



# Efficacy and safety of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers in diabetic nephropathy: a systematic review and meta-analysis

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**Background:** Diabetic nephropathy (DN) is one of the most typical microangiopathies caused by diabetes. It often leads enormous physiological and psychological burdens for patients and seriously affects their quality of life. Therefore, effective combination therapy is necessary for these patients. In this study, we performed a meta-analysis to systematically evaluate and discuss the efficacy and safety of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) in the treatment of DN.

**Methods:** The PubMed, Embase, Web of Science, and Medline databases were selected as the sources of the literature search, and the search was limited to studies published in English. Studies related to ACEIs and ARBs in the treatment of DN published from January 2001 to January 2021 were included in this analysis. Meta-analysis was performed to calculate the reinforcement mean difference.

**Results:** In total, eight articles involving 1,893 cases with DN were included in this study. The results of this systematic review and meta-analysis showed that for patients with diabetic nephropathy, there were significant differences in 24-hour proteinuria [mean difference (MD) = -78.46, 95% confidence interval (95% CI): -80.25 to -76.66,  $P < 0.00001$ ], systolic blood pressure (MD = -9.11, 95% CI: -13.44 to -4.78,  $P < 0.0001$ ), and diastolic blood pressure (MD = -3.39, 95% CI: -5.68 to -1.11,  $P = 0.004$ ) between the combined ACEI and ARB group and the single ACEI or ARB group ( $P < 0.05$ ). In terms of safety, in addition to the significant difference in serum potassium (MD = 0.1, 95% CI: 0.05 to 0.15,  $P = 0.0001$ ) between the combined ACEI and ARB group and the single drug group ( $P < 0.1$ ), there were no notable differences in serum creatinine (MD = 0.66, 95% CI: -8.0 to 2.12,  $P = 0.37$ ), creatinine clearance (MD = -0.25, 95% CI: -0.62, 0.11,  $P = 0.17$ ), or the incidence of adverse reactions [odds ratio (OR) = 1.19, 95% CI: 0.81 to 1.75,  $P = 0.37$ ].

**Discussion:** A total of eight studies were included in this meta-analysis. The results showed that for patients with diabetic nephropathy, the combination of ACEI and ARB was more effective than ACEI or ARB alone, and also had higher safety.

**Keywords:** Angiotensin-converting enzyme inhibitors (ACEIs); angiotensin II receptor blockers (ARBs); diabetic nephropathy (DN); meta-analysis

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## Introduction

Diabetic nephropathy (DN) is not only one of the most typical microangiopathies caused by diabetes, but is also an important cause of end-stage renal disease. Patients with diabetes complicated with this disease often show persistent albuminuria, lower limb edema, hypertension, and various progressive renal dysfunction (1-3), which not only imposes physical and psychological burdens on patients' premature delivery, but also seriously affects their quality of life. Therefore, adoption of reasonable drug treatment is valuable. At present, the treatment of such diseases mainly includes angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) (see *Figure 1*). ACEI drugs, such as captopril, benazepril, and enalapril, can achieve therapeutic effects by inhibiting ACE, preventing the transformation of (angiotensin I) Ang I to (angiotensin II) Ang II, so as to reduce the production of Ang II (4,5). ARB drugs, such as candesartan, losartan, and valsartan, can block the binding of Ang II to receptor 1 (AT1), thereby reducing the biological activity of Ang II to achieve therapeutic benefits (6,7). Both of these drug types can act on different levels of Renin-Angiotensin-Aldosterone System (RAAS). However, for patients with advanced DN, it is often difficult to achieve the clinical effect of protecting the kidneys via ACEI or ARB monotherapy (8). Therefore, an increasing number of clinical researchers began to explore new drug treatment schemes on this basis, and consistently investigated the clinical effect of ACEI and ARB combined treatment (9,10). In this study, we performed a meta-analysis to evaluate the efficacy and safety of ACEIs and ARBs in the treatment of DN. We present the following article in accordance with the PRISMA reporting

checklist (available at <https://apm.amegroups.com/article/view/10.21037/apm-22-212/rc>).

