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ORIGINAL ARTICLE

# Antihypertensive effect of azilsartan versus olmesartan in patients with essential hypertension: a meta-analysis

Di Zhao [1] · Hui Liu [2] · Pingshuan Dong [3]

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## Abstract

**Objective** The comparison of antihypertensive effects between azilsartan and olmesartan in patients with essential hypertension has been investigated in several studies. The results were not consistent. We performed this meta-analysis determining the antihypertensive effect of azilsartan versus olmesartan in patients with essential hypertension.

**Methods** Pubmed, Web of Science, and Cochrane Central were searched for all published randomized studies comparing the antihypertensive effects between azilsartan and olmesartan in patients with essential hypertension.

**Results** The antihypertensive effects were assessed in 1402 patients included in five trials. The reduction of office systolic blood pressure treated with azilsartan was greater than olmesartan (weighted mean differences (WMD) − 2.15 (95% confidence interval (CI), − 3.78, − 0.53) mm Hg, $p < 0.01$). There was no significant difference in reduction of office diastolic blood pressure between azilsartan and olmesartan (WMD − 0.99 (95% CI, − 2.06, 0.08) mm Hg, $p > 0.05$). The reduction of office systolic blood pressure treated with azilsartan was greater than olmesartan at same dose for both drugs (WMD − 2.24 (95% CI, − 4.03, − 0.44) mm Hg, $p < 0.05$), whereas there was no significant difference in reduction of office diastolic blood pressure between azilsartan and olmesartan (WMD − 0.55 (95% CI, − 1.76, 0.66) mm Hg, $p > 0.05$).

**Conclusions** This meta-analysis provides the evidence that the reduction of office systolic blood pressure treated with azilsartan was greater than olmesartan in patients with essential hypertension. These findings suggest the importance of strict designed randomized controlled trials in determining antihypertensive effects of angiotensin II receptor blockers in clinical practice.


**Keywords** Azilsartan · Essential hypertension · Meta-analysis · Olmesartan

## Introduction

Renin-angiotensin-aldosterone system plays a major role in the regulation of blood pressure (BP). Angiotensin II receptor blockers (ARBs) are the first line of antihypertensive agent. Each ARB has different pharmacokinetic properties [1]. Obviously, it is important to investigate the differences in effects of ARBs to determine the optimal treatment in the patients with hypertension [2].

Azilsartan medoxomil is the eighth approved member of ARBs [3] and is a safe and effective ARB with a unique pharmacologic profile versus other agents, including slowed angiotensin II type 1 (AT1) receptor dissociation rates and improved receptor specificity [4]. Azilsartan is well tolerated over the long term and provides stable BP improvements when used in a treat-to-target BP approach with thiazide-type diuretics [5]. Compared to other ARBs including valsartan, olmesartan, candesartan, and presumably losartan, azilsartan may increase the BP target control and response rate by an absolute value of 8–10%. Greater antihypertensive effects of azilsartan might be due in part to its unusually potent and persistent ability to inhibit binding of angiotensin II to AT1 receptors [6].

Di Zhao and Hui Liu contributed equally to this work.

✉ Di Zhao
emaildizhao@163.com

[1] Division of Hypertension, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, 24 Jinghua Avenue, Luoyang 471003, China

[2] Division of Endocrinology, Luoyang Central Hospital Affiliated to Zhengzhou University, 288 Zhongzhouzhong Avenue, Luoyang 471000, China

[3] Division of Cardiology, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, 24 Jinghua Avenue, Luoyang 471003, China

Olmesartan medoxomil was approved by FDA in April 2002 [7]. The most efficacious drug in reducing BP is olmesartan as compared with telmisartan and losartan [8]. Among ARBs, olmesartan stands out for a wide choice of effective fixed-dose combinations [9]. Kario et al. [8] reported that olmesartan-based treatment robustly reduced baseline high morning home BP, similar to clinic BP, and the effect was associated with baseline BP but unaffected by patient background factors. Olmesartan was also found to be cost-effective compared with other ARBs, though this area has yet relatively poor evidence and needs to further be explored [10].

