Angiotensin II Receptor Blockers Improve Peripheral Endothelial Function: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Objective(s): Several studies have assessed the effect of angiotensin II receptor blockers (ARBs) on peripheral endothelial dysfunction as measured by flow-mediated vasodilatation (FMD), a widely-used indicator for endothelial function. We conducted a meta-analysis to investigate the effect in comparison to placebo or no treatment and other antihypertensives.

Methods: MEDLINE, Cochrane library and EMBASE were searched to September 2013 for randomized controlled trials (RCTs) that assessed the effect of ARBs versus placebo or no treatment and other antihypertensives (angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), β-blockers, diuretics) by forearm FMD. Furthermore, we also use meta-regression to analyze the relationship between the endothelial function and the duration of ARBs treatments.

Results: In 11 trials including 590 patients, ARBs (n = 315) significantly improved FMD (1.36%, 95% confidence internal [CI]:1.28 to 1.44) versus placebo or no treatment (n = 275). In 16 trials that included 1028 patients, ARBs (n = 486) had a significant effect (0.59%, 95% CI: 0.25 to 0.94) on FMD when compared with other antihypertensives (n = 542). In 8 trials, ARBs (n = 174) had no significant effect (−0.14%, 95% CI: −0.32 to 0.03) compared with ACEI (n = 173). Compared with others, the benefits of ARBs, respectively, were 1.67% (95% CI: 0.65 to 0.93) in 7 trials with CCBs, 0.79% (95% CI: 0.42 to 1.01) with β-blockers in 3 trials and 0.9% (95% CI: 0.77 to 1.03) with diuretics in 3 trials. Importantly, we found ARBs were less effective in a long time span (95% CI: −1.990 to −0.622) than the first 6 months (95% CI: −0.484 to 0.360).

Conclusions: This study shows that ARBs improve peripheral endothelial function and are superior to CCBs, β-blockers and diuretics. However, the effect couldn’t be maintained for a long time. In addition, there was no significant difference between ARBs and ACEI.

Introduction

Endothelial dysfunction is an early marker for atherosclerosis and could be detected before structural changes to the vessel wall are apparent on angiography or ultrasound [1]. Several pathological conditions can lead to impairment of endothelial function, such as hypertension, diabetes, coronary artery disease and metabolic syndrome [2]. Examination of endothelium-dependent FMD using high-resolution ultrasonography is a widely-used noninvasive method of detecting endothelial dysfunction. It has also emerged that impaired FMD has a close correlation with the systemic nature of atherosclerosis and the future development and outcome of cardiovascular events [1,2,3].

The renin angiotensin system (RAS) plays a vital role in cardiovascular disease [1,4,5]. Angiotensin II receptor blockers (ARBs) inhibit the receptor of angiotensin II that stimulates the synthesis of nitric oxide (NO) and increases the levels of bradykinin to play a key role in vasodilatation and inhibition of vascular hypertrophy [5]. ARBs also promote an elastogenic profile in the extracellular matrix of the arterial wall by increasing elastin and decreasing the levels of matrix metalloproteinases. Similar mechanisms involved in regulating on RAS activity, ARBs and angiotensin-converting enzyme inhibitors (ACEIs) are both recommended first-line drugs for hypertension by guidelines [6,7]. A prior meta-analysis [8] pooled that ACEIs could improve endothelial function in patients with endothelial dysfunction caused by various conditions. Whether ARBs are protective on endothelial function or superior to other antihypertensives remains unclear.

Over the last decades, intensive research has investigated the potential clinical benefits of ARBs. Several clinical trials [9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30] have tested the effect of ARBs on endothelial dysfunction using forearm FMD (brachial or radial artery) in patients with...
endothelial dysfunction caused by different pathological lesions. In this meta-analysis we investigated the ARBs compared with placebo or no treatment or other antihypertensives (ACEIs, CCBs, β-blockers, diuretics) on peripheral endothelial function as measured by FMD in patients with endothelial dysfunction.

Materials and Methods

Search strategy

Studies were eligible to be included in our meta-analysis if they were: (1) randomized controlled trials which compared any kinds of ARBs with monotherapy of placebo or no treatment or with other anti-hypertensives (ACEIs, CCBs, β-blockers or diuretics); (2) included patients with endothelial dysfunction (hypertension, type 2 diabetes, coronary artery disease, chronic kidney disease or elderly) as either the study population or a subgroup; (3) Used forearm FMD (Flow mediated vasodilatation or Flow mediated dilatation or Flow mediated dilation) measured by high-resolution ultrasound to assess peripheral endothelial function; (3) Minimum period of treatment with ARBs is more than 4 weeks or 1 month; (4) articles published in English until to September 2013.

Data extraction

The following data were recorded for each study: first author, year of publication, country of research, number of participants randomized to ARBs and controls (not the total number that participated in the RCTs), age and gender, number of participants randomized into ARBs, placebo or no treatment and other antihypertensives respectively, ARBs type and dose, duration of treatment, controls type and dose, FMD at baseline and at the end of the study period, outcome. Authors of included studies were contacted when data was not available as appropriate (2 crossover trials as missing baseline FMD and 1 parallel double-blind trial as missing FMD change value). 2 independent reviewers (Shuang Li and Yan Wu) extracted and checked the data separately. Disagreements were resolved by consensus with the third reviewer, prof. Yawei Xu.

