Network of direct comparisons between various angiotensin-receptor blockers for office (upper panels) and ambulatory (lower panels) systolic (left panels) and diastolic (right panels) blood pressure. Abbreviations: AZL-M 20, AZL-M 40, and AZL-M 80 indicate azilsartan medoxomil 20, 40, and 80 mg daily, respectively; CAN 8, CAN 16, and CAN 32, candesartan 8, 16, and 32 mg daily, respectively; IRB 150 and IRB 300, irbesartan 150 and 300 mg daily, respectively; LOS 50 and LOS 100, losartan 50 and 100 mg daily, respectively; OLM 10, OLM 20, and OLM 40, olmesartan 10, 20, and 40 mg daily, respectively; TEL 40 and TEL 80, telmisartan 40 and 80 mg daily, respectively; VAL 40, VAL 160, and VAL 320, valsartan 40, 160, and 320 mg daily, respectively

3.5 | Efficacy evaluations

Figure 3A shows the differences in office systolic blood pressure reductions on various angiotensin-receptor blockers from valsartan 80 mg, being in favor of azilsartan medoxomil (20 mg, 40 mg, and 80 mg), irbesartan 300 mg, olmesartan 20 mg and 40 mg, telmisartan 80 mg, and valsartan 160 mg and 320 mg. The ranking plots shows that azilsartan medoxomil 80 mg had a 99% probability of being the best in class for systolic blood pressure reduction (Figure S2A), followed by azilsartan medoxomil 40 mg (90%) and irbesartan 300 mg (85%). There was no difference between direct and indirect pairwise comparisons of mean office systolic blood pressure (Figure S3).

There was no heterogeneity (Figure S5) except for the comparisons of telmisartan 80 mg with valsartan 80 mg ($I^2 = 53.2\%$) and 160 mg ($I^2 = 80.2\%$). Similar results were observed for diastolic blood pressure (Figure 3B, Tables S3 and Figures S2B and S6).

Similar results were also observed for 24-hour ambulatory blood pressure (Figure 4 and Table S4). The ranking plots show that azilsartan medoxomil 80 mg had a 93% and 86% possibility of being the best in class for 24-hour systolic and diastolic blood pressure reductions, respectively. Further adjustment for the duration of treatment and baseline blood pressure values did not materially change the results for either clinic or ambulatory blood pressure (data not shown).

