

Effects of different types of antihypertensive agents on arterial stiffness: a systematic review and meta-analysis of randomized controlled trials

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Background: This system review and meta-analysis was conducted to systematically review and analyze the clinical benefits of different antihypertensive agents in improving arterial stiffness in hypertensive patients.

Methods: PubMed database was searched for randomized controlled trials (RCTs) evaluating the effects of angiotensin receptor blockers (ARB) or other types of antihypertensive agents on pulse wave velocity (PWV). The main indicators were the improvements of PWV and augmentation index (AI) before and after randomized treatments with antihypertensive agents. For the studies that only provided the mean and standard deviation of the indicators before and after randomization, the standardized mean difference (SMD) method was directly applied to combine the mean and standard deviation of various indicators after the treatment. For the studies provided the mean and standard deviation of the changes of the indicators, the weighted mean difference (MD) method was applied to combine the mean and standard deviation of the therapeutic effect.

Results: Ten RCT studies were included and the sample sizes range from 40 to 201 (total: 938). Four studies provided the changes of PWV before and after randomization, the pooled analysis showed that the changes of PWV in ARB group were not significantly higher than other antihypertensive agents [MD: 125.76, 95% confidence interval (CI): -78.70 to 330.23, P=0.23]; 4 studies provided the PWV values before and after randomization, the PWV values in ARB group were not significantly superior (SMD: 0.04, 95% CI: -0.16 to 0.24, P=0.71). Three studies provided the changes of AI before and after randomization, the ability of ARB to lower the level of the AI was superior to other antihypertensive agents (MD: 8.94, 95% CI: 2.18-5.71, P=0.01); 2 studies provided the AI value after randomization, the abilities of ARB and other antihypertensive agents to improve the AI were similar (SMD: 0.03, 95% CI: -1.20 to 1.26, P=0.06).

Conclusions: The effect of ARB on the improvement of the PWV level is not superior to other types of antihypertensive agents, but ARB is superior to other types of antihypertensive agents for improving the AI level. Overall, to improve of arterial stiffness, ARB maybe is superior to other antihypertensive agents.

Keywords: Hypertensive; antihypertensive agents; vascular stiffness; meta-analysis

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Introduction

Hypertension is a major risk factor for cardiovascular diseases and death (1,2). Pathologically, hypertension leads to vascular disease, which represents the key step in the progression to clinical cardiovascular events. In patients with hypertension, increased blood pressure can increase arterial stiffness downstream of increased mechanical stress on vessel walls, endothelial dysfunction, and the excessive activation of the renin-angiotensin-aldosterone system. Furthermore, increased arterial stiffness can cause elasticity loss, reduced compliance, and lowered pressure reflectivity in the arteries, which can further increase the blood pressure, thereby causing a vicious cycle. Significant evidence suggests that the increase in arterial stiffness is an independent risk factor for cardiovascular diseases (3,4), and an ideal antihypertensive agent should both lower blood pressure and improve arterial stiffness.

As methods of monitoring arterial stiffness, pulse wave velocity (PWV) and augmentation index (AI) have been used as indicators in routine arteriosclerosis monitoring. The 2013 guidelines for the management of arterial hypertension by the European Society of Cardiology (ESC) assigned PWV as a new indicator in the risk classification (5), AI was also identified as a risk factor for all-cause mortality and cardiovascular disease in several populations (5). Improvements in PWV have become assessment indicators for the treatment of hypertension (5). Studies have demonstrated that antagonists of angiotensin II receptor, angiotensin converting enzyme inhibitors (ACEIs), beta-blockers and calcium channel blockers (CCBs) may improve arterial stiffness to varying degrees, thereby improving clinical prognosis (6-8).

Previous studies demonstrated that antihypertensive agents of different types or even antihypertensive agents of the same type exhibit differing effects on arterial stiffness (9-11). However, large-scale clinical studies comparing the effect of different types of antihypertensive agents on arterial stiffness are lacking. Thus, this system review and meta-analysis was conducted to systematically review and analyze the clinical benefit of different antihypertensive agents in improving arterial stiffness in hypertensive patients.