Assessment of methodological quality

Two reviewers (Shuang Li and Yan Wu) assessed the methodological quality assessment independently and any incongruity was discussed and resolved. The methodological quality of the included studies was assessed by the elements of the Cochrane collaboration tool, by which the risk of bias in each trial was assessed [19]. A total of 7 domains were reported for each study including: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, follow-up, selective reporting and other bias. Jadad scoring system was adopted in the same time.

Statistical methods for the meta-analysis

A random-effect model was obtained to conduct a meta-analysis of all the relevant RCTs to get a conservative conclusion. For continuous variables, weighted mean difference (WMD) was measured along with 95% CI, which is a measure of the likelihood of chance effects leading to random errors. A P value <0.05 was considered significant. The inter study heterogeneity was examined by both chi-squared test and I² statistics. The heterogeneity was considered statistically significant when P<0.1 or I²>50%.
Table 1. Characteristics of included trials.

| First author, Year [Ref #] | Country | Protocol | Participants (n) | ARBs (n) | ARBs Dose/Day | Duration | Control (n) | Control Dose/Day | Outcome |
|----------------------------|---------|----------|------------------|----------|---------------|----------|-------------|------------------|---------|
| **ARBs vs. placebo or no treatment** | | | | | | | | | |
| L.Ghiadoni, 2003 [17] | Italy | R,PSB | 69 | 29 | telmisartan, 80–160 mg | 6 m | 40 | no treatment | No effect on FMD |
| K.K.Koh, 2004 [9] | Korea | R,DB,PC | 122 | 92 | Losartan, 100 mg/ irbesartan, 300 mg/ candesartan, 16 mg | 2 m | 30 | placebo | Improved FMD |
| J.Trevelyan, 2005 [18] | UK | R,DB | 33 | 18 | Losartan, 50 mg | 5 m | 15 | no treatment | Improved FMD |
| S.Sola, 2005 [10] | USA | R,DB,PC | 28 | 14 | irbesartan, 150 mg | 4 w | 14 | placebo | Improved FMD |
| L.A.Souza-Barbosa, 2006 [19] | Brazil | R,O,P,PC | 39 | 14 | irbesartan, 150 mg | 12 w | 25 | no treatment | Improved FMD |
| S.Rajagopalan, 2005 [11] | USA | R,DB,PC,CO | 33 | 33 | Valsartan, 160–320 mg | 26 w | 33 | placebo | Improved FMD |
| A.Warnholtz, 2007 [12] | Germany | R,DB,PC | 63 | 30 | irbesartan, 300 mg | 6 m | 33 | placebo | Improved FMD |
| P.P.Filardi, 2009 [13] | Italy | R,DB,PC | 26 | 13 | Candesartan, 16 mg | 2 m | 13 | placebo | Improved FMD |
| F.Pelliccia, 2010 [14] | Italy | R,DB,PC | 40 | 20 | Telmisartan, 160 mg | 4 w | 20 | placebo | Improved FMD |
| K.K.Koh, 2010 [15] | Korea | R,B,PC,P | 34 | 34 | Candesartan, 16 mg | 8 w | 31 | placebo | Improved FMD |
| M.Lunder, 2011 [16] | Slovenia | R,DB,PC | 40 | 20 | Valsartan, 20 mg | 30 d | 20 | placebo | Improved FMD |
| **ARBs vs. other antihypertensives (ACEI, CCB, β-blocker, diuretic)** | | | | | | | | | |
| B.Hornig, 2001 [20] | Germany | R | 35 | 17 | Losartan, 100 mg | 4 w | 18 | Ramipril, 10 mg | FMD improved under both treatments |
| L.Ghiadoni, 2003 [17] | Italy | R,SB,P | 57 | 29 | Telmisartan, 160 mg | 6 m | 28 | Perindopril, 4 mg | FMD improved only under ACEI |
| D.Yavuz, 2003 [21] | Turkey | R,O,P | 18 | 9 | Losartan, 100 mg | 6 m | 9 | Enalapril, 40 mg | FMD improved under both treatments |
| J.Trevelyan, 2005 [18] | UK | R,DB | 34 | 18 | Losartan, 50 mg | 5 m | 16 | Enalapril, 10 mg | FMD improved under both treatments |
| L.A.Souza-Barbosa, 2006 [19] | Brazil | R,O,PC | 30 | 14 | Irbesartan, 150 mg | 12 w | 16 | Quinapril, 20 mg | FMD improved under both treatments |
| K.K.Koh, 2007 [22] | Korea | R,DB,CO,PC | 34 | 34 | Candesartan, 16 mg | 4 m | 34 | Ramipril, 10 mg | FMD improved under both treatments |
| A.B.SOZVEN, 2009 [23] | Turkey | R | 44 | 22 | Irbesartan, 300 mg/ Valsartan, 160 mg | 36 m | 22 | Fosinopril, 10 mg/ Quinapril, 20 mg | FMD improved under both treatments at the start of the trial but not maintained |
| K.K.Koh, 2010 [16] | Korea | R,SB,PC,P | 61 | 31 | Candesartan, 16 mg | 8 w | 30 | Ramipril, 10 mg | FMD improved under both treatments |
| **2. ARB vs. CCB** | | | | | | | | | |
| L.Ghiadoni, 2003 [17] | Italy | R,P | 85 | 29 | Telmisartan, 80–160 mg | 6 m | 56 | Nifedipine, 30–60 mg/ Amlodipine, 5–10 mg | No effect on FMD either. |
| S.Morimoto, 2006 [24] | Japan | R | 43 | 21 | Telmisartan, 40 mg | 24 w | 22 | Amlodipine, 5 mg | ARB improved FMD than CCB |
| R.A.Benndorf, 2007 [25] | Germany | R,SB,P | 25 | 12 | Telmisartan, 40–80 mg | 6 w | 13 | Nisoldipine, 10–20 mg | ARB improved FMD than CCB |
| First author, Year [Ref #] | Country | Protocol | Participants (n) | ARBs (n) | ARBs Dose/Day | Duration | Control (n) | Control Dose/Day | Outcome |
|--------------------------|---------|----------|------------------|----------|---------------|----------|-------------|------------------|---------|
| K.K.Koh, 2010 [15]       | Korea   | R,SB,PC,P| 61               | 31       | Candesartan,16 mg | 8 w      | 30          | Amlodipine,10 mg | ARB improved FMD than CCB |
| M.I.Yilmaz, 2010 [26]    | Turkey  | R        | 72               | 37       | Valsartan,160 mg | 12 w     | 35          | Amlodipine,10 mg | FMD improved under both treatments |
| D.Wei, 2011 [27]         | China   | R,PSB    | 55               | 27       | Olmesartan,20 mg | 8 w      | 27          | Nisoldipine,10 mg | FMD improved under both treatments |
| S.Takiguchi, 2011 [28]   | Japan   | R,CO     | 31               | 15       | Olmesartan,40 mg | 12 w     | 16          | Amlodipine,10 mg | ARB improved FMD than CCB |

