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ORIGINAL ARTICLE

# The impact of angiotensin receptor blockers on arterial stiffness: a meta-analysis

Feng Peng[1,4], Hongming Pan[2,4], Bin Wang[2], Jinxiu Lin[1] and Wenquan Niu[3]

**Some studies reported a protective role of angiotensin receptor blockers (ARBs) against arterial stiffness. Therefore, we performed a meta-analysis of published clinical trials to systematically assess the impact of ARBs on arterial stiffness as measured by using pulse wave velocity (PWV). Eligible articles were identified by searching PubMed, EMBASE, Cochrane, Wanfang and CNKI databanks before 31 July 2014. The data were extracted independently and in duplicate. Forty articles including 53 clinical trials qualified, including 1650 and 1659 subjects in ARB treatment and control groups, respectively. Overall reductions in carotid-femoral PWV (cfPWV) and brachial-ankle PWV (baPWV) were statistically significant, with an average of $-42.52\ cm\ s^{-1}$ (95% CI: −81.82 to −3.21; $P=0.034$) and $-107.08\ cm\ s^{-1}$ (95% CI: −133.98 to −80.18; $P<0.0005$), respectively, after receiving ARBs. Subgroup analysis by ARB type revealed that telmisartan (weighted mean difference or WMD $=-100.82\ cm\ s^{-1}$; $P<0.0005$) and valsartan (WMD $=-104.59\ cm\ s^{-1}$; $P<0.0005$) significantly reduced baPWV, but only valsartan reduced cfPWV (WMD = −65.58; $P=0.030$). cfPWV was significantly reduced in comparisons of ARBs with placebo (WMD $=-79.65\ cm\ s^{-1}$; $P=0.001$), and baPWV was significantly reduced with calcium channel blockers (WMD $=-130.74\ cm\ s^{-1}$; $P<0.0005$). There were low probabilities of publication bias. Taken together, our findings support the important role of ARB treatment in improving arterial stiffness.**
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**Keywords:** angiotensin receptor blocker; arterial stiffness; blood pressure; meta-analysis; pulse wave velocity

## INTRODUCTION

It is well established that arterial stiffness is an independent predictor for future cardiovascular events and all-cause mortality in general populations.[1–3] Mounting evidence suggests that the renin–angiotensin system (RAS) has a pivotal role in the progression of arterial stiffness, and blockade of this system can alleviate its progression.[4,5] Angiotensin II receptor antagonists, which are known as angiotensin receptor blockers (ARBs), are a group of pharmaceuticals that inhibit the negative impact of angiotensin II. Angiotensin II is a potent vasoactive peptide on the endothelium in RAS, which lowers blood pressure and improves arterial elasticity.[6,7] The beneficial impact of ARBs on arterial stiffness extends beyond the resulting blood pressure reduction.[8] However, the exact mechanisms underlying the ARB-dependent improvement in arterial stiffness remain poorly understood.

The heart is the primary site of damage of elevated arterial stiffness. Heart contraction produces a pulse or energy wave that travels through the circulation. Arterial stiffness is predominantly reflected by the traveling speed of this pulse wave, which is termed pulse wave velocity (PWV). PWV is established as a simple, well-validated and reproducible technique of applanation tonometry.[9] PWV measurement is a general clinical tool that has yielded some of the strongest evidence of the prognostic significance of large artery stiffening. Several clinical trials explored the potential impact of ARBs on arterial stiffness in various populations.[10–13] However, a comprehensive evaluation of this impact is lacking. Therefore, we systematically performed a meta-analysis of all published clinical trials that assessed the impact of ARBs on arterial stiffness as measured by PWV compared with other types of drugs.

## METHODS

This meta-analysis conformed to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[14]

### Search strategy

We obtained potentially relevant articles by searching PubMed, EMBASE (Excerpta Medica Database), Cochrane (http://www.thecochranelibrary.com), Wanfang (http://www.wanfangdata.com.cn) and CNKI (China National Knowledge Infrastructure, http://www.cnki.net) as of 31 July 2014 by using

[1]Department of Cardiology, The First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian, China; [2]Basic Medical Science College, Qiqihar Medical University, Qiqihar, Heilongjiang, China and [3]State Key Laboratory of Medical Genomics, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[4]These authors contributed equally to this work.
Correspondence: Professor J Lin, Department of Cardiology, The First Affiliated Hospital of Fujian Medical University, Chazhong Road 20, Fuzhou 350005, China.
E-mail: linjinxiu@medmail.com.cn
or Professor W Niu, State Key Laboratory of Medical Genomics, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Ruijin Second Road 197, Shanghai 200025, China.
E-mail: niuwenquan_shcn@163.com
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the subject terms 'pulse wave velocity,' 'arterial stiffness,' 'angiotensin receptor blocker,' 'angiotensin II antagonism' and 'sartan.' We additionally obtained the citations of relevant articles by reviewing the references of retrieved studies and review articles. We restricted search results to clinical trials on humans that were published in English or Chinese.

### Selection

Two authors (Feng Peng and Wenquan Niu) independently read the titles and abstracts of all retrieved articles and assessed article eligibility. If an article could not be rejected with certainty from the title or abstract, we obtained its full text to decide whether data on the topic of interest were provided. If more than one publication was based on the same study group, the data from the most recent or complete article were extracted. If results were provided according to different drug types in either the treatment or control group, we treated the results separately.

### Inclusion/exclusion criteria

Our analyses were restricted to clinical trials that met all of the following inclusion criteria: designed in a randomized manner and compared the ARB treatment with a placebo or other types of drugs on arterial stiffness as measured by PWV. Trials were excluded (one was sufficient for exclusion) if they were duplicate publications, conference abstracts, proceedings, case reports, case series, editorials, review articles or non-English and non-Chinese articles.

### Data extraction

Two authors (Feng Peng and Wenquan Niu) independently completed the data inclusion sheets using a standard Excel spreadsheet template (Microsoft, Redmond, WA, USA). We resolved disagreements during data extraction and reached consensus after a discussion and review of original articles.