Methods

Literature retrieval

The relevant studies published in the PubMed database

were retrieved by two of the authors. A Mesh table combined with a keyword search was used as the retrieval method. The Mesh table retrieval formula was as follows: "Pulse Wave Analysis" [Mesh] OR "Vascular Stiffness" [Mesh], "Antihypertensive Agents" [Mesh]. The keyword search included the following terms: arterial stiffness index [Title/Abstract] OR pulse pressure index [Title/Abstract] OR ambulatory pulse pressure index [Title/Abstract] OR arterial stiffness [Title/Abstract] OR artery stiffness [Title/Abstract] OR aortic stiffness [Title/Abstract] OR augmentation index [Title/Abstract] OR pulse wave velocity [Title/Abstract] combined with antihypertensive treatment [Title/Abstract] OR angiotensin-converting enzyme inhibitors [Title/Abstract] OR angiotensin receptor blocker [Title/Abstract] OR beta blockers [Title/Abstract] OR calcium antagonists [Title/Abstract] OR diuretics [Title/Abstract]. The retrieved literature did not include case reports, comments, editorials, letters, or reviews. The language restriction of "English" was added to the search criteria. The reference lists of the included studies were manually searched, and the referenced studies were included in the analysis if they met the inclusion criteria.

Literature screen

The inclusion criteria for the screened literature were as follows: (I) study design: randomized controlled trials (RCTs); (II) study subjects: patients with hypertension; (III) treatment: angiotensin receptor blockers (ARBs) or other types of antihypertensive agents; and (IV) prognostic evaluation of the patients according to improvement in PWV and the AI after receiving different antihypertensive agents. The exclusion criteria for the screened literature were as follows: the presences of diseases other than hypertension, failure to report the research endpoint of the study, and a follow-up time <30 days.

Data extraction

The following data were independently extracted by two authors: first author, year of publication, characteristics of the included subjects, number of enrolled patients, study design, experimental group (number of patients, the used agent and dose), control group (number of patients, the used agent and dose), duration of the intervention treatment, and changes in PWV and the AI. The extracted data were entered into a standard EXCEL file (Microsoft Crop) and were checked by another author. Disagreements

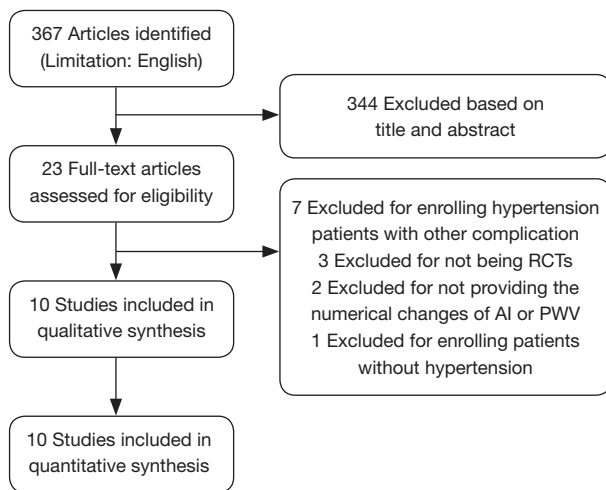


Figure 1 Selection process for the articles included in the meta-analysis.

in the process of data extraction were resolved by consensus among authors.

The main indicators in this study were improvements of PWV and AI before and after treatment with antihypertensive agents.

Quality evaluation

The two authors who screened the RCTs independently assessed the studies using the Cochrane risk-of-bias tool (12). We assigned a value of low, unclear or high risk of bias according the following domains: random sequence generation, allocation concealment, participants and personnel blinding, outcome assessment blinding, incomplete outcome data, selective reporting and other bias. Disagreements were resolved by consensus.

