

Angiotensin Receptor Blockades Effect on Peripheral Muscular and Central Aortic Arterial Stiffness: A Meta-Analysis of Randomized Controlled Trials and Systematic Review

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Background: Previous clinical trials have demonstrated the impact of blocking upstream renin-angiotensin-axis with angiotensin converting enzyme inhibitors (ACEIs) on arterial stiffness as evaluated by pulse-wave velocity (PWV). We ran a meta-analysis to evaluate the anti-stiffness effect of powerful downstream angiotensin receptor blockades (ARBs) on peripheral and central arterial stiffness (brachial to ankle, ba-PWV; carotid to femoral, cf-PWV, respectively), using a systematic review to assess the clinical arterial stiffness issues.

Methods: For our study, we searched the PubMed and Cochrane Library databases from inception to June 2013, targeting randomized controlled trials. ARBs along with other antihypertensive agents, ACEIs, calcium channel blockers (CCBs), beta-blockers and diuretics were evaluated to ascertain their comparable effect on ba-PWV and cf-PWV, respectively. A meta-analysis was conducted utilizing the fixed or random effect of the weighted mean change difference between the ARB and comparator groups, depending on the I^2 statistic heterogeneity measurement.

Results: In 2 trials treating patients with ARBs ($n = 30$), the ARBs insignificantly reduced levels of ba-PWV (pooled mean change difference -188 , 95% CI $-687, 311$, $p = 0.24$ with significant heterogeneity) as compared to other hypertensive agents (ACEIs and CCBs, $n = 77$). Interestingly, ARBs ($n = 20$) had a superior capacity to reduce levels of ba-PWV than CCBs ($n = 20$) in single study results (mean change difference -400 , 95% CI $-477, -322$, $p < 0.05$). In 7 trials which included a total of 653 patients, treatment with ARBs ($n = 308$) also insignificantly reduced cf-PWV (pool mean change difference -0.197 , 95% CI $-0.54, 0.14$, $p = 0.218$) as compared to other anti-hypertensive agents.

Conclusions: Our data suggested that ARBs had a similar effect as other anti-hypertensive agents in reducing ba-PWV and cf-PWV. Upon systematic review, the renin-angiotensin-axis system mechanism seems more significant than the direct vessel dilatation system in anti-arterial stiffness mechanism.

Key Words: Angiotensin receptor blockage • Arterial stiffness • Meta-analysis • Systematic review

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INTRODUCTION

Arterial stiffness assessment demonstrates the relationship between the stiffness severity of the central carotid and abdominal aorta and higher cardiovascular event rates in many high-risk¹⁻³ and community-based populations.⁴⁻⁶ Several methods were evaluated in clinical trials, and pulse wave velocity (PWV) was considered the gold standard non-invasive method.⁷ The PWV method was measured by two sites: the waveform tra-

velling distance was divided by the spending time as manifested by the tonometric method.⁸ Peripheral muscular ba-PWV was assessed by two sites, between the brachial artery and the ankle anterior tibial artery;⁹ meanwhile, central aortic cf-PWV was evaluated by two sites between the carotid artery and the femoral artery.¹⁰

In prior decades, arterial stiffness was strongly related to age, blood pressure and renal function impairment, and aggressive anti-hypertensive treatment was beneficial to arterial resilience beyond blood pressure control.¹¹ The renin-angiotensin-system (RAS) involved the arterial stiffness mechanism and provided the treatment target.¹² The angiotensin converting enzyme inhibitors (ACEIs) was the leading choice in anti-stiffness hypertensive treatment strategies.¹³ However, the adverse coughing effect and the modest blood pressure lowering effect limited the prescription frequency and raised the angiotensin receptor blockades (ARBs), of which there was greater usage than ACEIs in Asian hypertensive patients. The comparative effect of ARB and other hypertensive agents including ACEIs and calcium channel blockers (CCBs) on arterial stiffness is inconclusive in peripheral muscular ba-PWV and central aortic cf-PWV.