3. ARB vs. β-blocker

| First author, Year [Ref #] | Country | Protocol | Participants (n) | ARBs (n) | ARBs Dose/Day | Duration | Control (n) | Control Dose/Day | Outcome |
|--------------------------|---------|----------|------------------|----------|---------------|----------|-------------|------------------|---------|
| L.Ghiadoni, 2003 [17]    | Italy   | R,P      | 86               | 29       | Telmisartan,80–160 mg | 6 m      | 57          | Atenolol,50–100 mg/ Nebivolol,5–10 mg | No effect on FMD either. |
| A.J. Flammer, 2007 [29]  | Switzerland | R,CO  | 14               | 14       | Losartan,100 mg | 4 w      | 14          | Atenolol,100 mg | ARB improved FMD than β-blocker |
| K.K.Koh, 2010 [15]       | Korea   | R,SB,PC,P| 62               | 31       | Candesartan,16 mg | 8 w      | 31          | Atenolol,100 mg | ARB improved FMD than β-blocker |

4. ARB vs. diuretics

| First author, Year [Ref #] | Country | Protocol | Participants (n) | ARBs (n) | ARBs Dose/Day | Duration | Control (n) | Control Dose/Day | Outcome |
|--------------------------|---------|----------|------------------|----------|---------------|----------|-------------|------------------|---------|
| N.A.Chung, 2004 [30]     | UK      | R,DB     | 40               | 21       | Losartan,50–100 mg | 12 w     | 19          | Hydrochlorothiazide,12.5–25 mg | ARB improved FMD than diuretics |
| L.A.Souza-Barbosa, 2006 [19] | Brazil | R,PC     | 32               | 14       | Irbesartan,150 mg | 12 w     | 18          | Hydrochlorothiazide,20 mg | FMD improved under both treatments |
| K.K.Koh, 2010 [15]       | Korea   | R,SB,PC,P| 62               | 31       | Candesartan,16 mg | 8 w      | 31          | Hydrochlorothiazide,50 mg | ARB improved FMD than diuretics |

FMD: flow mediated dilatation; O: open; P: parallel; CO: crossover; PC: placebo-control; DB: double-blind; SB: single-blind; R: randomized; ARB: angiotensin receptor blocker; ACEI: angiotensin-converting enzyme inhibitors; CCB: calcium channel blocker; NR: not reported; m: month; w: week; d: day.
Table 2. Characteristics of participants.