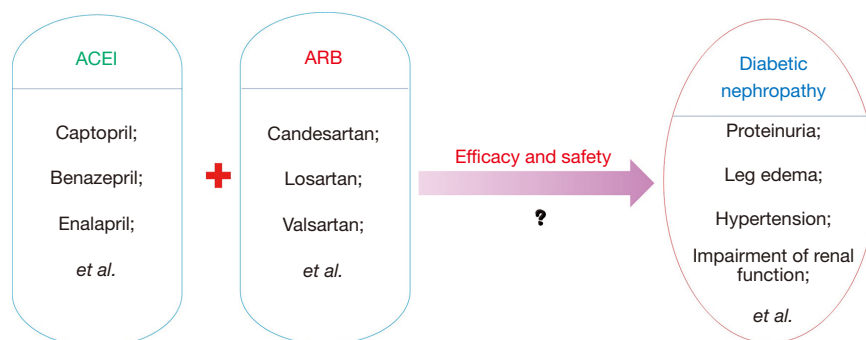
## Methods

### Data sources and search strategy

The PubMed, Embase, Web of Science, and Medline databases were selected as the data sources for this study. The literature search was limited to studies published in English. The literature search methods involved a rapid search of English words as well as a combinatorial search of literature keywords. The keywords were as follows: "angiotensin converting enzyme inhibitors", "angiotensin II receptor antagonist", "diabetic nephropathy", "combined medication", "clinical efficacy", "safety", and "randomized controlled trial". A free combination of these keywords was utilized for database full-text retrieval. At the same time, the relevant citations were tracked by manual retrieval. The literature search and retrieval were conducted on November 20, 2021.

### Inclusion criteria

The inclusion criteria were as follows: (I) randomized controlled trials evaluating the clinical efficacy and safety of ACEIs and ARBs in the treatment of DN; (II) articles with no lack of data on the clinical efficacy and safety of combined treatment of ACEIs and ARBs in DN; (III) the intervention measures involved the administration of ACEI and ARB combined treatment in the test group patients, and ACEI or ARB single-drug treatment for patients in the control group. If the control group was given ACEI plus placebo or ARB plus placebo, it was considered to be



**Figure 1** The possible efficacy and safety of ACEIs plus ARBs in patients with diabetic nephropathy. ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.

equivalent to ACEI or ARB single-drug treatment; (IV) studies involving subjects diagnosed with DN. Patients in the treatment and control groups received regular diet control and oral hypoglycemic agents or insulin therapy to control blood glucose, accompanied by persistent microalbuminuria, and other secondary renal diseases were excluded; and (V) articles that included the main outcome indicators set out in this study.

### *Exclusion criteria*

The exclusion criteria were as follows: (I) studies involving non-DN patients; (II) non-randomized controlled trials; (III) articles with incomplete analysis data; (IV) repeatedly published studies; and (V) studies involving early DN patients with non-microalbuminuria.

### *Selection of literature*

Two researchers independently performed the literature screening. Firstly, the titles and abstracts of the articles were read to exclude studies that obviously did not meet the inclusion requirements. Subsequently, we read the full texts of the remaining literatures for further screening. Next, two researchers performed cross-checking to exclude doubtful articles. Lastly, a third researcher was invited to assist in arbitration.

### *Data extraction*

Two researchers independently extracted the relevant data and information, including the first author, publication time, trial design, intervention measures, follow-up time, endpoint events, sample size, as well as the average age, sex ratio, and duration of disease of patients. All data were independently extracted and analyzed by two authors. In cases of divergent opinions, a comprehensive evaluation was conducted by a third party.

### *Literature quality assessment*

The Newcastle-Ottawa scale (NOS score method) was used for treatment evaluation of the included articles, with higher scores indicating better quality literature and less bias. We found that four articles scored 5 points, two articles scored 4 points, and two articles scored 2 points, which was of good quality.

### *Statistical analysis*

RevMan5.3 software provided by Cochrane Collaboration Network was used for meta-analysis. The weighted mean difference (MD) was used for measurement data, the odds ratio (OR) and 95% CI were used for counting data to report the size of combined effect, and forest maps were used to display the results. Also, the *Q* statistic test was used to examine the heterogeneity among the studies; if there was no statistical heterogeneity ( $P > 0.1$ ,  $I^2 \leq 50\%$ ), the fixed effects model is used to analyze the data. However, if there was statistical heterogeneity ( $P \leq 0.1$ ,  $I^2 > 50\%$ ), the data included in the study was preliminarily analyzed and evaluated. We then judged whether there was obvious research heterogeneity or methodological heterogeneity by reading the full texts of the included literature several times. Subsequently, sensitivity analysis was carried out on the outcome indicators of each study one-by-one, and new data were merged after excluding unqualified studies. Finally, we checked whether the overall effect amount had changed. If the result after each elimination was the same as the previous total consolidation result, this indicates that the result was relatively stable. However, if the aforementioned methods could not explain the causes of heterogeneity, the data was combined and analyzed using a random effects model.  $P < 0.05$  was considered statistically significant for all the above effect analyses.