In this meta-analysis, we investigated the effect of ARBs compared with other anti-hypertensive agents in two primary ways: to ACEIs and CCBs in peripheral muscular arterial stiffness (ba-PWV), and to ACEIs, CCBs, beta-blockers and diuretics in central arterial stiffness (cf-PWV).

As a result of the meta-analysis, we further briefly reviewed the clinical application of PWV to add the substantial benefit of predicting the outcome in renal disease, coronary arterial disease, heart failure and metabolic syndrome, and the important treatment role of ARB in arterial anti-stiffness mechanism.

METHODS

Search strategy

We reviewed the existing literature primarily researched through PubMed and Cochrane publications. We use the mesh terms and key words "arterial stiffness", "arterial elasticity", "pulse wave velocity", "central hemodynamic blood pressure", "clinical trial", "randomized trial", "hypertensive" and "medical treatment".

We also expanded the search from just reference lists of relevant papers, to avoid missing articles that might be obtained through an internet search. The searching procedure was performed repeatedly by two experienced cardiovascular physicians working independently. We only searching the articles published in English and human-related data (Figure 1).

Inclusion and exclusion criteria

The studies which were eligible to be included in the meta-analysis were the following: Hypertension with arterial stiffness PWV data and treatment with ARBs. Comparable studies and crossover studies were all included but only randomized clinical trials were optimal. Single ARB usage was better, but combination with other anti-hypertensive agents was also included. The articles were divided into peripheral and central groups in terms of ba-PWV and cf-PWV data. We excluded patients with chronic kidney disease, pulmonary hypertension, ocular hypertension, stroke (cerebral infarction), cardiovascular surgery, liver transplantation, endothelial function, pregnancy, invasive measurement, no PWV data, duplicated papers, exercise, diet treatment, Chinese herb medicine, ginseng, ambulatory blood pressure, and not currently taking ARBs medicine. The summary articles were listed in Tables 1 and 2.

Statistical analysis

We included randomized clinical trials, which also incorporated parallel-group and cross-over design. The articles were combined in the same meta-analysis with a standard recommendation.¹⁴ We calculate the absolute difference of mean changes in ba-PWV and cf-PWV and standard errors by the inverse variance method. Also, unpaired t-test was performed in parallel-groups studies. We ran a sensitivity analysis to measure the contribution of every study to the pooled treatment effect by excluding each study at one time. We then reran the meta-analysis model to assess the treatment effect for the remaining studies. A p-value < 0.05 was considered significant. Heterogeneity was calculated by I^2 method and essential heterogeneity was defined as > 50%. Random-effects model was performed if I^2 value > 50%. Fixed-effects model was then used when studies did not reveal significant heterogeneity. Stata version 11 was performed for the data analysis.

