Angiotensin-converting enzyme inhibitors versus angiotensin II receptor blockers on insulin sensitivity in hypertensive patients: A meta-analysis of randomized controlled trials

Jia Yao¹*, Simin Fan²*, Xiaoyan Shi³‡, Xiayu Gong⁴‡, Jia Zhao¹, Guanjie Fan⁵*

¹ School of Second Clinical Medicine, Guangzhou University of Chinese Medicine, Guangzhou, China, ₂ School of First Clinical Medicine, Guangzhou University of Chinese Medicine, Guangzhou, China, ³ School of Medicine, Southern University of Science and Technology, Shenzhen, China, ⁴ Research Center for Basic Integrative Medicine, Guangzhou University of Chinese Medicine, Guangzhou, China, ⁵ Department of Endocrinology, Guangdong Provincial Hospital of Chinese Medicine, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China

* These authors contributed equally to this work.
‡ These authors also contributed equally to this work.
* fanguanjiegz@163.com

Abstract

Introduction
This meta-analysis aimed to summarize the available evidence to compare angiotensin-converting enzyme (ACE) inhibitors with angiotensin II receptor blockers (ARBs) on improving insulin sensitivity in hypertensive patients.

Methods
Randomized controlled trials (RCTs) comparing ACE inhibitors versus ARBs published with outcomes on homeostasis model assessment of IR (HOMA-IR), glucose infusion rate (GIR), the quantitative insulin sensitivity check index (QUICKI), insulin sensitivity index (ISI) composite, fasting plasma glucose (FPG), fasting plasma insulin (FPI), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were searched through 5 databases. Data were searched from their inception to July 5, 2020. Stata 14.0 was used to perform the meta-analysis.

Results
Eleven RCTs (n = 1015) were included in this meta-analysis. Pooled analysis of studies showed no significant difference in HOMA-IR between ARBs and ACE inhibitors (WMD = -0.09, 95% CI: -0.69 to 0.50, P = 0.755); however, subgroup analysis of therapeutic duration showed a significant difference in HOMA-IR between ARBs and ACE inhibitors among the long-term intervention subgroup (>12 weeks) (WMD = 0.41, 95% CI: 0.06 to 0.76, P = 0.022) and hypertensive patients with diabetes mellitus subgroup (WMD = 0.55, 95% CI: 0.49 to 0.61, P < 0.001); results showed no significant difference between ARBs and ACE...
inhibitors on QUICKI score (WMD = -0.00, 95% CI: -0.03 to 0.03, P = 0.953) in hypertensive
patients; however, the efficacy of ACE inhibitors on improving GIR and ISI composite was
significantly better than that of ARBs (WMD = -1.09, 95% CI: -1.34 to -0.85, P < 0.001;
WMD = -0.80, 95% CI: -1.24 to -0.36, P < 0.001, respectively). Furthermore, no significant
differences were noted on FPG (WMD = 0.72, 95% CI: -1.39 to 2.83, P = 0.505), FPI
(WMD = -0.48, 95% CI: -1.60 to 0.64, P = 0.398), SBP (WMD = -0.65, 95% CI: -1.76 to 0.46,
P = 0.254), and DBP (WMD = -0.30, 95% CI: -1.70 to 1.10, P = 0.675) between ARBs and
ACE inhibitors.

Conclusion
Results from this meta-analysis showed that ACE inhibitors resulted in more effective
improvement of HOMA-IR compared with ARBs among the long-term intervention and
hypertensive patients with DM subgroup; furthermore, the efficacy of ACE inhibitors on
improving GIR and ISI composite was significantly better than that of ARBs in hypertensive
patients. However, ARBs had no significant difference in QUICKI score, FPG, FPI, SBP,
and DBP compared with ACE inhibitors. Larger and better-designed studies are needed to
further verify this conclusion.

1. Introduction
Insulin resistance (IR) can be defined as the inability of insulin to stimulate glucose disposal,
and when IR occurs, insulin sensitivity (IS) will decrease, the sensitivity of tissues and target
organs to insulin will decrease, and normal doses of insulin will not produce the normal hypo-
glycemic effect [1]. IR is considered as the common core pathological basis of metabolic disor-
ders including hypertension, diabetes mellitus (DM), and metabolic syndrome (MS), which
seriously threaten human health [2, 3]. Thus, improving IS represents one of the major path-
ways for drug development.

The close relationship between IR and the renin-angiotensin system (RAS) is not a recent
observation. The overactivation of the RAS can lead to IR by affecting insulin signaling path-
ways, inhibiting fat formation, promoting oxidative stress and inflammation, reducing tissue
blood flow, and activating the sympathetic nervous system [4–6]. Furthermore, the effect of
RAS blockers including angiotensin-converting enzyme (ACE) inhibitors and angiotensin II
(Ang II) receptor blockers (ARBs) on improving IS has gradually received attention. Experi-
mental and clinical studies have shown that ACE inhibitors and ARBs can inhibit the activa-
tion of Ang II, improve blood perfusion, reduce oxidative stress and beta-cell apoptosis, and
thus improve IS [3, 7]. However, although ACE inhibitors and ARBs both belong to the class
of RAS blockers, differences between these two kinds of drugs exist. A meta-analysis com-
pared studies that used ACE inhibitors or ARBs and found that the former was more effect-
ive in improving IS in hypertensive patients without diabetes [8]. However, this analysis
was limited because only 4 randomized controlled trials (RCTs) with 203 hypertensive
patients without DM were included. Therefore, more research is needed to better under-
stand which class of drugs (ACE inhibitors or ARBs) has a stronger effect on IS in hyperten-
sive patients.

To date, some RCTs have compared ACE inhibitors with ARBs on the efficacy of improving
IS in hypertensive patients, however, the findings have been inconsistent. On this basis, we
aim to conduct a meta-analysis of the available evidence to inform clinical practice.
2. Materials and methods

The current meta-analysis with its peer-reviewed protocol published online [9] was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. INPLASY registration number was INPLASY202050032.

2.1 Literature search

Four databases (PubMed, the Cochrane Library, Embase, and Web of Science) were searched for RCTs published from the database inception through July 5, 2020. Search terms were as follows: (“angiotensin-converting enzyme inhibitor” OR “ACE inhibitor” OR “ACEI”) AND (“angiotensin receptor antagonists” OR “angiotensin II type 1 receptor blockers” OR “angiotensin receptor blockers” OR ARB) AND (“hyperinsulinemic euglycemia clamp” OR “euglycemic clamp” OR “glucose clamp” OR HOMA OR “homeostasis model assessment” OR QUICKI OR “minimal model analysis” OR “minimal model” OR “index of insulin sensitivity” OR “insulin resistance” OR “insulin sensitivity”). The ClinicalTrials.gov registry was also searched for unpublished trials and the authors were contacted for additional information if necessary. Relevant references from included studies were sought to retrieve additional eligible studies. No limits were set on language, publication year, and type of publication.

