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
Angiotensin-receptor blockers are recommended by the current hypertension guidelines as one of the first-line antihypertensive drug classes. Angiotensin-receptor blockers lower blood pressures through inhibiting the actions of angiotensin II and exhibit good tolerability. Until recently, a number of agents in this class are available for the treatment of hypertension. 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.

## 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. 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.

### 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). 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. 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. 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
### Table 1: Characteristics of the included studies

| Author, year of publication | Country                          | Sample size | Trial design | Treatment                                                                 | Study duration | Efficacy variable |
|-----------------------------|----------------------------------|-------------|--------------|---------------------------------------------------------------------------|----------------|-------------------|
| Kalikar et al, 2017        | 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           | 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 |
| Flack et al, 2012           | 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           | US                               | 945         | PD           | Olmesartan 20 mg, Losartan 50 mg                                         | 8 weeks        | Mean change in SBP and DBP from baseline |
| Bakris et al, 2011          | 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            | US                               | 941         | PD           | Olmesartan 20 mg, Losartan 50 mg                                         | 8 weeks        | Mean change in SBP and DBP from baseline |
| White et al, 2011           | US, Guatemala, Mexico & 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        | US                               | 1940        | DB           | Olmesartan 10 mg; 20 mg; 40 mg Amlodipine 5 mg; 10 mg Olmesartan/amlo/dipine 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          | Italy                            | 126         | PO           | Olmesartan 20 mg, Telmisartan 80 mg                                      | 8 weeks        | Mean change in SBP and DBP from baseline |
| Bahadir et al, 2007         | Turkey                           | 42          | RCT          | Losartan 50 mg, Telmisartan 80 mg                                        | 8 weeks        | Mean change in SBP and DBP from baseline |
| Giles et al, 2007           | 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         | Study1: 6 countries               | 1911        | DB           | Amlodipine 2.5 mg; 5 mg Valsartan 40 mg; 80 mg; 160 mg; 320 mg           | 8 weeks        | Mean change in SBP and DBP from baseline |
| Baguet et al, 2006          | France                           | 256         | DB           | Candesartan 8 mg, Losartan 50 mg, Placebo                               | 6 weeks        | Mean change in SBP and DBP from baseline |
| Zhu et al, 2006             | 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 |
|----------------------------|---------|-------------|--------------|------------|----------------|------------------|
| 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[^29,24]    | 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[^30]   | 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)
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 ≤ .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 (±SD) values of systolic blood pressure at baseline ranged from 140.0 mm Hg (±12.7) to 170.5 mm Hg (±12.6) and diastolic blood pressure from 86.0 mm Hg (±10.1) to 104 mm Hg (±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 | SBP (SD) | DBP (SD) |
|              |                |           |               |         |     |                |                           |           |           |
| Kalikar et al, 2017 | 57       | Olmesartan 20 mg, Telmisartan 40 mg, Losartan 50 mg | 46.2  48.26  49.94 | 65  63.2  66.7 | —   —   — | — | SBP 140-159 or DBP 90-99 | 148.3 (6.07) | 95.05 (2.15) |
| Perez et al, 2017  | 183      | AM 20 mg, AM 40 mg, AM 80 mg, Olmesartan 20 mg | 54.6  55.3  53.5  53.4 | 53  47  56  46 | 31.2  31.5  31.4  29.3 | — | DBP 95-114 | 140.3 (12.7) | 86.0 (11.4) |
| Flack et al, 2012  | 922      | Olmesartan 20-40 mg, Losartan 50-100 mg (Stage 1-2 hypertension) | 50.1  52.4  51.4  52.4 | 47.5  56.6  55.2  54.9 | 33.2  32.2  31.5  32.6 | 12.8%  8.6%  11.2%  12.5% | SBP 140-159 or DBP 90-99 & SBP ≥ 160 or DBP ≥ 100 | 149.5 (12.7) | 97.9 (1.3) |
| Punzi et al, 2012  | 934      | Olmesartan 20 mg (Naïve, non-naïve), Losartan 50 mg (Naïve, non-naïve) | 48.6  52.8  49.3  52.1 | 64.2  54.8  56  55.1 | 32.8  32.4  31.8  32.3 | 2.1%  11.9%  3.3%  14.3% | DBP 95-114 or SBP < 180 | 157.4 (10.89) | 101.8 (4.26) |
| Bakris et al, 2011 | 1109     | AM 20 mg, AM 40 mg, AM 80 mg, Olmesartan 40 mg | 57.1  57.4  58.1  58.9 | 47  50.2  52.3  49.6 | 30.4  30.6  30  29.8 | — | SBP 150-179 & 24-h SBP 130-169 | 158.2 (10.4) | 101.1 (4.0) |
| Weir et al, 2011   | 934      | Olmesartan 40 mg, Losartan 100 mg | 51.7  52.1 | 53.8  55 | 32.5  32.3 | 9.9%, 12.2% | DBP 95-114 & SBP < 180 | 158.3 (10.2) | 101.3 (4.1) |
| White et al, 2011  | 1093     | AM 40 mg, AM 80 mg, Valsartan 320 mg, Olmesartan 40 mg | 57  56  55  56 | 53  53  54  55 | 31.7  30.7  31.1  31.1 | — | SBP 150-179 & 24-h SBP 130-169 | 157 (13) | 93 (11) |
| Chrysant et al, 2008 | 484    | Olmesartan 10 mg, Olmesartan 20 mg, Olmesartan 40 mg | 53.8  53.6  53.9 | 54  55.9  50.6 | 33.5  32.9  33.6 | — | Not specified | 162.9 (16.7) | 101.8 (5.9) |
| Fogari et al, 2008 | 126      | Olmesartan 20 mg, Telmisartan 80 mg | 60.1  59.9 | 54  55.6 | 25.6  25.4 | — | DBP ≥ 90 | 170.5 (12.6) | 104.1 (7.5) |
| Bahadir et al, 2007 | 42     | Losartan 50 mg, Telmisartan 80 mg | 47.7  52.3 | 33.3  28.6 | 32.8  31.5 | — | SBP 140-169 or DBP 90-109 | 144.3 (6) | 94.8 (5.1) |
| Giles et al, 2007  | 596      | Olmesartan 40 mg, Losartan 100 mg, Valsartan 160 mg | 52.2  52.2 | 62.8  66 | — | — | DBP 100-114 | 155.4 (11.2) | 103.5 (3.1) |