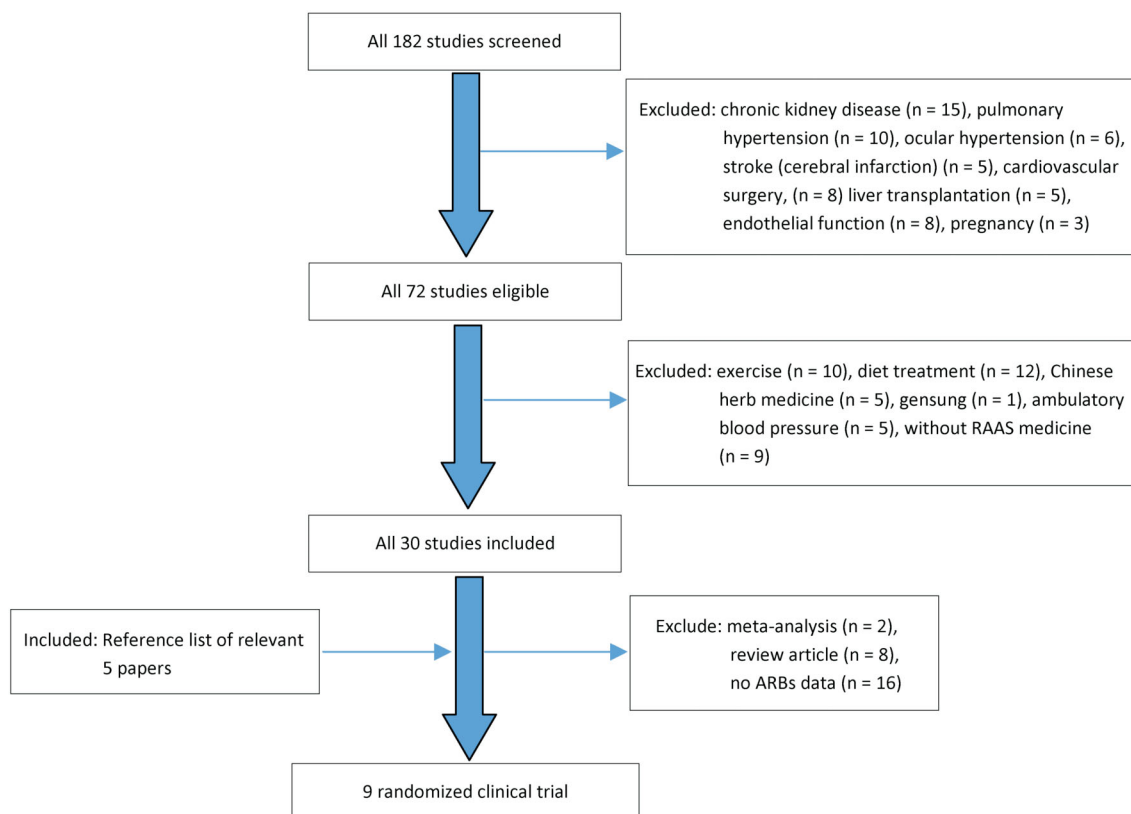


Figure 1. Flow diagram. ARBs, angiotensin receptor blockades; RAAS, renin-angiotensin-aldosterone system.

RESULTS

Epidemiology of patients and studies

We comprehensively reviewed 9 randomized control trials with 760 participants from 2002 to 2010 (Tables 1 and 2). The search identified 182 potentially eligible studies of which 152 studies were excluded by review of title and abstract. Full articles of the remaining 30 studies were collected and evaluated. Finally, 9 studies met our inclusion criteria. In the two trials that evaluated the effects of ARBs on ba-PWV, one compared ARBs with ACEIs or a combination of both drugs; the other compared it with ACEIs and CCBs. In the seven trials that assessed these effects on cf-PWV, four of them compared ARBs with ACEIs, two compared it with beta-blockers, and one compared it with thiazides. The basic demographics of patients were mostly similar between the study groups, with the exception of two studies that focused solely on elderly males (Takami, 2003; Ali, 2009). The mean patient age ranged from 49 to 61 years, and the mean follow-up duration

ranged from 4 to 40 weeks.

Ba-PWV measurement

In 2 trials including a total of 107 patients, no significant difference in peripheral ba-PWV reduction was observed with ARBs ($n = 30$, pooled mean change difference -188 , 95% CI $-687, 311$, $p = 0.25$ with significant heterogeneity) than other hypertensive agents (ACEIs and CCBs, $n = 77$). ARBs ($n = 20$) had comparatively superior effects on peripheral stiffness than CCBs ($n = 20$) in one study results (mean change difference -400 , 95% CI $-477, -322$, $p < 0.05$) (Figure 2).

Cf-PWV measurement

In 7 trials including a total of 653 patients, treatment with ARBs ($n = 308$) also insignificantly reduced central cf-PWV (pool mean change difference -0.19 , 95% CI $-0.54, 0.14$, $p = 0.21$ with insignificant heterogeneity) than other hypertensive agents (ACEIs, CCBs, beta-blockers, and thiazides) (Figure 3).

