# Original Article
# Effect of valsartan on insulin resistance in patients with hypertension: a systematic review and meta-analysis

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**Abstract:** Objective: The aim of the present meta-analysis was to evaluate the effect of valsartan on insulin resistance in patients with hypertension. Methods: We searched the electronic databases, including PubMed, EMBASE and The Chorance Library, for randomized controlled trials (RCTs) comparing the effect of valsartan and the other antihypertensive drugs on insulin resistance in patients with hypertension. We carried out statistical analyses using RevMan version 5.3 and used the Cochrane bias risk evaluation tools to assess the risk of bias. Results: A total of eight studies involving 935 subjects were included in the present meta-analysis. The results showed that compared with other antihypertensive drugs, valsartan possessed a slight but non-significant trend to reduce the level of HOMA-IR [WMD=-0.42; 95% confidence interval (CI) -0.84, -0.01 (P=0.05)], glycated hemoglobin [WMD=-0.06; 95% CI: -0.27, 0.14; (P=0.55)] and fasting plasma glucose [WMD=-0.11; 95% CI: -0.27, 0.05; (P=0.18)]. However, valsartan was found to be more effective at reducing the insulin level [WMD=-1.15; 95% CI -2.00, -0.31]. In addition, systolic blood pressure [WMD=-4.09; 95% CI: -8.83, 0.66], but not diastolic blood pressure [WMD=-2.41; 95% CI: -3.53, -1.30], was significantly different between the two groups. Conclusions: The present meta-analysis suggested that valsartan showed a tendency to be superior to other antihypertensive drugs in the improvement of insulin resistance, but the difference was not statistically significant. More large-scale studies with longer follow-up durations are warranted to confirm this effect.

**Keywords:** Valsartan, hypertension, insulin resistance, diabetes, meta-analysis

## Introduction

Hypertension threatens human health worldwide, with an incidence of 25% in adults. By 2025, the morbidity of hypertension is projected to reach 60% [1]. Patients with hypertension often co-present with insulin resistance, which may increase the risk of renal impairment [2, 3] and the morbidity [4] and mortality [5] of cardiovascular and cerebrovascular diseases. Studies have shown that insulin resistance, which is present in more than 50% of the patients with hypertension [6, 7], plays an important role in the development and progression of hypertension and diabetes. In addition to its role in increasing the incidence of impaired glucose tolerance and diabetes [8], insulin resistance is also directly associated with the severity of hypertension [6]. Therefore, to clarify the question whether antihypertensive drugs can improve insulin resistance has important implications for patients with hypertension.

Previous studies showed that compared with beta-blockers [9], calcium antagonists [10, 11] and diuretics [9, 10], angiotensin receptor antagonists (the first-line antihypertensive drugs recommended by the international guidelines for the management of arterial hypertension [12] not only had good antihypertensive effects but also improved insulin resistance. Valsartan, an angiotensin receptor antagonist, was found to can improve insulin resistance in patients with hypertension [11].

Studies have confirmed that valsartan improve insulin resistance, but large-scale studies are needed to further validate this effect. Moreover, it is unknown whether valsartan is superior to other antihypertensive drugs in improving insulin resistance in patients with hypertension. Thus, we conducted a systematic review and meta-analysis of clinical studies to figure out this question.
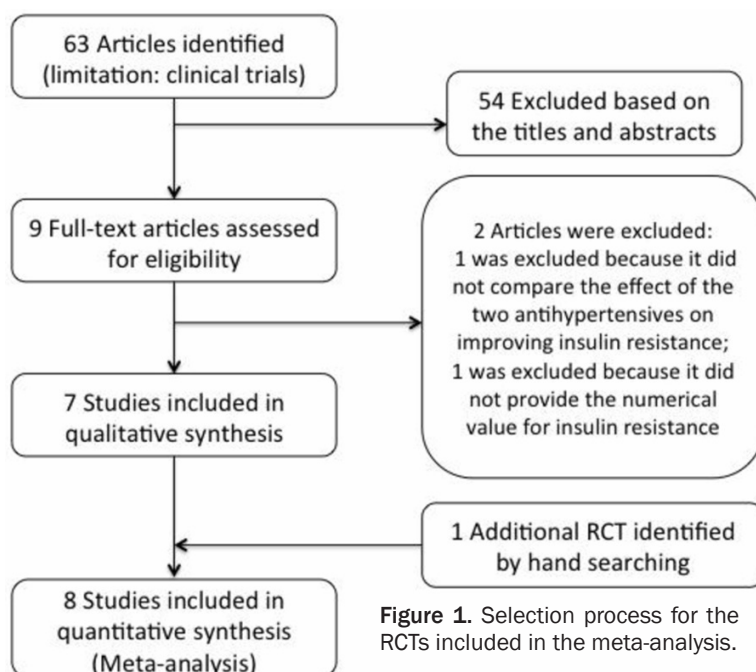
Figure 1. Selection process for the RCTs included in the meta-analysis.

by searching for opinions from a third party.