2.2 Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) RCTs published with any follow-up duration and sample size; (2) participants: hypertensive patients with or without other metabolic diseases (such as DM, IR, and MS); hypertension defined using the current and previously accepted definitions based on recommendations of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [10–12]; we also adopted studies with a subjective definition of hypertension based on physician-diagnosed hypertension or use of antihypertensive medication due to elevated systolic or diastolic blood pressure measurement; DM and IR defined using the American Diabetes Association (ADA) or World Health Organization (WHO) criteria [13, 14]; MS defined using the current and previously accepted definitions [15–17]; age, gender, and other general conditions are not limited; (3) intervention: one group was given ARBs, the other group was given ACE inhibitors; and (4) studies that assessed IS using recognized methods such as the glucose clamp technique, homeostasis model assessment of IR (HOMA-IR), the quantitative insulin-sensitivity check index (QUICKI), or insulin sensitivity index (ISI) composite.

The exclusion criteria were as follows: (1) participants that did not meet the relevant diagnostic criteria; (2) interventions combined use of ACE inhibitors and ARB drugs, or treated with additional anti-hypertensive drugs, or studies involving other interventions; (3) outcome measures were not appropriate, relevant data could not be obtained from the original author; (4) non-randomized controlled trials, animal experiments or review articles; and (5) repeated published literature.

Outcomes. The primary outcome measure was IS. Several methods were used to assess IS, among them, the hyperinsulinemic-euglycemic clamp technique represents currently the ‘gold standard’ for quantifying IS in vivo because it directly measures the effects of insulin to promote glucose utilization under steady state conditions [18]; furthermore, alternatives for estimating IS include some simple surrogate indexes (e.g., QUICKI, HOMA-IR, ISI composite) that are derived from blood insulin and glucose concentrations under fasting conditions (steady state) or after an oral glucose load (dynamic) [19]. In our study, we included several methods (glucose clamp technique, HOMA-IR, QUICKI, and ISI composite) to estimate IS. The secondary outcomes were fasting plasma glucose (FPG), fasting plasma insulin (FPI), systolic blood pressure (SBP), and diastolic blood pressure (DBP).
2.3 Data extraction

Literature search and data extraction were performed by two researchers (J.Y. and S.F.) independently using predesigned forms, and the third researcher (X.S.) was involved in a discussion for any disagreements. The following information of eligible articles was extracted to a data extraction form: author, publication year, sample size, intervention, dosage, duration, mean age, body mass index (BMI), study population, and outcomes. When relevant details were insufficiently reported in studies, authors were contacted by email, and the ClinicalTrials.gov register was searched for further information.

2.4 Quality assessment

According to the Cochrane collaboration’s updated tool for assessing the risk of bias (version 5.1.0; updated March 2011), two reviewers (J.Y. and S.F.) assessed the quality of the included studies independently, and the senior reviewer (X.S.) was consulted for any disagreements. Each RCT was assigned a low, high, or unclear risk of bias for 6 specific domains (random sequence generation, allocation concealment, blinding of outcome assessment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting, and other potential threats), using information identified from the published articles and supplementary materials and by contacting the study authors when needed.

2.5 Statistical analysis

Stata, version 14.0 (StataCorp LLC) was used for statistical analysis. To compare the effects of ARBs with ACE inhibitors on improving IS in patients; data for glucose infusion rate (GIR), QUICKI, HOMA-IR, ISI composite, FPG, FPI, SBP, and DBP were retrieved from the included RCTs. The mean and SD values of the ARBs group and ACEI inhibitors group were extracted to calculate the effect size. If SEs were reported rather than SDs, then SDs were calculated by equation SD = SE × \sqrt{n}. If 95% CI was reported, SD was calculated by equation SD = \sqrt{n} × (upper−lower)/2×t, where n is the number of subjects [20]. Continuous data (HOMA-IR, GIR, QUICKI, ISI composite, FPG, FPI, SBP, and DBP) used the weighted mean difference (WMD) with 95% CI after the units were standardized [21]. Heterogeneity was tested by \chi^2-based Cochran Q statistic (P < 0.10 indicated statistically significant heterogeneity) and I^2 statistic. If I^2 < 50%, a fixed-effects model was used to pool the estimations across studies. If I^2 ≥ 50%, after excluding clinical heterogeneity between studies, the random-effects model was used. Subgroup and sensitivity analyses were conducted to explore potential sources of heterogeneity, to assess the reliability and stability of the pooled results. Sensitivity analysis was performed by excluding low-quality studies, trials recruiting participants with particular conditions or trials with characteristics different from the others. When possible and appropriate, planned subgroup analyses included the therapeutic duration, sample size, and study population of the included studies. The funnel plot and Egger’s and Begg’s tests were used to judge publication bias, and the trim and fill method was used to correct the funnel asymmetry caused by publication bias. P < 0.05 was considered statistically significant.

3. Results

3.1 Search results

As displayed in Fig 1, in total, we identified 3093 citations with 325 duplicates. After preliminary screening of the titles and abstracts, 118 studies were selected for full-text review, and then 107 studies were excluded since 19 of them were reviews or meta-analyses, 12 of them were not RCTs, 36 studies didn’t provide quantitative outcomes, and the rest were those with
undesirable interventions. Correspondence with the authors via e-mail was done to obtain the needed information for the study with no specific data on an outcome. Unfortunately, no reply from the authors was obtained until the time of this writing. Ultimately, 11 RCTs [22–32] were determined to be included in this meta-analysis.

3.2 Study characteristics
Eleven studies involving 1015 subjects were included in this meta-analysis. Sample size ranged from 18 to 466 participants, duration varied from 6 weeks to 12 months, mean age ranged from 33.0 to 59.7 years, BMI varied from 23.8 to 33.4 kg/m². 1 (9%) RCT included hypertensive patients with left ventricular hypertrophy, 1 (9%) RCT included hypertensive patients with IR, 1 (9%) RCT included hypertensive patients with DM, 1 (9%) RCT included hypertensive postmenopausal women, 6 (55%) RCTs included patients with hypertension, 1 (9%) RCT included hypertensive patients with MS. A total of 7 (64%) RCTs reported HOMA-IR as an outcome, 2 (18%) RCTs reported QUICKI as an outcome, 2 (18%) RCTs reported GIR as an outcome, 1 (9%) RCT reported ISI composite as an outcome (Table 1). Changes of outcome measures extracted from excluded studies are summarized in Table 2.