Statistical methods

Because some studies only provided the mean and standard deviation of the detected indicators in the two groups of patients before and after the treatment (i.e., did not provide the mean and standard deviation of the therapeutic effect), the data were processed as follows, based on the recommendation of Cochrane Handbook: (I) for the studies that only provided the mean and standard deviation of the indicators before and after randomization, the baseline characteristics were assumed to be equal, and the standardized mean difference (SMD) method was directly applied to combine the mean and standard deviation of

various indicators after the treatment; (II) for the studies providing the mean and standard deviation of the change of the indicators before and after randomization, the weighted mean difference (MD) method was applied to combine the mean and standard deviation of the therapeutic effect. The therapeutic effect was defined as follows: the results after the treatment-the result before the treatment. The differences were presented as relative risks (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes and as MDs with 95% CIs for continuous outcomes. Heterogeneity across the studies was tested by the I^2 statistic, which is a quantitative measure of inconsistency across studies. Studies with an I^2 statistic of 25–50% were considered to have low heterogeneity, those with an I^2 statistic of 50–75% were considered to have moderate heterogeneity, and those with an I^2 statistic of 75% or greater were considered to have high heterogeneity (13). A random effects model was used, regardless of the heterogeneity. A P value <0.05 was considered statistically significant, except where otherwise specified. All statistical analyses were performed using Review Manager Software (Rev Man version 5.2; Nordic Cochrane Centre, Cochrane Collaboration).

Results

The included studies

A total of 367 articles were obtained by the search, 344 articles of which were excluded based on the title and abstract. The full text of the remaining 23 articles was reviewed, and 13 articles were excluded. Seven of the articles (14–20) were excluded because they involved the patients with hypertension and other associated diseases, one study (21) included non-hypertensive patients, three studies (22–24) were not RCT studies, and two studies (25,26) did not provide AI or PWV values. No study meeting the inclusion criteria was obtained by the manual searching. Eventually, a total of 10 RCT studies (6,8,27–34) met the inclusion criteria and were included in this meta-analysis. The literature retrieval process is presented in *Figure 1*.

Characteristics of the selected studies

The characteristics of the 10 included RCT studies are presented in *Table 1*. These RCT studies were published between 2002 and 2014. The number of included subjects was in the range of 40–201 (total: 893). Among the 10 included RCT studies, 7 studies (6,8,29–31,33,34)

Table 1 Characteristic of included studies in this meta-analysis

Author	Year	Country	No.	Participant	Treatment	Control	Duration
Hayoz (34)	2012	Switzerland	125	Aged 50-75 years; SBP \geq 140 mmHg, DBP $<$ 110 mmHg, and PP \geq 50 mmHg	Valsartan	Amlodipine	38 weeks
Ichihara (6)	2006	Japan	100	Untreated hypertensive patients; SBP \geq 140 mmHg and/or DBP $<$ 110 mmHg; 24-h ambulatory SBP of \geq 135 mmHg and/or 24-h ambulatory DBP of \geq 80 mmHg	Valsartan	Amlodipine	12 months
Kim (33)	2014	Korea	201	Age \geq 18 years; SBP $>$ 140 mmHg and/or DBP $>$ 90 mmHg	Losartan	Carvedilol	24 weeks
Klingbeil (32)	2002	Germany	60	Age: 20-70 years; SBP: 160-220 mmHg; DBP: 95-115 mmHg	Valsartan	HCTZ	6 weeks
Kosch (31)	2008	Germany	68	DBP: 90-110 mmHg	Valsartan	Metoprolol	12 weeks
Morimoto (30)	2006	Japan	43	Untreated essential hypertension	Telmisartan	Amlodipine	24 weeks
Munakata (29)	2004	Japan	41	Age 20-70 years; SBP $>$ 140 mmHg; DBP $>$ 90 mmHg	Valsartan	Nifedipine	12 weeks
Pozzobon (28)	2014	Brazil	47	Systemic arterial hypertension and type 2 diabetes mellitus; age 40-70	Losartan	Amlodipin	6 weeks
Schneider (27)	2008	Germany	168	Age of 25-65 years; SBP: 150-200 mmHg; DBP: 95-115 mmHg	Irbesartan	Atenolol	18 months
Takami (8)	2003	Japan	40	Male hypertensive patients aged 65 years or older	Valsartan	Nifedipine	24 weeks

reported the improvement of PWV with the hypertensive patients randomly assigned to the control group and the experimental (valsartan) group, of which four studies (8,29,33,34) reported the changes of PWV before and after the drug intervention and four studies (6,30,31,33) reported the pre-treatment and post-treatment PWV levels. The improvement in the AI after the randomized treatment was reported in four studies (27,28,32,33), of which three studies (27,32,33) reported the changes of AI before and after the drug intervention, and two studies (28,33) provided the post-treatment AI levels. The evaluation of the quality of the included studies is presented in *Table 2*.