As for the comparison of antihypertensive effects between azilsartan and olmesartan, non-consistent results were reported in several studies. In fact, until now, there are only two large clinical trials that compare the antihypertensive effects between azilsartan and olmesartan. The choice of ARBs as antihypertensive therapy is an important issue in clinical practice. Therefore, we performed this meta-analysis from previous studies to compare the antihypertensive effects between azilsartan and olmesartan in patients with essential hypertension.

## Methods

### Data sources

We searched Pubmed (1966–2018), Web of Science (1986–2018), and Cochrane library (Cochrane Central Register of Controlled Trials: Issue 1 of 12 January 2018) up to February 26, 2018, for all published articles comparing the antihypertensive effects between azilsartan and olmesartan in patients with hypertension. Search keywords were "hypertension," "azilsartan," and "olmesartan." Studies with duplicate publication of results were excluded. The final selection yielded five clinical trials for current analysis [11–15].

### Study selection criteria

Randomized studies were selected for this meta-analysis according to the following inclusion criteria: a diagnosis of essential hypertension at study entry (i.e., studies on secondary hypertension were excluded); BP assessed at office, home, or with ambulatory monitor; a follow-up of at least 6 weeks; clear description of inclusion and exclusion criteria; comparable baseline characteristics between azilsartan and olmesartan; clear description of outcome measures as well as of patient withdrawals and dropouts; and statistical method accurately described.

### Data extraction and quality assessment

Two authors (D. Zhao and H Liu) independently collected data from each study and entered onto a structured spreadsheet. Disagreements were resolved through discussion or by a third investigator (P. Dong) as required. We extracted the following data from each trial: year of publication; demographic and methodological data; total number, mean age, gender distribution, and race of enrolled patients; baseline systolic and diastolic BP (SBP and DBP); number of patients assigned to each intervention; duration of therapy; incidence and type of adverse events; number of dropouts or withdrawals because of adverse events; and change from baseline of SBP and DBP.

The characteristics and quality of the studies included herein are shown in Table 1. Two reviewers (D. Zhao and H Liu) independently assessed study quality using a validated scale (JADAD scale) based on the following criteria: methods used to generate the randomization sequence, methods of double blinding, and description of patient withdrawals and dropouts [16, 17]. A score of 1 point was given for each criterion satisfied, and 1 additional point was given for high quality of randomization and double blinding, for a maximum of 5 points. Studies with a score > 2 were considered high quality, and studies with a score ≤ 2 were considered low quality. In addition, risk of bias summary for each included study is shown in Fig. 1.

### Outcome measures

The outcomes of interest were changes from baseline of both SBP and DBP during follow-up. Incidence of any adverse event was used for safety measures. Serious adverse events were considered as withdrawal of study treatment.

### Statistical analysis

We combined data at the study level for this meta-analysis and analyzed data utilizing the Review Manager 5.3 software (available from The Cochrane Collaboration at http://www.cochrane.org) and STATA software package (version 12.0; Stata Corp., College Station, TX), respectively. Weighted mean differences (WMD) with 95% confidence intervals (CI) were considered for comparisons between changes in SBP and DBP. Heterogeneity of the included studies was tested with Q statistics [18]. We also tested the extent of inconsistency between results with $I^2$ statistics [18]. If an $I^2 > 50\%$, heterogeneity was considered significant. We used a random-effect model for calculating summary estimates and their 95% CI if there was significant heterogeneity. Publication bias was detected with funnel plots. We performed the analysis of publication bias test using the Egger's test [19]. Significance was set at $p < 0.05$.