3.3 Quality assessment
The risk of bias data for the included RCTs is presented in Table 3. Randomization was categorized as low risk in 1 (9%) RCT with appropriate use of random sequence generation. The

![Flow diagram of study selection](https://doi.org/10.1371/journal.pone.0253492.g001)
remaining 10 (91%) studies did not provide details about the method of randomization and were categorized as unclear risk. Allocation concealment was categorized as low risk in 2 (18%) studies with a detailed description. The remaining 9 (82%) studies were categorized as unclear risk due to no relevant description. Furthermore, 5 (45%) studies were conducted using the double-blinded method, 1 (9%) study followed in an unblinded fashion, 1 (9%) study was conducted using the open-label, blinded-endpoint method, and the remaining studies did not mention the blinding of participants, personnel, and outcome assessment. Incomplete outcome data were categorized as low risk in 11 (100%) studies with no missing outcome data or reasons for missing outcome data balanced in numbers across intervention groups. As for selective reporting, 7 (64%) studies with all expected outcomes, the remaining 4 (36%) were classified as an unclear risk because of insufficient information to permit judgment of “low risk” or “high risk”. As for other bias, 11 (100%) studies were classed as low risk.

### 3.4 Pooled results

#### 3.4.1 ARBs versus ACE inhibitors on IS

(1) HOMA-IR. A total of 7 RCTs [22–24, 27, 30–32] with 664 patients reported HOMA-IR as an outcome, and significant heterogeneity was observed (P < 0.001; I² = 92.3%). Pooled results with a random-effects model showed that ARBs had no significant difference on HOMA-IR compared with ACE inhibitors (WMD = -0.09, 95% CI: -0.69 to 0.50, P = 0.755) (Fig 2). Results of sensitivity and subgroup analysis
Table 2. Changes of outcomes in individual studies.

| Author, year | Groups          | IS          | FPG | FPI | SBP | DBP |
|--------------|-----------------|-------------|-----|-----|-----|-----|
| Anan (2005)  | Valsartan       | HOMA-IR     | 2.4±0.6 | 2.1±0.6 | 6.8±0.9 | 6.4±0.9 | 8.0±1.0 | 7.1±1.2 | 157±7 | 134±7 | 97±7 | 85±7 |
|              | Perindopril     |             | 2.3±0.6 | 1.9±0.6 | 6.6±0.8 | 6.1±0.9 | 7.9±0.9 | 6.9±1.0 | 156±9 | 133±6 | 97±6 | 85±5 |
| Brown (2002) | Losartan        |             | 3.6±0.7 * | 4.2±0.8 * | 5.6±0.2 | 5.8±0.2 * | 101±21 | 119±24 * | 140±64 | 123.7±2.6 * | 96.9±2.2 | 86.4±2.1 * |
|              | Ramipril        |             | 3.4±0.8 * | 4.8±1.1 * | 5.5±0.4 | 5.4±0.2 | 166±68 | 137±28 * | 144±83 | 127.0±3.1 * | 98.6±2.5 | 91.4±3.3 * |
| Derosa (2003)| Candesartan     |             | 3.99±2.5 | -0.25±0.08 | 160±13 | -8±2 | 10.6±6.1 | -0.7±0.4 | 148±6 | -12±4.1 | 93±5 | -8±2.9 |
|              | Perindopril     |             | 3.86±2.2 | -0.8±0.2 | 155±15 | -15±4 | 10.2±5.8 | -1.4±0.9 | 147±6 | -13±4.5 | 94±4 | -11±3.6 |
| Gilowski (2018)| Telmisartan     |             | 3.1±1.9 | 2.6±1.6 | 101±15 | 97±12 | / | / | 154±15 | 136±13 | 93±7 | 85±8 |
|              | Perindopril     |             | 2.6±1.1 | 2.4±1.2 | 97±7 | 95±8 | / | / | 149±12 | 136±14 | 90±8 | 84±7 |
| Napoli (2016)| Irbesartan      |             | 3.7±3.7 | 0.2 (-0.6,1.1) * | 117±40 | 2.6 (-3.4,8.7) * | 13.8±11.4 | 0.2 (-2.0,2.3) * | 132.9±142 | -18.8 (-21.0,16.6) * | 83.4±8.5 | -10.4 (11.8,9.0) * |
|              | Zofenopril      |             | 4.1±5.3 | 0.5 (-0.3,1.3) * | 117.9±42 | 1.9 (-1.7,7.9) * | 14.6±15.6 | 1.1 (-1.1,3.2) * | 131.7±146 | -17.0 (19.2,14.8) * | 83.9±10.0 | -9.8 (11.1,8.4) * |
| Sanchez (2008)| Telmisartan     | MHT         | 2.76±0.16 | 2.24±0.18 | 92±8 | 94±2.8 | 9.2±2 | 8.8±1.3 | 154±8 | 137±16 | 96±5 | 84±8 |
|              |                | NMHT        | 4.4±1 | 2.3±0.7 | 99±10 | 88±8.8 | 16±4 | 8.4±2 | 161±9 | 137±5 | 96±5 | 86±3 |
|              | Ramipril        | MHT         | 2.76±0.16 | 2.6±0.75 | 92±8 | 89±8 | 9.2±2 | 9.0±2 | 159±10 | 142±6 | 102±4 | 93±3 |
|              |                | NMHT        | 4.4±1 | 4.2±0.7 | 99±10 | 96±5.2 | 16±4 | 14±5.6 | 162±12 | 139±7 | 97±4 | 89±2 |
| Yavuz (2003)| Losartan        |             | 2.3±0.6 | 1.5±0.7 | / | / | / | / | 150±21 | 126±14 | 100±5 | 80±2 |
|              | Enalapril       |             | 2.9±1.7 | 1.2±0.6 | / | / | / | / | 149±11 | 126±11 | 98±7 | 79±3 |
| Fogari (2001)| Losartan        | Gir         | 6.74±0.47 | 6.96±0.50 | 93±9 | 92±10 | 77±39 | / | 160±6 | 145±11 | 100.5±5 | 88.6±5 |
|              | Trandolapril    |             | 6.67±0.56 | 7.99±0.65 | 92±10 | 89±10 | 74±36 | / | 162.1±12 | 145±10 | 101.2±5 | 88.1±4 |
| Fogari (2011)| Candesartan     |             | 5.2±1.8 | 5.3±1.7 | 89.1±8.9 | 89.2±8.8 | 9.5±2.8 | 9.4±2.7 | 149.0±4 | 132.9±4.4 | 98.5±4.0 | 86.3±0.2 |
|              | Imidapril       |             | 5.2±2.0 | 6.3±1.8 | 88.9±8.8 | 88.4±8.7 | 9.4±2.7 | 9.1±2.6 | 148±4.8 | 132±4.1 | 98.7±4 | 86.1±2.6 |
| Koh (2007)   | Candesartan     | QUICKI      | 0.406±0.011 * | 0.423±0.011 * | 85±2 | 84±3 | 4.6±0.42 | 4.28±0.57 | 156±1 | 137±2 | 95±1 | 85±1 * |
|              | Ramipril        |             | 0.428±0.023 * | 0.448±0.026 | 84±2 | 85±2 | 4.38±0.51 | 4.02±0.53 | 155±1 | 142±2 | 95±1 | 88±2 * |
| Koh (2010)   | Candesartan     |             | 0.348±0.008 * | 0.362±0.008 | 104±2 | 101±3 | 9.7±0.88 | 8.4±1.10 | 156±1 | 136±2 | 94±1 | 84±1 * |
|              | Ramipril        |             | 0.382±0.016 * | 0.396±0.018 | 101±2 | 103±3 | 8.4±1.04 | 7.5±1.05 | 155±1 | 143±2 | 94±1 | 87±1 * |
| Yavuz (2003)| Losartan        | ISI composite | 1.1±0.3 | 1.3±0.4 | / | / | / | / | 150±21 | 126±14 | 100±5 | 80±2 |
|              | Enalapril       |             | 0.9±0.3 | 1.9±0.6 | / | / | / | / | 149±11 | 126±11 | 98±7 | 79±3 |