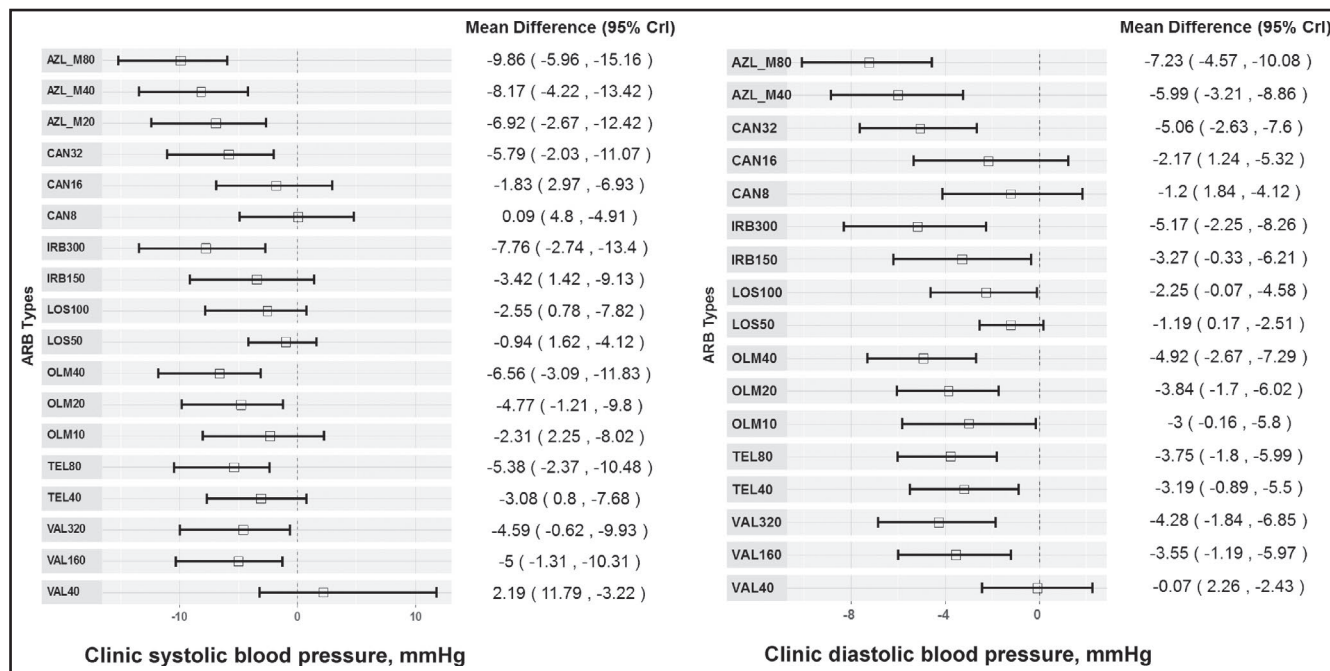


FIGURE 3 Absolute mean (95% credible interval, CRI) difference in office systolic (left panel) and diastolic (right panel) blood pressure for various angiotensin-receptor blockers in comparison with valsartan 80 mg daily. For explanations on the abbreviations of drugs, see the legend to Figure 2

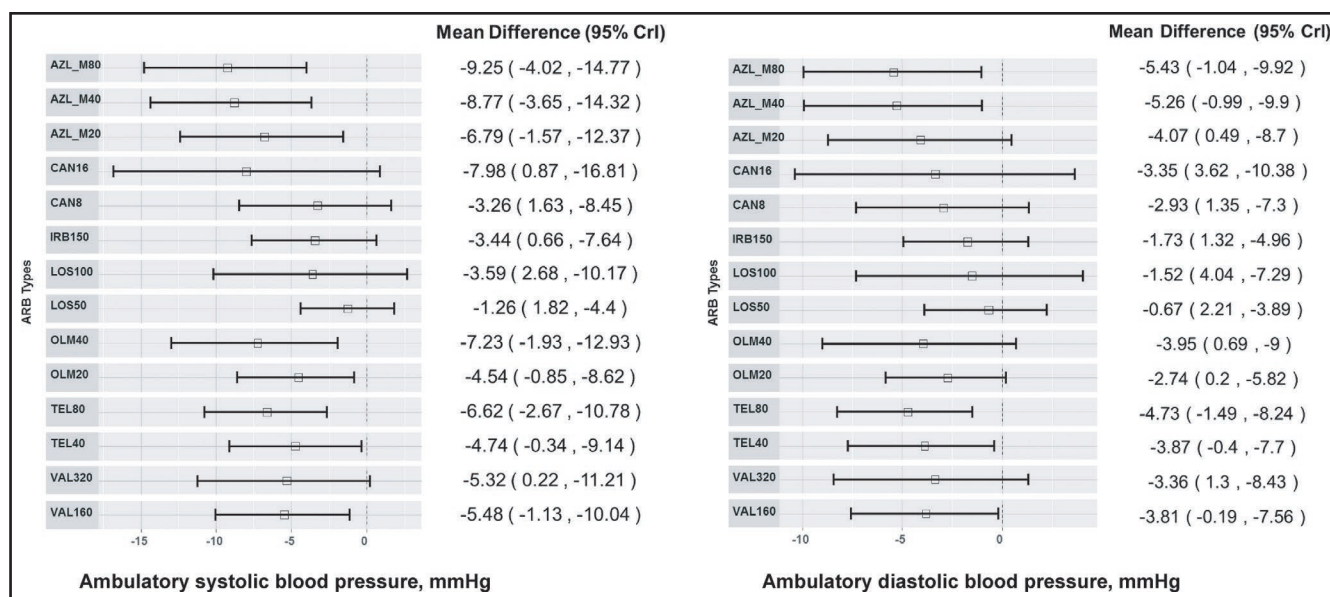


FIGURE 4 Absolute mean (95% credible interval, CRI) difference in ambulatory systolic (left panel) and diastolic (right panel) blood pressure for various angiotensin-receptor blockers in comparison with valsartan 80 mg daily. For explanations on the abbreviations of drugs, see the legend to Figure 2