We extracted detailed information for the impact of ARBs on arterial stiffness from each eligible article, including the first author, publication year, ethnicity and disease status of study patients, sample size in each arm, PWV type, study design, masking status, the type and dose of drugs used in each group, age, gender, body mass index, follow-up duration, levels and changes of systolic blood pressure (SBP) and diastolic blood pressure, pulse pressure, heart rate and PWV at the baseline and follow-up.

### Statistics

Quantitative parameters were compared by using weighted mean difference (WMD) and 95% confidence interval (95% CI) when hinged on a random-effects model by using the DerSimonian and Laird method[15] for patients taking ARBs versus placebo or other drugs. Pearson correlation analysis was used to examine the relationship between quantitative parameters of interest. The inconsistency index ($I^2$) statistic was calculated to assess between-study heterogeneity, and this statistic is defined as the percentage of the observed between-study variability that is because of heterogeneity rather than chance.

Predefined subgroup analyses were performed according to the types of drugs used in ARB treatment (mainly including valsartan, telmisartan, losartan, candesartan and irbesartan) and control (mainly including calcium channel blockers, angiotensin converting enzyme inhibitor or ACEI, placebo, non-RAS drugs, diuretics and β-blocker) groups to explore the potential sources of heterogeneity. Only subgroups involving two or more clinical trials were summarized in this meta-analysis.

We performed influential analysis by sequentially omitting each trial one at a time and computing differential estimates for the remaining trials to quantify the contribution of individual trials to the pooled estimates. We further resorted to meta-regression analysis to explore the other sources of heterogeneity from the divergence of baseline continuous characteristics across trials, including age, male percentage, body mass index and during of treatment.

We assessed the probability of publication bias by using Begg's test. The significance level was defined as $P<0.10$ for the $\chi^2$-test of $I^2$ and Begg's test.[16] The statistical analyses described above were completed using STATA software (StataCorp, College Station, TX, USA, version 11.2 for Windows).

## RESULTS

### Eligible trials

We illustrated the characteristics of all eligible trials and study patients in Tables 1 and 2, respectively. A flow diagram schematizing the process of article exclusion for specific reasons is summarized in Figure 1. In total, 40 articles with 53 clinical trials qualified, including 1650 subjects in the ARB treatment group and 1659 subjects in the control.[8,10–13,17–51] Of all clinical trials, 41 were performed in East Asians, and 12 trials were performed in Caucasians. For the ARB type, 24 trials adopted valsartan, 10 trials adopted telmisartan, 9 trials adopted losartan, 7 trials adopted candesartan and 3 trials adopted irbesartan. Control subjects included 20 trials that adopted calcium channel blockers, 9 trials that adopted ACEIs, 7 trials that adopted a placebo, 5 trials that adopted diuretics, 5 trials that adopted non-antihypertensive drugs, 3 trials that adopted beta blockers and 1 trial that adopted beraprost sodium, eplerenone, renin inhibitor and statins. The average follow-up of all clinical trials was 18.75 (s.d.: 13.25) months with a range from 2 to 48 months.

### Changes in pulse wave velocity

Overall and stratified changes in PWV between ARB treatment and control groups are provided in Figure 2 and Table 3. PWV is a validated method to quantify arterial stiffness, and it can be measured in different arterial segments. baPWV and cfPWV are the most common indices. We separately analyzed changes in brachial-ankle PWV (baPWV) and carotid-femoral PWV (cfPWV) in this meta-analysis. Overall reductions in cfPWV and baPWV were statistically significant by an average of $-42.52\ \mathrm{cm\,s^{-1}}$ (95% CI: $-81.82$ to $-3.21$; $P=0.034$) and $-107.08\ \mathrm{cm\,s^{-1}}$ (95% CI: $-133.98$ to $-80.18$; $P<0.0005$), respectively, after treatment with ARBs (Figure 2). There was strong evidence of heterogeneity in both comparisons. Overall reductions were strengthened for cfPWV and baPWV by $-49.03\ \mathrm{cm\,s^{-1}}$ (95% CI: $-92.78$ to $-5.28$; $P=0.028$) and $-121.17\ \mathrm{cm\,s^{-1}}$ (95% CI: $-151.39$ to $-90.96$; $P<0.0005$), respectively, after the removal of clinical trials that included controls who received ACEI or renin inhibitors, which might have exerted an effect similar to ARBs.

Stratified analyses by the type of ARBs detected significant reductions in baPWV for telmisartan (WMD $=-110.82\ \mathrm{cm\,s^{-1}}$; 95% CI: $-145.66$ to $-55.98$; $P<0.0005$) and valsartan (WMD $=-104.59\ \mathrm{cm\,s^{-1}}$; 95% CI: $-154.01$ to $-55.18$; $P<0.0005$), and reductions in cfPWV for valsartan (WMD $=-65.58$ cm/s; 95% CI: $-124.84$ to $-6.32$; $P=0.030$) with evident heterogeneity (Table 3). Stratification by the type of drugs taken by controls revealed a significant reduction in cfPWV for placebo (WMD $=-79.65\ \mathrm{cm\,s^{-1}}$; $P=0.001$; $I^2=70.6\%$), and baPWV was significantly reduced for comparisons of ARBs with diuretics (WMD $=-77.83\ \mathrm{cm\,s^{-1}}$; $P<0.0005$), calcium channel blockers (WMD $=-130.74\ \mathrm{cm\,s^{-1}}$; $P<0.0005$) and non-RAS drugs (WMD $=-81.66\ \mathrm{cm\,s^{-1}}$; $P<0.001$) (Figure 2).

### Changes in blood pressure and heart rate

Overall and stratified changes in blood pressure and heart rate between the ARB treatment and control groups are provided in Tables 4 and 5. Overall changes in SBP, diastolic blood pressure, pulse pressure and heart rate were not obvious between the two groups, and there was strong evidence of heterogeneity. Moreover, changes in PWV regressed with changes in pulse pressure in the ARB treatment group, and there was no observable significance for either cfPWV ($P=0.229$) or baPWV ($P=0.228$), even after adjusting for age, gender, body mass index and treatment duration.