Table 1. ARBs' effects on peripheral ba-PWV

First author year, country	Population	No	Mean age	F (%)	Treatment (ARB) N	Control group N	Followed up duration	Study method	Masking method	Modality	Before PWV (cm/s)	After PWV/mean difference (cm/s)	Reference
Futoshi, 2005 ¹⁵	Hypertension	31	59 ± 5	14 (45%)	Valsartan (V) N = 10	Perindopril (P) N = 11 Combine (V + P) N = 10	40 weeks	Randomized comparable	single	ba-PWV volume-plethysmographic, Colin, Japan	1853 ± 107	1615 ± 103	Eur J Clin Pharmacol 2005;61:353-9
Takami, 2003 ⁹	Elderly male hypertension	76	71 ± 3	0 (%)	Valsartan N = 20		12 weeks	Randomized comparable	single	ba-PWV volume-plethysmographic, Colin, Japan	1818 ± 137	1613 ± 94	Hypertens Res 2003;26:609-14
Japan						Temocapril N = 20 Cilnidipine N = 20 Nifedipine-CR N = 16						281 ± 99 209 ± 82 9 ± 146	

ARB, angiotensin receptor blockade; ba-, brachial to ankle; PWV, pulse wave velocity.

Heterogeneity

Heterogeneity was calculated by use of the I² method and essential heterogeneity was defined as > 50%. The random-effects model was performed if I² value > 50%, and the fixed-effects model was used when studies did not reveal significant heterogeneity.

Risk of bias and publication bias

Risk of bias and study quality was evaluated for all of the articles using the Jadad scoring system¹⁶ (Table 3). The Jadad score in our study was no more than 2, suggesting a less than excellent study quality. The effect sizes of PWV were plotted against the standard errors through use of Forest plotting (Figures 2 and 3). Publication bias was assessed by the funnel plot method (Supplementary figure).

DISCUSSION AND SYSTEMATIC REVIEW

Clinical pulse pressure, arterial stiffness, and PWV

Enthusiasm in the medical community contributing to primary prevention for cardiovascular disease and risk measurement in asymptomatic people had fueled substantial discussion about preventive research. By 1999, peripheral pulse pressure (PP) had become a better predictor for coronary heart disease according to the Framingham Heart Study, and a better predictor for risk of heart failure in the elderly study rather than conventional peripheral arterial blood pressure (BP) measurement.^{17,18} However, many factors other than PP such as heart rate, cardiac contractility, and venous pressure can influence the value of PP to predict clinical cardiovascular events.¹⁹ Apart from the limitation of PP, central pressure is more strongly associated with vascular disease and outcome than brachial pressure.²⁰ Some investigators have suggested a surrogate measure of large artery stiffness with the stroke volume/pulse pressure, which had been shown to be the better prediction marker of all-cause and cardiovascular mortality. But other authors considered the stroke volume/pulse pressure poorly correlated with central PWV.²¹ Central aortic PWV was a strong predictor of future cardiovascular events and all-cause mortality.²² Meanwhile, central aortic PWV was considered the gold standard method for assessing aortic stiffness and sub-clinical target organ damage as well.⁷