The change in PWV values before and after the treatment

Four studies (8,29,33,34) provided the changes in PWV before and after the drug intervention. Considering the substantial heterogeneity among these studies, a random effect model was used to combine the results. Although the ability of ARB to reduce PWV was superior to other antihypertensive agents (MD: 125.76, 95% CI: -78.70 to 330.23), the difference was not statistically significant

($P=0.23$), as shown in *Figure 2A*.

Four studies (6,30,31,33) provided pre-treatment and post-treatment PWV levels, and the PWV values after the treatment were combined using the SMD method. Because the heterogeneity among studies was minor, a fixed effect model was applied. Compared with other antihypertensive agents, the ability of ARB to reduce the PWV was not significant (SMD: 0.04, 95% CI: -0.16 to 0.24, $P=0.71$), as shown in *Figure 2B*.

The range of AI variation before and after the treatment

Three studies (27,32,33) provided the changes of AI before and after the drug intervention. Considering the substantial heterogeneity among these studies, a random effect model was used to combine the results. The ability of ARB to lower the level of the AI was superior to other antihypertensive agents (MD: 8.94, 95% CI: 2.18-5.71, $P=0.01$), as shown in *Figure 3A*.

Two studies (28,33) provided the AI values after the treatment, and the studies were combined using SMD method. The abilities of ARB and other anti-hypertensive

Table 2 Quality of included studies in this meta-analysis

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting and other bias
Hayoz (34)	Unknown	Unknown	Low	Low	High	Low
Ichihara (6)	Unknown	Unknown	High	High	Unknown	Low
Kim (33)	Low	Unknown	High	Low	Low	Low
Klingbeil (32)	Unknown	Unknown	Low	Low	Low	Low
Kosch (31)	Unknown	Unknown	Low	Low	Low	Low
Morimoto (30)	Unknown	Unknown	High	Unknown	Low	Low
Munakata (29)	Unknown	Unknown	High	Unknown	Low	Low
Pozzobon (28)	Unknown	Unknown	High	Unknown	Low	Low
Schneider (27)	Unknown	Unknown	Low	Low	High	Low
Takami (8)	Unknown	Unknown	High	Unknown	Low	Low

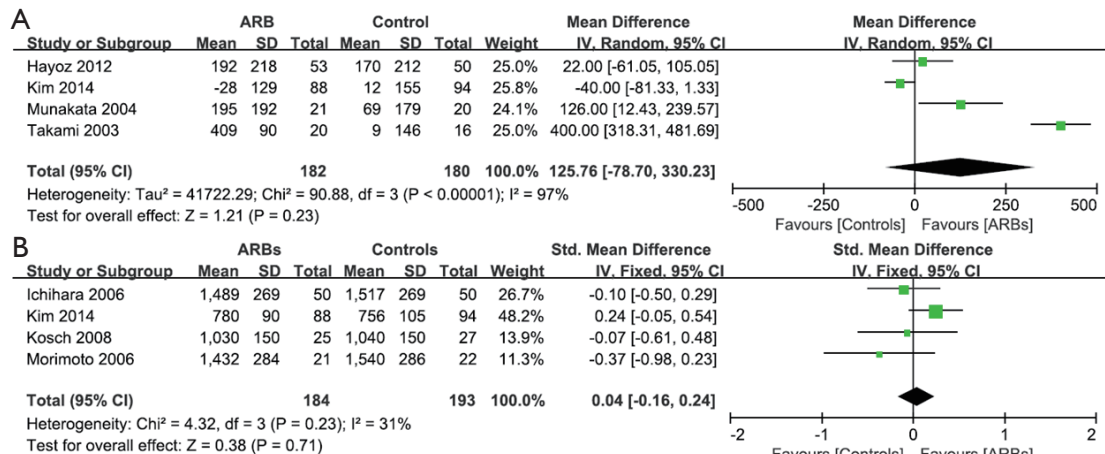


Figure 2 Meta-analysis of articles evaluating the effects of ARB and other types of antihypertensive agents on the levels of PWV. (A) Based on the random-effects model; (B) based on the fixed effect model.