The grouping of studies by ARB type revealed an obvious reduction in SBP for telmisartan (WMD $=-1.12$ mm Hg; 95% CI: $-1.82$ to

−0.42; $P=0.002$; $I^2=0.0\%$) (Table 4) but a significant increase in heart rate for losartan (WMD = 6.66 beats per minute; 95% CI: 0.77 to 12.55; $P=0.027$) (Table 5). Subgroup analysis by the type of drugs taken by controls revealed significant reductions in SBP for comparisons of ARBs with placebo (WMD = −3.81 mm Hg; 95% CI: −6.70 to −0.91; $P=0.010$; $I^2=77.2\%$) and diuretics (WMD = −1.31 mm Hg; 95% CI: −2.33 to −0.27; $P=0.013$; $I^2=0.0\%$), and reductions in diastolic blood pressure for placebo

**Table 1 The baseline characteristics of all eligible trials in this meta-analysis**

| *Author (year)* | *Ethnicity* | *Status* | *PWV type* | *Design* | *Masking* | *ARB type* | *Drugs in controls* | *Treatment* | *Control* | *Follow-up (months)* |
|---|---|---|---|---|---|---|---|---|---|---|
| Mahmud and Feely[8] | Caucasian | Hypertension | cfPWV | Crossover | Open | Valsartan | ACEI | 12 | 12 | 4 |
| Mahmud and Feely[8] | Caucasian | Hypertension | cfPWV | Crossover | Double | Losartan | Diuretics | 11 | 11 | 4 |
| Asmar *et al.*[26] | Caucasian | Hypertension | cfPWV | Crossover | Double | Telmisartan | Placebo | 20 | 20 | 3 |
| Suzuki *et al.*[36] | East Asian | Others | baPWV | Parallel | Double | Valsartan | Placebo | 14 | 10 | 48 |
| Takami and Shigemasa[37] | East Asian | Hypertension | baPWV | Parallel | NA | Valsartan | CCB | 20 | 16 | 12 |
| Takami and Shigemasa[37] | East Asian | Hypertension | baPWV | Parallel | NA | Valsartan | CCB | 20 | 20 | 12 |
| Takami and Shigemasa[37] | East Asian | Hypertension | baPWV | Parallel | NA | Valsartan | ACEI | 20 | 20 | 12 |
| Munakata *et al.*[32] | East Asian | Hypertension | baPWV | Parallel | NA | Valsartan | CCB | 21 | 20 | 12 |
| Anan[25] | East Asian | Hypertension | baPWV | Parallel | NA | Valsartan | ACEI | 10 | 11 | 40 |
| Ichihara *et al.*[27] | East Asian | Hypertension | baPWV | Parallel | Open | Losartan | ACEI | 22 | 21 | 48 |
| Ichihara *et al.*[27] | East Asian | Hypertension | baPWV | Parallel | Open | Losartan | Placebo | 22 | 21 | 48 |
| Ichihara *et al.*[28] | East Asian | Hypertension | baPWV | Parallel | NA | Valsartan | CCB | 50 | 50 | 48 |
| Rajagopalan *et al.*[34] | Caucasian | Healthy | cfPWV | Crossover | Double | Valsartan | Placebo | 33 | 33 | 13 |
| Morimoto *et al.*[31] | East Asian | Hypertension | baPWV | Parallel | Open | Telmisartan | CCB | 21 | 22 | 24 |
| Zhao[50] | East Asian | Hypertension | cfPWV | Parallel | NA | Valsartan | Placebo | 20 | 20 | 12 |
| Rehman *et al.*[35] | Caucasian | Hypertension | cfPWV | Parallel | Double | Losartan | ACEI | 19 | 20 | 12 |
| Nakayama *et al.*[33] | East Asian | Hypertension | baPWV | Parallel | Double | Telmisartan | Beraprost sodium | 20 | 20 | 12 |
| Kosch *et al.*[29] | Caucasian | Hypertension | cfPWV | Parallel | Double | Valsartan | Beta blocker | 25 | 27 | 12 |
| Zheng and Lin[51] | East Asian | Hypertension | baPWV | Parallel | Open | Valsartan | Diuretics | 21 | 18 | 12 |
| Zheng and Lin[51] | East Asian | Hypertension | baPWV | Parallel | Open | Valsartan | Beta blocker | 21 | 20 | 12 |
| Zheng and Lin[51] | East Asian | Hypertension | baPWV | Parallel | Open | Valsartan | CCB | 21 | 24 | 12 |
| Zheng and Lin[51] | East Asian | Hypertension | baPWV | Parallel | NA | Valsartan | ACEI | 21 | 22 | 12 |