**Table 1** Characteristics of studies included in this meta-analysis

| Study | Origin of people | Design (blind) | Setting | Drug | Doses | Other drugs (antihypertensive) (%) | Duration (weeks) | JADAD scale |
|---|---|---|---|---|---|---|---|---|
| Bakris et al. 2011 | USA | Randomized, blind | Multicenter | Azilmisartan | 80 mg/day | No | 6 | 3 |
| | Peru | | | Olmesartan | 40 mg/day | No | | |
| | Argentina | | | Azilmisartan | 40 mg/day | No | | |
| | Mexico | | | | | | | |
| Kakio et al. 2017 | Japan | Randomized, open | Multicenter | Azilmisartan | 20 mg/day | No | 16 | 2 |
| | | | | Olmesartan | 20 mg/day | No | | |
| Shiga et al. 2017 | Japan | Randomized, open | Single center | Azilmisartan | 20 mg/day | CCB (61) | 12 | 1 |
| | | | | | | β-Blocker (21) | | |
| | | | | | | α-Blocker (7) | | |
| | | | | Olmesartan | 20 mg/day | CCB (46) | | |
| | | | | | | β-Blocker (18) | | |
| | | | | | | α-Blocker (11) | | |
| Sezai et al. 2016 | Japan | Randomized, open | Single center | Azilmisartan | | ACE inhibitor | 52 | 3 |
| | | | | | | CCB, β-blocker | | |
| | | | | | | α-Blocker | | |
| | | | | | | Renin antagonist | | |
| | | | | Olmesartan | | ACE inhibitor | | |
| | | | | | | CCB, β-blocker | | |
| | | | | | | α-Blocker | | |
| | | | | | | Renin antagonist | | |
| White et al. 2011* | USA | Randomized, blind | Multicenter | Azilmisartan | 80 mg/day | No | 6 | 3 |
| | Guatemala | | | Olmesartan | 40 mg/day | No | | |
| | Mexico | | | Azilmisartan | 40 mg/day | No | | |
| | Peru | | | | | | | |
| | Puerto Rico | | | | | | | |

*Azilsartan was given at 40 or 80 mg in two groups of patients, respectively. *CCB* calcium channel blocker, *ACE* angiotensin-converting enzyme

## Results

### Search strategy

One hundred one screened articles initially met the search inclusion criteria (33 from Pubmed, 43 from Web of Science, and 25 from Cochrane databases). After excluding 44 duplicate articles, 57 articles were further evaluated. The majority of these articles ($n = 48$) were excluded after reviewing the abstract or title, mostly due to trial design, antihypertensive agent choice or because were reviews, letter, or comments. We evaluated 9 articles with full text and 4 articles were discarded due to combination treatment or lacking individual data with ARB treatment. Finally, 5 articles were included in this meta-analysis [11–15]. The progress of candidate article selection is documented as flow diagram in Fig. 2.

### Study participants and included studies

A total of 1402 patients were included in these five studies. Tables 1 and 2 show the main characteristics of included studies and study participants. All the five studies investigated the antihypertensive effects of azilsartan and olmesartan in patients with essential hypertension [11–15]. The duration of these studies ranged from 6 to 52 (18 ± 19) weeks.

### Comparisons of office SBP and DBP reduction between azilsartan and olmesartan

As shown in Fig. 3, the reduction of office SBP treated with azilsartan was greater than olmesartan (WMD −2.15 (95% CI, −3.78, −0.53) mm Hg, $p < 0.01$). There was no significant difference in reduction of office DBP between azilsartan and olmesartan (WMD −0.99 (95% CI, −2.06, 0.08) mm Hg, $p > 0.05$).

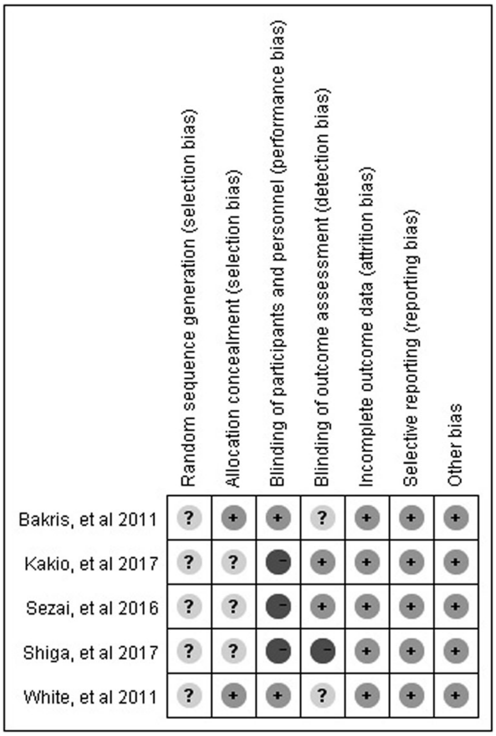


**Fig. 1** Risk of bias summary for each included study. "+" circle: low risk of bias, "-" circle: high risk of bias, "?" circle: unclear risk of bias