Table 2. ARBs' effects on central cf-PWV

First author, year, country	Population	No	Mean age, F (%)	Treatment (ARB) N	Control group N	Followed up duration	Study method	Masking method	Modality	Before PWV (m/s)	After PWV (m/s)	SBP change	DBP change	Reference
Mahmud-A 2002 ²³ Ireland	Hypertension	11	57 ± 36 (55%)	Losartan 50 mg, 11		4 weeks	Randomize crossover	Single blind	cf-PWV pressure transducer, (Complior) and AI (sphygmoCor device)	11.75 ± 0.64	10.35 ± 0.55	164	94	7 AJH 2001;15: 1092-5
Mahmud-B 2002 ¹⁰ Ireland	Hypertension	12	49 ± 116 (50%)	Valsartan 160 mg, 12	hydrochlorthi azide 12.5 mg, 11	4 weeks	Randomize crossover	Single blind	cf-PWV pressure transducer, (complior)	11.07 ± 0	10.04 ± 0	157	96	10 AJH 2002;15: 321-5
Ali 2009 ²⁴ UK	Hypertension	15	65 ± 90 (0%)	Irbesartan 300 mg, 15	Captopril 100 mg, 12	12 weeks	Randomize crossover	Double blind	cf-PWV pressure transducer, (complior)	11.07 ± 0	10.04 ± 0	157	98	6
Vitale 2011 ²⁵ Italy	Newly-diagnosed hypertension	65	52 ± 12 23 (35%)	Irbesartan 150 mg (thiazide base), 34	Lisinopril 20 mg, 15	8 weeks	Randomize parallel	Double blind	cf-PWV pressure transducer, (complior)	15.1 ± 5	13.3 ± 2.6	162	98	20 Vascular Health and Risk Management 2009;5:587-92
Rajzer 2003 ²⁶ Poland	Hypertension	118	53 ± 96 (54%)	Losartan 100 mg, 24	Nebivolol 5mg (beta-blocker), (thiazide base), 31	24 weeks	Prospective parallel	Open	cf-PWV pressure transducer, (complior)	11.23 ± 1.67	9.55 ± 1.32	155	91	7 AJH 2003;16:439-44
Boutouyrie 2010 ²⁷ France	Hypertension	393	57 ± 9.9 183 (47%)	Valsartan 160 mg (amlodipine base), 193	Quinapril 20 mg, 37 Amlodipine 10 mg, 38	24 weeks	Randomize parallel	Double blind	cf-PWV pressure transducer, (complior)	11.23 ± 1.67	10.53 ± 1.05	149	94	9
Rehman 2007 ²⁸ Malaysia	Hypertension	39	52 NR	Losartan 50 mg, 19	Perindopril 4 mg, 20	24 weeks	Randomize parallel	Double blind	cf-PWV pressure transducer, (complior)	11.23 ± 1.67	10.54 ± 1.67	154	97	11
										12.5 ± 3	11.52 ± 0.18	158	91	6 Hypertension 2010;55:1314-22
										11.9 ± 10.8	10.95 ± 0.17	156	92	7
										12 ± 1.75	11.17 ± 1.19	151	94	8 AJH 2007;20: 184-9
										11 ± 1.69	10.43 ± 1.22	152	92	9

ARB, angiotensin receptor blockade; cf-, carotid to femoral; DBP, diastolic blood pressure; F, female; PWV, pulse wave velocity; SBP, systolic blood pressure.

PWV and coronary heart disease

Despite the decline of the coronary heart disease (CHD) rate in the United States and major European countries, heart attack event prevention remains a challenge.²⁹ Optimal medical treatment and aggressive revascularization strategy have substantially reduced the mortality rate of acute myocardial infarction and coronary heart disease. Additionally, proper identification of the target population for primary prevention has led to more timely and appropriate intervention treatment. Arterial artery stiffness measured by PWV implying subclinical atherosclerosis had been performed in asymptomatic individuals to predict CHD,³⁰ and to potentially help foresee severe cardiovascular events in patients that underwent percutaneous coronary interventions.³¹