| Nakamura *et al.*[12] | East Asian | Hypertension | baPWV | Parallel | Open | Telmisartan | CCB | 15 | 15 | 48 |
| Ishii *et al.*[17] | East Asian | Hypertension | baPWV | Parallel | Open | Candesartan | CCB | 11 | 11 | 12 |
| Shigenaga *et al.*[22] | East Asian | Hypertension | baPWV | Parallel | NA | Valsartan | Non-RAS | 15 | 15 | 24 |
| Shigenaga *et al.*[22] | East Asian | Hypertension | baPWV | Parallel | NA | Candesartan | Non-RAS | 15 | 15 | 24 |
| Ruan *et al.*[46] | East Asian | heart failure | baPWV | Parallel | Open | Irbesartan | Non-RAS | 25 | 22 | 12 |
| Li *et al.*[43] | East Asian | Hypertension | baPWV | Parallel | Open | Telmisartan | ACEI | 34 | 34 | 12 |
| Li *et al.*[43] | East Asian | Hypertension | baPWV | Parallel | Open | Telmisartan | CCB | 34 | 34 | 12 |
| Mitsuhashi *et al.*[11] | East Asian | Hypertension | baPWV | Parallel | Open | Losartan | Non-RAS | 20 | 20 | 48 |
| Long and Liu[45] | East Asian | Others | baPWV | Parallel | NA | Valsartan | CCB | 35 | 40 | 24 |
| Li and Wang[44] | East Asian | Hypertension | baPWV | Parallel | Open | Telmisartan | CCB | 48 | 45 | 12 |
| Li and Wang[44] | East Asian | Hypertension | baPWV | Parallel | Open | Telmisartan | Diuretics | 48 | 42 | 12 |
| Ruan *et al.*[47] | East Asian | Hypertension | baPWV | Parallel | Open | Candesartan | Non-RAS | 23 | 19 | 12 |
| Han *et al.*[19] | East Asian | Others | baPWV | Parallel | Open | Valsartan | Statins | 57 | 57 | 24 |
| Lunder *et al.*[21] | Caucasian | Healthy | cfPWV | Parallel | Double | Valsartan | Placebo | 20 | 20 | 4 |
| Wu *et al.*[48] | East Asian | Hypertension | baPWV | Parallel | NA | Valsartan | CCB | 48 | 50 | 2 |
| Wu *et al.*[48] | East Asian | Hypertension | baPWV | Parallel | NA | Valsartan | ACEI | 48 | 49 | 2 |
| He *et al.*[39] | East Asian | Hypertension | baPWV | Parallel | NA | Valsartan | CCB | 44 | 44 | 12 |
| Feng[38] | East Asian | Hypertension | baPWV | Parallel | Open | Telmisartan | CCB | 44 | 49 | 12 |
| Tomiyama *et al.*[20] | East Asian | Hypertension | baPWV | Parallel | Open | Candesartan | CCB | 56 | 57 | 32 |
| Hayoz *et al.*[10] | Caucasian | Hypertension | baPWV | Parallel | Double | Valsartan | CCB | 63 | 62 | 38 |
| Spanos *et al.*[13] | Caucasian | Hypertension | cfPWV | Parallel | NA | Valsartan | Renin inhibitor | 14 | 15 | 24 |
| Yang *et al.*[49] | East Asian | Hypertension | baPWV | Parallel | NA | Valsartan | Diuretics | 42 | 40 | 24 |
| Kong *et al.*[41] | East Asian | Hypertension | baPWV | Parallel | Open | Irbesartan | ACEI | 34 | 34 | 12 |
| Kong *et al.*[41] | East Asian | Hypertension | baPWV | Parallel | Open | Irbesartan | CCB | 34 | 34 | 12 |
| Li and Ma[42] | East Asian | Hypertension | baPWV | Parallel | Open | Telmisartan | CCB | 33 | 34 | 24 |
| Huang *et al.*[40] | East Asian | Hypertension | baPWV | Parallel | Double | Losartan | Eplerenone | 40 | 37 | 12 |
| Kim *et al.*[11] | East Asian | Hypertension | cfPWV | Parallel | Open | Losartan | Beta blocker | 88 | 94 | 24 |
| Ihm *et al.*[24] | East Asian | Hypertension | cfPWV | Parallel | Open | Losartan | CCB | 99 | 101 | 24 |
| Agnoletti *et al.*[23] | Caucasian | Hypertension | cfPWV | Parallel | Open | Candesartan | CCB | 33 | 33 | 12 |
| Agnoletti *et al.*[23] | Caucasian | Hypertension | cfPWV | Parallel | Open | Candesartan | Diuretics | 33 | 44 | 12 |
| Agnoletti *et al.*[23] | Caucasian | Hypertension | cfPWV | Parallel | Open | Candesartan | Placebo | 33 | 35 | 12 |