| First author, Year(Ref #) | Participants                              | Mean Age | Male/Female | Mean SBP mmHg | Mean DBP mmHg | Smokers n (%) | Diabetes mellitus n% |
|---------------------------|-------------------------------------------|----------|-------------|----------------|---------------|---------------|---------------------|
| **ARBs vs. placebo or no treatment** |                                           |          |             |                |               |               |                     |
| L.Ghiadoni, 2003 [17]     | essential hypertension;                  | 49.8     | 42/27       | 132.4          | 87.1          | NR            | NR                 |
| K.K.Koh, 2004 [9]         | mild-to-moderate hypertension            | 48.5     | 96/26       | 162.8          | 100           | 0             | 0                  |
| J.Trevelyan, 2005 [18]    | stable CAD awaiting CABG                 | 63.2     | 33/0        | 140            | 82            | 0             | 3(9.1)             |
| S.Sola, 2005 [10]         | metabolic syndrome                      | 41.5     | 12/16       | 133            | 77.5          | NR            | NR                 |
| L.A.Souza-Barbosa, 2006 [19] | hypertension                           | 47.9     | 17/22       | 138.9          | 83.5          | NR            | NR                 |
| S.Rajagopalan, 2006 [11]  | healthy normotensive elders              | 71       | 21/14       | 123            | 70            | NR            | NR                 |
| A.Warnholtz, 2007 [12]    | stable CAD                              | 60       | 63/19       | NR             | NR            | 24(29.3)      | 11(13.4)           |
| P.P.Filardi, 2009 [13]    | hypertension with stable CAD             | 58       | 27/1        | 123            | 78            | 25(89.2)      | NR                 |
| F.Pelliccia, 2010 [14]    | normotensive patients with CAD           | 57       | 27/13       | 133            | 86            | NR            | 9(22.5)            |
| K.K.Koh, 2010 [15]        | hypertension                            | 46.5     | 43/19       | 154            | 93.5          | NR            | 0                  |
| M.Lunder, 2011 [16]       | healthy                                 | 43       | 40/0        | 123            | 75            | 0             | 0                  |
| **ARBs vs. other antihypertensives** |                                   |          |             |                |               |               |                     |
| B.Hornig, 2001 [20]       | CAD                                      | 59.5     | NR          | NR             | NR            | NR            | NR                 |
| L.Ghiadoni, 2003 [17]     | hypertension                             | 50.5     | 36/21       | 152            | 100           | NR            | NR                 |
| D.Yavuz, 2003 [21]        | hypertension                             | 40       | 9/9         | 149            | 98            | 0             | 0                  |
| J.Trevelyan, 2005 [18]    | stable CAD awaiting CABG                 | 63.8     | 34/0        | 143            | 81.6          | 21(5.9)       | 3(8.8)             |
| L.A.Souza-Barbosa, 2006 [19] | hypertension                           | 49.5     | 13/17       | 158.4          | 92.1          | NR            | NR                 |
| K.K.Koh, 2007 [22]        | hypertension                             | 46       | 23/11       | 155.5          | 95            | 11(32)        | 0                  |
| A.B. SOZEN, 2009 [23]     | mild-to-moderate hypertension            | 45       | 18/24       | NR             | NR            | 12(27.3)      | 20(45.5)           |
| K.K.Koh, 2010 [15]        | hypertension                             | 46.5     | 42/19       | 155            | 94            | NR            | NR                 |
| **2. ARB vs. CCB**        |                                           |          |             |                |               |               |                     |
| L.Ghiadoni, 2003 [17]     | essential hypertension; normotensive subjects as control | 51.6     | 52/33       | 152            | 100           | NR            | NR                 |
| S.Morimoto, 2006 [21]     | untreated hypertensive patients          | 57       | 18/25       | 162.5          | 94            | 11(25.6)      | NR                 |
| R.A.Benndorf, 2007 [25]   | essential hypertension                   | 57.9     | 13/12       | NR             | NR            | 14(4%)        | NR                 |
| M.I.Yilmaz, 2010 [26]     | diabetic CKD stage I patients with hypertension | 47       | 33/39       | 149            | 91            | NR            | 72(100%)           |
| K.K.Koh, 2010 [15]        | hypertension                             | 49       | 41/20       | 155.5          | 95            | NR            | NR                 |
| D.Wei, 2011 [27]          | hypertension                             | 58.6     | 41/14       | 148            | 87.8          | NR            | NR                 |
| S.Takiguchi, 2011 [28]    | essential hypertension                   | 56       | 27/4        | 150.5          | 92.9          | 10(32.2)      | 7(22.6)            |
| **3. ARB vs.  β-blocker** |                                           |          |             |                |               |               |                     |
| L.Ghiadoni, 2003 [17]     | hypertension                             | 52       | 53/33       | 153            | 99            | NR            | NR                 |
| A.J.Flammer, 2007 [29]    | type 2 diabetes and hypertension         | 61.3     | 10/3        | 133            | 82            | 6(46.2)       | 13(100)            |
funnel plot and Egger’s test. The STATA (version 11.0; StataCorp) were used to conduct this meta-analysis. We also used meta-regression to test for a duration–effect relationship between duration of ARBs treatment and the change percent of FMD.

To explore the source of heterogeneity, each included study was removed one by one to detect its contribution on the heterogeneity. Besides, the meta-regression was also conducted to evaluate the source of heterogeneity. The sensitivity analysis was conducted excluding each study one at a time and then detecting the efficiency of ARBs on the FMD. The results would be considered robust when the results didn’t change significantly.

Results

1 Literature searching

The searching protocol identified 1594 potentially eligible studies of which 281 were duplicated and 1230 studies were excluded on title and abstract. Full articles of the remaining 62 studies were collected and evaluated. 22 studies [9–30] met our inclusion criteria and were included in the meta-analysis. (see Fig. 1). We classified included trials into two groups: 11 trials compared ARBs with placebo [9–16] or no treatment [17,18,19], 16 trials [15–30] compared ARBs with other antihypertensives [15,17–30] (with ACEI in 8 trials [16–23], CCBs in 7 trials [15,17,24–28] β-blockers in 3 trials [15,17,29], diuretics in 3 trials [15,19,30], 21 studies detected brachial FMD and 1 study detected radial FMD [20].

2 Characteristics of patients and trials

Our meta-analysis included 1737 patients of 11 countries and 22 trials totally (Table 1). In all trials, major characteristics of patients at baseline were similar between study groups. The mean age of patients ranged from 40 [21] to 71 [11] years old. 2 studies assessed ARBs effect on brachial FMD in male only [16,18]. The mean systolic blood pressure ranged from 123 to 162.8 mmHg and the diastolic blood pressure ranged from 70 [11] to 100 mmHg [9,17] at baseline. Mean follow-up duration ranged from 4 weeks [10,14,20,29] to 3 years [23]. Patients’ characteristics are summarized in Table 2.