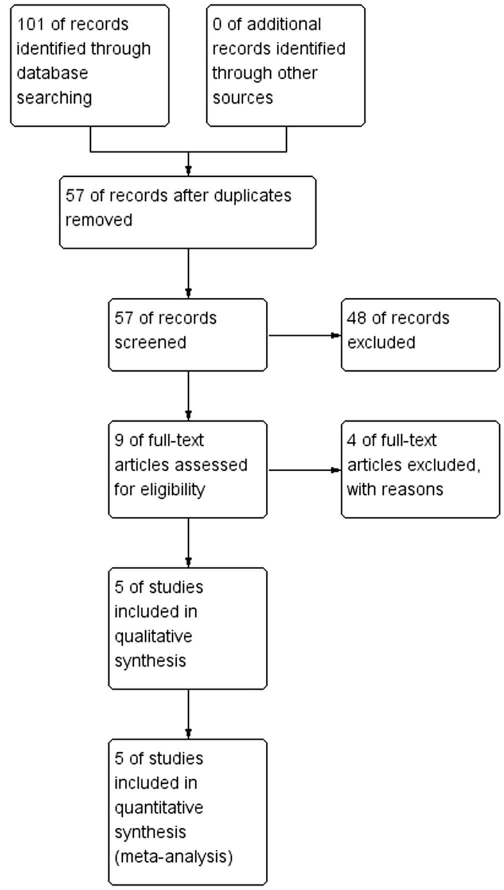


**Fig. 2** Flow diagram demonstrating the study selection process in the meta-analysis

The doses of azilsartan and olmesartan were not shown in Sezai et al.'s study. Therefore, this study was excluded in the following analysis. Azilsartan was also given at 40 mg in one group patients as the dose of olmesartan in White et al.'s study. Only data in this group was included in the following analysis, in which the doses of azilsartan and olmesartan were same in each study. As shown in Fig. 4, the reduction of office SBP treated with azilsartan was greater than olmesartan (WMD − 2.24 (95% CI, − 4.03, − 0.44) mm Hg, $p < 0.05$), whereas there was no significant difference in reduction of office DBP between azilsartan and olmesartan (WMD − 0.55 (95% CI, − 1.76, 0.66) mm Hg, $p > 0.05$).

### Publication bias

No publication bias was found by funnel plots. Furthermore, the Egger's test did not show any significant publication bias for outcome measures in this meta-analysis.

## Discussion

This meta-analysis provides the evidence that the reduction of office SBP treated with azilsartan was greater than olmesartan in patients with essential hypertension. Additional 2 mmHg SBP reduction may not really affect the cardiovascular prognosis. However, cardiovascular risk should increase with the elevation of BP. Although the difference of SBP reductions for these two drugs was smaller, the antihypertensive effect of azilsartan was stronger than olmesartan. Satoh et al. [20] reported that the maximum effect and the stabilization time differed among ARBs used at the mid-level dose in Japan. An ARB should be chosen based on its desired characteristics [20]. In addition, azilsartan is the most expensive ARB. If the benefit of azilsartan is only additional 2 mmHg SBP reduction, the price may affect the choice between these two antihypertensive drugs. Perhaps the cost of taking azilsartan impedes the extensive use of it in clinical practice.

While most ARBs have common molecular structures (biphenyl-tetrazol and imidazole groups), they also show slightly different structures. Their slightly different structures may be important for promoting molecule-specific effects [21]. Azilsartan is a safe and effective treatment option for every stage of hypertension, both alone or in fixed-dose combination tablets with chlorthalidone or amlodipine [22]. The bioavailability of azilsartan is about 60% and it has a $t_{max}$ of 1.5–3 h and a half-life of approximately 11 h [23]. With its IC50 of 7.4 nM after 5 h of drug washout in radioligand assays, azilsartan has a tighter and longer-lasting binding to the AT1 receptor by several orders of magnitude than other ARBs, which might lead to a more effective reduction in BP [23].