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; baPWV and cfPWV, brachial-ankle and carotid-femoral pulse wave velocity; CCB, calcium channel blocker; NA, not available; RAS, renin–angiotensin system.

**Table 2 The baseline characteristics of all study patients between the treatment and control groups in this meta-analysis**

| | *Age (years)* | | *Gender (male, %)* | | *BMI (kg m$^{-2}$)* | | *PWV in treatment group* | | *PWV in control group* | |
|---|---|---|---|---|---|---|---|---|---|---|
| *Author* | *Treatment* | *Control* | *Treatment* | *Control* | *Treatment* | *Control* | *Baseline* | *Follow-up* | *Baseline* | *Follow-up* |
| Mahmud and Feely[8] | 49 | 49 | NA | NA | NA | NA | 1110 | 1050 | 1110 | 1040 |
| Mahmud and Feely[8] | 57 | 57 | 45.5 | 45.5 | NA | NA | 1175 | 1035 | 1155 | 1170 |
| Asmar *et al.*[26] | NA | NA | NA | NA | NA | NA | 1253 | NA | 1307 | NA |
| Suzuki H (2003) | 56 | 57 | NA | NA | NA | NA | 1700 | 1470 | 1670 | 1440 |
| Takami and Shigemasa[37] | 71 | 72.8 | 100 | 100 | 22.8 | 23.2 | NA | NA | NA | NA |
| Takami and Shigemasa[37] | 71 | 72 | 100 | 100 | 22.8 | 22.7 | NA | NA | NA | NA |
| Takami and Shigemasa[37] | 71 | 71.4 | 100 | 100 | 22.8 | 22.9 | NA | NA | NA | NA |
| Munakata *et al.*[32] | 53 | 55 | 47.6 | 50 | 24.8 | 25.3 | 1669 | NA | 1622 | NA |
| Anan *et al.*[25] | 59 | 59 | 10 | 54.5 | 25.5 | 25.4 | 1853 | 1615 | 1818 | 1613 |
| Ichihara *et al.*[27] | 65 | 61 | 59.1 | 52.4 | 20.8 | 20.1 | 2004 | 1898 | 2012 | 1870 |
| Ichihara *et al.*[27] | 65 | 63 | 59.1 | 57.1 | 20.8 | 20.8 | 2004 | 1898 | 2008 | 2144 |
| Ichihara *et al.*[28] | 54.3 | 53.9 | 72 | 76 | 24.2 | 24.6 | 1671 | 1489 | 1723 | 1517 |
| Rajagopalan *et al.*[34] | 71 | 71 | 60 | 60 | NA | NA | 787 | 730 | 789 | 786 |
| Morimoto *et al.*[31] | 56 | 58 | 43 | 41 | 24.8 | 24 | 1699 | 1432 | 1611 | 1540 |
| Zhao[50] | 66.5 | 66.5 | 62.5 | 62.5 | NA | NA | 1280 | 800 | 1300 | 1128 |
| Rehman *et al.*[35] | 52.5 | 53.1 | NA | NA | 26.6 | 27.7 | 1200 | NA | 1100 | NA |
| Nakayama *et al.*[33] | 71.7 | 70.7 | 60 | 60 | 23.4 | 21.9 | 1985 | NA | 2011 | NA |
| Kosch *et al.*[29] | 45.4 | 46.2 | 51.4 | 57.6 | 29 | 28.2 | 1090 | 1030 | 1100 | 1040 |
| Zheng and Lin[51] | 52 | 50 | 61.9 | 55.6 | 24.8 | 24.7 | 1090 | 842.6 | 1060 | 967.8 |
| Zheng and Lin[51] | 52 | 51 | 61.9 | 60 | 24.8 | 24.2 | 1090 | 842.6 | 1120 | 945.3 |
| Zheng and Lin[51] | 52 | 52 | 61.9 | 62.5 | 24.8 | 25.1 | 1090 | 842.6 | 1080 | 706.3 |
| Zheng and Lin[51] | 52 | 50 | 61.9 | 54.5 | 24.8 | 24.5 | 1090 | 842.6 | 1110 | 868 |
| Nakamura *et al.*[12] | 45 | 47 | 60 | 60 | 25.4 | 24.8 | 1680 | 1460 | 1620 | 1660 |
| Ishii *et al.*[17] | 68.4 | 68 | NA | NA | 23.9 | 23.5 | 2007.8 | 1364 | 1985.7 | 1813 |
| Shigenaga *et al.*[22] | 53.1 | 53.3 | 66.7 | 73.3 | 25.1 | 25.8 | 1953 | 1820 | 1981 | 1888 |
| Shigenaga *et al.*[22] | 52.9 | 53.3 | 60 | 73.3 | 25.1 | 25.8 | 1985 | 1837 | 1981 | 1888 |
| Ruan *et al.*[46] | 64.8 | 63.5 | 68 | 59 | NA | NA | 1716.5 | 1482.7 | 1731.6 | 1610.4 |
| Li *et al.*[43] | 58.3 | 58 | 64.7 | 61.8 | NA | NA | 1859 | 1566 | 1859 | 1702 |
| Li *et al.*[43] | 58.3 | 57.1 | 64.7 | 67.6 | NA | NA | 1859 | 1566 | 1780 | 1559 |
| Mitsuhashi *et al.*[11] | 68.8 | 63.3 | 60 | 60 | 24.6 | 25.6 | 2011 | 1791 | 2008 | 1907 |
| Long and Liu[45] | 59.3 | 57.4 | 65.7 | 65 | 28.9 | 24.9 | 1260 | 1080 | 1210 | 1140 |
| Li and Wang[44] | 72 | 73 | NA | NA | NA | NA | 2177 | 2085 | 2195 | 2117 |
| Li and Wang[44] | 72 | 74 | NA | NA | NA | NA | 2177 | 2085 | 2186 | 2174 |
| Ruan *et al.*[47] | 64.8 | 63.5 | 69 | 63 | NA | NA | 1764.4 | 1524.3 | 1759.7 | 1634.5 |
| Han *et al.*[19] | 48.8 | 48.8 | 51.2 | 45.9 | 22.8 | 22.8 | 1691.5 | 1635 | 1617 | 1528.9 |
| Lunder *et al.*[21] | 42.8 | 43.1 | 100 | 100 | 25.9 | 26.6 | 582 | 519 | 577 | 580 |
| Wu *et al.*[48] | NA | NA | 77.1 | 76 | NA | NA | 1797.8 | 1027.8 | 1850.6 | 1411.6 |
| Wu *et al.*[48] | NA | NA | 77.1 | 79.6 | NA | NA | 1797.8 | 1027.8 | 1870.8 | 1170.8 |
| He *et al.*[39] | 60.5 | 59.4 | 0 | 0 | 24.5 | 25.4 | 2007.8 | 1370.5 | 1985.7 | 1812.7 |
| Feng[38] | 57.2 | 56.3 | 61 | 61 | NA | NA | 1829.5 | 1464.8 | 1875.6 | 1578.4 |
| Tomiyama *et al.*[20] | 56 | 58 | 64.2 | 63.1 | 24.1 | 23.5 | 1741 | 1576 | 1774 | 1662 |
| Hayoz *et al.*[10] | 62.3 | 60.4 | 0 | 0 | 27.5 | 27 | NA | NA | NA | NA |
| Spanos *et al.*[13] | 60 | 55 | 71.4 | 66.7 | 27.5 | 29.6 | 1110 | 1000 | 940 | 950 |
| Yang *et al.*[49] | 57.3 | 56.8 | 69 | 67.5 | 24.5 | 24.4 | 1230 | 1090 | 1250 | 1180 |
| Kong *et al.*[41] | 52.4 | 52.2 | 64.7 | 67.6 | NA | NA | 1864 | 1553 | 1856 | 1623 |
| Kong *et al.*[41] | 52.4 | 52 | 64.7 | 61.8 | NA | NA | 1864 | 1553 | 1862 | 1562 |
| Li and Ma[42] | 58.6 | 58.1 | 54 | 58 | NA | NA | 1763.5 | 1436.5 | 1722.7 | 1465.7 |
| Huang *et al.*[40] | 49.2 | 48.6 | NA | NA | NA | NA | 1718.9 | 1610.1 | 1648.1 | 1570.7 |
| Kim *et al.*[11] | 48.7 | 50.5 | 62.5 | 56.4 | 26 | 26 | 752 | 780 | 768 | 756 |
| Ihm *et al.*[24] | 50.6 | 51.1 | 61.6 | 54.5 | 25.1 | 25.4 | 900 | 890 | 850 | 860 |
| Agnoletti *et al.*[23] | 57.2 | 59.5 | 55 | 52 | NA | NA | 960 | 970 | 1030 | 980 |
| Agnoletti *et al.*[23] | 57.2 | 59.2 | 55 | 57 | NA | NA | 960 | 970 | 970 | 980 |
| Agnoletti *et al.*[23] | 57.2 | 56.6 | 55 | 46 | NA | NA | 960 | 970 | 970 | 960 |

Abbreviations: BMI, body mass index; NA, not available; PWV, pulse wave velocity.