*Data extraction and quality assessment*

The same two investigators reviewed the full texts of eligible studies independently and collected data for study and patient characteristics, interventions and items for bias risk assessing. We independently extracted the following data: first author, year of publication, the characteristics of the enrolled population, the number of patients enrolled, study design, the experimental group (number of patients, drug(s) and dose(s)), the control group (number of patients, drug(s) and dose(s)), treatment time, definition of blood pressure and the incidence of adverse events and related definitions. Extracted data were entered into a standard EXCEL file (Microsoft Corp.; Redmond, Washington, America) and were confirmed by another author of this manuscript. During data extraction, any discrepancies were resolved through discussions between the authors of this manuscript.

The primary efficacy endpoint of the studies was an improvement in insulin resistance, as determined by insulin resistance index, blood glucose and serum insulin. And the secondary efficacy endpoint was the presence of changes in blood pressure before and after randomized treatment.

The two authors who selected the RCTs independently assessed the studies for the risk of bias using the Cochrane risk-of-bias tool [13]. We assigned a value of low, unclear or high risk of bias to the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. Disagreements were resolved by consensus.

*Data synthesis and analysis*

The meta-analysis was performed by software RevMan 5.3 (Nordic Cochrane Centre, Cochrane

## Methods

*Eligibility criteria*

The literature was screened according to the following criteria: (i) study design: randomized controlled trials (RCTs), (ii) study population: patients with hypertension, (iii) treatment: valsartan or other antihypertensive drugs and (iv) prognosis evaluation: improvement in blood pressure and insulin resistance (insulin resistance index, blood glucose, serum insulin) and adverse events in patients with hypertension after treatment with different antihypertensive drugs. The exclusion criteria were no information about endpoints or a follow-up time was less than 30 days.

*Search strategy and study selection*

We searched the databases (PubMed, EMBASE, the Cochrane Library) for studies published up to July 2015, using the following search items: valsartan, hypertension, insulin resistance, diabetes, abnormal glucose tolerance, impaired glucose tolerance. This search was supplemented with citation tracking of the reference lists including articles and relevant review articles. Two investigators reviewed all the databases searched and retrieved the literature which met our eligibility criteria by title and abstract, and then the full texts independently. Disagreements were solved by discussion or

**Table 1.** Study characteristics

| Author | Year | Setting | N | Subjects | Experimental | | Control | | Duration |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Treatment | N | Treatment | N | |
| Boschmann [18] | 2006 | Germany | 18 | SBP of 150-179 mmHg or DBP of 95-109 mmHg; BMI of 30-40 kg/m$^2$ | Valsartan | 8 | Atenolol | 10 | 13 weeks |
| Fogari [17] | 2005 | Italy | 96 | BMI > 30 kg/m$^2$; DBP > 90 and < 110 mmHg | Valsartan | 48 | Felodipine | 48 | 16 weeks |
| Ichikawa [19] | 2007 | Japan | 53 | Metabolic syndrome; fasting plasma glucose < 140 mg/dl | Valsartan | 27 | Telmisartan | 26 | 4 weeks |
| Jordan [16] | 2005 | Germany | 132 | SBP of 150-179 mmHg or DBP of 95-109 mmHg; BMI of 30-40 kg/m$^2$ | Valsartan | 67 | Atenolol | 65 | 13 weeks |
| Kintscher [21] | 2010 | Germany | 109 | Age of 30-80 years; SBP of 140-159 mmHg and/or DBP of 90-99 mmHg; controlled type 2 diabetes mellitus on stable treatment for at least 4 weeks | Valsartan | 55 | Placebo | 54 | 16 weeks |
| Ozaki [22] | 2010 | Japan | 308 | SBP > 130 mmHg and/or DBP > 80 mmHg; HbA1c > 8.0% | Valsartan | 74 | Telmisartan (n=74) Candesartan (n=79) | 74 79 | 3 months |
| Yilmaz [20] | 2007 | Turkey | 96 | Metabolic syndrome and hypertension | Valsartan | 20 | Doxazosin (n=18) Metoprolo I (n=18) Ramipril (n=20) Amlodipine (n=20) | 76 | 3 months |
| Hanefeld [15] | 2001 | Germany | 123 | Subjects with mild-to-moderate hypertension between the ages of 35 and 78 years | Valsartan | 63 | Placebo | 60 | 12 weeks |

SBP: systolic blood pressure, DBP: diastolic blood pressure, BMI: body mass index, N: number.