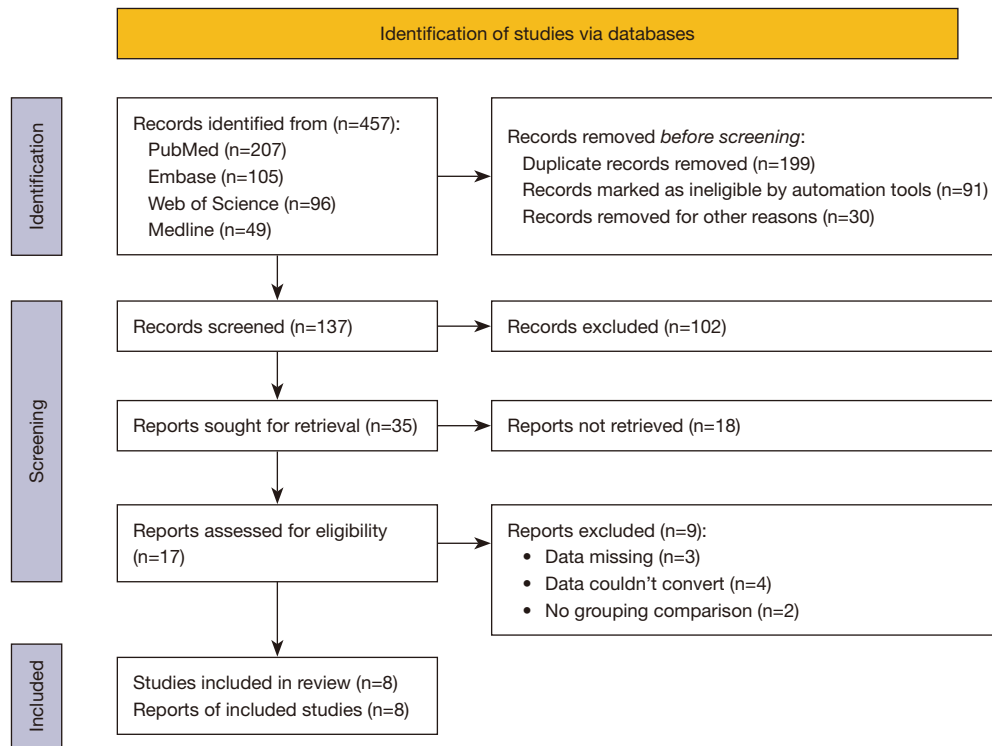
## **Results**

### *Literature search and screening results*

In total, 457 articles were initially retrieved. 199 repetitive literatures, 91 ineligible literatures, and 30 other irrelevant studies were removed. After reading the titles and abstracts of the remaining studies, 102 articles that did not meet the inclusion criteria were removed. Furthermore, 18 reviews and articles with incomplete data were excluded after intensive reading. The references of the included studies were also searched and read. Finally, eight articles were included, with a total of 1,893 DN patients (*Figure 2*). The basic and common characteristics of the included studies, as well as the excluded literature and the reasons for exclusion are listed in *Table 1*.

### *Basic characteristics of literatures*

The basic characteristics and NOS scores of the included articles are shown in *Table 2*.