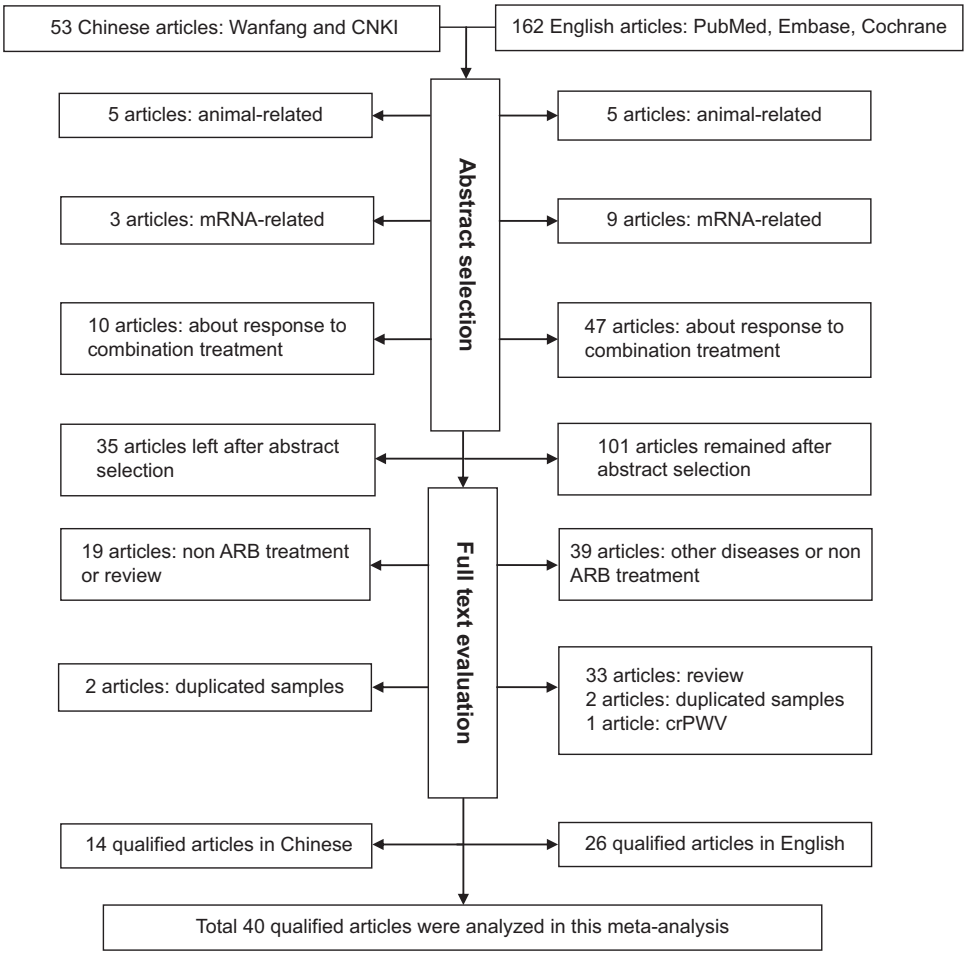


**Figure 1** Flow diagram of search strategy and trial selection.

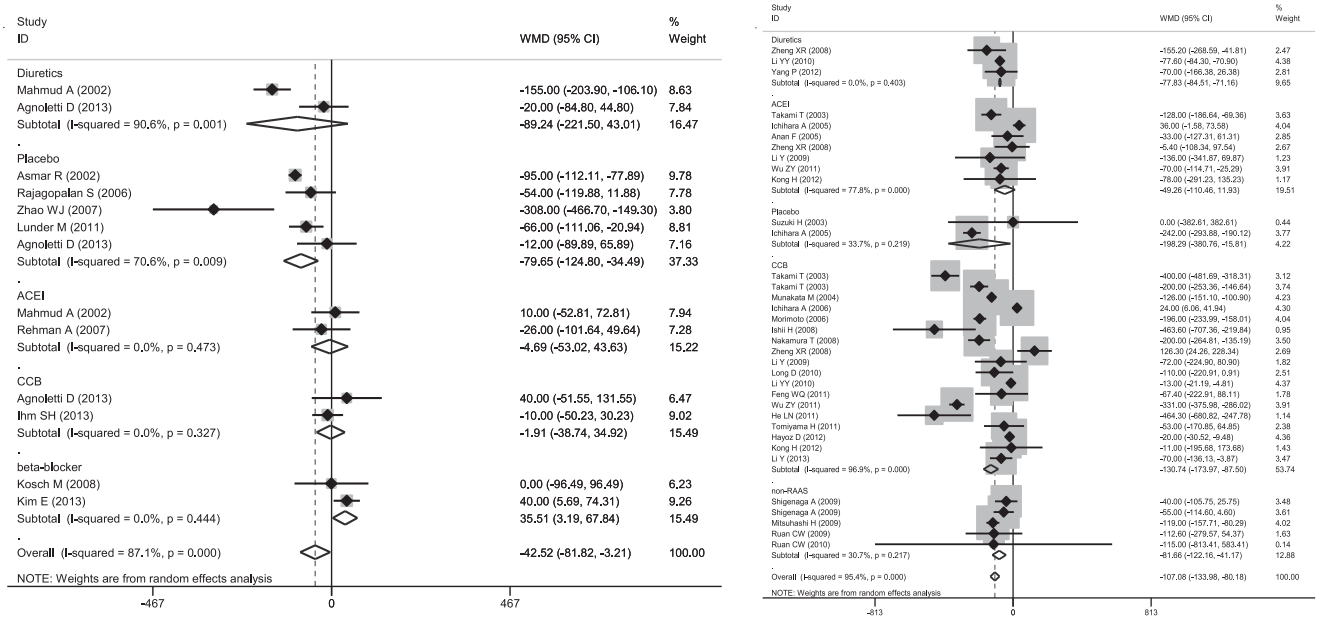


**Figure 2** Forest plots of carotid-femoral and brachial-ankle pulse wave velocity (left and right) changes between angiotensin receptor blocker treatment and control groups according to the types of drugs used in the controls.