**Figure 2.** Summary of risk of bias for each included study. "+", low risk of bias; "-", high risk of bias; "?", unknown risk of bias.

Collaboration) and the statistics were calculated by the Mantel-Haenszel statistical method. For continuous variables (change from baseline to follow-up), we used weighted mean differences (WMD) with 95% CI to express the outcomes. Statistic heterogeneity was measured using the $\chi^2$ (Cochran Q) statistic and $I^2$ test [14]. Heterogeneity was not considered as significant when $I^2 < 50\%$. Pooled analyses were conducted within fixed effect models, whereas random effect models were applied in conditions of significant heterogeneity among included studies. A *P* value < 0.05 was considered to be statistically significant, except where otherwise specified.

**Results**

*Eligible studies*

A total of 63 relevant clinical studies were searched and retrieved, of which 54 studies

were excluded based on the title and abstract and two studies were excluded based on the full text (one study did not compare the effect between valsartan and another antihypertensive drug on improving insulin resistance, and one study did not specify changes in the measures of insulin resistance). One study was added by manual search and retrieval. Thus, a total of eight RCTs [15-22] met the inclusion criteria and were included in this meta-analysis. The literature search and retrieval process was shown in **Figure 1**.

*Characteristics of the selected studies*

The characteristics of the eight RCTs included are shown in **Table 1**. These RCTs were published in 2001-2010 and had sample sizes of 18-308 subjects (total: 935 subjects). Regarding improvements in the insulin resistance of patients with hypertension randomly assigned to the valsartan group or the control group, of the eight RCTs [16-22], seven studies reported the insulin resistance index (homeostasis model assessment of insulin resistance (HOMA-IR)) before and after randomized treatment, six studies [15, 16, 18-20, 22] reported blood glucose levels before and after randomized treatment, five studies [16, 18-20, 22] reported insulin levels before and after randomized treatment, and three studies [15, 19, 22] reported glycated hemoglobin levels. Fogari-2005 [17] and Yilmaz-2007 [20] had a high risk of bias for two aspects: investigator and subject blinding and the blinded evaluation of study results. The Ozaki-2010 [22] study had a high risk of bias for three aspects: investigator and subject blinding, blinded evaluation of study results and integrity of study data. Other aspects of these studies and the remaining studies had a low or unknown risk of bias. The summary of the risk of bias for each included study was shown in **Figure 2**.

Among the eight RCTs [15-22], Ozaki-2010 [22] and Yilmaz-2007 [20] had multi-arms, in other words, the two trials compared valsartan with other two or more antihypertensive drugs on the change of insulin resistance indexes and blood pressure before and after the treatment respectively.