(Continues)
| Author, year | Sample analyzed | Treatment | Demographics | Baseline Office Blood Pressure, mmHg |
|-------------|----------------|-----------|--------------|-----------------------------------|
| Phillip et al, 2007 | 922 | **Study 1:** Valsartan 320 mg, Valsartan 160 mg, Valsartan 80 mg, Valsartan 40 mg | 56.7, 56.8 | 154.6 (11.41) |
|              |                | **Study 2:** Valsartan 320 mg, Valsartan 160 mg | 56.7, 56.8 | 154.6 (11.41) |
| Baguet et al, 2006 | 176 | Candesartan 8 mg, Losartan 50 mg | 54 | 154.6 (11.5) |
| Zhu et al, 2006 | 253 | Olmesartan 40 mg, Losartan 100 mg | 53.29, 54.78 | 154.6 (11.5) |
| Destro et al, 2005 | 107 | Olmesartan 20 mg, Valsartan 160 mg | - | 154.6 (11.5) |
| Liau et al, 2005 | 106 | Olmesartan 20 mg, Losartan 50 mg | 48.5, 48.1 | 154.6 (11.5) |
| Smith et al, 2005 | 534 | Olmesartan 20 mg, Losartan 50 mg, Valsartan 80 mg, Irbesartan 150 mg | 52.3, 52 | 154.6 (11.5) |
| Calvo et al, 2004 | 70 | Telmisartan 80 mg, Valsartan 160 mg | 45.7, 49.2 | 154.6 (11.5) |
| Ding et al, 2004 | 78 | Telmisartan 40 mg, Losartan 50 mg | 50.5, 52.7 | 154.6 (11.5) |
| Lee et al, 2004 | 176 | Telmisartan 80 mg, Losartan 100 mg | 52.1, 54.3 | 154.6 (11.5) |
| White et al, 2004 | 490 | Telmisartan 80 mg, Valsartan 160 mg | 54, 55 | 154.6 (11.5) |
| Bai et al, 2002 | 330 | Telmisartan 80 mg, Losartan 100 mg | 50.8, 50.8 | 154.6 (11.5) |
| Bakris et al, 2002 | 426 | Telmisartan 80 mg, Valsartan 80 mg | 53.6, 53.1 | 154.6 (11.5) |
| Bakris et al, 2001 | 654 | Candesartan 32 mg, Losartan 100 mg | 54.2, 54.1 | 154.6 (11.5) |
| Elliot et al, 2001 | 486 | Losartan 50 mg, Valsartan 80 mg | 53, 54 | 154.6 (11.5) |