Data are shown as mean ± SD
* Data are shown as mean ± SE
* Data are shown as mean changes (95% confidence interval).

Abbreviations: IS, insulin sensitivity; FPG, fasting plasma glucose; FPI, fasting plasma insulin; SBP, systolic blood pressure; DBP, diastolic blood pressure; B, before treatment; A, after treatment; MHT: modulating hypertension; NMHT: nonmodulating hypertension; HOMA-IR, homeostasis model assessment of insulin resistance; GIR, glucose infusion rate; QUICKI, quantitative insulin sensitivity check index; ISI, insulin sensitivity index.

https://doi.org/10.1371/journal.pone.0253492.t002
were shown in Table 4. Sensitivity analysis showed that after excluding Derosa et al. [24] and Sanchez et al. [31], heterogeneity was decreased (P = 0.240; I² = 27.2%). Pooled results with a fixed-effects model showed that the HOMA-IR still didn’t differ in two groups (WMD = -0.18, 95% CI: -0.42 to 0.05, P = 0.123). Subgroup analysis was performed based on the therapeutic duration (< = 12 weeks or > 12 weeks), sample size (< = 80 or > 80), and study population (hypertension with left ventricular hypertrophy, hypertension with IR, hypertension with DM, hypertension with DM or IS, hypertension with IS, hypertension without DM or IS, hypertension without DM, hypertension without IS).

Table 3. Risk of bias assessment in the included studies.

| Study (year)       | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
|--------------------|-----------------------------|------------------------|----------------------------------------|-------------------------------|-------------------------|---------------------|-----------|
| Anan (2005) [22]   | U                           | U                      | U                                      | U                            | L                       | L                   | L         |
| Brown (2002) [23]  | U                           | U                      | U                                      | U                            | L                       | U                   | L         |
| Derosa (2003) [24] | U                           | L                      | L                                      | L                            | L                       | L                   | L         |
| Fogari (2001) [25] | U                           | U                      | L                                      | L                            | L                       | L                   | L         |
| Fogari (2011) [26] | U                           | U                      | H                                      | L                            | L                       | L                   | L         |
| Gilowski (2018) [27]| U                           | U                      | U                                      | U                            | L                       | U                   | L         |
| Koh (2007) [28]    | U                           | U                      | L                                      | L                            | L                       | L                   | L         |
| Koh (2010) [29]    | U                           | L                      | L                                      | L                            | L                       | L                   | L         |
| Napoli (2016) [30] | U                           | U                      | L                                      | L                            | L                       | L                   | L         |
| Sanchez (2008) [31]| U                           | U                      | U                                      | U                            | L                       | U                   | L         |
| Yavuz (2003) [32]  | L                           | U                      | H                                      | H                            | L                       | U                   | L         |

H, high risk; L, low risk; U, unclear risk.

https://doi.org/10.1371/journal.pone.0253492.t003

were shown in Table 4. Sensitivity analysis showed that after excluding Derosa et al. [24] and Sanchez et al. [31], heterogeneity was decreased (P = 0.240; I² = 27.2%). Pooled results with a fixed-effects model showed that the HOMA-IR still didn’t differ in two groups (WMD = -0.18, 95% CI: -0.42 to 0.05, P = 0.123). Subgroup analysis was performed based on the therapeutic duration (< = 12 weeks or > 12 weeks), sample size (< = 80 or > 80), and study population (hypertension with left ventricular hypertrophy, hypertension with IR, hypertension with DM, hypertension with DM or IS, hypertension with IS, hypertension without DM or IS, hypertension without DM, hypertension without IS).

Fig 2. Effect of ARBs versus ACE inhibitors on HOMA-IR.

https://doi.org/10.1371/journal.pone.0253492.g002
hypertension, or hypertension with MS). The subgroup analysis did not show any significant differences within subgroups based on sample size. However, subgroup analysis of therapeutic duration showed a significant difference in HOMA-IR between ARBs and ACE inhibitors group among the long-term intervention subgroup (> 12 weeks) (WMD = 0.41, 95% CI: 0.06 to 0.76, P = 0.022) rather than the short-term intervention subgroup (< 12 weeks) (WMD = -0.71, 95% CI: -1.47 to 0.05, P = 0.069). Furthermore, results showed a significant difference in HOMA-IR between two groups in hypertensive patients with DM (WMD = 0.55, 95% CI: 0.49 to 0.61, P < 0.001), but there was no significant difference between the two groups among hypertensive patients, hypertensive patients with left ventricular hypertrophy, hypertensive patients with IR, and hypertensive patients with MS (Table 4).

(2) GIR. A total of 2 RCTs [25, 26] with 145 patients reported GIR as an outcome, and no heterogeneity was observed (P = 0.856; I² = 0%). Pooled results with a fixed-effects model showed that the efficacy of ACE inhibitors on improving GIR was significantly better than that of ARBs (WMD = -1.09, 95% CI: -1.34 to -0.85, P < 0.001) (Fig 3).