**Table 2** Main characteristics of patients included in this meta-analysis

| Study | Treatment group | No. of pts. | Age (years) | Gender | | SBP/DBP (mm Hg) | BMI (kg/m$^2$) | FPG (mmol/L) | HbA1c (%) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Male | Female | | | | |
| Bakris et al. 2011# | Azilmisartan | 285 | 58.1 ± 11.6 | 149 | 136 | 149.5 ± 1 | 30.0 ± 5.5 | None | None |
| | Olmesartan | 282 | 58.9 ± 11.6 | 140 | 142 | 150.6 ± 1 | 29.8 ± 5.3 | None | None |
| | Azilmisartan | 283 | 57.4 ± 9.6 | 142 | 141 | None | 30.6 ± 5.9 | None | None |
| Kakio et al. 2017 | Azilmisartan | 44 | 68.7 ± 11.1 | 22 | 22 | 150.4 ± 10.4/83.0 ± 9.8 | 25.2 ± 3.3 | None | 6.0 ± 0.7 |
| | Olmesartan | 40 | 66.6 ± 11.8 | 18 | 22 | 150.1 ± 14.1/83.2 ± 11.8 | 25.9 ± 3.9 | None | 6.1 ± 0.8 |
| Shiga et al. 2017 | Azilmisartan | 28 | 72 ± 9 | 10 | 18 | 132 ± 12/75 ± 9 | 23 ± 4 | 107 ± 26 | 5.9 ± 0.7 |
| | Olmesartan | 28 | 70 ± 9 | 14 | 14 | 136 ± 11/77 ± 8 | 25 ± 4 | 117 ± 38 | 6.1 ± 0.7 |
| Sezai et al. 2016 | Azilmisartan | 60 | 68.8 ± 8.8 | 39 | 21 | 126.3 ± 6.2 /69.3 ± 6.2 | None | None | None |
| | Olmesartan | 60 | 68.8 ± 8.8 | 39 | 21 | 126.3 ± 6.2 /69.3 ± 6.2 | None | None | None |
| White et al. 2011* | Azilmisartan | 285 | 56 ± 11 | 151 | 134 | 158 ± 12/92 ± 11 | 30.7 ± 5.9 | None | None |
| | Olmesartan | 290 | 56 ± 11 | 160 | 130 | 158 ± 13 /92 ± 9 | 31.1 ± 5.5 | None | None |
| | Azilmisartan | 280 | 57 ± 12 | 148 | 132 | 157 ± 13/93 ± 11 | 31.7 ± 6.0 | None | None |

*pts* patients, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BMI* body mass index, *FPG* fasting plasma glucose, *HbA1c* hemoglobin A1c

*Azilsartan was given at 40 or 80 mg in two groups of patients, respectively

# The data of SBP/DBP was mean 24-h baseline BPs

Furthermore, azilsartan has been reported to have greater antihypertensive effects than some other ARBs including candesartan and valsartan [12, 24, 25]. Azilsartan appears to be characterized by a superior ability to control 24-h SBP relative to other widely used ARBs including valsartan, olmesartan, and candesartan, and presumably others as well (e.g., losartan) [6]. Bakris et al. [15] reported that reduction in 24-h mean SBP was greater with azilsartan 80 mg than olmesartan 40 mg, while azilsartan 40 mg was noninferior to olmesartan 40 mg. In addition, the reduction in clinic DBP was greater with azilsartan 80 mg compared with olmesartan 40 mg [15]. The authors concluded that azilsartan is well tolerated and more efficacious at its maximal dose than the highest dose of olmesartan [15]. In five trials of this meta-analysis, only White et al. [11] found that azilsartan at its maximal dose (80 mg/day) had superior efficacy to both olmesartan (40 mg/day) and valsartan (320 mg/day) on reduction in 24-h mean or clinic SBP at their maximal, approved