*Primary efficacy endpoints*

*HOMA-IR:* Five studies reported HOMA-IR in the experimental group and the control group
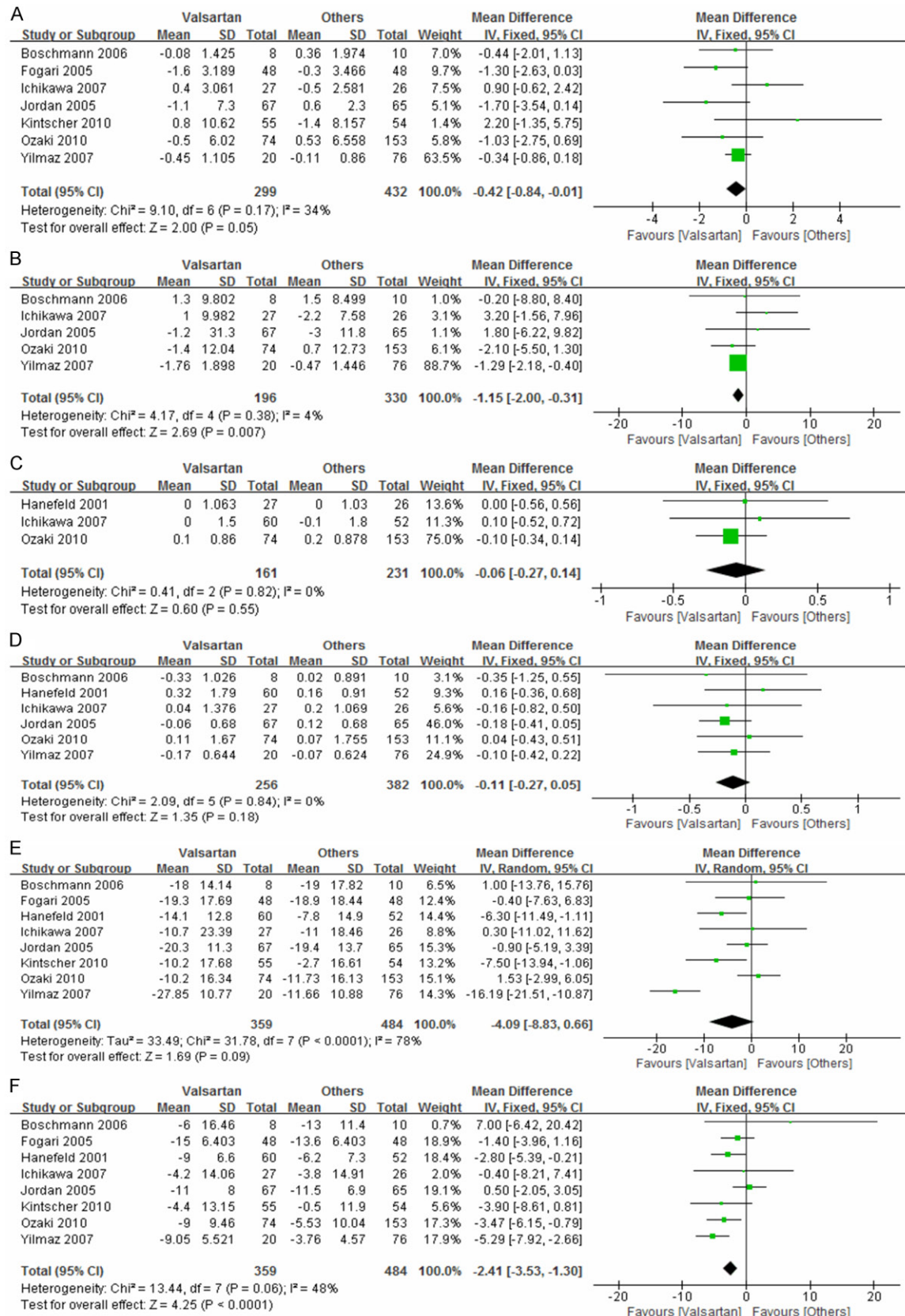
**Figure 3.** Forest plots of primary and secondary outcomes of meta-analysis. A. HOMA-IR; B. Insulin level; C. Glycated hemoglobin; D. Fasting plasma glucose; E. Systolic blood pressure (SBP); F. Diastolic blood pressure (DBP). The squares and horizontal lines correspond to the study-specific WMD and 95% CI, respectively. The area of the

squares reflects the study-specific weight. The diamond represents the pooled results of WMD and 95% CI. If 95% CI cross with 0, there was no statistical significance. 95% CI located in the left, valsartan was superior to other antihypertensive drugs, whereas other antihypertensive drugs were superior to valsartan.

before and after treatment. Two studies reported changes in HOMA-IR. **Figure 3A** shows a summary of the HOMA-IR changes before and after treatment. Statistical analysis showed that the WMD was -0.42 (95% CI: -0.84, -0.01), which did not reached statistical significance (P=0.05) and suggested that valsartan was not less effective than other antihypertensive drugs at improving HOMA-IR.

*Insulin level:* Three studies reported the insulin level in the experimental group and the control group before and after treatment. Two studies reported the changes of insulin level in the experimental group and control group. **Figure 3B** summarizes the changes of insulin level. Statistical analysis of this parameter showed that the WMD was -1.15 (95% CI: -2.00,-0.31) (P=0.007), suggesting that valsartan was more effective than other antihypertensive drugs in its effect on insulin level in patients with hypertension.

*Glycated hemoglobin:* Only one study reported the level of glycated hemoglobin before and after treatment in the experimental group and the control group. Two studies reported changes in the level of glycated hemoglobin in the experimental group and the control group. Statistical analysis (**Figure 3C**), suggested that valsartan was not less effective than other antihypertensive drugs at reducing the level of glycated hemoglobin in patients with hypertension [WMD=-0.06; 95% CI: -0.27, 0.14; (P= 0.55)].