**Table 3 Weighted mean differences in pulse wave velocity between the ARB treatment and control groups according to the type of drugs in treatment group**

| *Subgroups* | *Studies (n)* | *WMD; 95% CI;* P | $I^2$ (P) |
|---|---|---|---|
| *baPWV* | | | |
| Telmisartan | 9 | −100.82; −145.66 to −55.98; 0.000 | 96.3% (0.000) |
| Losartan | 4 | −81.30; −204.54 to −41.95; 0.196 | 96.4% (0.000) |
| Valsartan | 19 | −104.59; −154.01 to −55.18; 0.000 | 95.7% (0.000) |
| Candesartan | 4 | −139.49; −288.74 to 9.76; 0.067 | 71.0% (0.016) |
| Irbesartan | 3 | −69.70; −176.80 to 37.40; 0.202 | 0.0% (0.723) |
| *cfPWV* | | | |
| Losartan | 4 | 37.02; −122.88 to 48.86; 0.398 | 92.7% (0.000) |
| Valsartan | 6 | −65.58; −124.84 to −6.32; 0.030 | 69.0% (0.006) |
| Candesartan | 3 | −3.77; −47.53 to 39.99; 0.866 | 0.0% (0.559) |

Abbreviations: 95% CI, 95% confidence interval; ARB, angiotensin receptor blocker; baPWV and cfPWV, brachial-ankle and carotid-femoral pulse wave velocity; $I^2$, inconsistency index; WMD, weighted mean difference.

**Table 4 Weighted mean differences in systolic and diastolic blood pressure between the ARB treatment and control groups according to the types of drugs taken in both groups**

| | *Systolic blood pressure (mm Hg)* | | | *Diastolic blood pressure (mm Hg)* | | |
|---|---|---|---|---|---|---|
| *Groups* | *Studies (n)* | *WMD; 95% CI;* P | $I^2$ (P) | *Studies (n)* | *WMD; 95% CI;* P | $I^2$ (P) |
| Overall | 52 | −0.74; −1.58 to 0.11; 0.086 | 68.9% (0.000) | 52 | −0.58; −1.15 to −0.02; 0.042 | 78.8% (0.000) |
| *By drugs in treatment group* | | | | | | |
| Valsartan | 25 | −0.16; −1.50 to 1.19; 0.821 | 74.1% (0.000) | 25 | −0.71; −1.63 to 0.20; 0.128 | 88.0% (0.000) |
| Telmisartan | 8 | −1.12; −1.82 to −0.42; 0.002 | 0.0% (0.911) | 8 | 0.35; −0.10 to 0.80; 0.123 | 0.0% (0.975) |
| Losartan | 9 | −1.93; −4.08 to 0.22; 0.078 | 63.1% (0.006) | 9 | −0.68; −1.53 to 0.17; 0.117 | 21.0% (0.256) |
| Candesartan | 7 | −1.73; −5.29 to 1.83; 0.340 | 49.7% (0.064) | 7 | −1.07; −3.47 to 1.32; 0.380 | 60.9% (0.018) |
| Irbesartan | 3 | 0.51; −2.42 to 3.45; 0.731 | 56.8% (0.099) | 3 | −0.49; −4.26 to 3.27; 0.798 | 62.2% (0.071) |
| *By drugs in control group* | | | | | | |
| ACEI | 9 | −0.92; −2.74 to 0.91; 0.325 | 50.8% (0.039) | 9 | −0.90; −2.41 to 0.62; 0.248 | 57.7% (0.015) |
| Placebo | 6 | −3.81; −6.70 to −0.91; 0.010 | 77.2% (0.001) | 6 | −2.65; −3.89 to −1.40; 0.000 | 36.1% (0.166) |
| Diuretics | 5 | −1.31; −2.33 to −0.27; 0.013 | 0.0% (0.777) | 5 | −1.49; −3.63 to 0.64; 0.170 | 83.8% (0.000) |
| CCB | 20 | 0.51; −0.72 to 1.75; 0.417 | 65.6% (0.000) | 20 | 0.50; −0.23 to 1.23; 0.179 | 79.8% (0.000) |
| Beta blocker | 4 | −0.78; −2.88 to 1.32; 0.469 | 0.0% (0.991) | 4 | −2.11; −3.43 to −0.78; 0.002 | 4.4% (0.371) |
| Non-RAS | 5 | −2.30; −6.12 to 1.52; 0.238 | 58.3% (0.048) | 5 | −0.73; −2.77 to 1.31; 0.482 | 33.2% (0.200) |

Abbreviations: 95% CI, 95% confidence interval; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; $I^2$, inconsistency index; NA, not available; RAS, renin–angiotensin system; WMD, weighted mean difference.

(WMD = −2.65 mm Hg; 95% CI: −3.89 to −1.40; $P<0.0005$; $I^2=36.1\%$) and beta blockers (WMD = −2.11 mm Hg; 95% CI: −3.43 to −0.78; $P=0.002$; $I^2=4.4\%$), with improved heterogeneity (Table 4). In contrast, comparisons of ARBs with beta blockers revealed a significant increase in heart rate (WMD = 8.47 beats per minute; 95% CI: 0.87–16.08; $P=0.029$; $I^2=87.1\%$) (Table 5).

### Publication bias

Publication bias was only calculated for overall estimates because of the small number of studies involved in subgroup analyses. There was a low probability of publication bias for the overall comparisons of baPWV and cfPWV between the ARB treatment and control groups, as reflected by Begg's test ($P=0.479$ and 0.631, respectively). Similarly, there was no observable publication bias for the overall comparisons of SBP ($P$ for Begg's test: 0.877), diastolic blood pressure ($P=0.350$), pulse pressure ($P=0.921$) and heart rate ($P=0.718$) between the two groups.