**Figure 2** Literature search and selection flow chart.

**Table 1** Excluded literatures and reasons for exclusion (not exhaustive)

Serial number	Author	Date of publication	Reason for exclusion
1	Krairittichai U <i>et al.</i> (11)	2009	No group comparison data
2	Stanton RC (12)	2013	No enough data
3	Luno J <i>et al.</i> (13)	2005	No group comparison data
4	Rodriguez F <i>et al.</i> (14)	2021	Data could not be transformed

## Meta-analysis results

### Efficacy

#### Twenty-four-hour proteinuria

Six articles (15,17,18,19,21,22) reported the clinical effect of ACEI and ARB combination therapy on the 24-hour proteinuria in patients with DN. There were 492 cases in the combined drug group and 492 cases in the single drug group. There was heterogeneity among the literatures ( $I^2=99\%$ ,  $P<0.00001$ ). No cause of heterogeneity was identified through analysis, so the random effect model was used for data analysis. The results showed that the urinary protein in the combined drug group was lower than that in the single drug group within 24 hours, and the difference

was statistically significant (MD = -78.46, 95% CI: -80.25 to -76.66,  $P<0.00001$ ), as shown in *Figure 3*.

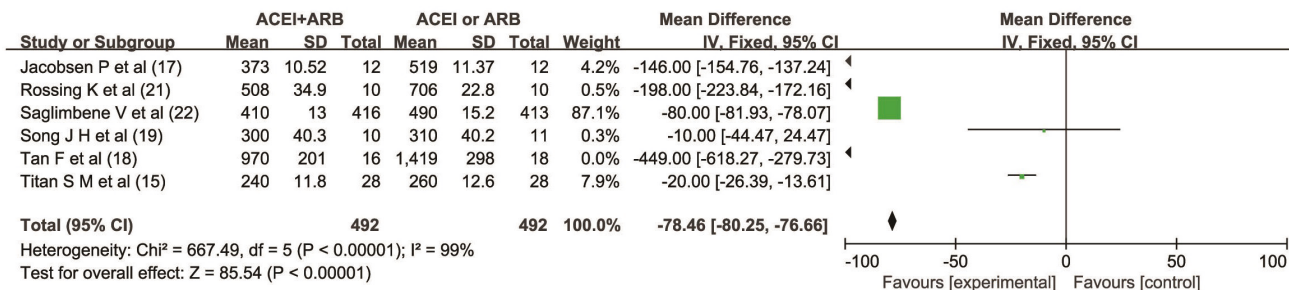
#### Systolic blood pressure

Three articles (15,16,18) reported the clinical effect of the combined use of ACEIs and ARBs on systolic blood pressure in patients with DN. There were 92 cases in the combined drug group and 94 cases in the single drug group. There was no heterogeneity between the literatures ( $I^2=0\%$ ,  $P=0.69$ ), so the fixed effect model was used for data analysis. The results showed that the clinical index of systolic blood pressure in the combined ACEI and ARB group was lower than that in the ACEI or ARB monotherapy group, and the difference was statistically significant (MD = -9.11, 95%

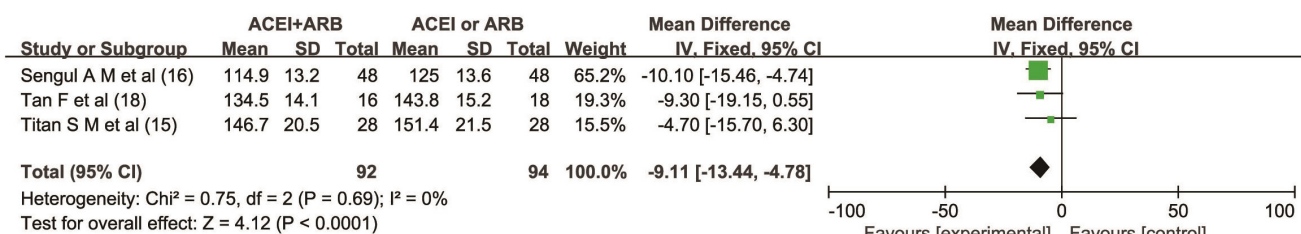
**Table 2** Summary of the basic characteristics of the included literature

Serial number	Author	Study location	Date of publication	Total cases	Efficacy and safety	Quality score (points)
1	Titan SM <i>et al.</i> (15)	Brazil	2011	56	(I)(II)(III)(V)(VII)	5
2	Sengul AM <i>et al.</i> (16)	Istanbul, Turkey	2006	192	(II)(III)(IV)(V)(VI)	5
3	Jacobsen P <i>et al.</i> (17)	Denmark	2002	24	(I)(IV)(VI)(VII)(VIII)	5
4	Tan F <i>et al.</i> (18)	Singapore	2010	34	(I)(II)(III)(V)	4
5	Song JH <i>et al.</i> (19)	Republic of Korea	2006	21	(I)(IV)(V) (VI)(VII)	5
6	Fernandez Juarez G <i>et al.</i> (20)	Oviedo, Spain	2013	133	(IV)(VI)(VII)	3
7	Rossing K <i>et al.</i> (21)	Denmark	2003	20	(I)(IV)(VI)	3
8	Saglimbene V <i>et al.</i> (22)	Sydney, Australia	2018	1,413	(I)(IV)(VII)(IX)	4