4 | DISCUSSION

The findings of our meta-analysis was that azilsartan medoxomil was superior to the other angiotensin-receptor blockers in lowering both office and ambulatory blood pressures. The mean difference in office systolic/diastolic blood pressure in comparison with valsartan

80 mg was $-9.9/-7.2$ mmHg and $-8.2/-6.0$ mmHg for azilsartan medoxomil 80 mg and 40 mg, respectively. The corresponding mean values for ambulatory systolic/diastolic blood pressure were $-9.2/-5.4$ mmHg and $-8.8/-5.3$ mmHg, respectively. Such differences are appreciable in the control of hypertension and in the prevention of cardiovascular events.

Our finding is in keeping with the results of three previously published meta-analyses on the basis of randomized comparisons.⁴²⁻⁴⁴ In an analysis that included seven studies with four angiotensin-receptor blockers, azilsartan medoxomil (including azilsartan) reduced systolic and diastolic blood pressure more than the other three angiotensin-receptor blockers by an overall difference of -3.7 mmHg (95% confidence interval [CI]: $-5.7, -1.7$) and -2.9 mmHg (95% CI: $-3.8, -1.9$), respectively.⁴² In another analysis that also included four angiotensin-receptor blockers (candesartan, irbesartan, losartan, and valsartan) but without azilsartan medoxomil,⁴³ the four angiotensin-receptor blockers had similar blood pressure lowering efficacy, with a maximum between-drug difference of $1.4/0.7$ mmHg in office systolic/diastolic blood pressure. In the third analysis that included 31 studies with six angiotensin-receptor blockers (candesartan, irbesartan, losartan, olmesartan, telmisartan and valsartan), valsartan 160 or 320 mg per day was more effective in lowering blood pressure than losartan 100 mg per day and as effective as the other angiotensin-receptor blockers.⁴⁴

The finding of our analysis is also consistent with the results of individual trials that involved azilsartan medoxomil (prodrug, 40-80 mg approved in most countries) or azilsartan (active drug, 20-40 mg approved in Japan). In all these trials, azilsartan medoxomil^{35,37} or azilsartan⁴⁵ showed significantly greater blood pressure lowering efficacy, regardless of the comparator angiotensin-receptor blocker or the blood pressure measurement technique, whether clinic or ambulatory blood pressure. Indeed, in the study with the largest sample size ($n = 1291$), azilsartan medoxomil 80 mg per day was superior to valsartan 320 mg per day and olmesartan 40 mg.³⁷ The corresponding placebo-adjusted mean changes in 24-hour systolic blood pressure were -14.3 mmHg, -10.0 mmHg ($P < .001$ vs. azilsartan medoxomil), and -11.7 mmHg ($P = .009$) from baseline, respectively. For office systolic blood pressure, azilsartan medoxomil at both lower (40 mg) and higher dosages (80 mg) were superior to the two comparator angiotensin-receptor blockers.

Although the mechanisms for the between-drug differences in blood pressure lowering effects within the same mode of action are not entirely understood, there are several possible explanations. A key mechanism that makes the difference between angiotensin-receptor blockers in blood pressure lowering is whether the angiotensin type II receptor is surmountable or insurmountable.⁴⁶ Insurmountable antagonist forms tight sartan-receptor complexes, and makes the dissociation half-life longer. Such a mechanism increases the duration of action and is potentially beneficial in cardiovascular protection and prevention. In a recent follow-up study in patients with myocardial infarction and treatment of various angiotensin-receptor blockers, the one-year risk of major cardiovascular events (14.3% vs. 11.2% , $P = .025$) and mortality (13.3% vs. 11.4% , $P = .031$) was significantly higher in patients on surmountable than insurmountable angiotensin-receptor blockers.⁴⁷

Our study has to be interpreted within the context of its limitations. First, network meta-analysis disregards randomization of each individual trial. The results of the analysis may be confounded

by the heterogeneity of the study participants at baseline, especially blood pressure and comorbid diseases. Second, our analysis included short-term studies only. Whether such a short-term difference would remain in long-term studies, especially when combination therapy is initiated, requires further investigation. Third, our study did not evaluate safety profile. The choice of angiotensin-receptor blockers could be influenced by tolerability and side effects more than the other classes of antihypertensive drugs.⁴⁸ However, angiotensin-receptor blockers in general have the best treatment persistence, because of their better tolerability and less side effects.