(3) QUICKI. A total of 2 RCTs [28, 29] with 129 patients reported QUICKI as an outcome, and no heterogeneity was observed (P = 0.933; I² = 0%). Pooled results with a fixed-effects model showed that ARBs had no significant difference on QUICKI compared with ACE inhibitors (WMD = -0.00, 95% CI: -0.03 to 0.03, P = 0.953) (Fig 3).

(4) ISI composite. A total of 1 RCTs [32] with 18 patients reported ISI composite as an outcome. Pooled results with a fixed-effects model showed that the efficacy of ACE inhibitors on improving ISI composite was significantly better than that of ARBs (WMD = -0.80, 95% CI: -1.24 to -0.36, P < 0.001) (Fig 3).

3.4.2 ARBs versus ACE inhibitors on FPG. A total of 10 RCTs [22–31] with 955 patients reported FPG as an outcome, and small heterogeneity was observed (P = 0.249; I² = 21.1%). Pooled results with a fixed-effects model showed that ARBs had no significant difference on FPG compared with ACE inhibitors (WMD = 0.72, 95% CI: -1.39 to 2.83, P = 0.505) (Fig 4).

3.4.3 ARBs versus ACE inhibitors on FPI. A total of 8 RCTs [22–24, 26, 28–31] with 787 patients reported FPI as an outcome, and significant heterogeneity was observed (P = 0.013;
I² = 60.8%). Pooled results with a random-effects model showed that ARBs had no significant difference on FPI compared with ACE inhibitors (WMD = -0.48, 95% CI: -1.60 to 0.64, P = 0.398) (Fig 5). After excluding Sanchez et al. [31], heterogeneity was decreased (P = 0.981; I² = 0.0%); and the results of sensitivity analysis were not altered after excluding the trial by Sanchez et al. [31] (WMD = 0.10, 95% CI: -0.57 to 0.77, P = 0.765).

### 3.4.4 ARBs versus ACE inhibitors on SBP

A total of 11 RCTs [22–32] with 1015 patients reported SBP as an outcome, and moderate heterogeneity was observed (P = 0.032; I² = 49.3%). Pooled results with a fixed-effects model showed that ARBs had no significant difference compared with ACE inhibitors on SBP (WMD = -0.65, 95% CI: -1.76 to 0.46, P = 0.254) (Fig 6).
3.4.5 ARBs versus ACE inhibitors on DBP. A total of 11 RCTs [22–32] with 1015 patients reported DBP as an outcome, and obvious heterogeneity was observed (P = 0.002; I² = 63.9%). Pooled results with a random-effects model showed that ARBs had no significant difference compared with ACE inhibitors on DBP (WMD = -0.30, 95% CI: -1.70 to 1.10, P = 0.675) (Fig 7). After excluding Derosa et al. [24], heterogeneity was decreased (P = 0.513; I² = 0.0%); and the results of sensitivity analysis were not altered after excluding the trial by Derosa et al. [24] (WMD = -0.56, 95% CI: -1.45 to 0.33, P = 0.220).

3.4.6 Publication bias. Publication bias analysis was conducted on the outcome of FPG, SBP, and DBP. The funnel plots were symmetrical, most scatter points were inside the
confidence limit, and the p-value of Begg’s tests were 1.000, 0.640, and 0.640, respectively. As shown in Fig 8, each meta-analysis did not show significant publication bias.

4. Discussion

The present study focused on the effects of ARBs versus ACE inhibitors on IS, FPG, FPI, SBP, and DBP in hypertensive patients for resolving the conflicting results of the outcomes of earlier studies. In a meta-analysis done by Yang et al. [8], where the improvement of IS was compared among patients on ACE inhibitors versus ARBs, ACE inhibitors were shown to have a significant effect on improving IS in hypertensive patients without diabetes. However, this analysis was limited because it only included 4 RCTs with 203 hypertensive patients without diabetes, other study populations such as hypertensive patients with DM, IR, or MS were not included;
HOMA-IR outcome in the patients was not measured, and the results of the more recent RCTs were not yet included in the analysis. Therefore, the main findings of our study and this study were different from each other.

Eleven studies [22–32] involving 1015 subjects were finally included in the present meta-analysis. To examine the IS, those studies that investigated HOMA-IR, GIR, QUICKI index, and ISI composite were entered into the meta-analysis. Pooled results showed that ARBs had no significant difference on HOMA-IR compared with ACE inhibitors in general (95% CI: -0.69 to 0.50; \( P = 0.755 \)). However, heterogeneity of these studies in this area was high (\( P < 0.001; \ I^2 = 92.3\% \)). With the heterogeneity, we noted that the eligible trials varied in several respects, including differences in the study population, baseline comorbidities, intervention drugs, and methodological differences, which may contribute to substantial heterogeneity. Sensitivity analysis showed that after excluding Derosa et al. [24] and Sanchez et al. [31], heterogeneity was decreased (\( P = 0.240; \ I^2 = 27.2\% \)), pooled results with a fixed-effects model showed that the HOMA-IR still didn’t differ in two groups. The study with long-term intervention (12 months) conducted by Derosa et al. [24] included patients with hypertension and DM, and the RCT conducted by Sanchez et al. [31] was a crossover study and included both modulating and non-modulating hypertensive patients; these were how they differ from other studies and may be the cause of heterogeneity. Subgroup analysis of therapeutic duration showed that ACE inhibitors resulted in more effective improvement of HOMA-IR compared with ARBs among the long-term intervention subgroup (> 12 weeks) (\( P = 0.022 \)) rather than the short-term intervention subgroup (< 12 weeks) (\( P = 0.069 \)). Furthermore, Subgroup analysis of the study population showed that ACE inhibitors showed an improvement on HOMA-IR compared with ARBs in hypertensive patients with DM (\( P < 0.001 \)). For other IS indicators, pooled results showed no significant difference between ARBs and ACE inhibitors on QUICKI score in hypertensive patients; however, the efficacy of ACE inhibitors on improving GIR and ISI composite was significantly better than that of ARBs in hypertensive patients or hypertensive postmenopausal women.

In the meta-analysis of FPG and FPI, results showed that ARBs had no significant difference on FPG and FPI compared with ACE inhibitors. However, significant heterogeneity was observed in FPI outcome (\( P = 0.013; \ I^2 = 60.8\% \)); with the heterogeneity, we noted that Sanchez et al. [31] was a crossover study and included both modulating and non-modulating hypertensive patients. After excluding Sanchez et al. [28], the heterogeneity was eliminated (\( P = 0.981; \ I^2 = 0.0\% \)), and pooled results with a fixed-effects model showed that the FPI still didn’t differ in the two groups.