*Fasting plasma glucose:* Three studies reported fasting plasma glucose before and after treatment in the experimental group and the control group. Three studies reported a reduction in fasting plasma glucose in the experimental group and the control group. Statistical analysis of the changes in fasting plasma glucose (**Figure 3D**) showed that the WMD was -0.11 (95% CI: -0.27, 0.05) (P=0.18), suggesting that valsartan was not less effective than other antihypertensive drugs in its effect on fasting plasma glucose in patients with hypertension.

*Secondary efficacy endpoints*

*Systolic blood pressure (SBP):* Five studies reported SBP before and after treatment in the

experimental group and the control group. Three studies reported changes in SBP in the experimental group and the control group. **Figure 3E** showed a summary of the SBP changes before and after treatment. Due to significant heterogeneity ($I^2$=78%), a random effects model was used to compile the results. Statistical analysis of the changes in SBP showed that the WMD was -4.09 (95% CI: -8.83, 0.66) (P=0.09), which suggested that the effect of valsartan on SBP was not significantly different from that of other antihypertensive drugs.

*Diastolic blood pressure (DBP):* Five studies reported DBP before and after treatment in the experimental group and the control group. Three studies reported changes in DBP in the experimental group and the control group. Statistical analysis of the changes in DBP (**Figure 3F**) showed that the WMD was -2.41 (95% CI: -3.53, -1.30) (P < 0.0001), suggesting that valsartan was more effective at lowering DBP than other antihypertensive drugs.

*Safety*

Only one of the eight RCTs included reported adverse events [15]. In this article, there were 11 discontinuation patients (three in valsartan group and eight in placebo group). Reasons for discontinuation were adverse events such as acute bronchitis, feverish infection and hypotension. These events were not suspected to be related to study drug. And no significant difference was found between valsartan group and placebo group with respect to frequency of adverse events. The adverse events were not reported in the other seven RCTs. With limited data, we could not evaluate adverse events through meta-analysis method.

**Discussion**

This study was a meta-analysis of eight RCTs conducted to evaluate improvements of insulin resistance and blood pressure in patients with hypertension and also to determine whether the incidence of adverse events was higher with valsartan compared with other antihypertensive drugs. The results showed that there was no significant difference in the improve-

ment of insulin resistance in hypertension patients between valsartan and other antihypertensive drugs. But, valsartan showed a tendency to be superior to other antihypertensive drugs in the improvement of insulin resistance, but the difference was not statistically significant. We thought that this might be related to the small number of studies included in the meta-analysis. Future researches with larger sample sizes are needed to assess the advantage of valsartan. And our findings illustrated that valsartan was more effective at reducing the insulin level than other antihypertensive drugs in patients with hypertension. We thought that Valsartan might improve insulin resistance by lowering insulin levels. Furthermore, valsartan was more potent than other antihypertensive drugs at lowering the DBP of patients with hypertension but showed no stronger effects on SBP than other antihypertensive drugs.

Many clinical studies have reported that valsartan was effective at lowering blood pressure and improving insulin resistance in patients with hypertension, but this is the first meta-analysis of such studies. Moreover, to ensure quality, this meta-analysis included only RCTs and excluded cohort studies.

Compared with previous clinical studies, this meta-analysis reached a different conclusion on whether valsartan improves insulin resistance in patients with hypertension. Previous cohort studies [23] showed that valsartan lowered blood pressure and improved insulin resistance in patients with hypertension, however, these cohort studies only assessed whether valsartan improves insulin resistance and did not compare the effect of valsartan with that of other antihypertensive drugs. As a result, these studies only indicated that valsartan could improve insulin resistance in patients with hypertension, but contained no information about whether valsartan was superior to other antihypertensive drugs in improving insulin resistance. This meta-analysis of compiled results showed that valsartan was not significantly more effective than other antihypertensive drugs at improving insulin resistance, suggesting that although valsartan improves insulin resistance, it was not superior to other antihypertensive drugs. In addition, some cohort studies [24] did not include a valsartan monotherapy group and thus are unable to show the

correlation between improvement in insulin resistance and valsartan. Some cohort studies investigated the efficacy of valsartan in patients with hypertension who also had diabetes. However, these studies also used different measures. For example, these studies investigated the effect of valsartan on different measures such as soluble Klotho [25], serum proteins [26, 27] and adiponectin [28] or on the incidence and mortality of cardiovascular events in diabetic patients [29]. Although these measurements, to some extent, indicated the protective effect of valsartan on the kidneys and glucose metabolism of diabetic patients, they did not directly reflect improvement in insulin resistance. In some studies, the study population received other antihypertensive drugs in addition to valsartan without specific protocols on the use of other antihypertensive drugs; thus, these studies could not exclude the interference of other antihypertensive drugs while evaluating the effect of valsartan on improving glucose metabolism in diabetic patients. In summary, current studies only show that valsartan improves insulin resistance in patients with hypertension but are unable to show whether valsartan is superior to other antihypertensive drugs in improving insulin resistance, which requires validation from additional clinical studies.