In conclusion, our study showed that angiotensin-receptor blockers had different blood pressure lowering efficacy, with the newest one, azilsartan medoxomil, being most efficacious in reducing both office and ambulatory blood pressures, at the least during short-term treatment (<12 weeks). With the increasing availability, azilsartan medoxomil might improve blood pressure control. Nonetheless, more evidence on this new angiotensin-receptor blocker is still needed.

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CONFLICT OF INTEREST

Ji-Guang Wang reports having received lecture and consulting fees from Takeda and from Astra-Zeneca, Novartis, Omron, and Servier. Tzung-Dau Wang has received honoraria for lectures from AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Novartis, Omron, Pfizer, and Sanofi. The other authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

Ji-Guang Wang contributed to the conception of the study. Miao Zhang did literature search, acquired the data, performed statistical analyses, and together with Ji-Guang Wang prepared the first draft of the manuscript. All authors critically commented and revised the manuscript and gave the final approval.

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REFERENCES

1. Oparil S, Silfani TN, Walker JF. Role of angiotensin receptor blockers as monotherapy in reaching blood pressure goals. *Am J Hypertens.* 2005;18:287-294.
2. Kurtz TW, Kajiya T. Differential pharmacology and benefit/risk of azilsartan compared to other sartans. *Vasc Health Risk Manag.* 2012;8:133-143.
3. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating

- network meta-analyses of health care interventions: Checklist and explanations. *Ann Intern Med.* 2015;162:777-784.
- Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
 - Lumley T. Network meta-analysis for indirect treatment comparisons. *Stat Med.* 2002;21:2313-2324.
 - van Valkenhoef G, Kuiper J. *Package GeMTC: Network meta-analysis using Bayesian methods.* R package version 0.8-2. 2016 (URL <http://github.com/gertvv/gemtc>)
 - Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol.* 2011;64:163-171.
 - Andersson OK, Neldam S. The antihypertensive effect and tolerability of candesartan cilexetil, a new generation angiotensin II antagonist, in comparison with losartan. *Blood Press.* 1998;7:53-59.
 - Kassler-Taub K. Comparative efficacy of two angiotensin II receptor antagonists, irbesartan and losartan, in mild-to-moderate hypertension. *Am J Hypertens.* 1998;11:445-453.
 - Gradman AH, Lewin A, Bowling BT, et al. Comparative effects of candesartan cilexetil and losartan in patients with systemic hypertension. Candesartan Versus Losartan Efficacy Comparison (CANDLE) Study Group. *Heart Dis.* 1999;1:52-57.
 - Hedner T, Oparil S, Rasmussen K, et al. A comparison of the angiotensin II antagonists valsartan and losartan in the treatment of essential hypertension. *Am J Hypertens.* 1999;12:414-417.
 - Lacourcière Y. A comparison of the efficacy and duration of action of candesartan cilexetil and losartan as assessed by clinic and ambulatory blood pressure after a missed dose, in truly hypertensive patients: A placebo-controlled, forced titration study. *Am J Hypertens.* 1999;12:1181-1187.
 - Mallion J, Siche J, Lacourcière Y. ABPM comparison of the antihypertensive profiles of the selective angiotensin II receptor antagonists telmisartan and losartan in patients with mild-to-moderate hypertension. *J Hum Hypertens.* 1999;13:657-664.
 - Monterroso VH, Chavez VR, Carbajal ET, et al. Use of ambulatory blood pressure monitoring to compare antihypertensive efficacy and safety of two angiotensin II receptor antagonists, losartan and valsartan, Losartan Trial Investigators. *Adv Ther.* 2000;17:117-131.
 - Bakris G, Gradman A, Reif M, et al. Antihypertensive efficacy of candesartan in comparison to losartan: the CLAIM study. *J Clin Hypertens (Greenwich).* 2001;3:16-21.
 - Elliott WJ, Calhoun DA, DeLuca PT, Gazdick LP, Kerns DE, Zeldin RK. Losartan versus valsartan in the treatment of patients with mild to moderate essential hypertension: data from a multicenter, randomized, double-blind, 12-week trial. *Clin Ther.* 2001;23:1166-1179.
 - Vidt DG, White WB, Ridley E, et al. A forced titration study of antihypertensive efficacy of candesartan cilexetil in comparison to losartan: CLAIM Study II. *J Hum Hypertens.* 2001;15:475-480.
 - Bakris G. Comparison of telmisartan vs. valsartan in the treatment of mild to moderate hypertension using ambulatory blood pressure monitoring. *J Clin Hypertens (Greenwich).* 2002;4:26-31.
 - Bai J, Zhu J, Cai N, et al. Clinical efficacy and safety of telmisartan in patients with mild to moderate hypertension: a multi-center randomized controlled clinical trial. *Chin J Cardiol.* 2002;30:738-742.
 - Calvo C, Hermida RC, Ayala DE, Ruilope LM. Effects of telmisartan 80 mg and valsartan 160 mg on ambulatory blood pressure in patients with essential hypertension. *J Hypertens.* 2004;22:837-846.
 - Ding PYA, Chu KM, Chiang HT, Shu KH. A double-blind ambulatory blood pressure monitoring study of the efficacy and tolerability of once-daily telmisartan 40 mg in comparison with losartan 50 mg in the treatment of mild-to-moderate hypertension in Taiwanese patients. *Int J Clin Pract.* 2004;58:16-22.
 - Lee YT, Lee CM, Lin CS, et al. A double-blind comparison of the efficacy and tolerability of telmisartan 40-80 mg vs. losartan 50-100 mg in Taiwanese hypertensive patients. *Int J Clin Pract.* 2004;58:40-45.
 - White WB, Lacourcière Y, Davidai G. Effects of the angiotensin II receptor blockers telmisartan versus valsartan on the circadian variation of blood pressure: impact on the early morning period. *Am J Hypertens.* 2004;17:347-353.
 - Zhu JR, Bai J, Cai NS, et al. Efficacy and safety of telmisartan vs. losartan in control of mild-to-moderate hypertension: a multicentre, randomised, double-blind study. *Int J Clin Pract.* 2004;58(Suppl. 145):46-49.
 - Destro M, Scabrosetti R, Vanasia A, Mugellini A. Comparative efficacy of valsartan and olmesartan in mild-to-moderate hypertension: results of 24-hour ambulatory blood pressure monitoring. *Adv Ther.* 2005;22:32-43.
 - Liau C-S, Lee C-M, Sheu S-H, et al. Efficacy and safety of olmesartan in the treatment of mild-to-moderate essential hypertension in Chinese patients. *Clin Drug Investig.* 2005;25:473-479.
 - Smith DH, Dubiel R, Jones M. Use of 24-hour ambulatory blood pressure monitoring to assess antihypertensive efficacy: a comparison of olmesartan medoxomil, losartan potassium, valsartan, and irbesartan. *Am J Cardiovasc Drugs.* 2005;5:41-50.
 - Baguet JP, Nisse-Durgeat S, Mouret S, Asmar R, Mallion JM. A placebo-controlled comparison of the efficacy and tolerability of candesartan cilexetil, 8 mg, and losartan, 50 mg, as monotherapy in patients with essential hypertension, using 36-h ambulatory blood pressure monitoring. *Int J Clin Pract.* 2006;60:391-398.
 - Zhu J, Cai N, Fan W, et al. Efficacy and safety of olmesartan medoxomil versus losartan potassium in Chinese patients with mild to moderate essential hypertension. *Chin J Cardiol.* 2006;34:877-881.
 - Bahadir O, Uzunlulu M, Oguz A, Bahadir MA. Effects of telmisartan and losartan on insulin resistance in hypertensive patients with metabolic syndrome. *Hypertens Res.* 2007;30:49-53.
 - Giles TD, Oparil S, Silfani TN, Wang A, Walker JF. Comparison of increasing doses of olmesartan medoxomil, losartan potassium, and valsartan in patients with essential hypertension. *J Clin Hypertens (Greenwich).* 2007;9:187-195.
 - Philipp T, Smith TR, Glazer R, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. *Clin Ther.* 2007;29:563-580.
 - Chrysant SG, Melino M, Karki S, Lee J, Heyrman R. The combination of olmesartan medoxomil and amlodipine besylate in controlling high blood pressure: COACH, a randomized, double-blind, placebo-controlled, 8-week factorial efficacy and safety study. *Clin Ther.* 2008;30:587-604.
 - Fogari R, Zoppi A, Mugellini A, et al. Effectiveness of hydrochlorothiazide in combination with telmisartan and olmesartan in adults with moderate hypertension not controlled with monotherapy: a prospective, randomized, open-label, blinded end point (PROBE), parallel-arm study. *Curr Ther Res Clin Exp.* 2008;69:1-15.
 - Bakris GL, Sica D, Weber M, et al. The comparative effects of azilsartan medoxomil and olmesartan on ambulatory and clinic blood pressure. *J Clin Hypertens (Greenwich).* 2011;13:81-88.
 - Weir MR, Punzi HA, Flack JM, et al. A randomized, double-blind, forced-titration study to compare olmesartan medoxomil versus losartan potassium in patients with stage 1 and 2 hypertension. *Postgrad Med.* 2011;123:80-87.
 - White WB, Weber MA, Sica D, et al. Effects of the angiotensin receptor blocker azilsartan medoxomil versus olmesartan and valsartan on ambulatory and clinic blood pressure in patients with stages 1 and 2 hypertension. *Hypertension.* 2011;57:413-420.