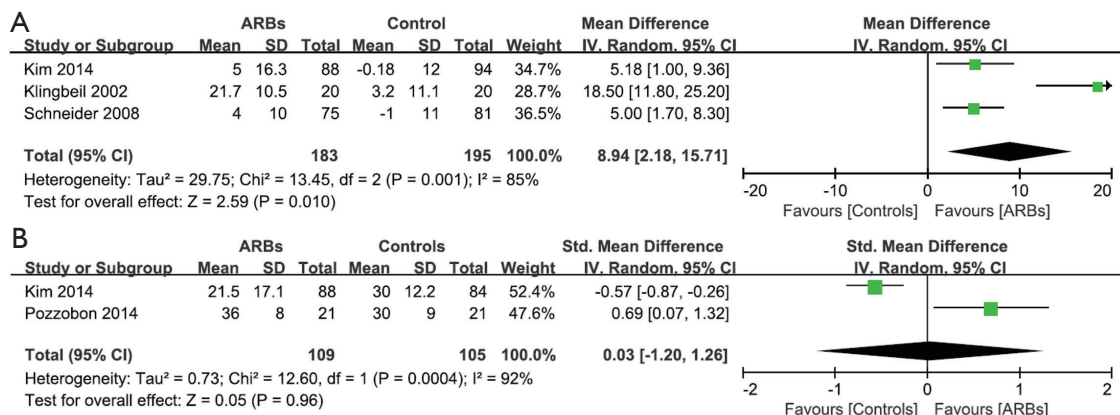


Figure 3 Meta-analysis of articles evaluating the effects of ARB and other types of antihypertensive agents on the levels of the AI. (A) Based on the random-effects model; (B) based on the fixed effect model.

agents to improve the AI were similar (SMD: 0.03, 95% CI: -1.20 to 1.26, $P=0.06$), as shown in *Figure 3B*.

Discussion

This study is a meta-analysis of ten RCT studies to assess the changes in arterial stiffness in patients with hypertension after treatment with the drugs of the ARB class or other types of antihypertensive agents. In the present study, two indicators, PWV and the AI, were used to assess the arteries stiffness. The ability of ARB to improve the PWV level was not observed to be superior to other types of antihypertensive agents, but the ability of ARB to improve the AI level was superior to other types of antihypertensive agents.

Although many clinical studies have reported that compared with other types of antihypertensive agents, the ARB class of antihypertensive agents may improve the arterial stiffness levels in the patients with hypertension. To the best of our knowledge, this is the first meta-analysis to compare the effect of the ARB class of drugs and other types of antihypertensive agents on the improvement of arterial stiffness in the patients with hypertension. The relevant clinical studies included cohort studies and RCTs. To ensure the quality of our study, only the RCTs were included in our meta-analysis.

In this study, the ability of ARB to improve the AI level was superior to other types of antihypertensive agents, but no significant advantage of ARB was observed in improving the PWV compared with other types of antihypertensive agents. The potential reasons for the results are list as follows. First, the antihypertensive drugs in control group include CCB, diuretics, β -blocker, all of these drugs can have effect on heart rate. Although PWV and AI are both indicators for arterial stiffness, the impact factors of the two indicators are different. The biggest difference is that PWV was not influenced by heart rate, whereas AI was influenced by heart rate. Second, the study population in the included studies is different, some study only included elder patients, some studies didn't set limitation on ages. Considering different kinds of patients have different respond to those kinds of antihypertensive drugs, this heterogeneity may have influence on the results. Third, on purely statistical grounds, as shown in *Figure 2A*, the actual degree of PWV improvement by ARB was higher than that by other antihypertensive agents. The difference was not statistically significant, primarily due to the small sample size and poor statistical power, suggesting that future research in this area

of research is necessary. In addition, *Figure 2A* presented the results of the meta-analysis based on the changes of PWV in the control group and the ARB group before and after the treatment, which take into consideration the baseline values, whereas *Figure 2B* is based on the statistics of the PWV values of the ARB group and the control group after the treatment only (the baseline PWV values were assumed to be the same); therefore, the results presented in *Figure 2A* are more convincing than those presented in *Figure 2B*.