3 The methodological quality of the included trials

The methodological quality of the included studies ranged from poor to moderate, with a median Jadad score of 3, range (1–3). This resulted from poor description of randomization and allocation concealment methods and the lack of double-blinding. Three studies [17,19,23] lacked adequate reporting on loss to follow up and withdrawals. In 2 studies [14,30], diuretics were added to study treatments to normalize blood pressure in patients remaining hypertensive in spite of being on study treatments which might have affected the results too. Two studies [16,18] included males only which might result in selective bias. Other aspects of methodological quality of the included trials are summarized in Table 3.

4 FMD measurement

There was certain variation in the values of FMD among included studies. FMD change percent ranged from -0.3% [11] to 2% [19] in the placebo or no treatment group and 0.3% [17] to 5.9% [19] in relative ARBs groups. Also, when compared between ARBs with other antihypertensives, FMD ranged from −3.8% [23] to 5.6% [21] and −3.95% [23] to 5.9% [19] in relative ARBs groups. Other aspects of FMD measurements across included studies are summarized in Table 4.
Table 3. Risk of bias assessment.

| First author, Year(Ref #) | Adequate sequence generation | Allocation concealment | Blinding (observer) | Blinding (patient) | Adequate report on loss to follow-up | Free of other sourced of bias | Jadad score |
|----------------------------|-------------------------------|------------------------|---------------------|--------------------|------------------------------------|-----------------------------|--------------|
| **ARBs vs. placebo or no treatment** | | | | | | | |
| L.Ghiadoni,2003 [17] | Yes | NR | Yes | NO | NO | NO | 1 |
| K.K.Koh,2004 [9] | Yes | NR | Yes | Yes | Yes | NO | 3 |
| J.Trevelyan,2005 [18] | Yes | NR | Yes | NO | Yes | NO | 3 |
| S.Sola,2005 [10] | Yes | Yes | Yes | Yes | Yes | NO | 3 |
| L.A.Souza-Barbosa,2006 [17] | Yes | NO | NO | NO | NO | Yes | 2 |
| S.Rajagopalan,2006 [11] | Yes | NR | Yes | Yes | Yes | NO | 3 |
| A.Warnholtz,2007 [12] | Yes | NR | Yes | Yes | Yes | NO | 3 |
| P.P.Filardi,2009 [13] | Yes | NR | Yes | Yes | Yes | NO | 3 |
| F.Peliccia,2010 [14] | Yes | NR | Yes | Yes | Yes | NO | 3 |
| K.K.Koh,2010 [15] | Yes | Yes | NO | Yes | Yes | Yes | 3 |
| M.Lunder,2011 [16] | Yes | NR | Yes | Yes | Yes | NO | 3 |
| **ARBs vs. other antihypertensives** | | | | | | | |
| B.Hornig,2001 [20] | Yes | NR | NO | NO | Yes | NO | 1 |
| D.Yavuz,2003 [21] | Yes | NO | NO | NO | Yes | Yes | 2 |
| K.K.Koh,2007 [22] | Yes | NR | Yes | Yes | Yes | Yes | 3 |
| A.B.SOZEN,2009 [23] | Yes | NO | NO | NO | NO | NO | 1 |
| S.Morimoto,2006 [24] | Yes | NO | NR | NR | NR | NO | 1 |
| R.A.Benndorf,2007 [25] | Yes | NR | NO | Yes | NR | NO | 2 |
| M.I.Yilmaz,2010 [26] | Yes | NR | NR | NR | NR | NO | 1 |
| D.Wei,2011 [27] | Yes | NR | NO | Yes | Yes | NO | 2 |
| S.Takiguchi,2011 [28] | Yes | NO | NO | NO | Yes | NO | 1 |
| A.J.Flammer,2007 [29] | Yes | NR | Yes | Yes | Yes | NO | 3 |
| N.A.Chung,2004 [30] | Yes | NR | Yes | Yes | Yes | NO | 3 |

A & b: A diuretic was added to study treatments to normalize blood pressure.

NR not reported; ARB Angiotensin receptor blocker; ACEI Angiotensin-converting enzyme inhibitors; CCB Calcium channel blocker.
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### Table 4. Technical aspects of forearm FMD measurement.