In the meta-analysis of SBP and DBP, results showed that ARBs had no significant difference on SBP and DBP compared with ACE inhibitors. However, significant heterogeneity was observed in DBP outcome (\( P = 0.002; \ I^2 = 63.9\% \)); after excluding the study conducted by Derosa et al. [24] which had a long-term intervention (12 months) and included patients with hypertension and DM, the heterogeneity was eliminated (\( P = 0.513; \ I^2 = 0.0\% \)), and pooled results with a fixed-effects model showed that the DBP outcome still didn’t differ in two groups.

Studies have revealed that the RAS is closely related to IR, and the overactivation of the RAS can lead to IR in the following ways: (1) Ang II can promote IR by affecting insulin signaling pathways, inhibiting fat formation, promoting oxidative stress and inflammation, reducing tissue blood flow, and activating sympathetic nervous system [4–6]. (2) Hyperinsulinemia associated with IR can activate RAS, increase the expression of angiotensinogen, Ang II, and AT1 receptors, and further aggravate IR [33]. (3) Another mechanism is through aldosterone, which is also a regulator of salt and water balance and is involved in IR by inhibiting the expression of insulin receptor and glucose transporters, as well as by degrading insulin
receptor substrate or inhibiting the insulin signaling pathway [34]. (4) Furthermore, the ACE2/ANG (1–7)/MAS receptor axis functions as a negative regulator of the classical RAS, which was recently discovered and is responsible for improving IS by antagonizing the biological effect of Ang II. Ang (1–7) can also improve IS via reducing oxidative stress through MAS receptor activation possibly via improved adiponectin secretion [35]. Furthermore, IR and RAS activation aggravate each other and a vicious IR-RAS activation-inflammation/endothelial dysfunction-IR cycle is present in patients with various metabolic disorders. Thus, breaking this vicious circle is crucial to the prevention and treatment of metabolic diseases.

The effects of RAS blockers on improving IS have gradually received attention, and massive studies have shown that RAS blockers could improve IS [7]. ACE inhibitors and ARBs are two kinds of RAS system blockers and were initially used as antihypertensive drugs in the clinic. ACE inhibitors and ARBs are both equally effective in lowering blood pressure and have beneficial effects on glucose metabolism. Therefore, the clinical guidelines recommend these two types of drugs for the first-line treatment of hypertension with diabetes [36]. Although substantial studies have confirmed the beneficial effects of ACE inhibitors and ARBs on the improvement of IS [3, 7], differences between the two kinds of RAS system blockers exist. Results from the present meta-analysis showed that ARBs had no significant difference on QUICKI score, FPG, FPI, SBP, and DBP compared with ACE inhibitors; however, ACE inhibitors resulted in more effective improvement of HOMA-IR compared with ARBs among the long-term intervention subgroup and hypertensive patients with DM subgroup; furthermore, the efficacy of ACE inhibitors on improving GIR and ISI composite was significantly better than that of ARBs in hypertensive patients or hypertensive postmenopausal women. Studies have shown that ARBs can bind to AT1 receptors with high affinity selectively and competitively, thus inhibiting the activation of Ang II, improving blood perfusion, reducing oxidative stress and beta-cell apoptosis, and accordingly improving IR [7]. In addition to inhibiting the conversion of angiotensinogen I into Ang II which can reduce the generation of Ang II and improves IS [3, 7], ACE inhibitors can improve IS in the following additional ways: (1) ACE inhibitors may be mediated by the increased bradykinin levels by inhibiting kallikrein II, which not only could enhance insulin signaling and translocation of the glucose transporter, GLUT-4 in skeletal muscle, but also could directly increase nitric oxide levels, which enhance insulin-stimulated glucose oxidation and transport [37]. Shiuchi et al [38] also verified ACE inhibitors improved IS by enhancing bradykinin and nitric oxide in the diabetic mouse. Indeed, some studies suggest that the positive effect of ACE inhibition on IR is predominantly mediated by increased bradykinin actions via the B2kinin receptor and therefore may not be observed with AT1 receptor blockade [39]. (2) ACE inhibitors could increase adiponectin and leptin concentrations and decrease TNF-α levels, substances that are believed to enhance IS [40]. (3) ACE inhibitors could improve IS by relaxing smooth muscle, promoting water and sodium excretion, and reducing sympathetic nervous system excitability [41]. (4) In addition, the favored ACE2 axis may mediate these additional effects of improving IS from ACE inhibitors through enhanced ANG (1–7) action [42]. The beneficial effects of ACE inhibitors rely on a higher ACE2/ACE ratio and reduce oxidative stress and glucotoxicity by improving glucose-stimulated insulin secretion and islet function while reducing oxidative stress and inflammation [7]. To sum up, we hypothesize that the additional ways mentioned above may represent a major reason why ACE inhibitors demonstrated a stronger effect of improving HOMA-IR, GIR, and ISI composite than ARBs in the current study. Furthermore, the absence of significant differences between ACE inhibitors and ARBs on QUICKI in this study does not mean that there is no evidence of a true difference. Only 2 RCTs [28, 29] were included, the relatively limited data for ACE inhibitors in comparison with ARBs and the short-term intervention (8 weeks) could still be underpowered to detect a true difference.
There are also limitations of the current analysis that should be taken into consideration. Firstly, the number of RCTs currently available comparing ARBs versus ACE inhibitors with regards to our outcomes of interest is limited. Secondly, some RCTs were of poor quality, for example, were single-center with short duration, and enrolled a few participants. Thirdly, there was significant heterogeneity among the included studies for the outcomes of HOMA-IR, FPI, and DBP, which may result from the differences in trial populations, treatment regimens, and methodological differences. Given the limitations of the included studies, the above conclusions need to be further verified by more high-quality RCTs.

5. Conclusion
Taken together, results from this meta-analysis showed that ACE inhibitors resulted in more effective improvement of HOMA-IR compared with ARBs among the long-term intervention subgroup and hypertensive patients with DM subgroup; furthermore, the efficacy of ACE inhibitors on improving GIR and ISI composite was significantly better than that of ARBs in hypertensive patients. However, ARBs had no significant difference in QUICKI score, FPG, FPI, SBP, and DBP compared with ACE inhibitors. Larger and better-designed studies comparing these two RAS system blockers and their effects on IS in the future could hopefully shed better light.