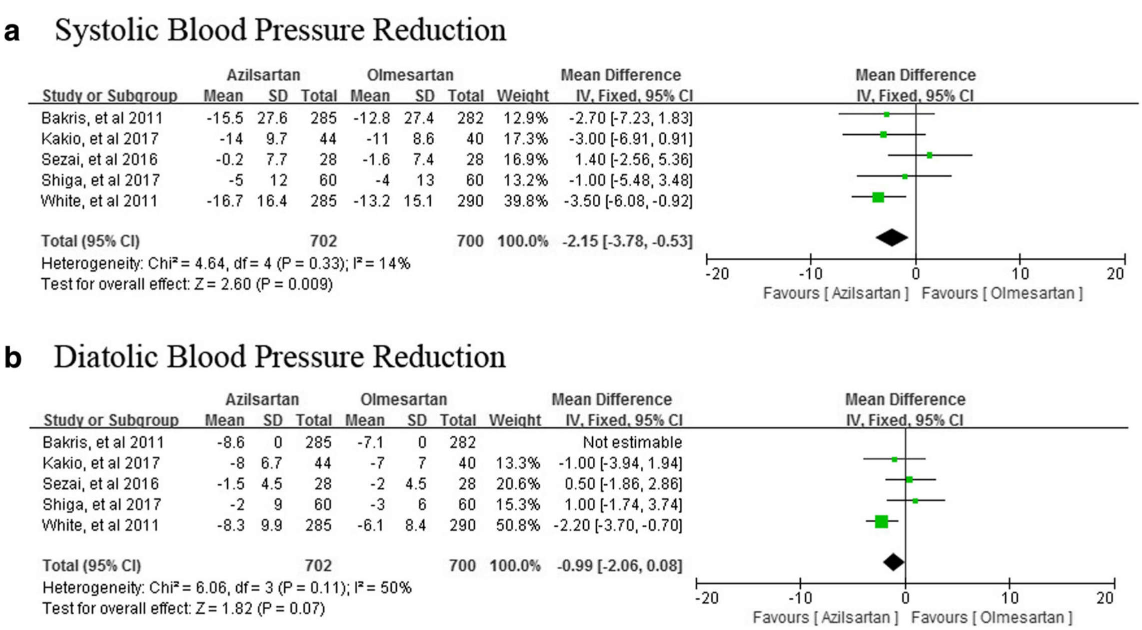


**Fig. 3** Comparison of office SBP and DBP reduction in patients with essential hypertension treated with azilsartan or olmesartan. WMD of data with 95% CI of difference between changes in SBP and DBP were considered. The data are presented as mean ± SD. SBP systolic blood pressure, DBP diastolic blood pressure, WMD weighted mean differences, CI confidence interval, SD standard deviation

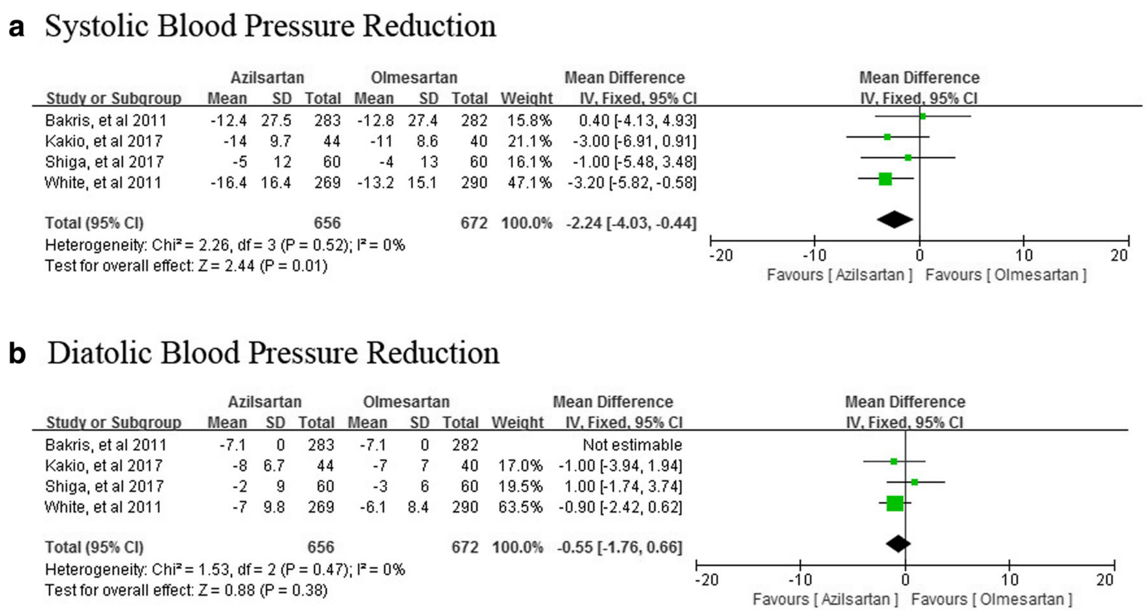


**Fig. 4** Comparison of office SBP and DBP reduction between azilsartan and olmesartan at same doses. WMD of data with 95% CI of difference between changes in SBP and DBP were considered. The data are presented as mean ± SD. SBP systolic blood pressure, DBP diastolic blood pressure, WMD weighted mean differences, CI confidence interval, SD standard deviation