The peripheral wave reflection was evaluated by the AI, and the AI is an indicator reflecting the amplitude and duration of the global reflected wave (3). PWV can affect the AI by increasing the velocity of the forward and reflected waves. Because the ARB class of drugs was not superior to other types of antihypertensive agents in the improvement of PWV, we can further assess the effect of antihypertensive drugs on arterial stiffness by studying the improvement in the AI. In this study, although the ARB class of drugs was not superior to other antihypertensive agents in the improvement of PWV, the ARB class of antihypertensive drugs was superior to other types of antihypertensive agents in improving the AI. Overall, ARB is superior to other antihypertensive agents in improving arterial stiffness.

Most existing studies have demonstrated that the ARB class of antihypertensive agents is superior to other antihypertensive agents in improving arterial stiffness. The ARB class of antihypertensive agents may improve arterial stiffness due, in part, to its antihypertensive effect; furthermore, ARB drugs can relax the vascular smooth muscle, improve endothelial function and reduce the thickness and collagen content of the arteries, thereby reversing cell hypertrophy in the smooth muscle (35-37). A study had demonstrated that (23) the short term application of the ARBs can improve arterial stiffness, and therefore the improvement of arterial stiffness by the ARBs may be related to the improvement of not only vascular structure but also vascular function. In addition, an *in vitro* study (38) indicated that angiotensin II can significantly inhibit the expression of adipocyte adiponectin in human, and the ARB class of drugs may improve arterial stiffness by increasing the concentration of serum adiponectin. Furthermore, ARB can reduce the concentration of TNF- α in skeletal muscle and mononuclear cells (although this function has not yet been confirmed), and TNF- α can inhibit the expression and secretion of 3T3-L1 adipocyte adiponectin; therefore, the

ARB class of drugs may also enhance the expression and secretion of adipocyte adiponectin through this pathway (39,40).

The clinical studies included in this meta-analysis are all RCTs and the selected articles for this meta-analysis were published between 2002 and 2014, which ensured, to some extent, that the findings of this study are applicable to current clinical practice. Nevertheless, the following limitations still exist in this study. First, the follow-up periods in the different studies are not the same, and previous studies have demonstrated that the mechanism of short-term and long-term drug therapy on arterial stiffness is not the same. Therefore, different follow-up periods may affect the results of the studies. Second, this meta-analysis didn't compare ARB with different kinds of antihypertensive drugs (such as CCB, diuretic, β -blockers). As mentioned before those antihypertensive drugs have different impact on heart rate, and the impacts of heart rate on PWV and AI are different. Third, this meta-analysis did not assess the improvement of blood pressure by different types of antihypertensive agents. Previous studies have demonstrated that blood pressure and arterial stiffness are correlated. Because the improvement of blood pressure was not assessed in this study, the correlation between the improvement of blood pressure and the improvement of arterial stiffness by different antihypertensive agents could not be analyzed. In addition, whether there are other factors independent of blood pressure in the change of the arterial stiffness by different antihypertensive drugs could not be analyzed. Last but not least, considering the heterogeneity in the included studies (study population and definition of hypertension), the results may be influenced to some degree.

Future research may further assess the change of arterial stiffness by different types of antihypertensive agents from the following aspects. First, future studies can further assess the changes of arterial stiffness by different types of antihypertensive agents with different treatment durations and further analyze the mechanism of these changes in short-term and long-term antihypertensive agent treatment. Second, whether different types of antihypertensive agents can affect arterial stiffness independent of blood pressure changes can be further assessed, and the corresponding mechanism can be further investigated. Finally, the existing studies analyzed hypertensive patients whose clinical conditions were complicated by dialysis, diabetes or obesity, suggesting that the ARB class of drugs may also improve arterial stiffness in these patients. Future studies

may further evaluate the change of arterial stiffness by different antihypertensive agents in hypertension patients complicated with other risk factors.

Conclusions

The effect of ARB on the improvement of the PWV level is not superior to other types of antihypertensive agents, but ARB is superior to other types of antihypertensive agents for improving the AI level. Overall, to improve of arterial stiffness, ARB maybe is superior to other antihypertensive agents.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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