### Meta-regression analysis

We performed meta-regression analyses to assess the confounding impact of age, gender, body mass index and treatment duration on the treatment of ARBs versus other types of drugs in terms of PWV and other related indexes and further explore potential sources of heterogeneity. Age explained some part of the heterogeneity for baPWV (regression coefficient: −5.18; $P=0.028$) but not cfPWV (regression coefficient: −2.87; $P=0.300$), which indicates that the change in PWV was negatively associated with increases in age. No significance was observed for the other confounders.

## DISCUSSION

The key finding of this study was that ARBs, particularly telmisartan and valsartan, significantly reduced baPWV and cfPWV relative to placebo, except SBP. To the authors' knowledge, this study is the most comprehensive meta-analysis to assess the comparison of ARBs with the other types of drugs in terms of PWV and related indices of arterial stiffness.

**Table 5 Weighted mean differences in pulse pressure and heart rate between the ARB treatment and control groups according to the types of drugs taken in both groups**

| | *Pulse pressure (mm Hg)* | | | *Heart rate (beats per minute)* | | |
|---|---|---|---|---|---|---|
| *Groups* | *Studies (n)* | *WMD; 95% CI;* P | $I^2$ (P) | *Studies (n)* | *WMD; 95% CI;* P | $I^2$ (P) |
| Overall | 28 | −0.45; −1.41 to 0.51; 0.359 | 44.0% (0.007) | 17 | 1.34; −0.57 to 3.26; 0.169 | 74.7% (0.000) |
| *By drugs in treatment group* | | | | | | |
| Valsartan | 13 | −0.58; −2.26 to 1.10; 0.501 | 70.2% (0.000) | 8 | 0.94; −0.30 to 2.18; 0.138 | 12.2% (0.335) |
| Telmisartan | 4 | −0.10; −2.35 to 2.16; 0.934 | 0.0% (0.706) | 2 | 0.98; −3.62 to 5.58; 0.675 | 0.0% (0.766) |
| Losartan | 3 | 0.45; −2.35 to 3.26; 0.751 | 22.9% 90.273) | 4 | 6.66; 0.77 to 12.55; 0.027 | 89.8% (0.000) |
| Candesartan | 5 | −0.36; −2.87 to 2.16; 0.782 | 0.0% 90.603) | 3 | −2.81; −5.85 to 0.23; 0.070 | 0.0% (0.755) |
| Irbesartan | 3 | −1.27; −3.46 to 0.93; 0.257 | 0.0% (0.866) | | | |
| *By drugs in control group* | | | | | | |
| ACEI | 6 | −1.27; −3.17 to 0.63; 0.189 | 0.0% (0.516) | 4 | 0.41; −1.51 to 2.32; 0.675 | 0.0% (0.786) |
| Placebo | 3 | −2.88; −6.40 to 0.64; 0.109 | 0.0% (0.869) | | | |
| Diuretics | 2 | 0.95; −2.62 to 4.52; 0.603 | 0.0% (0.432) | | | |
| CCB | 12 | −0.45; −1.91 to 1.0; 0.540 | 68.8% (0.000) | 7 | 1.00; −0.39 to 2.39; 0.159 | 20.8% (0.271) |
| Beta blocker | | | | 3 | 8.47; 0.87 to 16.08; 0.029 | 87.1% (0.000) |
| Non-RAS | 4 | 0.77; −1.93 to 3.47; 0.574 | 0.0% (0.563) | | | |

Abbreviations: 95% CI, 95% confidence interval; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; $I^2$, inconsistency index; RAS, renin–angiotensin system; NA, not available; WMD, weighted mean difference.

Angiotensin II is the terminal pressor effector molecular of RAS that plays an active role in blood pressure regulation via the induction of vasoconstriction and sodium and fluid retention and the initiation and progression of endothelial dysfunction and vascular remodeling.[52] Therefore, it is reasonably expected that ARBs may improve arterial compliance via blockade of the negative role of angiotensin II in the endothelium, as exemplified by the improvement in vascular compliance and endothelial function in healthy elderly subjects taking ARBs.[34] However, many, but not all, clinical studies documented the beneficial impact of ARBs on arterial stiffness. For example, Suzuki *et al.*[36] observed a comparative reduction in PWV between treatment with and without ARBs. As a caveat, this lack of reproducibility might be attributed to the diverse types of drugs taken by controls or the individually underpowered clinical trials. We performed a meta-analysis of data from 40 articles and 3309 subjects and demonstrated significantly lower levels of baPWV and cfPWV and SBP in patients taking ARBs, especially telmisartan and valsartan, than placebo, which reinforces the selection of ARBs as the first-line treatment for arterial destiffening in clinical routine. Moreover, Shahin and coworkers summarized the impact of ACEIs on arterial stiffness and found that ACEIs significantly reduced PWV relative to the placebo, but this difference was non-significant relative to other antihypertensive agents, including ARBs, calcium channel blockers, beta blockers and diuretics.[53] Consistent with the results of this meta-analysis, the impact of ARBs on improvements in arterial elasticity was superior, but insignificant, compared with ACEIs. It is also worth stressing that the modulatory impact of ARBs on arterial stiffness is independent of the resulting blood pressure decrease, which was confirmed by many previous studies.[8] These results suggest that additional mechanisms are invoked by ARBs in the treatment of arterial stiffness.

Several possible limitations should be acknowledged. First, a set of subgroup analyses was undertaken, but significant heterogeneity persisted in some subgroups. Second, we must have some reservations regarding the interpretation of our subgroup results because of the limited number of clinical trials with relatively small sample sizes in some subgroups. In fact, Hannah and colleagues suggested that the study power is low if the number of studies included in a meta-analysis is 10 or fewer.[54] Third, our statistical tests reported a low probability of publication bias, which is consistent with all meta-analyses, but selection bias cannot be completely excluded because we only retrieved published articles and trials written in English or Chinese. Therefore, our conclusions require further verification in larger, more targeted clinical trials.

Taken together, meta-analyses of the data from 40 articles and 3309 subjects support an important role of ARB treatment in improving arterial stiffness. For practical reasons, successful validation of the present results with accumulating data from large randomized clinical trials will shed more light on the widespread administration of ARBs in the treatment of arterial stiffness in daily clinical practice.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ACKNOWLEDGEMENTS

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