Supporting information
S1 Checklist. PRISMA 2009 checklist.
(DOC)

Author Contributions
Conceptualization: Jia Yao, Guanjie Fan.
Data curation: Jia Yao, Simin Fan, Xiaoyan Shi.
Formal analysis: Xiayu Gong.
Project administration: Guanjie Fan.
Validation: Jia Yao, Simin Fan, Xiaoyan Shi, Guanjie Fan.
Writing – original draft: Jia Yao, Simin Fan.
Writing – review & editing: Jia Zhao, Guanjie Fan.

References
1. Brown AE, Walker M. Genetics of Insulin Resistance and the Metabolic Syndrome. *Curr Cardiol Rep*. 2016; 18(8):75. https://doi.org/10.1007/s11886-016-0755-4 PMID: 27312935
2. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015. A systematic analysis for the Global Burden of Disease Study. *Lancet*. 2015; 2016:1545–1602. https://doi.org/10.1016/S0140-6736(16)31678-6 PMID: 27733282
3. Prabhakar SS. Inhibition of renin-angiotensin system: implications for diabetes control and prevention. *J Invest Med*. 2013 Mar; 61(3):551–7. https://doi.org/10.2310/JIM.0b013e31828298ce PMID: 23360847
4. Motley ED, Eguchi K, Gardner C, Hicks AL, Reynolds CM, Frank GD, et al. Insulin-induced Akt activation is inhibited by angiotensin II in the vasculature through protein kinase C-alpha. *Hypertension*. 2003 Mar; 41(3 Pt 2):775–80. https://doi.org/10.1161/01.HYP.0000051891.90321.12 PMID: 12623995
5. Furuhashi M, Ura N, Takizawa H, Yoshida D, Moniwa N, Murakami H, et al. Blockade of the renin-angiotensin system decreases adipocyte size with improvement in insulin sensitivity. J Hypertens. 2004 Oct; 22(10):1977–82. https://doi.org/10.1097/0004872-200410000-00021 PMID: 15361770

6. Blendea MC, Jacobs D, Stump CS, McFarlane SI, Ogrin C, Bahtiyar G, et al. Abrogation of oxidative stress improves insulin sensitivity in the Ren-2 rat model of tissue angiotensin II overexpression. Am J Physiol Endocrinol Metab. 2005 Feb; 288(2):E353–9. https://doi.org/10.1152/ajpendo.00402.2004 PMID: 15494608

7. Graus-Nunes F, Souza-Mello V. The renin-angiotensin system as a target to solve the riddle of endocrine pancreas homeostasis. Biomed Pharmacother. 2019; 109: 639–645. https://doi.org/10.1016/j.biopha.2018.10.191 PMID: 30404071

8. Yang Y, Wei RB, Wang ZC, Wang N, Gao YW, Li MX, et al. A meta-analysis of the effects of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers on insulin sensitivity in hypertensive patients without diabetes. Diabetes Res Clin Pract. 2015 Mar; 107(3):415–23. https://doi.org/10.1016/j.diabres.2014.11.007 PMID: 25649909

9. Yao J, Gong X, Shi X, Fan S, Chen J, Chen Q. The efficacy of angiotensin converting enzyme inhibitors versus angiotensin II receptor blockers on insulin resistance in hypertensive patients: A protocol for a systematic review and meta-analysis. Medicine (Baltimore). 2020; 99(24):e20674. https://doi.org/10.1097/MD.00000000000020674 PMID: 32541513

10. [No authors listed]. 1999 World Health Organization-International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. J Hypertens. 1999; 17:151–83. PMID: 10067786

11. Krakoff LR, Gillespie RL, Ferdinand KC, Fergus IV, Akinboboye O, Williams KA, et al. 2014 hypertension recommendations from the eighth Joint National Committee (JNC-8) panel members raise concerns for elderly black and female populations. J Am Coll Cardiol. 2014 Jul 29; 64(4):394–402. https://doi.org/10.1016/j.jacc.2014.06.014 PMID: 25060376

12. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003 May 21; 289(19):2560–72. https://doi.org/10.1001/jama.289.19.2560 PMID: 12748199

13. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020 Jan; 43(Suppl 1):S14–S31. https://doi.org/10.2337/dc20-S002 PMID: 31862745

14. World Health Organization, International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation, 2006. Available: http://www.who.int/diabetes/publications_diagnosis_diabetes2006/en/ [Accessed 29 Nov 2018].

15. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009 Oct 20; 120(16):1640–5. https://doi.org/10.1161/CIRCULATIONAHA.109.192644 PMID: 19805654

16. Kassi E, Pervandiou P, Kaltsas G, Chrousoos G. Metabolic syndrome: definitions and controversies. BMC Med. 2011 May 5; 9:48. https://doi.org/10.1186/1741-7015-9-48 PMID: 21542944

17. Ahmed A, Khan TE, Yasmeen T, Awan S, Islam N. Metabolic syndrome in type 2 diabetes: comparison of WHO, modified ATP III & IDF criteria. J Pak Med Assoc. 2012 Jun; 62(6):569–74. PMID: 22755342

18. Sarafidis PA, Lasaridis AN, Nilsson PM, Pikilidou MI, Stafilas PC, Kanaki A, et al. Validity and reproducibility of HOMA-IR, 1/HOMA-IR, QUICKI and McAuley’s indices in patients with hypertension and type II diabetes. J Hum Hypertens. 2007 Sep; 21(9):709–16. https://doi.org/10.1038/sj.jhh.1002201 PMID: 17443211

19. Katz A, Nambi SS, Mather K, Baron AD, Pollmann DA, Sullivan G, et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab. 2000 Jul; 85(7):2402–10. https://doi.org/10.1210/jcem.85.7.6661 PMID: 10902785

20. Sahebkar A. Effect of niacin on endothelial function: a systematic review and meta-analysis of randomized controlled trials. Vasc Med. 2014 Feb; 19(1):54–66. https://doi.org/10.1177/1358863X13515766 PMID: 24391126

21. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions version 5.0. 2. The Cochrane Collaboration, 2009; 2010, Available from www.cochranehandbook.org [updated September 2009].