| First author, Year(Ref #) | Mean change FMD (SD) | Probe (device) MHz | Position | Reproducibility |
|---------------------------|----------------------|--------------------|----------|-----------------|
| **ARBs vs. placebo or no treatment** | | | | |
| L.Ghiadoni,2003 [17] | 0.3±0.29 | 7(ESAOTE) brachial artery | | Intraobserver variability 14% | Mean difference between measures 0.9% |
| K.K.Koh,2004 [9] | 1.36±0.364 | 8.5(Logic 700) brachial artery | | Mean difference between measures 0.9% |
| J.Trevelyan,2005 [18],2m | 0.6±0.60 | 5-10(GE) brachial artery | | |
| J.Trevelyan,2005 [18],5m | 3.3±0.65 | 5-10(GE) brachial artery | | |
| S.Sula,2005 [10] | 2.7±0.82 | 7-12(ALT HDI) brachial artery | | Mean difference between measures 0.9%; Intraobserver variability <2% |
| L.A.Souza-Barbosa,2006 [19] | 5.9±2.81 | 7-12(ALT HDI) brachial artery | | |
| S.Rajagopalan,2006 [11] | 0.8±0.9 | 10(NR) brachial artery | | |
| A.Warnholtz,2007 [12] | 0.3±0.27 | NR(Aloka alfa) right brachial artery | | |
| P.P.Filardi,2009 [13] | 1.88±2.3 | 7.5 (NR) brachial artery | | |
| F.Pelliccia,2010 [14] | 4.9±3.5 | 7.5–12.5(Vivid 7) right brachial artery | | |
| K.K.Koh,2010 [15] | 1.62±0.29 | 10(ATL) right brachial artery | | Interobserver variability 0.07–1.27%; Intraobserver variability 0.15–1.24% |
| M.Lunder,2011 [16] | 2.7±0.37 | 7-12(ALT HDI) brachial artery | | |
| **ARBs vs. other antihypertensives (ACEI, CCB, β-blocker, diuretic) 1. ARB vs. ACEI** | | | | |
| B.Hornig,2001 [20] | 0.12±0.1 | 10(ASULAB) radial artery | | |
| L.Ghiadoni,2003 [17] | 0.3±2.9 | 7(ESAOTE) brachial artery | | Intraobserver variability 14%; Mean difference between measures 0.9% |
| D.Yavuz,2003 [21] | 4.5±3.06 | 8.5(Logic 700) brachial artery | | Mean difference between measures 0.9%; Intraobserver variability 1–3% |
| J.Trevelyan,2005 [18],2m | 0.6±0.60 | 5-10(GE) brachial artery | | |
| J.Trevelyan,2005 [18],5m | 3.3±0.65 | 5-10(GE) brachial artery | | |
| L.A.Souza-Barbosa,2006 [19] | 5.9±2.81 | 7–12(ALT HDI) brachial artery | | Mean difference between measures 0.9%; Intraobserver variability <2% |
| K.K.Koh,2007 [22] | 1.58±1.71 | 1.7±1.75 | 10(ATL) brachial artery | | Interobserver variability 0.07–1.27%; Intraobserver variability 0.15–1.24% |
| A.B.SOZEN,2009 [23] | −3.95±1.5 | −3.8±4.6 | 10(VingMed) brachial artery | | Intra-and inter-observer variabilities 1–3% |
| K.K.Koh,2010 [15] | 1.62±0.29 | 1.66±0.31 | 10(ATL) right brachial artery | | Interobserver variability 0.07–1.27%; Intraobserver variability 0.15–1.24% |
| **2. ARB vs. CCB** | | | | |
| L.Ghiadoni,2003 [17] | 0.3±2.9 | −0.4±2.24 | 7(ESAOTE) brachial artery | | Intraobserver variability 14%; Mean difference between measures 0.9% |
| S.Morimoto,2006 [24] | 3±0.92 | −0.9±0.82 | 7.5(GE) brachial artery | | |
| R.A.Benndorf,2007 [25] | 5.44±4.19 | −0.68±3.57 | 12(ATL) brachial artery | | Mean intraindividual coefficient 4.2% |
| K.K.Koh,2010 [15] | 1.62±0.29 | 1.22±0.29 | 10(ATL) right brachial artery | | Interobserver variability 0.07–1.27%; Intraobserver variability 0.15–1.24% |
| M.I.Yilmaz,2010 [26] | 1.2±0.747 | 0.375±0.954 | 12(Bethell) brachial artery | | The variability was 12% with a mean difference of 0.8% between the two measurements |
| D.Wei,2011 [27] | 2.91±4.48 | 4±7.06 | 7.5(Philips) brachial artery | | |
| S.Takiguchi,2011 [28] | 1.59±2.92 | 0.04±2.34 | 7.5(Aplio) right brachial artery | | |
| **3. ARB vs. β-blocker** | | | | |
| L.Ghiadoni,2003 [17] | 0.3±2.9 | 7(ESAOTE) brachial artery | | Intraobserver variability 14%; Mean difference between measures 0.9% |
| A.J.Flammer,2007 [29] | 0.73±0.43 | −0.11±0.45 | 10(WTS-2) brachial artery | | |
| K.K.Koh,2010 [15] | 1.62±0.29 | 0.8±0.35 | 10(ATL) right brachial artery | | Interobserver variability 0.07–1.27%; Intraobserver variability 0.15–1.24% |
| **4. ARB vs. diuretics** | | | | |
| N.A.Chung,2004 [30] | 1.15±4.6 | −0.26±4.571 | 10(GE) brachial artery | | |

**ARBs vs. placebo or no treatment**

**ARBs vs. other antihypertensives (ACEI, CCB, β-blocker, diuretic)**

**2. ARB vs. CCB**

**3. ARB vs. β-blocker**

**4. ARB vs. diuretics**
5 Outcome measures reporting

5.1 ARBs versus placebo or no treatment. Overall, 11 trials [9–19] assessed the effect of ARBs on FMD compared to placebo or no treatment, all using brachial arteries. These studies included 590 patients of which 315 patients received ARBs and 275 patients received placebo (8 trials [9–16]) or no treatment (3 trials [17,18,19]). Across the 11 trials we found significant heterogeneity (I² = 94.3%, p = 0.00001). A random effect model showed that treatment with ARBs significantly improved brachial FMD (pooled mean change difference = 1.36%) (see Fig. 2).

5.2 ARBs versus other antihypertensives. In 15 trials (14 using brachial FMD and 1 using radial FMD [20]) which included 1028 patients, treatment with ARBs (n = 486) had a significant effect on FMD when compared with other antihypertensives (ACEI, CCBs, β-blockers and diuretics) (n = 542) (pooled mean change difference 0.59%, 95% CI 0.25–0.94, I² = 95.7%, p for heterogeneity <0.00001) (see Fig. 3).