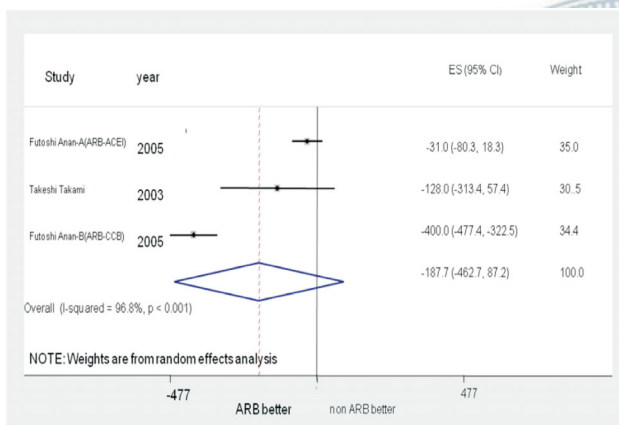


Figure 2. Forest plot of ba-PWV. ba-PWV, Brachial to ankle pulse wave velocity

PWV and chronic renal disease

Cardiovascular events were the leading complication risk in patient with chronic kidney disease (CKD). Vascular dysfunction, comprising carotid intima-medial thickness and aortic arterial stiffness, was the major predictor for fatal and non-fatal cardiovascular events and PWV through the aorta to femoral artery, and was the only arterial index independently associated with cardiovascular outcome in patients with CKD.³² The possible mechanisms associated with higher rate of cardiovascular events in patients with chronic renal disease

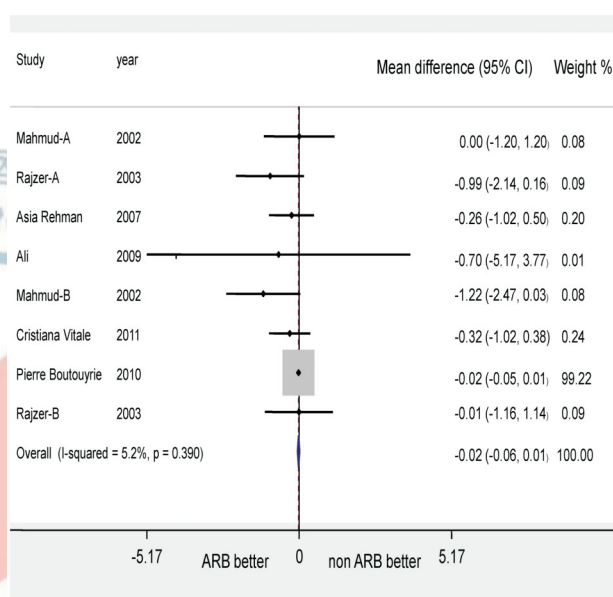


Figure 3. Forest plot of cf-PWV.

Table 3. Quality check-up with Jadad scores

	Risk of bias estimation					
	Adequate sequence generation	Allocation concealment	Blinding	Adequate report on loss to followed-up	Free of other resources of bias	Jadad score
Mahmud-A ²³ , 2002	Yes	No	single	No	Yes	1
Mahmud-B ¹⁰ , 2002	Yes	No	single	No	Yes	1
Ali ²⁴ , 2009	Yes	NR	double	No	Yes	2
Vitale ²⁵ , 2011	Yes	No	NR	No	Yes	1
Rajzer ²⁶ , 2003	Yes	No	open	No	Yes	1
Boutouyrie ²⁷ , 2010	Yes	No	double	No	Yes	2
Rehman ²⁸ , 2007	Yes	NR	double	No	Yes	2
Deary ³³ , 2002	Yes	NR	double	No	Yes	2
Mackenzie ³⁴ , 2009	Yes	NR	double	No	Yes	2
Futoshi ¹⁵ , 2005	Yes	No	single	No	Yes	1
Takami ⁹ , 2003	Yes	No	single	No	Yes	1

were disturbed calcium-phosphate metabolism, arterial calcification, anemia and increased systemic inflammatory changes.³² Even in end-stage renal disease (ESRD), Tetsuo et al. found the aortic PWV was a significant predictor for all-cause and cardiovascular mortality after adjusting for other risk factors such as age, gender, C-reactive protein, hematocrit, body mass index and diabetes.³⁵ In a previous study, aging, hypertensive risk factor and renal disease were the most frequently cited impacts on arterial stiffness that often coexisted with decreased carotid distensibility and the presence of calcification and plaques.¹¹