22. Anan F, Takahashi N, Ooie T, Yufu K, Hara M, Nakagawa M, et al. Effects of valsartan and perindopril combination therapy on left ventricular hypertrophy and arterial stiffness in patients with essential
23. Brown NJ, Kumar S, Painter CA, Vaughan DE. ACE inhibition versus angiotensin type 1 receptor antagonism: differential effects on PAI-1 over time. *Hypertension*. 2002 Dec; 40(6):859–65. https://doi.org/10.1161/01.hyp.000004264.15961.48 PMID: 12468570

24. Derosa G, Cicero AF, Ciccarelli L, Fogari R. A randomized, double-blind, controlled, parallel-group comparison of perindopril and candesartan in hypertensive patients with type 2 diabetes mellitus. *Clin Ther*. 2003 Jul; 25(7):2006–21. https://doi.org/10.1016/s0149-2918(03)80201-1 PMID: 12946547

25. Fogari R, Zoppi A, Preti P, Fogari E, Malamani G, Mugellini A. Differential effects of ACE-inhibition and angiotensin II antagonism on fibrinolysis and insulin sensitivity in hypertensive postmenopausal women. *Am J Hypertens*. 2001 Sep; 14(9 Pt 1):921–6. https://doi.org/10.1016/s0895-7061(01)02140-9 PMID: 11587159

26. Fogari R, Zoppi A, Salvaddeo SA, Mugellini A, Lazzari P, Santoro T, et al. Fibrinolysis and insulin sensitivity in imidapril and candesartan (FISIC study) recipients with hypertension. Hypertens Res. 2011 Apr; 34(4):509–15. https://doi.org/10.1038/hr.2010.260 PMID: 21179101

27. Gilowski W, Krysiak R, Marek B, Okopień B. The effect of short-term perindopril and telmisartan treatment on circulating levels of anti-inflammatory cytokines in hypertensive patients. *Endokrynol Pol*. 2018; 69(6):667–674. https://doi.org/10.5603/EP.a2018.0068 PMID: 30259507

28. Koh KK, Quon MJ, Lee Y, Han SH, Ahn JY, Chung WJ, et al. Additive beneficial cardiovascular and metabolic effects of combination therapy with ramipril and candesartan in hypertensive patients. *Eur Heart J*. 2007 Jun; 28(12):1440–7. https://doi.org/10.1093/eurheartj/ehm101 PMID: 17483542

29. Koh KK, Quon MJ, Han SH, Lee Y, Kim SJ, Koh Y, et al. Distinct vascular and metabolic effects of different classes of anti-hypertensive drugs. *Int J Cardiol*. 2010 Apr 1; 140(2):1239–8. https://doi.org/10.1016/j.ijcard.2008.11.017 PMID: 19059660

30. Napoli C, Omboni S, Borghi C; ZAMES (Zofenopril in Advanced Metabolic Syndrome) Study Group. Fixed-dose combination of zofenopril plus hydrochlorothiazide VS. irbesartan plus hydrochlorothiazide in hypertensive patients with established metabolic syndrome uncontrolled by previous monotherapy. The ZAMES study (Zofenopril in Advanced Metabolic Syndrome). *J Hypertens*. 2016 Nov; 34 (11):2287–97. https://doi.org/10.1097/HJH.0000000000001079 PMID: 27653164

31. Sanchez RA, Masnatta LD, Pesiney C, Fischer P, Ramirez AJ. Telmisartan improves insulin resistance in high renin nonmodulating salt-sensitive hypertensives. *J Hypertens*. 2008 Dec; 26(12):2393–8. https://doi.org/10.1097/HJH.0b013e328328317f PMID: 19008718

32. Yavuz D, Koç M, Toprak A, Akpınar I, Veliöğlu A, Deyneli O, et al. Effects of ACE inhibition and AT1-receptor antagonism on endothelial function and insulin sensitivity in essential hypertensive patients. *J Renin Angiotensin Aldosterone Syst*. 2003 Sep; 4(3):197–203. https://doi.org/10.3317/jrasi.2003.032 PMID: 14668527

33. Samuelsson AM, Boliano E, Mobini R, Larsson BM, Omerovic E, Fu M, et al. Hyperinsulinemia: effect on cardiac mass/function, angiotensin II receptor expression, and insulin signaling pathways. *Am J Physiol Heart Circ Physiol*. 2006 Aug; 291(2):H787–96. https://doi.org/10.1152/ajpheart.00974.2005 PMID: 16565309

34. Wada T, Ohshima S, Fujisawa E, Koya D, Tsuneki H, Sasaoka T. Aldosterone inhibits insulin-induced glucose uptake by degradation of insulin receptor substrate (IRS) 1 and IRS2 via a reactive oxygen species-mediated pathway in 3T3-L1 adipocytes. *Endocrinology*. 2009 Apr; 150(4):1662–9. https://doi.org/10.1210/en.2008-1018 PMID: 19095745

35. Cassis LA, Police SB, Yiannikouris F, Thatcher SE. Local adipose tissue renin-angiotensin system. Curr Hypertens Rep. 2010 Apr; 12(2):109–38. https://doi.org/10.1007/s11906-008-0019-9 PMID: 18474174

36. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014 Feb 5; 311(5):507–20. https://doi.org/10.1001/jama.2013.284427 PMID: 24352797

37. Dietze GJ, Wickimay M, Rett K, Jacob S, Henriksen EJ. Potential role of bradykinin in forearm muscle metabolism in humans. *Diabetes*. 1996 Jan; 45 Suppl 1:S110–4. https://doi.org/10.2337/dbi.45.1_s110 PMID: 8529790

38. Shiuichi T, Cui TX, Wu L, Nakagami H, Takeda-Matsubara Y, Iwai M, et al. ACE inhibitor improves insulin resistance in diabetic mouse via bradykinin and NO. *Hypertension*. 2002 Sep; 40(3):329–34. https://doi.org/10.1161/01.hyp.0000028979.98877.0c PMID: 12215475

39. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. Hypertension. 2001 Apr; 37(4):1053–9. https://doi.org/10.1161/01.hyp.37.4.1053 PMID: 11304502
40. Furuhashi M, Ura N, Higashiura K, Murakami H, Tanaka M, Moniwa N, et al. Blockade of the renin-angiotensin system increases adiponectin concentrations in patients with essential hypertension. *Hypertension*. 2003 Jul; 42(1):76–81. https://doi.org/10.1161/01.HYP.0000078490.59735.6E PMID: 12796280

41. Li J, He JR. Research progress on the biological effects of pancreatic RAAS system activation and blocking methods. *China Journal of Modern Medicine*. 2011; 13(5):125–127. http://kns-cnki-net-cjfd2011&filename=ZHTY201105076&v=xm2xqc4AJtP%25mmd2FllBmve0XjG4SQN%25mmd2FllBmve0XjG4SQNZgLYW9QHoA

42. Frantz ED, Crespo-Mascarenhas C, Barreto-Vianna AR, Aguila MB, Mandarim-de-Lacerda CA. Renin-angiotensin system blockers protect pancreatic islets against diet-induced obesity and insulin resistance in mice. *PLoS One*. 2013 Jul 22; 8(7):e67192. https://doi.org/10.1371/journal.pone.0067192 PMID: 23894285