5.3 ARBs versus ACEI. In 8 trials (7 with brachial FMD and 1 with radial FMD [20]), treatment with ARBs (n = 174) had no significant effect on FMD when compared with ACEI (n = 173) (pooled mean change difference = −0.14%, 95% CI 0.32 to 0.03, p = 0.082, I² = 37.52%).

5.4 ARBs versus CCB. In 7 trials [15,17,24–28], all using brachial FMD, ARBs (n = 172) significantly improved FMD when compared with CCBs (n = 199) (pooled mean change difference 1.67%, 95% CI 0.65–0.93, I² = 96.6%, p for heterogeneity <0.00001).

5.5 ARBs versus β-blockers. When compared with β-blockers in 3 trials [15,17,29], all using brachial FMD, ARBs also had a significant effect on FMD (pooled mean change difference

| Table 4. Cont. |
|----------------|
| **First author, Year(Ref #)** | **Mean change FMD (SD)** | **Probe (device) MHz** | **Position** | **Reproducibility** |
| L.A.Souza-Barbosa,2006 [19] | 5.9±2.81 | 5.5±2.722 | 7–12(ALT HDI) brachial artery | Mean difference between measures (0.9%); Intraobserver variability<2% |
| K.K.Koh,2010 [15] | 1.62±0.29 | 0.71±0.24 | 10(ATL) right brachial artery | Interobserver variability (0.07–1.27%); Intraobserver variability (0.15–1.24%) |

![Figure 2. Forest plot illustrating ARBs effect on brachial FMD change compared with placebo or no treatment.](doi:10.1371/journal.pone.0090217.g002)
5.6 ARBs versus diuretics. Three trials [15,19,30] which included 134 patients evaluated the effect of ARBs versus diuretics on FMD, all using brachial arteries, ARBs also had a significant effect on FMD (pooled mean change difference = 0.9%, 95% CI 0.77–1.03, \( I^2 = 0 \%), \ p \ for \ heterogeneity = 0.808).

5.7 Duration-effect relationship. We also analyze the relationship between the FMD change and the duration of ARBs treatments using meta-regression. In available 25 values of total 22 studies [J. Trevelyan [18] has 2 values of different time-points, A.B.SOZEN [23] has 3 values], of which 21 have results with follow-up less than or equal to 6 months and 2 trials [11,23] contributed data more than 6 months. We found that the FMD change percent was relatively stable in the first 6 months (95% CI 0.48 to 0.36, \( p = 0.764 \)) (see Fig. 4), but fell down quickly after 6 month (95% CI 1.065 to 0.549, \( p = 0.154 \)). In total, the benefit of ARBs on endothelial function wouldn’t be well maintained (95% CI −1.990 to −0.622, \( p = 0.001 \)) (see Fig. 4).

6 Publication bias
We found no significant evidence for publication bias. The Begg’s test (\( P = 0.350 \)) and the Egger’s test (\( P = 0.357 \)) also provided no statistical evidence for publication bias.

Discussion

Major findings
Our study is important in the sense that this is the first meta-analysis in the literature which assesses the effect of ARBs on peripheral endothelial function compared to placebo or no treatment and other antihypertensives. One of main findings of our meta-analysis is that treatments with ARBs could improve peripheral endothelial function compared with placebo or no treatment for patients who are suffering from endothelial dysfunction. When compared to other antihypertensives, ARBs show priority to CCBs, \( \beta \)-blockers and diuretics but have no significant difference with ACEI. Interestingly, although the antihypertensive targets of included RCTs have been well reached, we found the effect of ARBs on endothelial function still couldn’t be well maintained in a long span. This suggested the improvement of endothelial function is relatively weak by ARBs.

Figure 3. Forest plot illustrating ARBs effect on changes in FMD compared with other antihypertensive agents (ACEI, CCB, \( \beta \)-blockers and diuretics). In 16 trials that included 1028 patients, ARBs (n = 486) had a significant effect (0.59%, 95% CI: 0.25 to 0.94) on FMD when compared with other antihypertensives (n = 542). In 8 trials, ARBs (n = 174) had no significant effect (−0.14%, 95% CI: −0.32 to 0.03) compared with ACEI (n = 173). Compared with others, the benefits of ARBs respectively were 1.67% (95% CI: 0.65 to 0.93) in 7 trials with CCBs, 0.79% (95% CI: 0.42 to 1.01) with \( \beta \)-blockers in 3 trials and 0.9% (95% CI: 0.77 to 1.03) with diuretics in 3 trials.

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endothelial function and reduction of blood pressure are not paralleled, which shined a deep clinical thinking that how to well set anti-hypertensive target based on the purpose of improvement of endothelial function.

**ARBs improve endothelial function**

The mechanisms by which ARBs improve endothelial dysfunction are based on their ability of inhibiting angiotensin II receptor and to increasing bradykinin. On one hand, angiotensin II, by binding to angiotensin II type 1 receptor [5], leads to vascular constriction, endothelial cell migration, proliferation and hypertrophy and increases uptake and oxidation of LDL by endothelial cells as well as oxyradical production, thus leading to endothelial dysfunction [31]. On the other hand, bradykinin, via binding to the bradykinin B2 receptor, increases production and release of NO [32], prostacyclin [33] and the endothelium-derived hyperpolarizing factor [34] to cause vasodilatation, inhibition of vascular smooth muscle cell proliferation and platelet adhesion [35]. Therefore, inhibition of angiotensin II receptor and increasing bradykinin production by ARBs will result in an improvement in endothelial function.