PWV and metabolic syndrome, obesity and diabetes

Metabolic syndrome encompassing dyslipidemia, high blood pressure, increased waist circumference, and impaired glucose metabolism linked to cardiovascular events such as acute myocardial infarction, heart failure, and stroke and death have become the world's leading health burden.³⁶ However, the magnitude of metabolic syndrome (which can vary with the number of components of the syndrome presentation) may not predict metabolic risk in an African man in the United States.³⁷ Alternatively, vascular compliance assessment with arterial stiffness may be the appropriate avenue of evaluation, focusing on cardio-metabolic syndrome.³⁸ By 1997, Lehmann disclosed that diabetic patients show increased arterial stiffness in young age compared to a non-diabetic group. Arterial stiffness was considered to be an important and robust predictor for cardiovascular events for glucose intolerance and diabetes patients.^{3,39} At least one investigator suggested an association between obesity and arterial stiffness in young and older adults.⁴⁰ However, the long-term effect of weight-reduction in cardiovascular event was ambiguous in secondary prevention and thus necessitates additional investigation in the future.⁴¹

PWV and preserved EF heart failure

Heart failure, a major and virtually skyrocketing public health problem of epidemic proportion, comprising cardiac abnormal contraction, unmet oxygen demand of peripheral tissue, pulmonary congestion and volume overload, was the leading cause of epidemic hospitalization and associated with approximately 45% of post-discharge mortality and readmission within 3

months.^{42,43} Despite drug and device interventional treatment, the clinical outcome of heart failure has remained suboptimal.⁴⁴ Many investigators have agreed that the increasing percentage of preserved ejection fraction heart failure within an aging society has become an important epidemic problem now and in the near future.⁴³ In earlier Japanese and European studies, arterial stiffness was considered a risk factor for both atherosclerosis and diastolic heart failure.^{45,46} A coupling of ventricular-arterial stiffness encompassed mechanical interaction of the systemic and coronary flow balance, regulating endothelial function and smooth muscle tone.^{47,48} B-type natriuretic peptide (BNP) is comparable to N-terminal pro-BNP in predicting heart function in compensated renal dysfunction.⁴⁹ A treatment-guide by B-type BNP and heart echocardiography parameter has already proven useful in clinical practice.^{50,51} However, the combination of arterial stiffness, cardiac contractility with diastolic function and biochemical marker may offer additional prediction power for cardiovascular events in clinical settings.^{48,52}

Pulse pressure, PWV in hypertension pharmacology and therapy mechanism

Arterial stiffness was the consequence of progressive arterial dilatation and degeneration of the arterial wall along with aging process and increasing systolic pressure. Furthermore, peripheral brachial systolic pressure underestimated the rising in systolic pressure in the aorta and left ventricle, thus conferring differing vessel dilatation effect of anti-hypertensive drugs.⁵³ In addition to the effects of advancing years and hypertensive status on arterial wall elasticity, some evidence of atherosclerosis has further amplified these hardening effects in the distributed compliance model of arterial circulation, thus implying statin utility in elevated pulse pressure and arterial stiffness.⁵⁴ In previous studies, anti-hypertensive agents were divided into two categories: one group involved interference with the RAS system, endothelial NO synthase system and the α -adducin systems; the other group related to the aging process with elastin, collagen and telomere length, both supplying the protective effect in terms of gene polymorphisms.^{12,13} In clinical treatment of arterial stiffness, the effect of vasodilator drugs could directly relax smooth muscle in the arterial medial and indirectly respond to the dilata-

tion and increased compliance of small muscular arteries.⁵⁵ The treatment strategy in hypertension with congestive heart failure aims to increase arterial compliance, and lower pressure afterload with pulse pressure and reverse progression of the left ventricular and arterial wall hypertrophy.⁵⁵ Based on the HOPE and LIFE trials, inhibitors of the renin-angiotensin system may carry the better protective effect in minimizing cardiovascular outcome. Results of the REASON and CAFÉ trials suggested that beta-blocker (atenolol) usage was inferior to perindopril, indapamide and amlodipine in terms of central blood pressure lowering effect.⁵⁶