doses without increasing adverse events. Similar findings were also reported by White et al. [26] in patients with essential hypertension and prediabetes mellitus or type 2 diabetes mellitus. These findings have important clinical implications for this high-risk patient group [26]. However, this superior effect of azilsartan versus olmesartan in lowering BP was not found in other three included studies [12–14]. Sezai et al. [14] found that home BP exceeded 140/90 mmHg and additional antihypertensive medication was administered to 12 patients (20 episodes) in the azilsartan group versus 4 patients (4 episodes) in the olmesartan group, with the number being significantly higher in the azilsartan group. In this study, olmesartan reduced angiotensin II and aldosterone levels more effectively than azilsartan [14]. Perhaps non-consistent results may be related to the doses of azilsartan and olmesartan in each study, since the doses were not totally same in these studies. Secondly, the relative small sized sample in some studies may also affect the results. Thirdly, the comorbidities of patients were different. All the patients received different cardiac surgeries that included coronary artery bypass grafting, aortic valve replacement et al. in Sezai et al.'s study, although these patients were clinically stable after cardiac surgery [14]. In addition, before azilsartan or olmesartan was randomly assigned in these two studies, other ARBs were given in Shiga et al.'s study [12] and olmesartan was taken at least 1 year in Sezai et al.'s study [14]. This is the reason that the reduction of BP was less in these two studies. Interestingly, Iwanami et al. [27] reported that the hypotensive and antihypertrophic effects of azilsartan may involve activation of the angiotensin-converting enzyme 2 (ACE2)/Ang-(1-7)/Mas axis with AT1 receptor blockade [27]. These findings indicate potential new mechanisms of azilsartan on antihypertensive therapy. In addition, based on the pharmacokinetic and safety/tolerability findings, no azilsartan dose adjustments are required based on age, sex, or race (black/white) [28].

Twenty-four-hour ambulatory BP was reduced to a greater extent with olmesartan 80 mg than with amlodipine 5 mg [29], suggesting the greater antihypertensive effect of olmesartan 80 mg. Besides the antihypertensive effect, olmesartan treatment was found to generate beneficial effects on metabolic syndrome parameters in hypertension patients but did not produce any significant increases in serum peroxisome proliferator-activated receptor gamma transcription factor concentration [30]. Olmesartan significantly improves arterial stiffness as demonstrated by the reduction in pulse wave velocity and in central SBP [29]. This may relate to a mechanistic rationale for olmesartan's antioxidant/anti-inflammatory potential translation, in the long term, toward anti-atherosclerotic/anti-remodeling effects [31]. In contrast with other antihypertensive drugs, olmesartan may uniquely increase urinary ACE2 level, which could potentially offer additional renoprotective effects [32]. However, whether this contributes to olmesartan's renoprotective effect must be examined further [33]. These findings indicate the multiple mechanisms of olmesartan on cardiovascular and renal protection. Furthermore, olmesartan may be more cost-effective than other ARBs such as losartan, valsartan, irbesartan, and candesartan, having the potential of decreasing the overall medical costs of care for patients with hypertension [10].

Importantly, the major adverse reactions may be hypotension in patients with essential hypertension treated with azilsartan or olmesartan. No severe adverse reactions to azilsartan or olmesartan therapy were noted in these studies [11–15]. The side effect profiles of azilsartan [15, 22] and olmesartan [15] were similar to that of the placebo. These data suggest the safety of these two agents in antihypertensive therapy. However, sprue-like enteropathy induced by olmesartan should be addressed. It is critical for its early diagnosis and replacing olmesartan with an alternative antihypertensive drug [34].

This article had several limitations. The major limitation may be the inadequate trials and the small samples in some studies, which may relate to non-consistent results.

In conclusion, this meta-analysis provides the evidence that the reduction of office SBP treated with azilsartan was greater than olmesartan in patients with essential hypertension. These findings suggest the importance of strict designed and large sized randomized controlled trials in determining antihypertensive effects of ARBs in clinical practice.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

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