Among the trials included in this study, variant members of this class (Table 1) that showed benefit on endothelial function are involved, including telmisartan (40 mg [24], 40–80 mg [25], 160 mg [14]), losartan (50 mg [18], 50–100 mg [30], 100 mg [9,20,21,29]), irbesartan (150 mg [10,19], 300 mg [9,12,23]), candesartan (16 mg [9,13,15,22]) and valsartan (20 mg [16], 160 mg[23,26], 160–320 mg [11]), thus to confirm that the protective effect on endothelial function is the common feature of ARBs.

**ARBs versus ACEI**

Recently, several studies have assessed the effect of ARBs and ACEIs on endothelial function as measured by brachial or radial FMD. As two antihypertensives in the involvement of renin angiotensin system (RAS), they have similar mechanisms. ACEIs could reduce production of angiotensin (Ang) II by inhibiting angiotensin converting enzyme, a key enzyme affecting the transformation from angiotensin I to angiotensin II [36]. Also, the inhibition of the angiotensin converting enzyme also increased bradykinin production [37]. However, the findings of “ACE escape” phenomenon [38] and other pathways, i.e. chymotrypsin-like enzymes that also induce Ang I to Ang II indicated ACE was not the major Ang II-forming enzyme [39,40], thus directly given rise to the first member of ARBs, losartan. ARBs directly inhibited the binding between Ang II with its receptors, which seem more downstream and reliable. Consider the inhibition of Ang II is the leading mechanism of the improved endothelial function, ARB is seemed to superior to ACEIs. Since then, a wealth of clinical trial data has accumulated.

However, in this study, we pooled 8 studies that conducted ARBs and ACEI monotherapy on endothelial dysfunction and found that 7 trials [15,18,19,20,21,22,23] show they can both improve FMD without significant difference but 1 trial [17] showed ARBs were less effective than ACEI. That’s difficult to explain well using current mechanisms. Besides, some trials have compared the combination of ARBs and ACEI with monotherapy. K.K. Koh 2007 [22] demonstrated beneficial effects of the combination therapy superior to monotherapy with either drug and explained this by a greater extent of increased NO bioavailability. However, L.A. Souza-Barbosa [19] found that

![Figure 4. Relationship between the FMD change and the duration of ARBs treatments included all 22 trials. In available 25 values of total 22 studies, FMD change percent was relatively stable in the first 6 months (95% CI −0.484 to 0.360, p = 0.764), but felt down quickly after 6 month (95% CI −1.065 to 0.549, p = 0.154). In total, the benefit of ARBs on endothelial function wouldn’t be well maintained (95% CI −1.990 to −0.622, p = 0.001).](http://example.com/figure4.png)

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the combined effect of the two drugs on endothelial dysfunction was not better than either of these drugs separately. Hence, for this issue, we still need further evidence.

FMD for endothelial function

For clinical assessment of endothelial function, FMD using high-resolution ultrasound to the forearm artery diameter is a well-known noninvasive method of detecting endothelial dysfunction. The mechanism is that reactive hyperemia induces increased blood flow and shear stress, stimulating NO release and vasodilation [1]. The systemic nature of atherosclerosis is reflected by the close correlation between endothelial dysfunction in the forearm and coronary endothelial dysfunction [41]. However, FMD to evaluate endothelial function also has some shortcomings. It is poor resolution relative to arterial size, highly operator-dependent and variable in measurements [3]. So it is important to note that in this meta-analysis we effect of ARBs on peripheral endothelial function base on FMD and there may be some certain variation existence.

Duration-effect relationship between ARBs and endothelial function

A.B.SOZEN [23] indicated ARBs (irbesartan 300 mg/day or valsartan 160 mg/day) monotherapy improved endothelial function at 6 weeks after treatment, but this benefit fell below baseline at the one and three-year measurements, while there was no worsening in blood pressure control. Furthermore, our analysis all available data about the relationship between duration of ARBs therapy and FMD change percent and found that the FMD change percent was relatively stable within the first 6 months (95% CI −0.484 to 0.360, p = 0.764) (see Fig.4), but fell down quickly after 6 month (95% CI−1.065 to 0.549, p = 0.154). In total, the benefit of ARBs on endothelial function wouldn’t be well maintained (95% CI −1.990 to −0.622, p = 0.001) (see Fig. 4), while BP targets were well reached in all trials. These results suggested that the improvement of endothelial function and lowering BP are not paralleled. Similar finding was also supported by Panza et al. [42], who found that endothelial impairment persisted after antihypertensive treatment had produced a clinical effect. Additionally, two studies [43,44] suggested that very high doses of ARBs may exert a significantly greater anti-proteinuric action than standard doses, with no increment in the antihypertensive effect. Additionally, two studies [43,44] suggested that very high doses of ARBs may exert a significantly greater anti-proteinuric action than standard doses, with no increment in the antihypertensive effect.

Also, there are many widely-used methods to test endothelial function, including invasive methods, such as forearm blood flow, and non-invasive methods, such as FMD. In our study, we prefer to focus on the non-invasive methods and use FMD only for endothelial function, since it is more convenient for clinical application.

Supporting Information

Checklist S1 PRISMA checklist.

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