The RCTs included in these meta-analysis enrolled patients with hypertension who were randomly assigned to receive valsartan or other antihypertensive drugs and then investigated whether valsartan was superior to other antihypertensive drugs in improving insulin resistance. This meta-analysis showed that valsartan was superior to other antihypertensive drugs in decreasing the level of DBP in patients with hypertension, but was not significantly more effective at reducing SBP than other antihypertensive drugs. Previous studies [30] showed that valsartan significantly improved the SBP and DBP of patients with hypertension. However, more studies are needed to verify whether valsartan is superior to other antihypertensive drugs in improving DBP.

This meta-analysis had the following advantages in evaluating the effect of valsartan on insulin resistance in patients with hypertension: it used measures that directly reflect the improvement of insulin resistance, such as insulin

resistance index, blood glucose, insulin level, and glycosylated hemoglobin. In addition, in the RCTs included in this meta-analysis, other anti-hypertensive drugs were added only if valsartan treatment was ineffective for the management of hypertension, which, to some extent, minimized the effect of other antihypertensive drugs on insulin resistance. All of the clinical studies included in this meta-analysis were RCTs that used direct measures of insulin resistance, which helped ensure accurate and rigorous results. However, there still existed some limitations. First, although the results showed that valsartan did not significantly improve insulin resistance relative to other drugs, different studies used different time points. Past studies [31] had shown that the efficacy of valsartan was time and dose dependent. Due to the small number of studies included, this meta-analysis did not analyze the effect of treatment time on insulin resistance. The variation in treatment time between studies might affect the results of this meta-analysis. Second, studies [26, 27] had shown that high-dose valsartan was superior to low-dose valsartan in improving endocrine parameters in diabetic patients, and thus, more studies are needed to investigate whether the effect of valsartan on the improvement of insulin resistance is dose dependent. In this meta-analysis, the included studies differed in the dose of valsartan, but we did not analyze the effect of different doses of valsartan or the use of high-dose valsartan on improving insulin resistance due to the small number of included studies. Hence, more studies are needed to investigate the effect of different doses of valsartan on improving insulin resistance. Finally, only one of the included studies reported the incidence of adverse events, and thus, more studies are needed to confirm the safety of different doses of valsartan for hypertension.

Future research may further investigate the following topics to evaluate the effect of valsartan on improving insulin resistance in patients with hypertension to provide more detailed and precise evidence to support the clinical diagnosis and treatment of hypertension: 1) efficacy and safety of different doses and treatment times of valsartan and other antihypertensive drugs, 2) improvement in insulin resistance with valsartan in combination with other drugs, and whether combination therapy (and with which drugs) improves insulin resistance in patients who showed unsatisfactory improvements in insulin resistance with valsartan mono-therapy, 3) safety of valsartan and other antihypertensive drugs, as evaluated by adverse events or changes in biochemical parameters, and 4) previous studies [32] showed variations in the efficacy of valsartan in patients at different risk levels; thus, further research could be conduct to evaluate the efficacy and safety of valsartan in high-risk and medium-to-low-risk patients, different races, different age groups and different genders.

## Conclusion

In conclusion, results of this meta-analysis indicated that valsartan showed a tendency to be superior to other antihypertensive drugs in the improvement of insulin resistance, but the difference was not statistically significant. More large-scale studies with longer follow-up durations are warranted to confirm this effect. Compared with other antihypertensive drugs, valsartan had stronger efficacy in terms of reducing insulin level and the DBP of hypertension patients. Efficacy in the improvement of insulin resistance and safety of different doses and treatment times of valsartan are unclear and should be verified in further trials. Future researches, with more studies and larger sample sizes, are needed to investigate the efficacy and safety of valsartan in high-risk and medium-to-low-risk patients, different races, different age groups and different genders.

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## Disclosure of conflict of interest

None.

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