ARBs comparing with ACEIs

ACEIs have played the upstream role in the renin-angiotensin-axis system, and ARBs have taken the downstream part. Previous studies demonstrated ACEIs had a beneficial arterial anti-stiffness effect which was independent of blood pressure change.⁵⁷ The mechanism of how ACEIs improve arterial compliance was based on the ability to suppress angiotensin II and increase bradykinin. ACEIs also inhibited the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and reduced oxidative stress in the vascular tissue, implying a cardiovascular protective effect.⁵⁸ However, bradykinin tended to induce cough as an adverse effect and made the use of ACEIs intolerable in many Asian patients. Some investigators considered the endothelium dysfunction by ARBs, but this was not a consensus opinion.⁵⁹ In terms of balancing an effective anti-stiffness impact with a blood pressure lowering effect, our results showed that ARBs binding to angiotensin II type 1 receptor were similar to ACEIs.

ARBs comparing with CCBs

In an earlier study, despite the fact that CCBs (amlodipine) had a significant central blood pressure lowering effect with ARBs (valsartan), the anti-stiffness effect was no different between the two groups, and the CCBs coincided with a high prevalence of peripheral edema in post-menopausal women.⁶⁰ This suggested that the ARBs anti-stiffness effect was independent of central hemodynamic change. In our results, we calculated that the direct comparison effect in meta-analysis in peripheral muscular arterial stiffness and ARBs was better than CCBs in single study data. CCBs was the direct

vasodilatation agent which effected central hemodynamic change, ARBs played a similar role in the renin-angiotensin-axis system leading to vessel wall anti-hypertrophic change.³⁸

STRENGTH AND LIMITATIONS

The strength of our meta-analysis is its incorporated robust literature search including randomized clinical trials. However, after exclusions were applied, few studies were included in our final meta-analysis project (less than 10 articles). Second, most of the articles we referenced were lower quality publications intended for small audiences, where there was less double-blinding and fewer long-term followed-up results. Third, we were only able to include published data. Fourth, we worked with the study-level data rather than the patient-level data, and may approximate to biased measurement upon meta-analyses. In addition, we tried to contact the authors of the underlying articles for missing data, but received no replies to our requests.

CONCLUSIONS

Our data implied ARBs were similar to other anti-hypertensive agents in reducing ba-PWV and cf-PWV. Upon systematic review, the renin-angiotensin-axis system mechanism seemed to play a more important role than direct vessel dilatation system in anti-arterial stiffness mechanism, and ARBs improved arterial resilience independent of central hemodynamic change.

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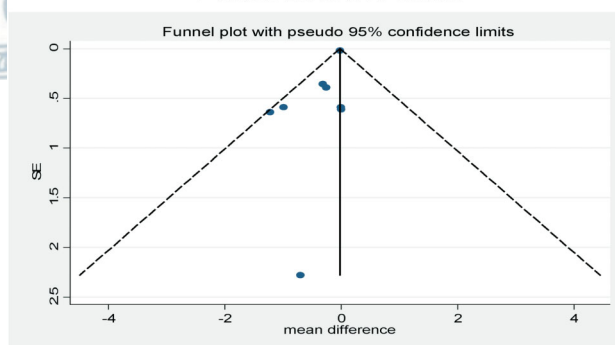
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SUPPLEMENT

Publication bias



Egger's test $p > 0.05$ denoted no significant publication bias

Supplementary Figure. Funnel plot of cf-PWV.