(I) 24 h proteinuria; (II) systolic blood pressure; (III) diastolic blood pressure; (IV) serum creatinine; (V) creatinine clearance; (VI) serum potassium; (VII) adverse event; (VIII) glomerular filtration rate; (IX) hyperkalemia.



**Figure 3** Effect of ACEI plus ARB group vs. ACEI or ARB group on 24-hour urinary protein. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.



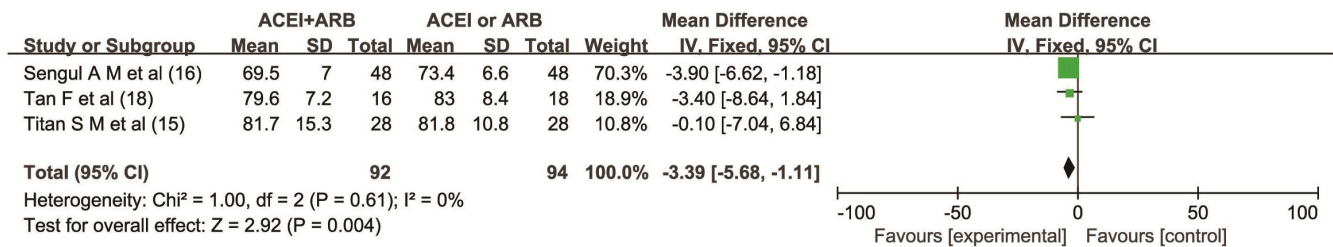
**Figure 4** Effect of ACEI plus ARB group vs. ACEI or ARB group on systolic blood pressure. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

CI: -13.44 to -4.78,  $P < 0.0001$ ) as shown in *Figure 4*.

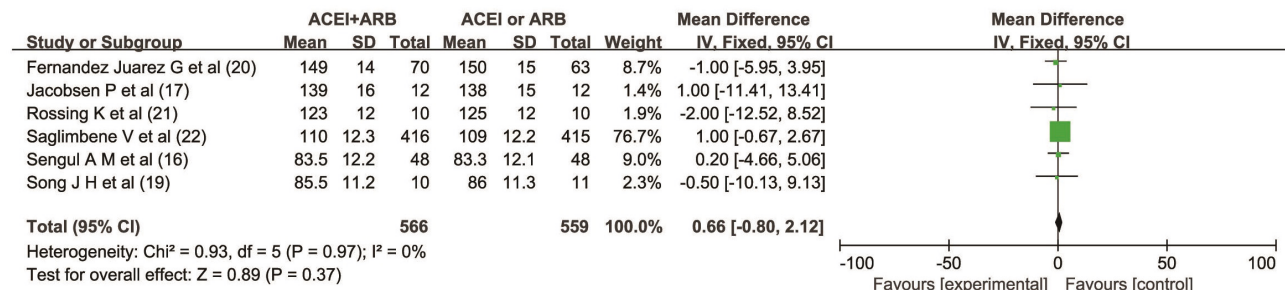
**Diastolic blood pressure**

Three articles (15,16,18) reported the clinical effect of combination therapy of ACEI and ARB on diastolic blood pressure in patients with DN. There were 92 cases in the combined drug group and 94 cases in the single drug group.

There was no heterogeneity among the articles ( $I^2=0\%$ ,  $P=0.61$ ), so the fixed effect model was used for data analysis. The results showed that the clinical index of diastolic blood pressure in the combined ACEI and ARB group was lower than that in the ACEI or ARB alone group, and the difference was statistically significant (MD = -3.39, 95%



**Figure 5** Effect of ACEI plus ARB group vs. ACEI or ARB group on diastolic blood pressure. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.