(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** | **SBP (SD)** | **DBP (SD)** |
| Vidt et al, 2001 | 611 | Candesartan 32 mg Losartan 100 mg | 55.5 | 58.3 | – | – | DBP 95-114 | 153.6 (11.7) | 100.4 (4.3) |
|               |                |           | 55.1 | 58.9 | – | – | 151.5 (11.7) | 97.8 (6.1) |
| Monterroso et al, 2000 | 187 | Losartan 50 mg Valsartan 80 mg | 54.6 | 58.1 | 48.9 | – | – | DBP 95-114 | – | 100.8 (5.6) |
|               |                |           | 54.1 | 57.1 | 48.9 | – | – | 100.8 (5.6) |
| Gradman et al, 1999 | 322 | Candesartan 32 mg Losartan 100 mg | 54 | 57 | – | – | DBP 95-114 | 152.9 | 100.3 |
|               |                |           | 57 | 58 | – | – | 154.1 | 100.5 |
| Hedner et al, 1999 | 1096 | Valsartan 160 mg Losartan 100 mg | 55.7 | 58.1 | 48.9 | – | – | DBP 95-114 | 157.4 (15.9) | 101.6 (5.1) |
|               |                |           | 54.9 | 56.8 | 48.9 | – | – | 157.4 (15.9) | 101.6 (5.1) |
| Lacourciere et al, 1999 | 215 | Candesartan 16 mg Losartan 100 mg | 55 | 62.1 | – | – | DBP 95-114 or SBP < 200 & 24-h DBP ≥ 85 | 155.1 | 101.8 |
|               |                |           | 55 | 62.6 | – | – | 153 | 100.2 |
| Mallion et al, 1999 | 167 | Losartan 50 mg Telmisartan 40 mg Telmisartan 80 mg | 56 | 58 | 29.1 | – | DBP 95-114 or SBP 140-199 & 24-h DBP > 85 | 162.4 (16.3) | 100.7 (4.5) |
|               |                |           | 58 | 67 | 28.5 | – | 161.9 (14.7) | 100.8 (4.2) |
|               |                |           | 57 | 65 | 29.3 | – | 164.2 (15.3) | 101.8 (4.9) |
| Andersson et al, 1998 | 249 | Candesartan 8 mg Candesartan 16 mg Losartan 50 mg | 60 | 57 | – | – | DBP 95-114 | 169 (14) | 102 (5) |
|               |                |           | 59 | 67 | – | – | 168 (15) | 103 (5) |
|               |                |           | 59 | 57 | – | – | 168 (16) | 104 (5) |
| Kassler-Taub et al, 1998 | 394 | Losartan 100 mg Irbesartan 150 mg Irbesartan 300 mg | 55 | 50 | – | – | DBP 95-109 | 153.3 (15.5) | 100.6 (4.4) |
|               |                |           | 53.1 | 54 | – | – | 155.3 (16.2) | 101.1 (4.6) |
|               |                |           | 55.6 | 57 | – | – | 155.4 (16) | 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.

*Clinic blood pressure in the sitting position, unless indicated otherwise.*
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).
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.

**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.\textsuperscript{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 \(-3.7\, \text{mmHg} (95\% \text{ confidence interval [CI]}: \text{−5.7, −1.7})\) and \(-2.9\, \text{mmHg} (95\% \text{ CI: −3.8, −1.9})\), respectively.\textsuperscript{45} In another analysis that also included four angiotensin-receptor blockers (candesartan, irbesartan, losartan, and valsartan) but without azilsartan medoxomil,\textsuperscript{46} the four angiotensin-receptor blockers had similar blood pressure lowering efficacy, with a maximum between-drug difference of \(1.4/0.7\, \text{mmHg}\) 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.\textsuperscript{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\textsuperscript{35,37} or azilsartan\textsuperscript{45} 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.\textsuperscript{37} The corresponding placebo-adjusted mean changes in 24-hour systolic blood pressure were \(-14.3\, \text{mmHg}, \text{−10.0 mmHg (P < .001 vs. azilsartan medoxomil)}, \text{and −11.7 mmHg (P = .009)}\) 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 form Takeda and from Astra-Zeneca, Novartis, Omron, and Servier. Tsung-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.

4. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.

5. Lumley T. Network meta-analysis for indirect treatment comparisons. Stat Med. 2002;21:2313-2324.

6. van Valkenhoef G, Kuiper J. Package GeMTC: Network meta-analysis using Bayesian methods. R package version 0.8-2. 2016 (URLhttp://github.com/gertv/gemtc)

7. 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.

8. 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.

9. Kassler-Taub K. Comparative efficacy of two angiotensin II receptor antagonists, irbesartan and losartan, in mild-to-moderate hypertension. Am J Hypertens. 1999;11:445-453.

10. 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.

11. 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.

12. 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.

13. Mallion J, Siche J, Lacourciere 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.

14. 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.

15. 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.

16. Elliott WJ, Calhoune DA, DeLucia 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.

17. Vldt 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.

18. 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.

19. 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.

20. Calvo C, Hermida RC, Ayala DE, Rulope 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.

21. 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.

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.

23. White WB, Lacourciere 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.

24. 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.

25. 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.

26. 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 Invest. 2005;25:473-479.

27. 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.

28. 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.

29. 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.

30. Bahadir O, Uzunulu 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.

31. 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.

32. 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.

33. Chrysant SG, Melino M, Karli 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.

34. Fogari R, Zoppa 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.

35. 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.

36. 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.

37. White WB, Weaver 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, Lowy A, 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, Sugiuara 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(2):291-297.

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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