38. Flack JM, Graff A, Li W, Chavanu KJ. Efficacy/safety of olmesartan medoxomil versus losartan potassium in patients by stage 1 or 2 hypertension. *Postgrad Med*. 2012;124:59-70.
39. Punzi HA, Lewin A, Li W, Chavanu KJ. Efficacy/safety of olmesartan medoxomil versus losartan potassium in naive versus previously treated subjects with hypertension. *Adv Ther*. 2012;29:524-537.
40. Kalikar M, Nivangune KS, Dakhale GN, et al. Efficacy and tolerability of olmesartan, telmisartan, and losartan in patients of stage I hypertension: A randomized, open-label study. *J Pharmacol Pharmacother*. 2017;8:106-111.
41. Perez A, Cao C. The impact of azilsartan medoxomil treatment (capsule formulation) at doses ranging from 10 to 80 mg: Significant, rapid reductions in clinic diastolic and systolic blood pressure. *J Clin Hypertens (Greenwich)*. 2017;19:312-321.
42. Takagi H, Mizuno Y, Niwa M, Goto SN, Umemoto T. A meta-analysis of randomized controlled trials of azilsartan therapy for blood pressure reduction. *Hypertens Res*. 2014;37:432-437.
43. Conlin P, Spence J, Williams B, et al. Angiotensin II antagonists for hypertension: Are there differences in efficacy? *Am J Hypertens*. 2000;4:418-426.
44. Nixon RM, Müller E, Falvey H. Valsartan vs. other angiotensin II receptor blockers in the treatment of hypertension: a meta-analytical approach. *Int J Clin Pract*. 2009;63:766-775.
45. Rakugi H, Enya K, Sugiura K, Ikeda Y. Comparison of the efficacy and safety of azilsartan with that of candesartan cilexetil in Japanese patients with grade I-II essential hypertension: a randomized, double-blind clinical study. *Hypertens Res*. 2012;35:552-558.
46. Van Liefde I, Vauquelin G. Sartan-AT1 receptor interactions: in vitro evidence for insurmountable antagonism and inverse agonism. *Mol Cell Endocrinol*. 2009;302:237-243.
47. Jeong HC, Jeong MH, Ahn Y, et al. Comparative assessment of angiotensin II type 1 receptor blockers in the treatment of acute myocardial infarction: surmountable vs. insurmountable antagonist. *Int J Cardiol*. 2014;170(291-297):48.
48. Catanzaro DF, Frishman WH. Angiotensin receptor blockers for management of hypertension. *South Med J*. 2010;103:669-673.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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