**Figure 6** Effect of ACEI plus ARB group vs. ACEI or ARB group on serum creatinine. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

CI: -5.68 to -1.11, P=0.004), as shown in *Figure 5*.

## Safety

### Serum creatinine

Six articles (16,17,19,20,21,22) reported the effect of combined use of ACEI and ARB on serum creatinine in patients with DN. There were 566 cases in the combined drug group and 559 cases in the single drug group. There was no heterogeneity among the literatures (I<sup>2</sup>=0%, P=0.97), so the fixed effect model was used for data analysis. The results showed that there was no significant difference in the clinical index of diastolic blood pressure between the ACEI and ARB combined group and the ACEI or ARB monotherapy group (MD =0.66, 95% CI: -0.80 to 2.12, P=0.37), as shown in *Figure 6*.

### Creatinine clearance

Four articles (15,16,18,19) reported the effect of the combined use of ACEI and ARB on the creatinine clearance rate in patients with DN. There were 102 cases in the combined drug group and 105 cases in the single drug group. There was heterogeneity among the literatures (I<sup>2</sup>=80%, P=0.002). No cause of heterogeneity was found through analysis, so the random effect model was used

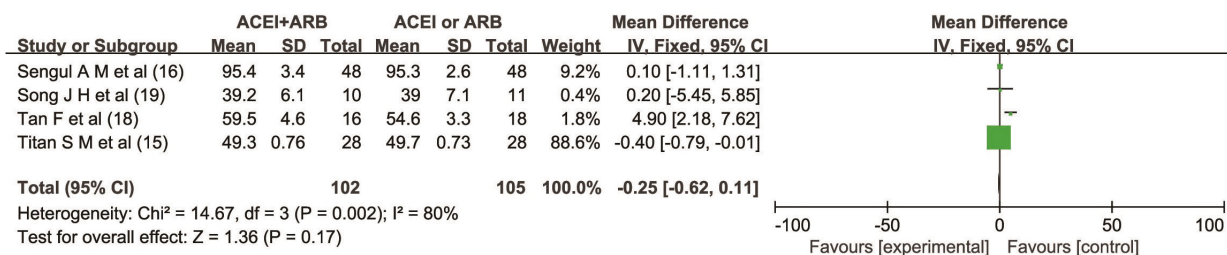
for data analysis. The results showed that there was no significant difference in the clinical index of creatinine clearance between ACEI and ARB combined group and ACEI or ARB monotherapy group (MD =-0.25, 95% CI: -0.62 to 0.11, P=0.17), as shown in *Figure 7*.

### Serum potassium

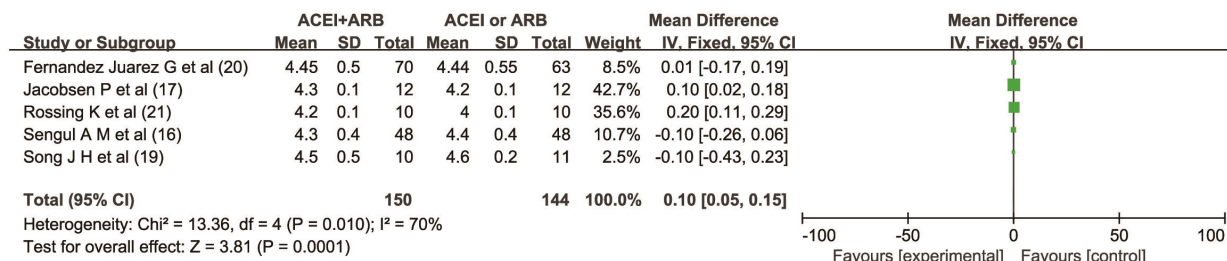
Five articles (16,17,19,20,21) reported the effect of the combined use of ACEI and ARB on serum potassium in patients with DN. There were 150 cases in the combined drug group and 144 cases in the single drug group. There was heterogeneity among the literatures (I<sup>2</sup>=70%, P=0.01). No cause of heterogeneity was found through analysis, so the random effect model was used for data analysis. The results showed that the serum potassium level in the combined drug group was lower than that in the single drug group, and the difference was statistically significant (MD =0.10, 95% CI: 0.05 to 0.15, P=0.0001), as shown in *Figure 8* below.

### Adverse events

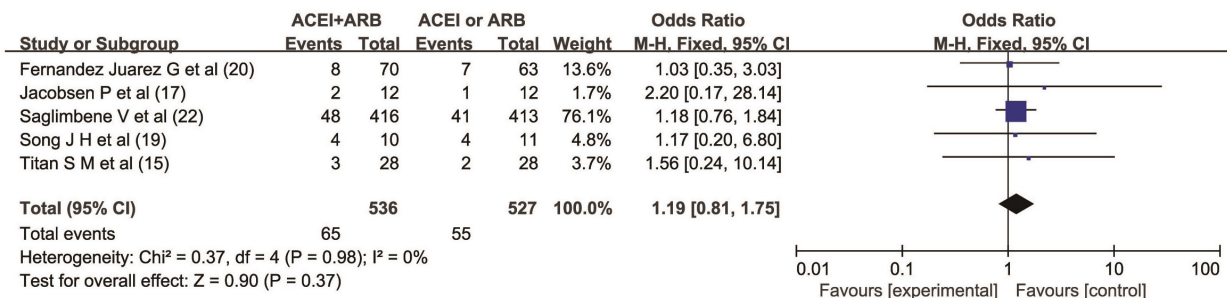
Five articles (15,17,19,20,22) reported the adverse reactions of ACEIs and ARBs in patients with DN. There were 536 cases in the combined drug group and 527 cases in the single drug group. There was no heterogeneity among the



**Figure 7** Effect of ACEI plus ARB group *vs.* ACEI or ARB group on creatinine clearance. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.



**Figure 8** Effect of ACEI plus ARB group *vs.* ACEI or ARB group on serum potassium. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.



**Figure 9** Effect of ACEI plus ARB group *vs.* ACEI or ARB group on adverse events. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

literatures (I<sup>2</sup>=0%, P=0.98), so the fixed effect model was used for data analysis. The results showed that there was no significant difference in the incidence of adverse reactions between the ACEI and ARB combined group and the ACEI or ARB monotherapy group (OR =1.19, 95% CI: 0.81 to 1.75, P=0.37), as shown in *Figure 9*.

### Publication bias

Publication bias analysis was not performed, as only a small number of articles were included in this study.

### Discussion

DN is one of the most common complications in diabetic patients. Its early pathological changes are mainly characterized by thickening of the glomerular basement membrane, increased permeability, proliferation of mesangial cells, and abnormal increase of extracellular matrix, leading to glomerular sclerosis in patients (23,24). If these patients do not receive effective means of clinical intervention and drug treatment, their condition may easily develop into the clinical stage of DN. At this time,

patients will not only be accompanied by a large amount of proteinuria, but also have clinical symptoms of hypertension and severe renal function impairment. Therefore, it has high research significance to improve the physiological status and quality of life of patients with DN through effective intervention (25,26).

At present, treatment of DN includes glucose lowering, lipid lowering, blood pressure control, administrative micro blog, anti-oxidative stress, and renal function (27). ACEI or ARB drugs are widely used in treatment. Clinical studies have confirmed that these two drug types can not only effectively reduce the excretion of urinary protein and reduce the level of blood pressure, but also have high safety (28). However, the clinical efficacy and safety of these two drugs in the treatment of DN are still in the exploratory stage (29). Therefore, this systematic analysis and evaluation of existing research materials/data is important for further clinical guidance.

The results of this systematic review and meta-analysis suggest that in terms of effectiveness of drug use, patients with DN who received combined therapy with ACEIs and ARBs had significantly lower 24 h urine protein, systolic blood pressure, and diastolic blood pressure than those treated with ACEIs or ARBs alone, and the difference between the two groups was statistically significant ( $P < 0.05$ ). In terms of safety, in addition to the significant difference in serum potassium between the combined ACEI and ARB group and the single-drug group ( $P < 0.05$ ), there were no significant differences in serum creatinine, creatinine clearance, and the incidence of adverse reactions ( $P > 0.05$ ).

## Conclusions

In this meta-analysis of the clinical efficacy and safety of ACEIs and ARBs in patients with DN, a total of eight articles were included. The results showed that the combination of ACEIs and ARBs had better clinical effects on the control of 24-hour urine protein, systolic blood pressure, and diastolic blood pressure in patients with DN, as well as higher safety and a lower incidence of adverse events.

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## Footnote

*Reporting Checklist:* The authors have completed the

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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